CARDIAC DRUGS

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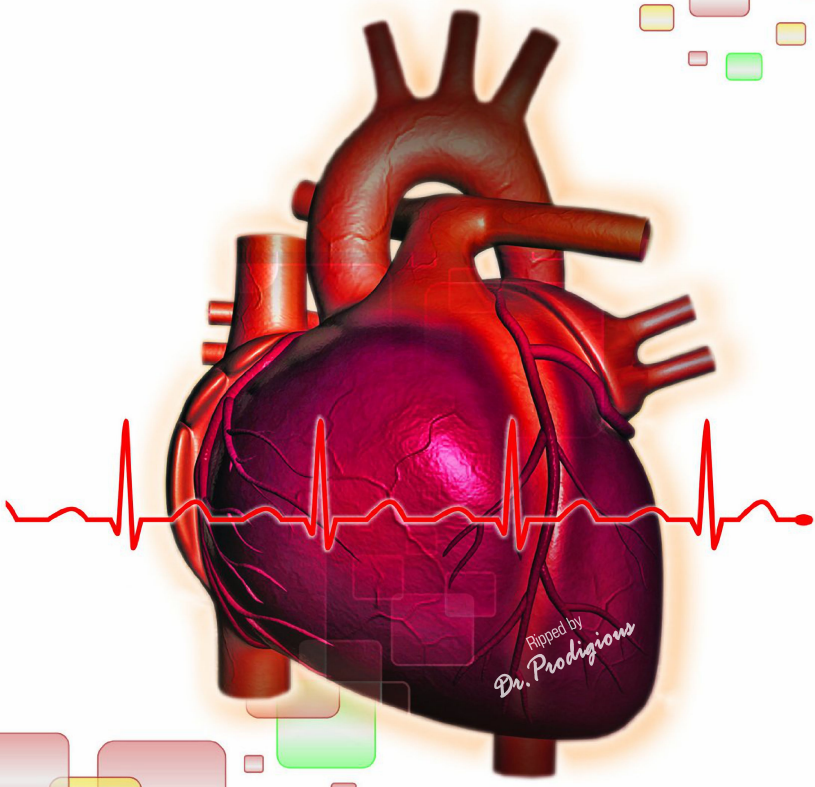
ERIC J TOPOL



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Our wives
Docey Chatterjee and Susan Topol

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PREFACE

The book *Cardiac Drugs* presents an evidence-based approach towards the pharmacologic agents that are used in various clinical conditions in cardiovascular medicine.

The classes of drugs, such as renin-angiotensin-aldosterone blocking drugs, positive inotropic drugs, diuretics, and anti-hypertensive drugs are discussed in great details with their pharmacokinetics, pharmacodynamics, indications, contra-indications, and doses. Drugs for heart failure, acute coronary syndromes, and pulmonary hypertension are also discussed similarly. Pharmacologic agents, which are in development for various clinical syndromes are also discussed. The unique feature of this book is the detailed discussion on the guidelines of the American College of Cardiology/American Heart Association for the use of pharmacologic agents in various clinical conditions.

Kanu Chatterjee

Eric J Topol

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1 CHAPTER

Angiotensin, Aldosterone, and Renin Inhibition in Cardiovascular Disease

Abdallah Kamouh,
Gary S Francis, Kanu Chatterjee

ANGIOTENSIN CONVERTING ENZYME INHIBITORS

Introduction

Angiotensin converting enzyme inhibitors (ACEIs) have emerged as one of the most important and high impact classes of drugs used today in cardiovascular medicine.[1] These agents were developed for use in patients with hypertension, but their penetration into cardiovascular medicine has been far beyond the treatment of high blood pressure. ACEIs protect the heart and prevent remodeling in acute myocardial infarction (MI), prevent the development of left ventricular (LV) remodeling in patients with progressive heart failure (HF), and reduce mortality in patients with a variety of cardiovascular risk factors.[2,3]

Although the renin-angiotensin-aldosterone system (RAAS) evolved over millions of years and affords a certain survival advantage, there is an overarching hypothesis that its activation in cardiovascular disease states may be maladaptive and may drive much of the pathophysiology. Over the years, it has become increasingly clear that the RAAS contributes importantly to cardiovascular diseases, including hypertension, acute MI, and HF.[4] Drugs that block the RAAS, such as ACEIs and angiotensin receptor blockers (ARBs) are associated with prevention of cardiac remodeling, less progression of HF, and reduced mortality.

The emergence of ARBs was important, because these agents are very well tolerated and appear to provide benefits similar to ACEIs in most clinical trials.[5,6] In recent years, it has become clearer that mineralocorticoid receptor (MR) blockers or aldosterone antagonists are also helpful in most patients with symptomatic HF. Direct renin inhibitors (DRIs) are emerging, and it is expected that these agents will also be useful in the treatment of selected patients with hypertension and possibly other cardiovascular disorders.

In summary, drugs that inhibit the RAAS are a very important form of therapy with a strong safety profile and a track record of improved survival across a wide array of acute and chronic cardiovascular disorders, especially hypertension, MI, and HF. They have been successful beyond our expectations and now form the cornerstone of treatment for many cardiovascular disorders.

The purpose of this chapter is to detail how these drugs, which are designed to block the RAAS, are used to treat patients with cardiovascular disease.

Mechanism of Action and Pharmacology

ACEIs provide both primary and secondary protection against cardiovascular diseases. Their mechanism of action is related to the reduction of the adverse effects of angiotensin II on multiple organs (Figure 1). Angiotensin I, a decapeptide, is a precursor of angiotensin II and is a product of the interaction between renin [molecular weight (MW) = 40,000] and angiotensinogen (MW = 60,000). Angiotensin I is cleaved by ACE to form the highly active octapeptide, angiotensin II. Most of this conversion takes place in the endothelial surface of the lung that is rich in ACE (Figure 2).

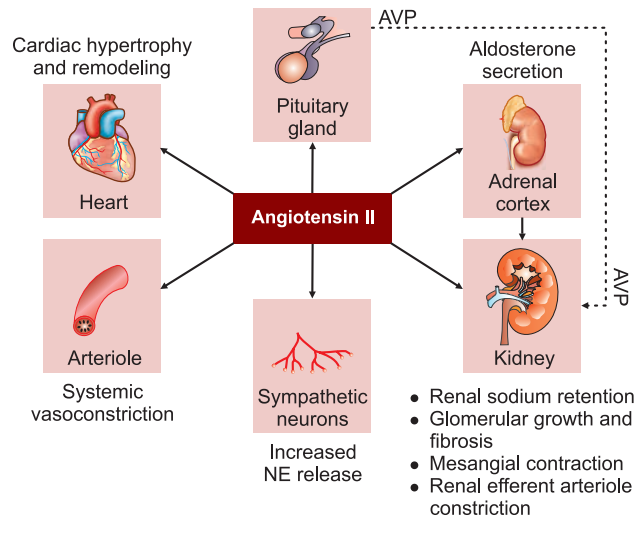
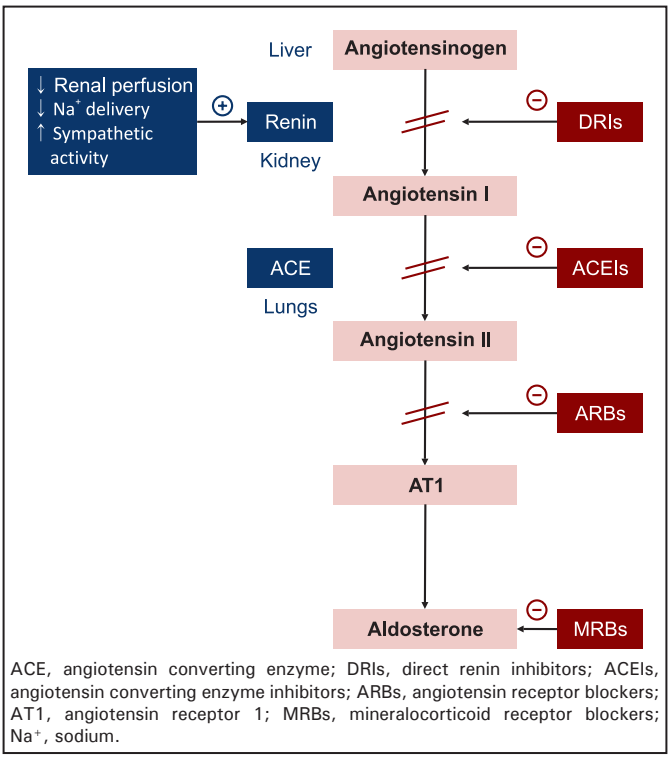


FIGURE 1. The biologic activities of angiotensin II on different organs. They include myocardial hypertrophy and remodeling, arteriolar vasoconstriction, facilitation of NE release from sympathetic neurons, release of AVP from the posterior pituitary gland, secretion of aldosterone from the adrenal cortex, sodium retention, glomerular fibrosis, mesangial contraction, and constriction of the renal efferent arteriole.



ACE, angiotensin converting enzyme; DRIs, direct renin inhibitors; ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers; AT1, angiotensin receptor 1; MRBs, mineralocorticoid receptor blockers; Na^+, sodium.

FIGURE 2. Renin-angiotensin-aldosterone system and different inhibitors. Renin is a proteolytic enzyme released primarily by the kidneys. This release is stimulated by decrease in kidney perfusion, decrease in Na^+ delivery to the distal tubules, and increase in sympathetic nerve activation. Renin acts upon its substrate angiotensinogen secreted by the liver to form angiotensin I. Vascular endothelium, particularly in the lungs, has ACE that cleaves off 2 amino acids to form the octapeptide angiotensin II. Angiotensin II acts on its receptor AT1 to generate a host of biological activities, including the release of aldosterone from the adrenal gland.

Angiotensin II Effects on Different Receptor Subtypes

Angiotensin II acts on its cognate receptor subtype 1 (AT1) to generate a host of biological activities (Figure 1). Angiotensin II releases aldosterone from the adrenal cortex, which regulates salt and water metabolism, facilitates the release of locally synthesized norepinephrine, causes direct vasoconstriction of arteries and veins, has a proliferative effect on vascular smooth vessel, promotes cardiac myocyte hypertrophy, and stimulates fibroblasts to synthesize collagen leading to fibrosis of tissues (Figure 1). Angiotensin II also acts directly on the central nervous system to drive thirst, and on the renal tubules to promote salt and water retention, that helps to regulate intravascular volume. Angiotensin II is an important participant in wound healing, but its long-term effects on myocardial "healing" can lead to changes

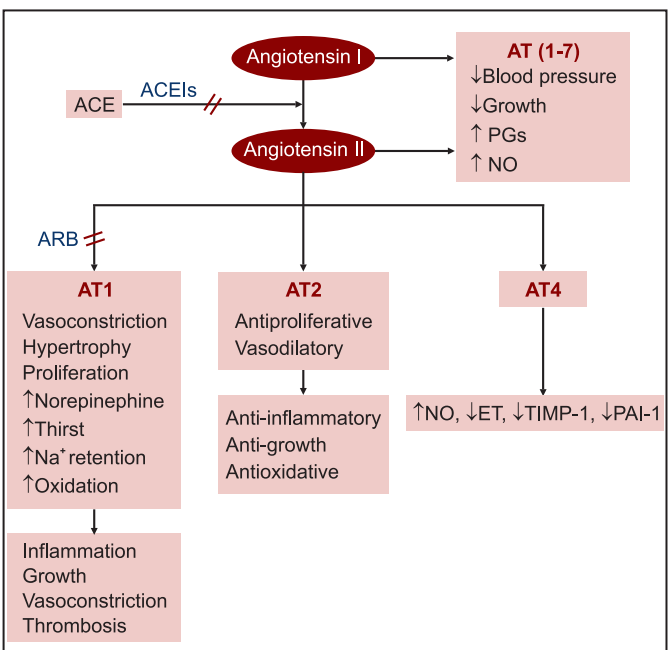
in cardiac geometry, including chamber enlargement and scar formation, a process referred to as myocardial remodeling. In contrast, angiotensin II receptor subtype 2 (AT2) has effects that counter AT1 receptor activation, as AT2 receptor activation subserves vasodilation, and is responsible for the antifibrotic and anti-inflammatory effects. Selective blockade of AT1 receptors with ARBs leaves the AT2 receptors open for stimulation by angiotensin II. The role of AT2 receptors in human physiology is less understood, whereas the role of AT1 receptors is more clearly linked to clinically recognized events (Figure 3).

Alternate Pathways of Angiotensin II Generation

Non-ACE pathways are also present in humans and involve chymase-like serine proteases that increase the formation of angiotensin II. Chymase inhibition like ACE inhibition prevents cardiac fibrosis and improves diastolic function,[7] but its quantitative role in the pathophysiology of cardiovascular disease is less clear.

Angiotensin Converting Enzyme Inhibitors and Bradykinin

ACEIs not only decrease the formation of angiotensin II, but also increase bradykinin at local tissue sites. ACE is identical to



ACEIs, angiotensin converting enzyme inhibitors; AT, angiotensin receptor; ET, endothelin; NO, nitric oxide; Na^+, sodium; PAI, plasminogen activator inhibitor; tPA, tissue plasminogen activator; PGs, prostaglandins; TIMP, tissue inhibitor of metalloproteinase.

FIGURE 3. Angiotensin II receptor subtypes and their roles.

TABLE 1

Therapeutic Uses of Angiotensin Converting Enzyme Inhibitors
▪ As antihypertensives
▪ Prevention or reversal of left ventricular hypertrophy and cardiac remodeling
▪ Provide protection against sudden death and second myocardial infarction after acute myocardial infarction
▪ Improvement in survival and hemodynamic parameters in systolic heart failure
▪ Prevention or delay in progression of diabetic and nondiabetic nephropathy

kininase II, an enzyme that inactivates bradykinin; therefore, ACEIs lead to an increase in local tissue bradykinin. Bradykinin acts on its receptors to release nitric oxide and prostaglandins, both of which promote vasodilation and may be important in preventing cardiac remodeling.[8] It is possible that the blood pressure lowering effect of ACEIs is in part through local nitric oxide production, which tends to have a favorable effect on the endothelium. The accumulation of bradykinin is perhaps responsible in part for some of the side effects of ACEIs, such as cough and angioedema.

Major Indications

ACEIs are indicated for the treatment of hypertension, chronic systolic HF, acute MI, chronic ischemic heart disease, and renal diseases, such as diabetic and hypertensive nephropathies (Table 1). These drugs also promote cardiovascular protection in patients with risk factors for cardiovascular diseases.[2]

Side Effects

Side effects of ACEIs are discussed in table 2.

Cough

One of the most common side effects of ACEIs is dry, nonproductive, and persistent cough. Patients with HF may also cough because of pulmonary congestion; therefore, one cannot assume that all cough in patients taking ACEIs is due to the drug. The incidence of cough in patients taking ACEIs is being reported to be as high as 15%, but the need to withdraw the drug because of cough arises in about 5% of patients.[2] The mechanism of the cough is not entirely clear but is likely due to the increased sensitivity of the cough reflex and to the formation of local bradykinin and prostaglandin in the proximal airways. The usual strategy when patient does not tolerate an ACEI is to change to an ARB.

TABLE 2

Side Effects of Angiotensin Converting Enzyme Inhibitors	
Side effects	*Comment*
Cough	5–15% of patients
Angioedema	1–2% of patients
Hypotension	Only 1–2% patients need to discontinue the drug
Hyperkalemia	More commonly seen in those with: ▪ Renal dysfunction ▪ Diabetics ▪ Concomitant use of nonsteroidal anti-inflammatory drugs ▪ Aldosterone antagonists ▪ Potassium supplementation
Worsening renal function and acute renal failure	High risk in patients with: ▪ Chronic kidney disease ▪ Hypertensive nephrosclerosis ▪ Diabetics
Allergic skin rash	Reported more with captopril (rare)
Neutropenia	▪ Mainly with captopril. ▪ High risk in patients with underlying renal dysfunction and connective tissue disorders
Dysgeusia	Mainly with captopril (rare)
Teratogenicity	In all trimesters of pregnancy

Hypotension

Hypotension, which can be symptomatic or asymptomatic, is a common consequence of ACEI therapy. In the ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) trial,[9] hypotensive symptoms sufficient to discontinue the drug occurred in 1.7% of the patients who received ramipril and/or telmisartan.

Low systolic blood pressure is perceived by many physicians to be a contraindication to the use of ACEIs, particularly in the setting of HF. However, in the absence of symptoms, asymptomatic low blood pressure is usually well tolerated and is typically not a reason to withdraw the drug. ACEIs are at least as effective in improving outcomes in patients with systolic blood pressure less than 100 mmHg as in those with normal or high blood pressure.[10] In patients with HF, hypotension and/or the inability to tolerate an ACEI due to symptomatic hypotension are powerful predictors of a poor prognosis.[10-12] Although patients with HF and low systolic blood pressure have a greater risk for developing symptoms, they also receive a similar benefit as patients without low blood pressure. This is probably because vasodilator can increase stroke volume, which then maintains or even increases systolic blood pressure in some patients with HF. Those patients with HF and the lowest systolic blood pressure are at the highest

risk of dying or being hospitalized independent of other baseline characteristics.[12] Patients with a marked hyperreninemic state, such as following a substantial recent diuresis, are especially prone to develop abrupt and sometimes severe symptomatic hypotension following the use of ACEIs.

When abrupt reduction in blood pressure occurs following the use of ACEIs, it may also be due to venous rather than arterial vasodilation. Symptomatic hypotension due to ACEIs can be minimized by beginning with the lowest dose of a short-acting drug, such as captopril. It can be often quickly treated by having the patient lie down and elevating the legs modestly.

In summary, asymptomatic low blood pressure should not be necessarily viewed as a contraindication for the use of ACEIs. However, if symptoms of low blood pressure persist, ACEIs may have to be withdrawn.

Hyperkalemia

ACEIs increase the serum potassium (K^+), mainly through the inhibition of aldosterone formation, which normally promotes urinary potassium excretion. The overall incidence of hyperkalemia (serum K^+ >5.5 mEq/L) in patients treated with an ACEI or ARB in carefully conducted clinical trials is approximately 3.3%.[2,9] Hyperkalemia is always a risk when patients are taking ACEIs, particularly, if there is associated impaired renal function, volume depletion, diabetes, recent use of contrast medium, and concomitant use of ARBs, MR blockers, or nonsteroidal anti-inflammatory drugs. Follow-up monitoring of serum K^+ is essential when managing patients taking ACEIs.

Renal Insufficiency

It can occur in patients receiving ACEIs, but is typically modest and reversible. It is believed that the transiently reduced renal function from ACEIs is a consequence of efferent arteriolar vasodilation. The efferent glomerular arterioles are normally tightly vasoconstricted by excessive angiotensin II in HF, leading to a helpful maintenance of intraglomerular hydraulic pressure and preserved filtration. When an ACEI or ARB is introduced in the setting of HF, there is dilation of efferent glomerular arterioles, thus, leading to reduced intraglomerular hydraulic pressure and reduced glomerular filtration. For example, it is not unusual to observe a 20% increase in serum creatinine with the use of ACEIs, but this is not usually a reason to reduce or stop the ACEI therapy. Often, the rise in serum creatinine occurs a few days after the institution of therapy; therefore, renal function should be checked after initiation of ACEI therapy. Rarely, irreversible renal failure

can occur when ACEIs are used in patients with bilateral renal artery stenosis or in patient with oliguric acute renal failure.

Angioedema

Therapy with ACEIs is rarely associated with the occurrence of angioedema. It is estimated to occur from 0.1 to 2%.[13,14] The exact mechanism behind the development of angioedema associated with ACEIs therapy is unknown; however, various theories have been proposed, including inhibition of bradykinin, antigen-antibody interactions, deficiency of complement 1-esterase inactivator, or impaired breakdown of substance P. The development of angioedema is more common in African-Americans and usually occurs within days of initiating ACEI therapy. However, it can take months or even years after initiating treatment. Very rarely, angioedema can be fatal. Although switching to ARB is the usual strategy, there have been rare, isolated instances whereby ARBs have also caused angioedema.[15,16]

Contraindications

Pregnancy

ACEIs and ARBs are contraindicated during each trimester of pregnancy, as they are known to be teratogenic.[17] Typically, one does not employ ACEI therapy in women of childbearing age unless there are unusual circumstances. Other contraindications of ACEIs are discussed in table 3.

Clinical Evidence

Angiotensin Converting Enzyme Inhibitors and Heart Failure

It is well established that the RAAS is highly active in patients with HF. The RAAS, like the sympathetic nervous system (SNS), likely represents an ancient evolutionary advantage. Presum-

TABLE 3

Contraindications of Angiotensin Converting Enzyme Inhibitors
▪ Bilateral renal artery stenosis
▪ Acute oliguric renal failure
▪ Pregnancy (all trimesters)
▪ History of angioedema or hypersensitivity to angiotensin converting enzyme inhibitor
▪ Cardiogenic shock
▪ History of neutropenia due to previous use of angiotensin converting enzyme inhibitors, especially in patients with collagen vascular disease

ably, the release of renin and the action of angiotensin II and aldosterone have a temporary favorable effect on maintaining blood pressure and intravascular volume in patients with low cardiac output. These are recognized as favorable short-term adaptations, as if the body is trying to maintain intravascular volume and perfusion pressure to vital organs in the face of a falling cardiac output and/or volume depletion. However, the RAAS and the SNS can become persistently active and eventually promote maladaptive effects on the heart and the vascular system. For example, sodium and fluid retention ensues, and heightened vascular tone contributes to higher impedance to LV ejection, which further reduces cardiac output. Importantly, the chronic effects of the RAAS and the SNS can be directly toxic to the myocardium and are associated with myocyte hypertrophy and the development of myocardial fibrosis. These changes are recognized clinically by increased peripheral vasoconstriction, tachycardia, LV remodeling, increased LV wall stress, release of brain natriuretic peptide, fluid and sodium retention, tissue congestion, dilutional hyponatremia, and anemia. This constellation of abnormalities represents the clinical syndrome of congestive HF. It then stands to reason that drugs designed to reduce excessive angiotensin II activity (ACEIs and ARBs), aldosterone activity (spironolactone and eplerenone), and SNS activity (β-blockers) should be highly effective in the treatment of patients with HF. The first group of these drugs to be widely used to treat HF was the ACEIs.

Beneficial effects of Angiotensin Converting Enzyme Inhibitors in Heart Failure: Vasodilators or Antiremodeling Agents

Although many believe that the acute vasodilator effects of ACEIs and the subsequent increase in cardiac output and fall in venous pressure represent the dominant mechanism of action, it is more likely that the highly favorable long-term effects of ACEIs are due to their ability to inhibit the consequences of excessive angiotensin II on various organs, especially remodeling. They also reduce SNS activity by desensitizing effectors organs to norepinephrine and by vitiating its release from sympathetic neurons. This inhibitory effect on the SNS might also be contributing to an antiarrhythmic effect of ACEIs and possibly to the reduction of sudden death observed in several HF trials.[18]

ACEIs should be considered more as antiremodeling agents than as acute vasodilators or afterload reducing drugs. The amount of vasodilation and improvement in cardiac output in response to ACEIs are relatively modest. Although there is a reduction in the vascular resistance, the direct antiremodeling

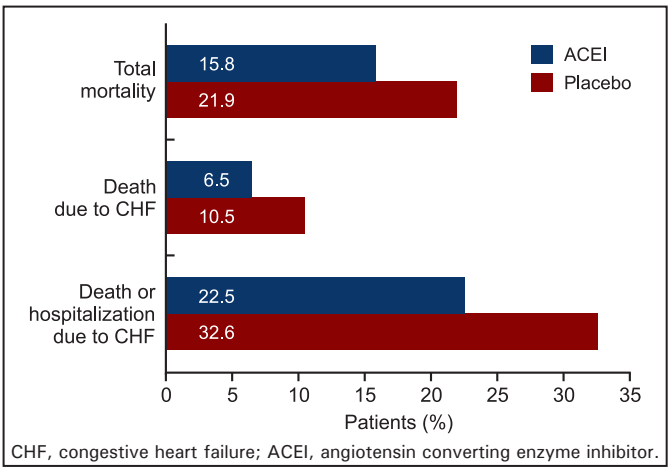


FIGURE 4. Results of treatment with ACEIs in patients with systolic heart failure are illustrated. The results of 32 randomized trials are summarized. Angiotensin converting enzyme inhibitors were shown to decrease mortality and morbidity of patients with systolic heart failure. *Data from* Garg R, Yusuf S. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. Collaborative Group on ACE Inhibitor Trials. *JAMA*. 1995;273:1450-6.

effect on the heart is probably more important with regard to patient survival over the long run. Other vasodilators that fail to block the RAAS, such as amlodipine and prazosin, provide no long-term survival benefits. The combination of hydralazine and isosorbide dinitrate however does have long-term survival benefits, possibly mediated by nitric oxide production.

ACEIs have become first line therapy for early HF. ACEIs decrease mortality in patients with systolic HF (Figure 4). Based on the SOLVD prevention (Studies Of Left Ventricular Dysfunction prevention) trial,[3] they are also beneficial in patients with stage B HF (cardiac structural changes but without symptoms). ACEIs are generally used in conjunction with diuretics and β-blockers for the treatment of HF. ACEIs should be used very cautiously, if at all, when the baseline serum creatinine exceeds 2.5–3.0 mg/dL (220–264 mmol/L). The real possibility of ACEIs aggravating baseline renal insufficiency must be balanced against the possible benefits on the kidney and the heart along with other structural attributes associated with their use. In general, the threshold to use ACEIs in patients with cardiovascular disease should be quite low.

Optimal Doses of Angiotensin Converting Enzyme Inhibitors in Heart Failure

ACEIs are usually begun with small doses that are gradually titrated (days to weeks) to the doses used in large clinical trials or

TABLE 4

Dosing and Indications for Various Angiotensin Converting Enzyme Inhibitors

Generic name	*Initial daily dose (mg)*	*Target dose (mg)*	*Indication*
Benazepril	5–10 OD	20–40 OD–BD	HTN
Captopril	6.25 TID	50 TID	HTN, HF, diabetic nephropathy
Enalapril	2.5 BD	20 BD 10 BD	HTN, HF
Fosinopril	5–10 OD	80 OD	HTN, HF
Lisinopril	2.5–5 OD	40 OD 20 OD	HTN, HF
Perindopril	0.5–1 BD	8 OD	HTN, CV protection*
Quinapril	10–20 OD	80 OD	HTN
Ramipril	1.25–2.5 OD	10 OD 20 OD	HF, CV protection#
Trandolapril	1 OD	4 OD	HTN, HF

*Perindopril reduces the risk of cardiovascular mortality and nonfatal myocardial infarction in patients with stable coronary artery disease.
#Ramipril reduce the risk of myocardial infarction, stroke, and death from CV causes in patients at high risk (>55 years with a history of coronary artery disease, stroke, peripheral vascular disease or diabetes).
HTN, hypertension; HF, heart failure; CV, cardiovascular; OD, once a day; BD, twice a day; TID, thrice a day.

recommended by the pharmaceutical manufactures (Table 4). This titration period typically occurs over 1–3 weeks, but there are no data to support how one should precisely titrate these drugs. In general, the dose-response curve to ACEIs is rather flat.

Although the optimal doses of ACEIs in patients with systolic HF have not always been clearly established by clinical trials, several studies have examined this question. In a study comparing enalapril 10 mg twice a day to 60 mg once a day, there was no benefit in terms of mortality or changes in hemodynamic status with the high dose.[19] The ATLAS (Assessment of Treatment with Lisinopril and Survival) study,[20] randomly allocated patients with HF to low or high-dose lisinopril. Although this study demonstrated no significant difference between groups for the primary outcome of all-cause mortality (HR 0.92; 95% CI 0.82, 1.03), the predetermined secondary combined outcome of all-cause mortality and HF hospitalization was reduced by 15% in patients receiving high-dose lisinopril compared with low-dose ($p < 0.001$). A reduction of 24% was observed in HF hospitalization ($p = 0.002$) with the higher dose. The survival benefits and the significant reduction in cardiovascular morbidity related to treatment with ACEIs are best achieved by uptitrating the dose of ACEIs to the target dose achieved in clinical trials. In routine practice, these doses are

rarely reached, in part due to side effects or concerns by patients, physicians or nurses regarding hypotension. Clinical endpoints including New York Heart Association (NYHA) class and HF-related hospitalizations have been reduced by higher doses, but a close dose-related survival benefit has not been demonstrated.[21]

Angiotensin Converting Enzyme Inhibitors and Hyponatremia

Hyponatremia can be a marker of intense activation of the RAAS and marked hyperreninemia. This may occur following substantial diuresis. Such patients are notoriously sensitive to ACEIs and may develop precipitous, symptomatic hypotension. If over-diuresis with volume depletion is clinically suspected and serum sodium is low, small doses of short-acting captopril may be safer to use than the long-acting ACEIs.

Angiotensin Converting Enzyme Inhibitors and Heart Failure with Preserved Ejection Fraction

There are no survival benefit data to support the use of ACEIs or any other neurohormonal blocking agents for the treatment of patients with HF and preserved ejection fraction.[22] All 3 major randomized trials of RAAS blocking agents in HF with preserved LV function—Candesartan in Patients with Chronic Heart Failure and Preserved Left Ventricular Ejection Fraction [CHARM-Preserved], Irbesartan in Patients with Heart Failure and Preserved Ejection Fraction [I-PRESERVE], and Perindopril in Elderly People with Chronic Heart Failure [PEP-CHF])[23-25]—demonstrated no clear benefit with regard to all-cause mortality and HF-related hospitalizations. However, RAAS inhibition continues to be valuable in the management of hypertension commonly found in this patient population. Patients with this form of HF continue to be a source of intensive investigations; however, no specific therapy has emerged as consistently successful. Blood pressure control and diuretics continue to be the mainstay of therapy.

Phosphodiesterase-5 inhibition has been reported to exert beneficial effects in patients with HF with preserved ejection fraction.[26] The patients in this prospective trial had overt HF and mixed type of pulmonary hypertension with increased pulmonary capillary wedge pressures as well as increased pulmonary vascular resistance. The patients were randomized to receive either sildenafil (50 mg thrice a day) or placebo. The long-term treatment with sildenafil was associated with a significant reduction in pulmonary capillary wedge pressure, pulmonary artery pressure, and pulmonary vascular resistance. There was a substantial reduction in right atrial pressure and

an improvement in right ventricular systolic function. There was also a substantial reduction in the lung water content due to treatment with sildenafil. Systemic vascular resistance and arterial pressure, however, remained unchanged, indicating that there was no systemic vasodilatation with sildenafil. The hemodynamic improvement was associated with clinical improvement and improved exercise tolerance.

Angiotensin Converting Enzyme Inhibitors and Hypertension

Under normal circumstances, the blood pressure is maintained through a variety of mechanisms, including the activation of RAAS. When there is sodium restriction or diuretic use, the RAAS can be further activated. This is especially true of patients with renal artery stenosis, hyponatremia, or volume depletion. ACEIs lower blood pressure through a variety of mechanisms, including vasodilation, reduced aldosterone production, release of bradykinin, and attenuation of SNS activity. They appear to be more effective in Caucasian than black patients, but, when used with diuretics, ACEIs are also quite effective in black patients. In elderly patients, they may control blood pressure better than diuretics.[27] Unlike diuretics, ACEIs and ARBs do not usually alter glucose tolerance and blood uric acid, or lipids.[28-30] Losartan, an ARB, actually lowers serum uric acid levels.

Angiotensin Converting Enzyme Inhibitors for Early-phase Acute Myocardial Infarction or Postinfarct Left Ventricular Dysfunction

ACEIs or ARBs are uniformly recommended for the treatment of LV dysfunction when patients are hemodynamically stable following MI. In general, the patients with the most advanced HF probably derive the most benefit from ACEIs. Such patients would include those with diabetes mellitus, anterior MI, persistent sinus tachycardia, or overt LV failure.[31-34] Many physicians choose to withhold ACEIs during the first 24 hours following MI until the patient is hemodynamically stable. Several large clinical trials, including GISSI-3 (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico)[35] indicated that ACEIs reduce mortality at 6 weeks, particularly, in patients with diabetes mellitus. The effectiveness of ACEIs in patients with MI is not off-set by the use of aspirin. Likewise, β-blockers are given concomitantly with ACEIs under most circumstances.

At least 3 major trials have demonstrated that mortality reduction occurs when ACEIs are used in patients with postinfarct LV dysfunction.[36-38] ACEIs attenuate LV remodeling, which likely contributes importantly to improved survival. This benefit is

similar in those patients with or without signs of HF.[39] In general, ACEIs are prescribed long-term for patients who have sustained LV dysfunction following MI.

Angiotensin Converting Enzyme Inhibitors and Long-term Cardiovascular Protection

At least 3 large international trials[2,40,41] have indicated that ACEIs protect against the development of coronary artery disease (CAD). This protection extends even to low risk patients. These trials found an 18% reduction in the odds ratio for the combined outcomes of cardiovascular death, nonfatal MI, or stroke, which is highly significant. In the Prevention of Events with ACE inhibition (PEACE) trial, trandolapril reduced total mortality in patients with CAD, a preserved ejection fraction, and cardiovascular risk factors.[41] Although ACEIs are not direct anti-ischemic agents, they seem to reduce ischemic events by indirectly reducing myocardial oxygen demand, SNS activity, and improving endothelial function.

Angiotensin Converting Enzyme Inhibitors and Renal Protection

It is now apparent that patients with diabetes mellitus benefit greatly from blood pressure control. Patients with type 1 diabetes and renal insufficiency also demonstrate less proteinuria and reduced further loss of renal function when treated with ACEIs.[42] Renal protection may be afforded by the decline in proteinuria. When microalbuminuria is observed, ACE inhibition is indicated. In fact, ACE inhibition can delay the onset of albuminuria.[43,44] Since angiotensin II may play a role in progressive impairment of renal function, ACEIs may delay the development of end-stage renal failure, in part, by reducing blood pressure.[45,46] ACEIs probably reduce the rate of decline in glomerular filtration rate (GFR) more than that expected by decline in blood pressure alone.[42,46] Even relatively, high level of serum creatinine may not be a contraindication of ACEIs in patients with renal disease, although it remains a point of controversy and uncertainty among physicians. Of interest, African-Americans with renal insufficiency treated with ACEIs are less likely to need hemodialysis.[47]

Choice of Angiotensin Converting Enzyme Inhibitors

Overall, there is a little reason to believe that there are specific advantages observed for one ACEI over another. In general, clinicians should choose ACEIs that have been vigorously

tested in clinical trials. Captopril, a very short-acting ACEI, has the disadvantage of requiring dosing thrice a day. However, it has the advantage of being relatively short-acting; therefore, it is preferable for hospitalized patients when hypotension is a potential concern. One of the unique side effects related to captopril is neutropenia, which is typically associated with high doses. It usually occurs in patients with underlying renal dysfunction and in especially those with a collagen vascular disease. Now that low doses of captopril are more commonly employed, neutropenia is much less common. Ramipril has undergone extensive testing in early postinfarction HF, in renoprotection studies, and in prevention studies of patients with cardiovascular risk factors. A disadvantage of ramipril is that the blood pressure lowering effect is not sustainable over 24 hours. Lisinopril is inexpensive, has relatively straightforward pharmacokinetics, is water soluble, and does not require liver transformation; thereby, making it easy to use. It has been widely studied in major clinical trials. Perindopril was used in EUROPA (the EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease), in patients with stable CAD, where it had a favorable effect on cardiovascular events.[40] It has shown benefit in secondary prevention for patients with previous stroke and in those with transient ischemic attack in the PROGRESS (perindopril protection against recurrent stroke study) trial.[48] It is widely used in Europe and other oversees countries.

ANGIOTENSIN II RECEPTOR BLOCKERS

Introduction

ARBs emerged in the late 1980s and early 1990s as alternative agents to ACEIs that could be used to directly block angiotensin II receptors. It was believed that ARBs would essentially have most of the favorable effects of ACEIs but without bradykinin induced side effects, such as cough and angioedema.

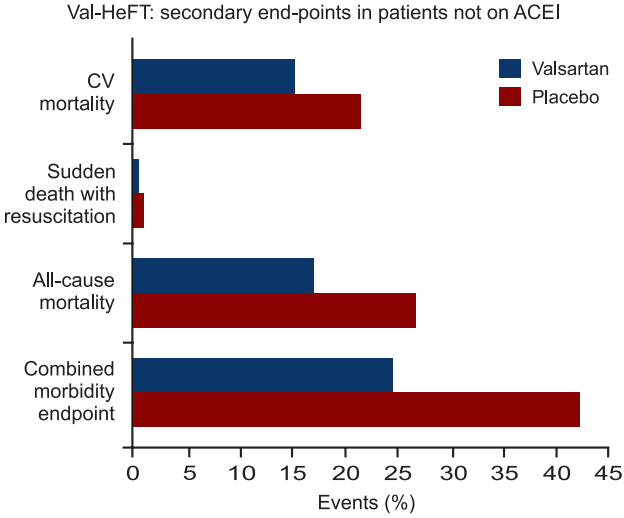
Mechanism of Action and Pharmacology

ARBs block the AT1 receptors and attenuate the deleterious pharmacodynamics effects of angiotensin II, such as vaso-constriction, hypertension, myocyte hypertrophy, ventricular and atrial adverse remodeling, renal dysfunction, and promotion of atherothrombosis. AT1-blockade is also associated with upregulation of the AT2 receptors which has the potential to produce beneficial effects on cardiovascular dynamics.

Indications and Clinical Evidence

The first ARB to be marketed was losartan and it is now widely used for patients with HF and hypertension. It is also used for the prevention of stroke and diabetic nephropathy. Over time, we have learned that ARBs are seemingly better tolerated than ACEIs. They have a remarkable lack of side effects and are regarded as first line therapy by many experienced physicians. The indications and contraindications of ARBs are essentially similar to ACEIs and include cardiogenic shock, pregnancy, and bilateral renal artery stenosis. Although better tolerated, ARBs are generally more costly than generic ACEIs. This is likely to change, as more ARBs become generic. Although ACEIs are generally preferred as first line therapy for HF, the well-known tolerability of ARBs is gradually allowing them to assume a primary choice of treatment by many cardiologists. ARBs reduce mortality of patients with systolic HF (Figure 5).

Many large trials have shown that ACEIs and ARBs are generally equivalent when used for patients with chronic HF or postinfarct LV dysfunction. The ONTARGET trial,[9] one of the largest trials to date, comparing an ACEIs and an ARB, provided additional evidence that ARBs are equal to ACEIs in the prevention of clinical end-points, such as cardiovascular mortality and morbidity,



Val-HeFT, valsartan heart failure trial; ACEI, angiotensin converting enzyme inhibitor; CV, cardiovascular.

FIGURE 5. Results of treatment with valsartan in comparison to placebo in patients with systolic heart failure in the Val-HeFT trial. *Data from* Cohn JN, Tognoni G; Valsartan Heart Failure Trial Investigators. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med*. 2001;345(23):1667-75.

MI, and stroke. This was also noted in the VALIANT (VALsartan In Acute myocardial iNfarction Trial) trial.[49] VALIANT suggested that valsartan is as effective as captopril for patients following an acute MI with HF and/or LV systolic dysfunction, and may be used as an alternative treatment in ACEI-intolerant patients.

Combination of Angiotensin Converting Enzyme Inhibitors and Angiotensin Receptor Blockers

Both the ONTARGET and the VALIANT trials demonstrated no survival benefit with the combination of an ACEI and an ARB over either agent used alone. On the other hand, both Val-HeFT (the Valsartan Heart Failure Trial)[6] and CHARM-ADDED (Candesartan in Heart failure: Assessment of Reduction in Mortality and Morbidity)[50] trials did indicate that combined RAAS inhibition with ACEI and ARBs (valsartan or candesartan) may reduce morbidity and mortality in certain patient subgroups with chronic HF. Accumulating evidence also points to the benefits of the combination therapy in individuals with proteinuric nephropathies. Despite these observations, combining ARBs with ACEIs has also been associated with more adverse effects in some studies, including hypotension, renal insufficiency, and hyperkalemia. These adverse effects occurred without additional benefit,[9,49] although there may be some exceptions to this rule.

Doses of Angiotensin Receptor Blockers

Although ARBs has been studied extensively in patients with hypertension and HF, the relation between dose and clinical outcomes has not been well studied. The dose of ARBs is largely based on clinical trials, and one dose does not fit all patients (Table 5). The HEAAL (Heart failure Endpoint evaluation of Angiotensin II Antagonist Losartan) study is one of the first studies done to assess the relation between the dose and the clinical outcome of an ARB (losartan) in patients with HF.[51] It indicated that losartan at 150 mg/day reduced the rate of death or admission to the hospital for HF more than the commonly used dose of losartan 50 mg/day. This supports the value of uptitrating the ARBs dose to achieve clinical benefit, but it is unlikely that additional large clinical trials comparing dose strength will be performed.

Choice of Angiotensin Receptor Blockers

Although different ARBs have different affinity for the AT1 receptors and may have different clinical effects, most ARBs studied in patients with systolic HF demonstrated a reduction in mortality and hospitalization. Various ARBs have not been

TABLE 5

Different Types of Angiotensin Receptor Blockers			
Generic name	*Initial daily dose (mg)*	*Target dose (mg)*	*Indication*
Candesartan	4–8 OD	32 OD	Hypertension, heart failure
Irbesartan	150 OD	300 OD	Hypertension, diabetic nephropathy
Losartan	12.5–25 OD	100 OD	Hypertension, diabetic nephropathy
		150 OD	Heart failure
Olmesartan	20 OD	40 OD	Hypertension
Telmisartan	40 OD	80 OD	Hypertension
Valsartan	40 BD	320 OD	Hypertension, diabetic nephropathy
		160 BD	Heart failure

OD, once a day; BD, twice a day.

studied in a comparative manner; however, candesartan compared with losartan has higher binding affinity for the AT1 receptors and is more effective at lowering blood pressure.[52] In a registry study of hypertension, candesartan compared with losartan was associated with less *de novo* HF,[53] and, in a registry study of elderly patients with HF, losartan was associated with a lower survival rate than irbesartan, valsartan, and candesartan.[54] A recently published registry from Sweden suggests that the use of candesartan compared to losartan is associated with a lower all-cause mortality in patients with HF.[55] Registries tend to be less reliable than large randomized trials. Nonetheless, it would be a value to have more comparative data among the various ARBs. This is not likely to happen in the current era of cost-containment.

Angiotensin Receptor Blockers and Atrial Fibrillation

Early observations suggested that ARBs prevented atrial fibrillation, but this has not been consistently confirmed in other large follow-up clinical trials. In a meta-analysis of 11 trials with ACEIs or ARBs involving 56,308 patients, both ACEIs and ARBs were demonstrated to reduce the relative risk of atrial fibrillation by 28% (95% CI, 15–40%; p = 0.0002).[56] Similar reductions in atrial fibrillation (ACEIs: 28%, p = 0.01; ARBs: 29%, p = 0.00002) were produced by both the group of drugs. The effect was greatest in patients with LV dysfunction or LVH, in whom the risk reduction was 44% (95% CI, 15–63%; p = 0.007). This reduction in atrial fibrillation with RAAS blockade could at least partly

account for the reduction in stroke that has consistently been observed in other large outcome trials. However, the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE I) trial[57] indicated that irbesartan did not reduce cardiovascular events in patients with atrial fibrillation. Overall, ARBs may reduce the incidence of atrial fibrillation in patients with HF, but this observation has not been consistently reported.

Angiotensin Receptor Blockers and Risk of Cancer

Although no studies were designed to specifically address cancer risk in patients taking ARBs, a large meta-analysis suggested an increased risk of cancer among patients taking ARBs.[58] A later meta-analysis from 70 randomized trials of 325,000 patients failed to confirm the findings of the previous study and demonstrated no increase in cancer incidence with ARBs or ACEIs.[59] Recently, the USFDA conducted a large meta-analysis from 31 trials and 156,000 patients, comparing outcomes in patients randomized to an ARB or "non-ARB treatment" with an average follow-up of 39 months.[60] This analysis also demonstrated no increase in patient's risk of developing cancer while taking ARBs.

Angiotensin Receptor Blockers and Aortic Aneurysm

AT1 receptor blockade is potentially beneficial in preventing aortic expansion and enlargement of aortic aneurysms.[61-66] The precise mechanism of this beneficial effect of AT1 receptors blockade has not been elucidated. The beneficial effects have been observed with doses of AT1 receptors blockers that do not lower arterial pressure.

Activation of transforming growth factor-β (TGF-β) has been implicated in the pathogenesis of aortic aneurysms. Angiotensin II stimulates TGF-β signaling pathways. The AT1 receptors blocking agents decrease expression of TGF-β in aortic walls.

It should be appreciated that the mechanisms involved in the aneurysm formation vary according to the anatomic location. In the tissues of the thoracic aortic aneurysms, high-grade inflammatory response is usually absent. In the abdominal aortic aneurysms, however, infiltration of macrophages with inflammatory and atherothrombotic changes are common. Angiotensin II promotes atherosclerosis and exerts proinflammatory responses in the aortic walls. AT1 receptors blockade can attenuate atherothrombotic and inflammatory responses in aortic aneurysms and decrease the risk of aneurysm expansion. In animal models of abdominal

aortic aneurysm, the tissue concentration of ACEs are increased and ACEIs decrease aortic dilatation.

In the animal model of Marfan's syndrome, angiotensin II causes progression of aortic aneurysm. The selective AT1 receptors blockers attenuated progressive dilatation of the aneurysms. It was also observed that the presence of AT2 receptors provide better protection. The activation of AT2 receptors decreases the deleterious effects of angiotensin II. The ACEIs decrease the formation of angiotensin II and attenuate activation of both AT1 and AT2 receptors and, thus, are less effective than selective AT1 receptors blocker in preventing dilatation of the aortic aneurysms.

In patients with Marfan's syndrome with severe annuloaortic ectasia, angiotensin II concentrations in the tissues of the affected aorta are increased but remains normal in the tissues of the unaffected aorta. This observation suggests that angiotensin II plays a role in the pathogenesis of aneurysms of ascending aorta in Marfan's syndrome and provides a rationale for the use of AT1 receptors blockers.

Serial echocardiographic studies in patients with Marfan's syndrome have revealed that treatment with AT1 receptors blockade is associated with a marked attenuation of the increase in the size of the aortic aneurysm. Based on these observations, the patients with Marfan's syndrome are frequently treated with AT1 receptors blockers.

In all aortic aneurysms, irrespective of location, there are changes in the extracellular matrix. There is an imbalance between matrix collagen synthesis and breakdown. Matrix degrading enzymes, matrix metalloproteinases (MMPs), particularly MMP-2 and MMP-9, are increased in thoracic and aortic aneurysms and have been suggested to be contributing factor in the pathogenesis of aortic aneurysms. In animal model, AT1 receptors blockade was associated with decreased expression of MMP-2 and MMP-9, which is another rationale for the use of AT1 receptors blocking agent for treatment of aortic aneurysms.

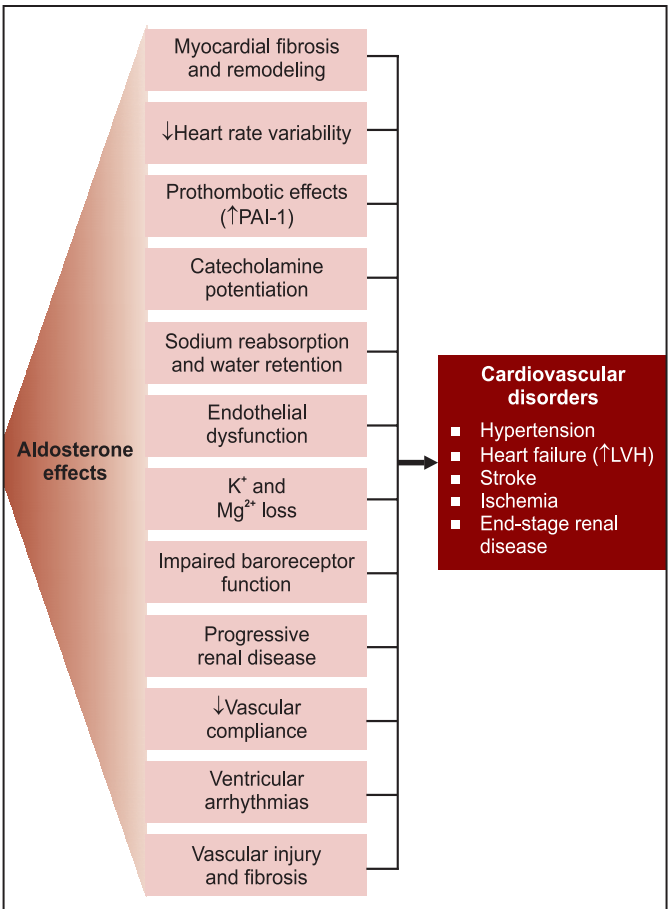
ALDOSTERONE INHIBITORS: SPIRONOLACTONE AND EPLERENONE

Introduction

Aldosterone, a mineralocorticoid hormone and product of the RAAS, has been linked to hypertension, cardiac remodeling, and vascular fibrosis. It is synthesized, stored, and released primarily from the adrenal cortex. It is widely believed that aldosterone is

active in many tissues, including the brain, heart, and vasculature, where it participates in wound healing and collagen deposition. It is also active on the distal tubules of the kidney, where it helps maintain sodium, water, and potassium balance. It has long been known to play a pathophysiological role in cardiovascular disease (Figure 6). Aldosterone has a steroidal chemical structure and has well-known effects on various endocrine organs, including breast tissue. The aldosterone or MR is widely expressed in tissues, which use both aldosterone and cortisol as ligands.

The Randomized Aldactone Evaluation Study (RALES),[67] the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS),[68] and the Eplerenone in Mild Patients Hospitalization And SurvIval Study in Heart Failure (EMPHASIS-HF)[69] trials have substantiated the fact that aldosterone is highly important in the syndrome of systolic HF.

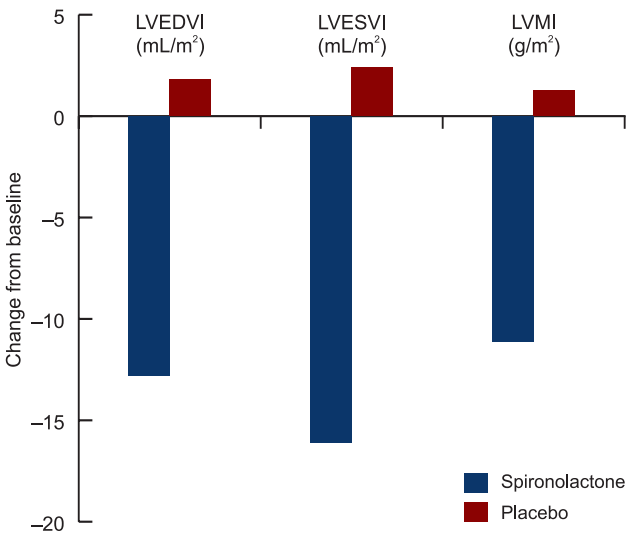


PAI-1, plasminogen activator inhibitor-1; LVH, left ventricular hypertrophy; K^+, potassium; Mg^{2+}, magnesium.

FIGURE 6. Biological action of aldosterone that contribute to cardiovascular disease.

Aldosterone appears to make major contributions to salt and water retention and remodeling of cardiac and vascular tissue. The overly active RAAS is associated with higher mortality in patients with systolic HF. Blocking aldosterone production (ACEIs) and inhibiting its receptor activity (spironolactone and eplerenone) have consistently improved survival in patients with systolic HF. In the RALES study, 1,663 patients with advanced chronic systolic heart failure were randomized to receive either spironolactone (25–50 mg/day) or placebo. Spironolactone treatment was associated with a 31% reduction in cardiovascular death, a 36% reduction in death due to progressive heart failure, and a 29% reduction in sudden death. Because chronic aldosterone inhibition by ACEIs may lead to "escape" of aldosterone production over time, it is believed that drugs, such as spironolactone and eplerenone, which directly block aldosterone receptors are associated with more durable antialdosterone pharmacologic effects over time compared to ACEIs or ARBs.

After many years of study, it has become apparent that aldosterone blockade in patients with systolic HF reduces LV hypertrophy and remodeling[70,71] (Figure 7). There is a reduction



LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index; LVMI, left ventricular mass index.

FIGURE 7. The effect of aldosterone antagonist on left ventricular reverse remodeling is illustrated. After treatment with aldosterone antagonist spironolactone, there was a reduction in LVEDVI, LVESVI, and LVMI. *Adapted from* Tsutamoto T, Wada A, Maeda K, Mabuchi N, Hayashi M, Tsutsui T, et al. Effect of spironolactone on plasma brain natriuretic peptide and left ventricular remodeling in patients with congestive heart failure. *J Am Coll Cardiol*. 2001; 37:1228-33, *with permission*.

in LV end-diastolic and end-systolic volumes and LV mass after treatment with spironolactone. Aldosterone blocking agent, spironolactone, reduces mortality of patients with systolic HF. Aldosterone blockade is now an established therapeutic strategy for the treatment of systolic HF. Unless contraindicated or not tolerated, aldosterone receptor blockers should be used virtually in all patients with symptomatic HF in conjunction with a RAAS blocker and a β-adrenergic receptor blocker. Selective aldosterone antagonist, eplerenone, decreases the mortality and morbidity of postinfarction patients with reduced LV ejection fraction. In the EPHESUS study, 6,642 patients with left ventricular ejection fraction of 40% or less were randomized within 3–4 days of incident infarction to receive either eplerenone (target dose 50 mg/day) or placebo. Following treatment with eplerenone for 30 days, all cause mortality decreased by 31% (risk ratio 0.69); death from cardiovascular causes decreased by 32% (risk ratio 0.68) and sudden cardiac death decreased by 37% (risk ratio 0.63).

Mechanism of Action

Aldosterone levels increase in response to angiotensin II stimulation and hyperkalemia (Figure 8). It is now clear that therapy with MR blockers reduces LV remodeling, possibly by limiting the amount of myocyte hypertrophy, cardiac collagen deposition, and myocardial fibrosis.[70,71]

Excessive aldosterone has been shown to have a number of other adverse effects, including activation of other neurohumoral

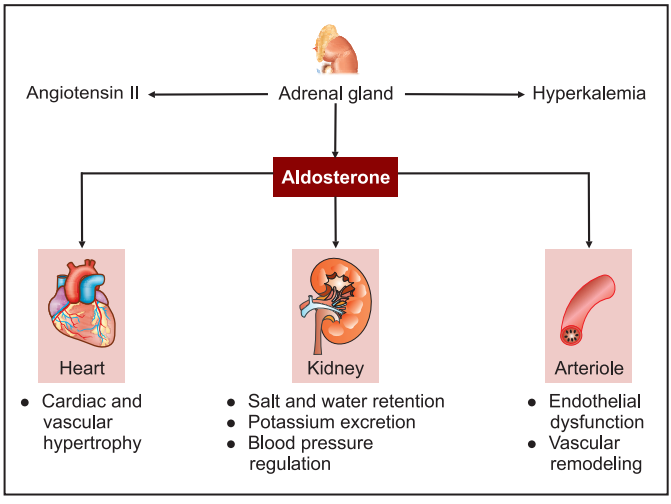


FIGURE 8. Effect of aldosterone on different organs. Aldosterone release from the adrenal gland is directly stimulated by angiotensin II and hyperkalemia. Aldosterone exerts multiple detrimental effects on the heart, vasculature, and the kidneys.

mediators, stimulation of reactive oxygen species, activation of the NF-κβ and the activator protein 1 (AP-1) signaling pathways, vascular inflammation and fibrosis, myocardial hypertrophy, autonomic imbalance, and a decrease in fibrinolysis.[70]

It is also noted that spironolactone and eplerenone reduce the incidence of arrhythmias and sudden death.[67-69] These important favorable effects may be mediated in part by inhibition of cardiac norepinephrine release and/or concurrent relative hyperkalemia.

Despite the benefits of MR blockade repeatedly demonstrated in clinical trials, it has been difficult to determine the precise mechanism by which MR blockade translates into improved survival in patients with systolic HF. The benefits are likely multifactorial.

Pharmacology

In addition to the many favorable attributes of MR blockers in patients with HF, spironolactone also has a long track record as a diuretic, a treatment for ascites, hyperaldosteronism, and a blood pressure lowering agent. This is the basis for its widespread use in patients with resistant hypertension. The starting dose of spironolactone for the treatment of systolic HF is typically 12.5 mg/day with titration to 25 or 50 mg/day if serum K^+ <5 mEq/L. The dose of spironolactone for resistant hypertension is typically higher at 50–100 mg/day.

Eplerenone received USFDA approval in 2002 and 2003 for the treatment of systolic HF and hypertension, respectively. Eplerenone is metabolized by the hepatic cytochrome P450 system and may interact with multiple drugs. No active metabolites of eplerenone are known to exist. The elimination half-life is 4–6 hours. Steady-state is achieved within 2 days. Blood levels are potentiated and increased with concomitant use of inhibitors of the cytochrome P450 3A4 pathway (e.g., ketoconazole, saquinavir, and erythromycin). A major advantage of eplerenone over the more nonselective aldosterone receptor antagonist, spironolactone, is a lack of binding to progesterone and androgen receptors. The usual dose of eplerenone in HF is 25–50 mg/day.

Side Effects

Hyperkalemia

The main factor that limits the use of both eplerenone and spironolactone is the increased risk of hyperkalemia, which rarely can be fatal.[72,73] The incidence of serious hyperkalemia defined as serum K^+ >6.0 mEq/L was reported to be 1, 1.6, and 0.6% greater than placebo in RALES, EPHESUS, and the EMPHASIS trials,

respectively.[67-69] This frequency of increase in serum K^+ >6 mEq/L was statistically significant except in the EMPHASIS trial (p = 0.29). Hyperkalemic events were most common during the first 30 days after introduction of the drug, coinciding with the period of drug titration, but occurred sporadically throughout the period of follow-up. The predictors of hyperkalemia were reduced baseline renal function (GFR <60 mL/min/1.73 m^2), diabetes mellitus, and advanced age. The highest reported rate of hyperkalemia was seen in trials using doses in excess of 50 mg/day of either eplerenone or spironolactone.[74] Patients who are receiving dual therapy with ACEIs and ARBs along with potassium chloride supplementation carry the highest risk of hyperkalemia, particularly, if there is underlying diabetic nephropathy and concomitant use of anti-inflammatory drugs. Hyperkalemia following aldosterone antagonists' administration is usually managed by lowering the dose of these drugs or discontinuing therapy. The frequency of hyperkalemia in the context of a controlled clinical trial may be less than expected in routine clinical practice. These observations should increase the vigilance regarding hyperkalemia and should enhance close laboratory surveillance of serum K^+ levels especially early after introducing the drug.

Gynecomastia

Gynecomastia was reported in 4.3% of the spironolactone-treated patients.[75] Due to the selectivity of eplerenone for the MR receptor, adverse effects, such as gynecomastia and vaginal bleeding, seem to be less likely in patients who take eplerenone than in those who take spironolactone.

Contraindications

Aldosterone antagonists are contraindicated in patients with shock, oliguric renal failure, and/or hyperkalemia.

Role of Aldosterone Inhibitors in Heart Failure: Clinical Evidence

Spironolactone was used as an adjunctive diuretic agent for HF until 1999, when it jumped to the forefront of medical therapy for patients with advanced HF following the publication of the RALES trial.[67] This trial demonstrated that spironolactone reduced mortality by 30% and HF hospitalizations by 35% in patients with severe HF on conventional medical therapy.

Further proof of the importance of MR blockade for the treatment of systolic HF comes from the EPHESUS trial.[68] In this study, eplerenone reduced the combined end-point of cardiovascular mortality and cardiovascular hospitalization by

13%, when administered at a mean of 7.3 days postinfarction to patients with systolic LV dysfunction and signs of HF. The majority of these patients were also treated with both an ACEI and a β-blocker. Both RALES and EPHESUS provide important proof of principle that aldosterone is of pathophysiological importance in patients with systolic HF.

Recently, the spectrum of aldosterone inhibitor benefit expanded to include patients with NYHA class II systolic HF. In the EMPHASIS trial,[69] eplerenone produced a 37% reduction in the primary end-point of the composite of death from cardiovascular causes or hospitalization for HF. A 24% reduction in cardiovascular death and a 42% reduction in hospitalization for HF compared with placebo were also observed in patients with systolic HF and mild symptoms. These results extend the benefit of aldosterone antagonists to patients with mild HF, a much broader population. It is widely expected that updated HF guidelines will incorporate the use of eplerenone for NYHA class II patients. Although these randomized trials provide compelling evidence for a change in clinical practice, data indicate that aldosterone antagonists are used in less than one-third of eligible patients.[76] This is in part related to concerns regarding hyperkalemia.

Spironolactone and Eplerenone: Are They the Same?

Both spironolactone and eplerenone have been shown to reduce mortality in patients with systolic HF. However, a few differences exist. Due to its relatively greater specificity for the MR, eplerenone lacks the progestogenic and antiandrogenic off-target actions of spironolactone. This is seemingly important and leads to fewer adverse effects. Investigations have shown that eplerenone and spironolactone have different effects on important metabolic activities.[77] Spironolactone has been found to increase glycosylated hemoglobin levels, decrease adiponectin, and increase cortisol levels in patients with HF and diabetes mellitus, while eplerenone does not. Recent experimental animal data indicate that testosterone reduces cardiomyocyte apoptosis.[78] This beneficial effect was not observed in this model after therapy with spironolactone, and may be unique to eplerenone. Thus, more data are needed to better understand if both agents provide equivalent clinical benefits. In practice, spironolactone is commonly substituted for eplerenone, as it is less expensive. Nonetheless, eplerenone may have unique advantages, and we are lacking head-to-head comparative clinical trials.

DIRECT RENIN INHIBITORS

Introduction

Although both ACEIs and ARBs block the RAAS, they are associated with an increase in plasma renin activity. This is referred as "reactive hyperreninemia." Over the years, there was some concern that elevated or so-called "reactive" plasma renin may then act to stimulate "unprotected" angiotensin II receptors. This elevated renin might limit the therapeutic effectiveness of ACEIs or ARBs.

Mechanism of Action and Pharmacology

DRIs were developed to decrease plasma renin activity. It is believed that they may provide an alternative or a complementary strategy for blocking upstream RAAS activity. Aliskiren is the first orally active DRI to appear in the market. It is currently approved for the treatment of hypertension in the USA and could potentially emerge as important therapy for HF.

Aliskiren is a nonpeptide piperidine that inhibits the enzyme renin by binding to its catalytic site producing about 50% reduction in renin activity. Virtually, all the subsequent messengers for the RAAS receptors are then attenuated. This tends to offset the heightened renin activity when concomitant diuretics, ACEIs or ARBs are used. Whether this provides an important clinical advantage over ACEIs or ARBs alone has been controversial.

Aliskiren has a low bioavailability, but its pharmacokinetics make the drug suitable for a once-a-day administration. Earlier observations indicate good tolerability of aliskiren, and the drug is expected to have a low likelihood of adverse effects. Moreover, renin inhibitors do not affect substance P or kinin metabolism and, hence, are not expected to cause cough or angioneurotic edema.

Indication and Clinical Evidence

Aliskiren and Hypertension

When used as monotherapy for hypertension, aliskiren reduces blood pressure more effectively than hydrochlorothiazide, and is at least as effective as an ACEI or ARB.[79-84] When assessed by a 24-hour ambulatory blood pressure monitoring, blood pressure lowering with aliskiren is statistically more effective than either an ACEI or an ARB.[85] It may be particularly useful for patients with

resistant hypertension or for patients who do not tolerate more typical RAAS blockers.

The antihypertensive effect of aliskiren is dose-dependent up to 300 mg/day, and 600 mg/day produces little additional blood pressure reduction, but can be associated with an increased incidence of adverse effects, particularly diarrhea. In most studies at doses up to 300 mg/day, aliskiren is as well tolerated as placebo.[86]

Direct Renin Inhibitors in Combination with Angiotensin Converting Enzyme Inhibitors and Angiotensin Receptor Blockers

Clinical trials evaluating the addition of aliskiren to ACEIs or ARBs have been of interest. Aliskiren suppresses the compensatory increase in plasma renin (so called "hyperreninemia") and causes additional blood pressure lowering when combined with a thiazide diuretic, an ACEI or ARBs.[79] When aliskiren is combined with valsartan at maximum recommended doses, it provides significantly greater reduction in blood pressure than monotherapy with either agent alone. The tolerability profile is similar to that of aliskiren or valsartan alone.[87] The risk of hyperkalemia and worsening renal function is higher with the combination than with either drug separately, which is to be expected. In general, combining two or more drugs that block ACE, angiotensin II receptors, or renin activity is prone to cause hyperkalemia, hypotension, and renal function impairment.

Aliskiren and Heart Failure

Preclinical studies in transgenic mice with the over-expression of RAAS appear to indicate that aliskiren possesses independent beneficial effects on cardiac hypertrophy, wall thickness, and diastolic dysfunction equivalent to or perhaps superior to valsartan.[88] The Aliskiren Observation of Heart Failure Treatment (ALOFT) study[89] indicated that direct renin inhibition with aliskiren 150 mg/day in patients with chronic HF was well tolerated and accompanied by a significant reduction in brain natriuretic peptide levels, reduced urine aldosterone, and improved cardiac remodeling by echocardiography.

Major adverse effects included hypotension, hyperkalemia, and renal impairment. The Aliskiren Trial to Minimize Outcomes in Patients with HEart failuRE (ATMOSPHERE) study[90] is an ongoing clinical trial addressing the benefits of direct renin inhibition with aliskiren relative to enalapril or aliskiren plus enalapril. This trial is expected to provide definitive data with regard to the use of aliskiren in patients with HF.

Results of several ongoing randomized clinical trials should provide additional insights into the potential of therapeutic efficacy and safety of aliskiren for patients with HF.

CONCLUSION

Angiotensin inhibition can be achieved by the ACEIs, ARBs, and DRIs. Angiotensin inhibition therapy has many clinical indications. Treatments of hypertension and of HF, however, are the two major indications for the use of angiotensin inhibition therapy. The major clinical indication for the use of aldosterone antagonists is for the treatment of HF.

HF is a complex clinical syndrome. Not all treatments or all doses fit each patient. Treatment must always be individualized, based on many factors, including age, pathophysiology, concomitant conditions, and cost. The large clinical trials that form the basis of guidelines are meant to be simply pathways, and not mandated algorithms of treatment. Nevertheless, these studies are the best evidence we have, and the use of these various proven therapies must be at least considered for all patients, recognizing that their use must be tailored to each patient's individual needs.

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2 CHAPTER

Positive Inotropic Drugs: A Limited but Important Role

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INTRODUCTION

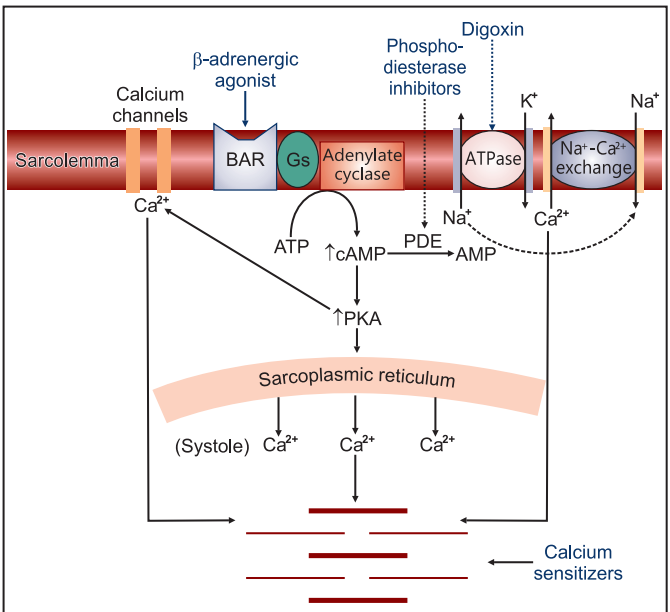
Positive inotropic agents are drugs that increase the velocity and strength of contraction of the cardiomyocyte in which the myocardium and heart are the primary target organ. The classic measurement of cardiac function is ejection fraction, but it only indirectly represents a measurement of contractility. It is also a way of determining the extent of contraction but does not account for the rate or strength of myocardial contraction. The more accurate measurements of myocardial contractility or inotropy include end-systolic elastance from the left ventricular (LV) pressure-velocity loop, ΔLV systolic upstroke pressure/Δ time, peak slope of LV developed pressure, and velocity of circumferential fiber shortening.

The positive inotropes will also augment the magnitude of contraction (i.e., ejection fraction), but this effect can also be achieved to varying degrees by a wide variety of non-inotropic agents (e.g., angiotensin converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers, and vasodilators). Therefore, this is not a unique characteristic of positive inotropic agents.

This chapter will discuss the pharmacologic drugs employed clinically to directly enhance cardiac contractility or the inotropic state of the myocardium, the so-called positive inotropic drugs. These agents are directed at the patients whose overall cardiovascular functions are impaired by loss of cardiac contractility to the extent that there are symptoms and signs of reduced stroke volume, cardiac output, often hypotension, and hypoperfusion of vital organs and systems.

Positive inotropic agents augment cardiac contractility through a number of different mechanisms, but most of them act by modulating calcium handling by the myocardial cell. The various mechanisms of action on the cardiomyocyte by the major positive inotropic drugs are presented in figure 1.

Enhancement of cardiac contractility by these agents with resultant improvement of compromised hemodynamics is not



BAR, β-adrenergic receptor; Gs, ATPase, adenosine triphosphatase; K^+, potassium; Na^+, sodium; Ca^{2+}, calcium; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; PDE, phosphodiesterase; AMP, adenosine monophosphate; PKA, protein kinase A.

FIGURE 1. Mechanisms of actions of positive inotropic drugs on cardiomyocytes. The major positive inotropic groups generally act through mechanisms that increase the concentration and availability of intracellular calcium for the actin-myosin contractile apparatus. β-adrenergic agonists attach to the β-adrenergic receptor, activating the Gs protein-adenylate cyclase complex to convert ATP to cAMP. cAMP activates protein kinase A, which phosphorylates several intracellular sites resulting in Ca^{2+} influx into the cell and Ca^{2+} release from sarcoplasma reticulum to augment systole. Phosphodiesterase inhibitors impair the breakdown of cAMP. Calcium sensitizers act by making the troponin-actin-myosin complex more responsive to available intracellular Ca^{2+}. By blocking the Na^+/K^+ ATPase pump, digoxin increases intracellular Na^+ loading of the Na^+-Ca^{2+} exchanger, resulting in less extrusion of Ca^{2+} from the myocyte. Dashed arrow indicates inhibition. The comprehensive mechanisms of actions of these positive inotropic agents are considerably more numerous and complex.

achieved without a price to be paid. Unless the positive inotropic agent also has substantial cardiac unloading properties (preload- and afterload-reduction) and/or substantially causes other favorable effects (e.g., increase of diastolic perfusion time and improvement of autonomic imbalance), these agents invariably increase the metabolic and oxygen demands of the heart. This undesirable characteristic is accentuated by other pharmacologic properties not uncommonly associated with positive inotropes, such as positive chronotropy (increase in heart rate), an increase in systemic vascular resistance, and cardiac dysrhythmias. These unfavorable properties can be especially troublesome in the

clinical setting of occlusive coronary artery disease (CAD), where the oxygen metabolic supply can be limited by the coronary obstructing lesions. For these reasons, intravenous positive inotropic therapy should generally be directed at acute short-term intervention and must be administered properly.

At present, chronic oral inotropic therapy is primarily delivered by digoxin, an agent with a relatively mild positive inotropic effect. It is quite possible that any favorable response to digoxin is largely secondary to other accompanying beneficial properties (see the heading "Digoxin"). The development of newer orally administered positive inotropic agents to enhance cardiac function has received a lot of attention and research activity over the past 4 decades, but to date, all have been burdened with adverse effects and outcomes.

For the purpose of clinical application, this chapter is divided into those agents directed at the short-term support of cardiac contraction and the intravenous inotropes, followed by a discussion on chronic long-term inotropic therapy with digoxin.

INTRAVENOUS SHORT-TERM POSITIVE INOTROPIC THERAPY

The drugs placed under this category represent a wide spectrum of pharmacologic effects in addition to their positive inotropic properties. The predominant distinguishing feature among these agents is their effect on peripheral vasculature, which can range from vasodilatation (milrinone) to balanced vascular tone (dobutamine) to vasoconstriction (norepinephrine) (Figure 2 and Table 1). The cellular mechanisms for the positive inotropic properties of these intravenous agents are centered on increasing intracellular cyclic adenosine monophosphate (cAMP) by either

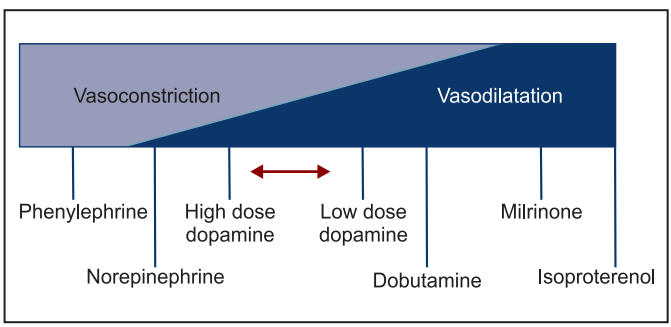


FIGURE 2. Effects of short-term positive inotropic agents on peripheral vasculature. The wide range of vascular effects is presented for the agents currently available for short-term positive inotropy and cardiovascular support. The vascular properties are the major determinants for selection of these agents in individual patients.

TABLE 1

Hemodynamic Profiles of the Agents Currently Employed to Deliver Short-term Inotropic and Vasoactive Support

	Phosphodiesterase inhibitor	*Adrenergic agonists*				
	Milrinone	*Dobutamine*	*Dopamine*		*Norepinephrine*	*Phenylephrine*
			Low dose	*Higher dose*		
Contractility (inotropy)	↑	↑↑↑	↑	↑↑	→↑	↗
Cardiac output	↑↑	↑↑↑	↑	↑	→↑	↗
Heart rate (chronotropy)	→↑	→↑	→↑	↑↑	→↑	→↗
LV filling pressure	↓↓↓	↓↓	↓	→↑	→↑	→↑
Systemic blood pressure	→↓	→↑	→	↑↑	↑↑↑	↑↑↑
Systemic vascular resistance	↓↓↓	↓↓	→	↑↑	↑↑	↑↑↑
Pulmonary vascular resistance	↓↓↓	↓↓	→	→↑	↑	↑

↓, decrease; →, minimal to no change; ↗, mild increase; ↑, increase.

adrenergic receptor stimulation or inhibition of cAMP degradation with subsequent elevation of intracellular calcium available for contraction (Figure 1).

ADRENERGIC AGENTS

Although the adrenergic receptor agonists can provoke tachycardia and dysrhythmias, they generally have a short elimination half-life. This is an ideal pharmacokinetic property for patients in the monitored critical care setting, where a quick onset and offset of cardiovascular effects allow immediate and tightly controlled hemodynamic support. An undesirable effect can be expected to be reversed shortly, within minutes, after the dose of the agent is lowered or discontinued.

The 3, 4-hydroxyphenyl ring is the essential structure of the catechols, the major component for the adrenergic agents employed for positive inotropic therapy. The molecular structures of the most commonly used adrenergic agents available and applied clinically are shown in figure 3.

The adrenergic receptor agonists evoke most of their pharmacodynamic effects through activation of β-and α-adrenergic receptors. The myocardium is heavily populated with β-adrenergic receptors and, to a lesser extent, with α-adrenergic receptors; all capable of augmenting cardiac contraction in varying degrees. Stimulation-activation of both β1- and 2-adrenergic receptors augments the inotropic and, in some instances, the chronotropic states of the cardiac cell through mechanisms shown in figure 1. β-adrenergic receptors are also present in other regions and organs of the body with the β2-adrenergic receptor being the most ubiquitous; accounting for concomitant vasodilatation and bronchodilation during β2-receptor agonism. α-adrenergic receptors are predominantly located in vasculature, such that their stimulation evokes vasoconstriction (also calcium-mediated) in excess of any positive inotropic effect.

The pharmacotherapeutic properties of the adrenergic receptor agonists used clinically for inotropic and hemodynamic support are individually presented under the heading of each. The pharmacologic properties are summarized in table 1.

Dobutamine

Dobutamine is discussed first, because it is currently the agent most commonly employed for short-term intravenous positive inotropic support. Its overall cardiovascular effects in the setting of LV systolic dysfunction and failure result predominantly from positive inotropic enhancement of depressed cardiac contractility.

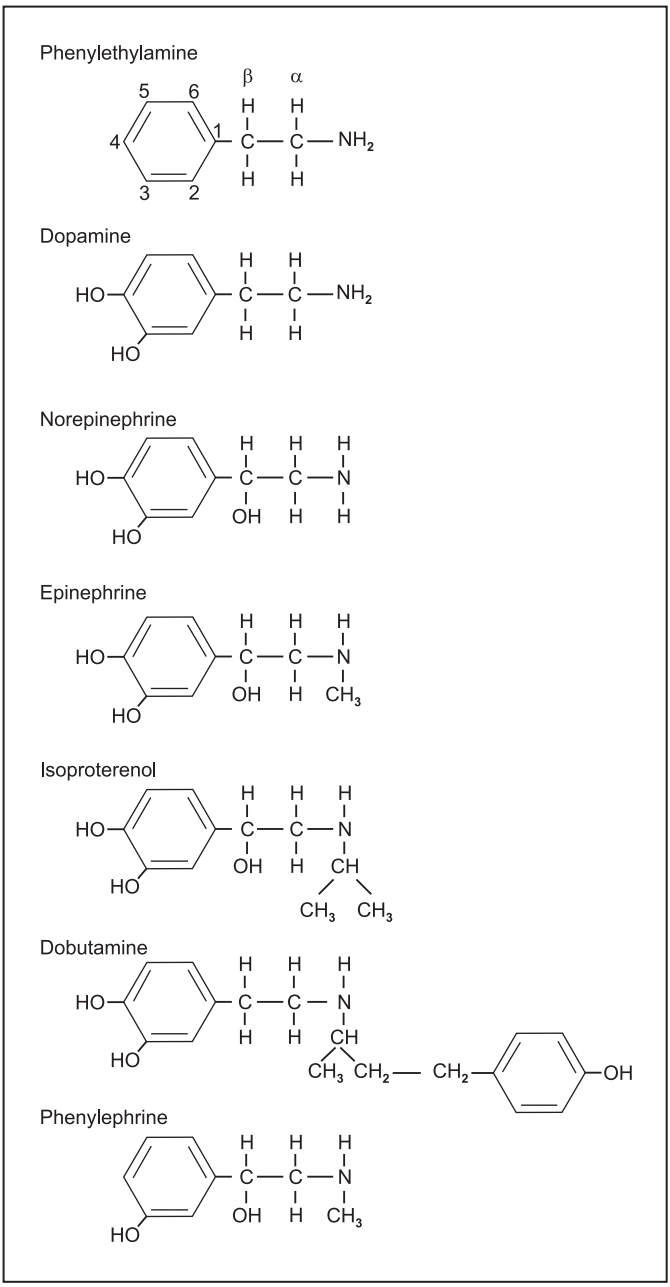


FIGURE 3. The molecular structures of the most commonly used adrenergic agents. The phenylethylamine molecule is the basic molecular structure for the adrenergic compounds under discussion. Variations in the hydroxyl attachment at the β-site and the groups at the amino end determine many of the pharmacologic properties and consequent clinical applications of the catechols. Very little modification of the molecular structure is needed to change an intense vasodilator (isoproterenol) to a strong vasopressor (norepinephrine). Deletion of the 4-hydroxyl group from the epinephrine molecule results in phenylephrine, a powerful vasoconstrictor.

Dobutamine was formulated and developed in the laboratory by Tuttle and Mills[1] from a methodical manipulation and branch substitutions of the basic catechol-phenyl ethylamine molecule. Out of over 15 molecules developed and then studied in large animal models, dobutamine achieved the greatest increase of cardiac contractility and performed with the least effect on vasculature and heart rate.

Pharmacologic Effects

Dobutamine is a racemic compound: dextro- and levo-isomers. It activates myocardial β1- and β2-adrenergic receptors to generate cAMP, which enhances calcium entry and release (the downstream mechanisms is depicted in figure 1); thereby, increases the velocity and extent of myocardial contraction. In chronic heart failure (HF), the number and responsiveness of β1-adrenergic receptors are depleted such that dobutamine's cardiac effects in this clinical setting are largely rendered by activation of β2-receptors.[2] β-adrenergic receptor stimulation also accounts for the chronotropic properties and any dysrhythmias noted with higher dose dobutamine.

In the setting of LV systolic dysfunction and HF, dobutamine generally evokes a mild overall vasodilatory effect, reducing systemic and pulmonic vascular resistance through arteriolar β2-receptor stimulation exceeding the relatively modest vasoconstricting effects of its α-receptor agonism (Figure 2 and Table 1). Studies by Binkley et al.[3-5] indicated that the pharmacology of dobutamine in human HF was considerably more complex. Their studies demonstrated that dobutamine favorably affected aortic impedance and vascular–ventricular coupling, allowing further enhancement of ventricular contractility and overall cardiac performance. In the total artificial heart model of the calf, dobutamine augmented cardiac output in the absence of myocardium and its associated positive inotropic mechanisms.[4] This response was the result of the vascular effects of dobutamine: its dextro-isomer (+enantiomer) reduced systemic vascular resistance and afterload via β2-adrenergic receptor stimulation, and its levo-isomer (–enantiomer) reduced venous capacitance with enhanced venous return via α-receptor agonism.[4,6] The result is augmentation of cardiac output.

Clinical Effects

The major clinical indication for dobutamine administration is short-term positive inotropic support in patients afflicted with ventricular systolic dysfunction and failure, resulting in a problematic drop in blood pressure and systemic perfusion (Table 2). Short-term support will vary somewhat, but generally,

TABLE 2

Clinical Indications and Applications of Dobutamine

- Major indications
  - Short-term (hours to days) positive inotropic and hemodynamic support for patients with ventricular systolic dysfunction resulting in a depressed stroke volume and cardiac output, mild to moderate systemic hypotension (systolic blood pressures of 70–100 mmHg), systemic hypoperfusion, and an elevated left ventricular diastolic filling pressure (≥18 mmHg)
  - The support is maintained until the patient recovers or is directed into more advanced cardiovascular support (e.g., intra-aortic balloon counterpulsation and ventricular assist device) and/or remedial intervention (e.g., coronary artery intervention, valvular repair or replacement, and cardiac transplantation)
- Additional considerations
  - Pharmacologic support as needed for patients with severe heart failure undergoing major diagnostic or surgical procedures
  - Cardiovascular hemodynamic support for the heart failure patient as needed during the course of a major illness
  - Pharmacologic bridge in severe heart failure to standard therapies (e.g., angiotensin converting enzyme inhibitor, β-adrenergic blockade)
  - As a continuous infusion via indwelling central venous catheter to provide the only means of stabilizing an unstable or decompensated heart failure patient to allow discharge from the hospital (to extended care, home, or hospice)
  - For hemodynamic support during weaning from cardiopulmonary bypass and during immediate recovery from cardiac surgery
  - To facilitate recovery of myocardial stunning in the setting of low-output cardiac failure
  - As a means of improving renal function and urine output in patients hospitalized for low-output, systemic hypoperfusion, and volume-overloaded congestive heart failure when renal responsiveness to standard therapy and diuretics is impaired
  - For hemodynamic support during management of cardiac transplant-rejection complicated by hemodynamic low-output and volume-overloaded decompensation
  - To augment systolic function of problematic systolic failure of the right ventricle
  - To assess ventricular (right or left) contractile reserve
  - To evaluate the severity of aortic valvular stenosis in low-flow and low-gradient aortic stenosis
  - As pharmacologic stress for myocardial perfusion imaging or echocardiographic imaging

until the patient recovers adequately or is advanced into more definitive interventions (e.g., mechanical support and remedial cardiac surgery). For the typical patient who presents with acute systolic HF or decompensated chronic HF, a reduced stroke volume and cardiac output, elevated ventricular filling pressures, mild-to-moderate reduction in systemic pressure (systolic

blood pressure 70–100 mmHg), and notably impaired systemic perfusion (e.g., prerenal azotemia, impaired mentation, and elevated liver enzymes), the clinical setting is as one of the "cold and wet"patients.[7]

The therapeutics in this general clinical setting can include diuretics for volume overload and elevated ventricular filling pressures (>18 mmHg), vasopressor infusion (e.g., norepinephrine, moderate-to-high dose dopamine and phenylephrine) for marked hypotension and shock, and combined with a positive inotrope—vasodilator or inodilator (e.g., milrinone) or a vasodilator (e.g., nitroprusside, nitroglycerin, and nesiritide) for patients with systolic blood pressure >90–100 mmHg. It is relatively common to administer two or more of these agents simultaneously or in succession to attain and maintain the optimal and safest clinical and hemodynamic stability on the way to more definitive interventions. For example, a patient may be receiving a diuretic, dobutamine and nitroprusside, and yet another patient, dobutamine and norepinephrine.

With proper patient selection, specifically the patient with ventricular systolic dysfunction resulting in a fall in stroke volume and cardiac output, an abnormal rise in LV end-diastolic filling pressure, systemic hypoperfusion, and mild-to-moderate reduction in systemic blood pressure, dobutamine increases stroke volume, cardiac output, systemic systolic blood pressure and pulse pressure, and systemic perfusion, while decreasing the elevated LV filling pressure and pulmonary and systemic vascular resistances[8-10] (Figure 4). In patients with concomitant mitral regurgitation, the reduction in systemic vascular resistance, ventricular volume and mitral orifice area likely account for the decrease in mitral regurgitation, the reduction in mitral regurgitation further augments stroke volume, and cardiac output during dobutamine administration.[10] While there appears to be a dose-related separation of positive inotropy or enhanced contractility with beneficial hemodynamic effects from the potential detrimental effects of positive chronotropy, higher dosing will elicit a faster heart rate and can provoke atrial and ventricular ectopic beats and various forms of tachydysrhythmias[8] (Figure 4).

Regional blood flow studies in decompensated chronic HF revealed that dobutamine increases limb blood flow proportional to the increase in cardiac output. Dobutamine augments renal blood flow, but generally less than the proportional rise in cardiac output. Dobutamine favorably affects renal function, glomerular filtration rate, and urine output, and can be expected to augment the renal effects (natriuretic and diuretic responses) of diuretics.[8]

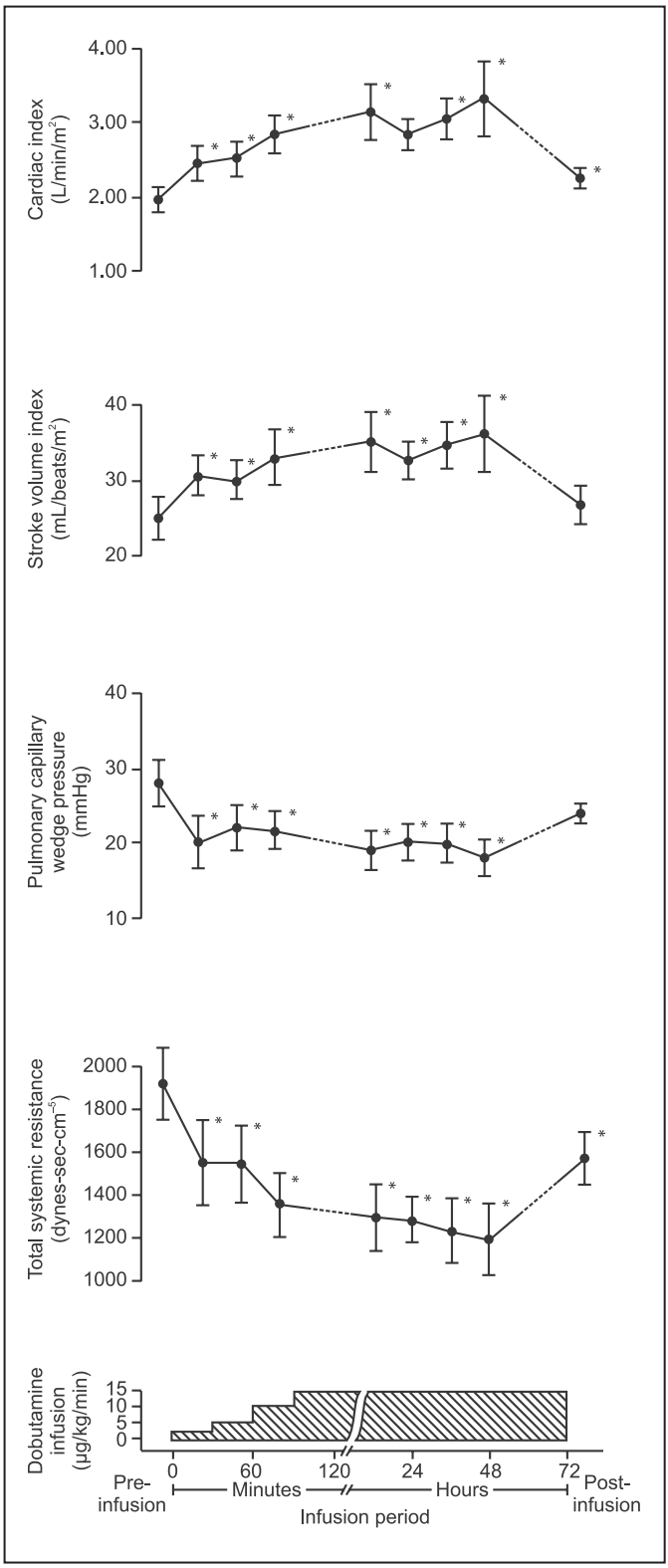


Figure 4 *(continued)*

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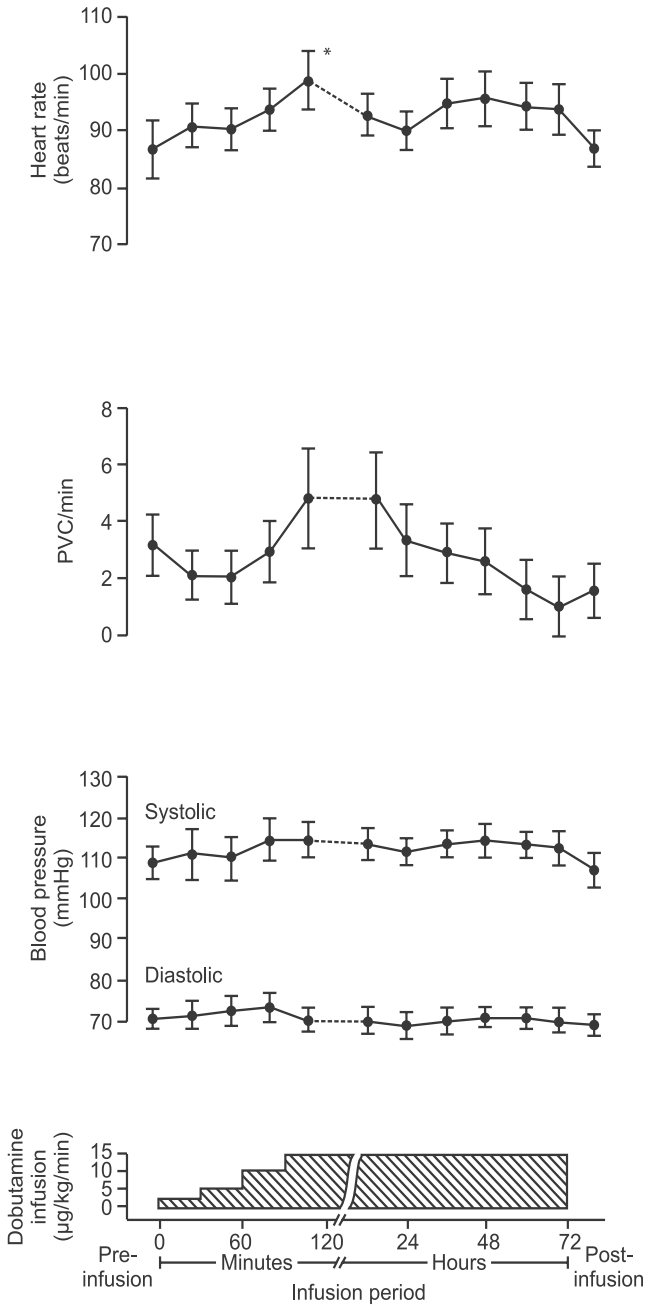

PVC, premature ventricular contraction.

FIGURE 4. Pharmacodynamic curves for the dose-response and sustained infusions (72 hours) of dobutamine in chronic systolic heart failure. The infused dose is presented in the bottom panel. *Adapted from* Leier CV, Webel J, Bush CA. The cardiovascular effects of the continuous infusion of dobutamine in patients with severe heart failure. *Circulation*. 1977;56(3):468-72, *with permission.* $\bar{X} \pm SD$, $n = 25$, $^*p < 0.05$ vs. preinfusion baseline.

There is no statistical change in hepatic-splanchnic flow with little information on how this system is clinically affected.[11]

In patients with LV systolic dysfunction and nonobstructed coronary arteries, dobutamine increases coronary blood flow proportionate to or greater than the augmented cardiac output and myocardial oxygen consumption.[12,13] This favorable effect on myocardial oxygen balance is related to several mechanisms, including dobutamine-induced enhancement of coronary perfusion pressure (reduction in LV diastolic pressure is more than the drop in systemic diastolic pressure), an increase in coronary diastolic perfusion time, and a decrease in coronary vascular resistance.[8,12-14] Furthermore, the reduction in aortic impedance, systemic and pulmonary vascular resistances, ventricular afterload, and ventricular systolic volume with dobutamine lowers myocardial oxygen consumption. Positive inotropy as such increases myocardial oxygen consumption. At doses short of evoking a clinically significant elevation in heart rate (>10% above baseline), the coronary blood flow—myocardial oxygen delivery—is equal to or exceeds the increase in myocardial oxygen consumption caused by the enhanced contractility of dobutamine.[12,13]

However, these favorable coronary-myocardial energetic properties of dobutamine can be negated in the setting of high-grade occlusive CAD, where a fixed obstructive lesion can prevent an increase of coronary blood flow in its region to match the rise in myocardial contractility and associated oxygen consumption. Any substantial increase in heart rate (>10% above baseline) imposes a threat to coronary artery perfusion and the balance of oxygen demand–oxygen delivery by increasing myocardial oxygen–energy consumption without an increase in coronary blood flow through shortening of diastolic coronary perfusion time.[14] The positive chronotropic and inotropic properties of high-dose dobutamine is now regularly employed during dobutamine-stress echocardiographic nuclear or magnetic resonance myocardial imaging to elicit evidence of inadequate coronary flow and myocardial ischemia in patients with occlusive CAD.

While the chronotropic properties of dobutamine are of major importance in all patients, they are particularly important in patients with occlusive CAD, where tachycardia will override the favorable coronary-myocardial energetic effects of dobutamine to evoke myocardial ischemia. For these reasons, proper patient- and dose-selection is extremely important in patients with LV systolic dysfunction and occlusive coronary disease. Using these pharmacologic considerations as a guide, dobutamine can be effectively and safely administered to decompensated

HF patients with occlusive CAD to achieve and maintain a more stable, short-term, clinical, and hemodynamic course until the patient is directed to more advanced intervention (e.g., intraaortic balloon counterpulsation, catheter-based coronary intervention, and coronary artery bypass surgery).[15-22] During this short-term "pharmacologic bridge", dobutamine has to be able to favorably alter the determinants of oxygen-metabolic consumption and supply (by reducing elevated ventricular diastolic pressures, pulmonic and systemic vascular resistances, ventricular volumes and wall stress, and increasing coronary artery perfusion pressure and diastolic perfusion time) comparable to and greater than the increase in myocardial oxygen-energy consumption of enhanced ventricular contraction. Nevertheless, even with proper patient-selection and dose-administration, a few patients with occlusive coronary disease can develop myocardial ischemia and potentially an infarction during dobutamine administration.[16,17,19]

Dobutamine appears to favorably affect and reverse myocardial stunning beyond the simple increase in coronary blood flow and myocardial perfusion of the affected region or whole heart.[23-25]

Clinical Indications

The most common clinical settings for appropriate dobutamine administration (to improve and then stabilize the patient's hemodynamic and clinical status) include patients treated for decompensated, hypoperfused, and typically hypotensive (generally systemic systolic blood pressure of 70–100 mmHg), chronic systolic HF, acute systolic HF (as can be seen with acute myocardial infarction or acute myocarditis), or immediately following cardiac surgery. The various considerations for the administration of dobutamine are presented in table 2.

Vasodilators or inodilators might be considered for augmentation and stabilization of hemodynamic- and clinical-status in symptomatic HF patients with systemic systolic pressures >90 mmHg.

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Under the recommendations for management of patients with refractory end-stage HF (stage D), dobutamine would fall under class IIb, as "continuous intravenous infusion of a positive inotropic agent may be considered for palliation of symptoms in patients with refractory end-stage HF (level of evidence: C)". The discussion that follows this narrow recommendation includes "...has been used in patients who are awaiting cardiac

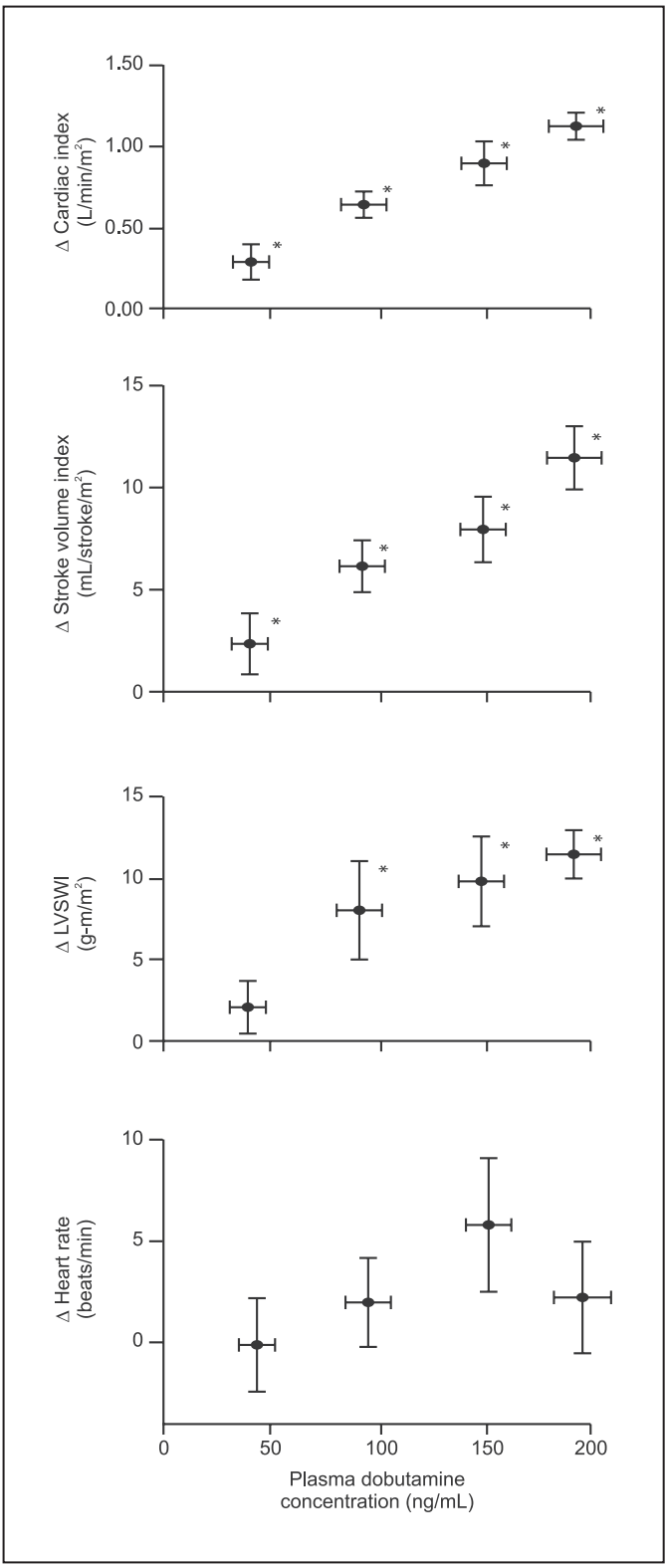
transplantation" (i.e., pharmacologic bridge) and for the end-stage patient with few remaining options; whereby, dobutamine "can be used in the outpatient setting in patients who otherwise cannot be discharged from the hospital".[26]

Administration and Dosing

Although the standard recommended dose range for dobutamine is 2.0–15.0 μg/kg/min, many patients can experience clinical and hemodynamic benefit at a lower initial dose of 0.5–1.0 μg/kg/min, and can achieve such with little to no increase in heart rate or the occurrence of dysrhythmias. Dosing can be increased incrementally by 1.0–2.0 μg/kg/min every 12–15 minutes (or more), until the desired clinical and hemodynamic responses are attained, but short of elevating heart rate >10% above baseline, provoking dysrhythmias, or inducing side effects. In the absence of β-adrenergic blockade, the inability to improve hemodynamic and clinical parameters in symptomatic, LV systolic dysfunction, and HF during incremental dobutamine infusion dosing up to 15 μg/kg/min seems to be associated with a poor prognosis.[8]

To discontinue dobutamine, maintenance doses of <2.0 μg/kg/min can generally be withdrawn without difficulty. Higher infusion rates administered over an extended period usually require gradual weaning over 12–72 hours to avoid hemodynamic and clinical deterioration with rapid discontinuation.[8,27] Prolonged higher infusion rates in patients treated for decompensated, chronic systolic dysfunction, and HF often require a longer weaning period or incremented oral administration of hydralazine to effectively withdraw dobutamine with less difficulty.[27] Although tolerance can develop to a mild-moderate degree during a prolonged administration, it is generally not enough of a factor to facilitate withdrawal of dobutamine.[28]

The pharmacodynamic and pharmacokinetic properties of dobutamine support its role as a short-term, positive inotropic agent. Its half-life in HF patients (averages 2.37 ± 0.07 minutes)[29] indicates that steady-state blood level for any dose is achieved in about 12–13 minutes, and an invaluable property if positive inotropic support of ventricular contraction is urgently needed. In human HF, there is a direct relationship between the infusion rate of dobutamine, the plasma levels of dobutamine, and its hemodynamic responses[30] (Figure 5). Furthermore, the drug is eliminated from circulation within 12–13 minutes upon discontinuation of administration, thus allowing for a rapid elimination of undesirable side effects, if encountered during dobutamine administration.



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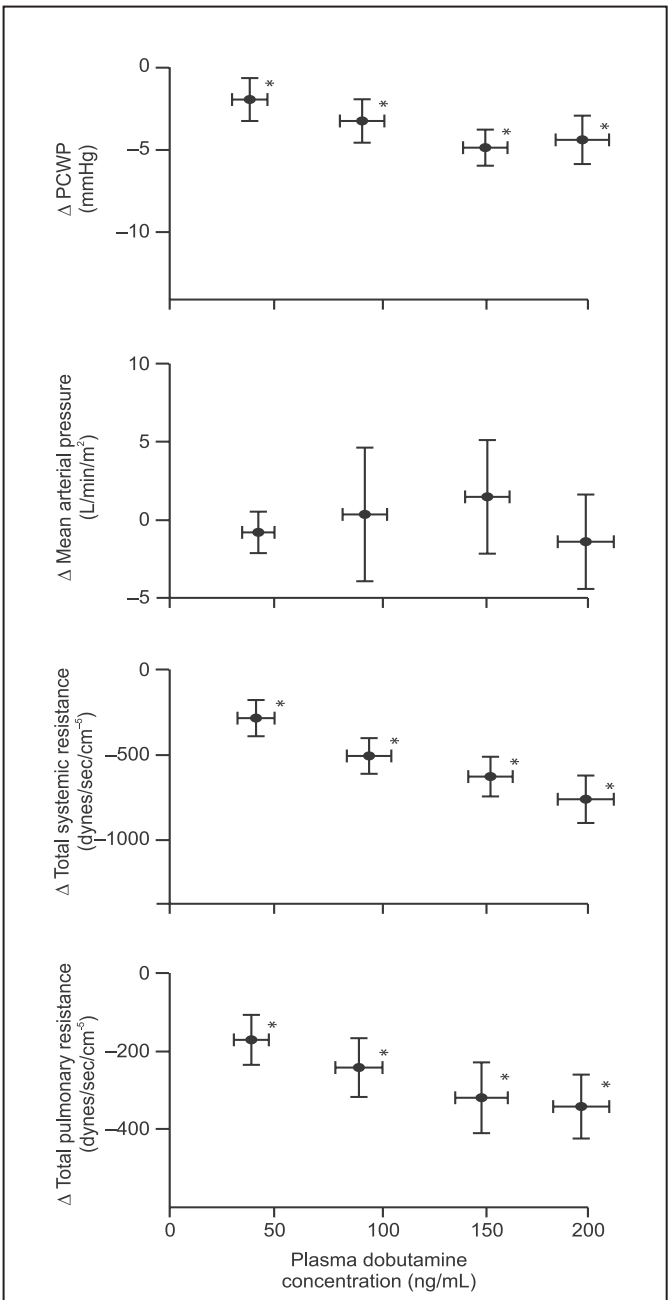

Δ, change in; LVSWI, left ventricular stroke work index; PCWP, pulmonary capillary wedge pressure.

FIGURE 5. Graphs depicting the relationship of dobutamine infusion dose, plasma concentration, and hemodynamic effects in patients with moderate to severe chronic systolic heart failure. The infusion rates for the 4 data points of each graph are 2.5, 5.0, 7.5, and 10.0 μg/kg/min, incremented every 20–30 minutes. *Adapted from* Leier CV, Unverferth DV, Kates RE. The relationship between plasma dobutamine concentrations and cardiovascular responses in cardiac failure. *Am J Med.* 1979;66(2):238-42, *with permission*. $\bar{X} \pm$ SED, *$p < 0.05$.

The addition of a phosphodiesterase inhibitor (e.g., milrinone) augments the inotropic effect of dobutamine by impairing the metabolism of dobutamine-induced elevation of intracellular cAMP.[31] The inotropic–hemodynamic properties of dobutamine are blunted in patients taking β-adrenergic blocking agents, especially the nonselective adrenergic receptor blockers (e.g., carvedilol).[32-34] This effect can be reversed with incremental dosing of dobutamine, which competitively replaces the adrenergic receptor blocker at the receptor site. The β1-selective β-blockers (e.g., metoprolol) do not interfere with the β2-agonism and hemodynamic effects of dobutamine. It is generally not necessary to stop the β-blocker or to substitute a nonadrenergic agent (e.g., milrinone) for dobutamine in most of these patients.

Adverse Effects

The most common undesirable responses to dobutamine are an increase in heart rate and dysrhythmias. From comparative studies and various registries, it is clear that improper patient- or dose-selection will evoke tachycardia, atrial and ventricular dysrhythmias, poor clinical outcomes, and other adverse effects.[35-38] In a number of retrospective studies, the apparent dobutamine-induced undesirable effect on outcomes is largely attributable to improper dosing and/or to its administration in a sicker, more compromised patient population than that served by the comparator.[38-40] Nevertheless, these reports[35-40] emphasize the importance of appropriate selections of patient, drug, and dose.

Other adverse effects, also usually dose-related, include anxiety, tremor, palpitations, headache, and nausea. A hypertensive response (elevated systemic systolic blood pressure) can be observed when dobutamine is administered to patients with a history of hypertension or peripheral vascular disease, even though they can initially present with hypotension and systemic hypoperfusion. As noted above, patients with high-grade occlusive coronary disease can develop angina, myocardial ischemia, and infarction, particularly those who do not meet the primary indication for use, receive excessive initial dosing or excessively rapid advancement of dose (Table 2). More prolonged dobutamine infusions can reduce plasma potassium concentrations.[41] Less common adverse effects include a generalized erythema-flushing, eosinophilia, and hypersensitivity myocarditis.[42,43] These do not appear to be dose-related, and the reactions are probably related to the bisulfite adjuvant. Dobutamine has been reported to induce stress-cardiomyopathy (also known as Takotsubo cardiomyopathy) in rare patients undergoing pharmacologic stress-testing with this agent.[44]

Dopamine

Dopamine is the endogenous precursor of norepinephrine and epinephrine. Although it is the simplest molecule of the clinically available adrenergic drugs, it has the most complicated pharmacology (Figures 2 and 3, and Table 1).

Pharmacologic Effects

Dopamine evokes most of its effects through activation of the adrenergic receptors (β1, β2, and α), through the neuronal release and reduced neuronal uptake of endogenous norepinephrine, and via stimulation of dopaminergic receptors (D1 and D2).[45-47] In human HF, dopamine at lower infusion rates of <4.0 μg/kg/min can act as a mild vasodilator (dopaminergic), particularly of renal and visceral arterial-arteriolar vascular beds. At higher doses, this effect is modulated by dopamine's stimulation of adrenergic receptors directly and through its release of norepinephrine from nerve endings. Although individual responses vary widely, in general, vasodilatation gives way to a net-balanced vascular effect and some positive inotropy at moderate dosing of 4.0–8.0 μg/kg/min and to considerable vasoconstriction with some retained positive inotropy at doses of >8.0 μg/kg/min.

Clinical Effects

In states of reduced cardiac output, systemic hypoperfusion, and elevated ventricular filling pressures, dopamine administered at doses of <4.0 μg/kg/min can enhance ventricular contraction, stroke volume and cardiac output, and drop systemic and pulmonary vascular resistances—all to a modest degree without much change in systemic blood pressure.[11,48-50] As infusion dosing moves to >4.0 μg/kg/min, stroke volume and cardiac output tend to plateau, systemic and pulmonary vascular resistances even out or increase, and a substantial dose-related rise in systemic blood pressure occurs in a dose-related manner. A rise in heart rate and the development of dysrhythmias are also dose-related and often become undesirable effects at >6.0 μg/kg/min. LV filling pressure can decrease in some patients but usually does not change or can rise with higher dosing. Indices of positive inotropy or ventricular contractility are reduced at higher doses and during a continuous infusion.[11] This presumably is related to the increase in blood pressure, pulmonary and systemic vascular resistances, ventricular afterload, and via depletion of myocardial norepinephrine stores from dopamine-induced norepinephrine release and reduced reuptake at nerve endings during high dose or prolonged dopamine infusions.

Clinical Indications

The vasoconstricting effects of moderate to high doses of dopamine are employed clinically to increase and stabilize systemic blood pressure in the clinical settings of cardiogenic or vasodilatory (e.g., septic) hypotension and shock.[51-55] This clinical application should predominate over its use as a primary inotrope and, thus, is its principal indication (as a vasopressor).

Interestingly, the *post hoc* analysis of a recently performed multicenter trial on shock suggests that dopamine may offer little advantage over norepinephrine and may be less effective in the cardiogenic shock group[55] (see the heading "Norepinephrine").

A multicenter study from Europe found that donor hearts from patients supported with dopamine (4.0 μg/kg/min) preharvested had an improved clinical course as allografts (less hemofiltration and graft failure) compared to the donor hearts not supported with dopamine infusions.[56]

Much of the clinical appeal for dopamine administration in problematic hypotension shock originates from what are thought to be favorable renal effects of dopaminergic stimulation. It has been demonstrated that dopamine, at lower doses of <5.0 μ/kg/min, can increase renal blood flow equal to or greater than the proportional increase in cardiac output.[11,57-59] Whether this increase in renal blood flow also evokes an increase in glomerular filtration rate, diuresis and natriuresis in HF, marked hypotension, or shock remains controversial and burdened by conflicting results of published reports.[11,48,57-61]

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Since dopamine is generally placed under the heading of "positive inotropes," its guidelines for recommended use are the same as those of dobutamine, even though the drugs are pharmacologically and therapeutically different. Clinically, dopamine is generally used as a vasopressor.

Administration and Dosing

Due to considerable variation with respect to individual responses to dopamine, this drug is generally started at 2.0 μg/kg/min and advanced as needed to attain the necessary increase in systemic blood pressure. Doses >4.0 μg/kg/min are generally required to achieve and maintain a systemic pressure >80 mmHg. Dopamine, like dobutamine, is a rapid-onset and rapid-offset agent, which is ideal for the acute management of critically ill patients in the intensive care unit.

Adverse Effects

The most common adverse effects seen during dopamine administration are comparable to those of dobutamine, namely, a rise in heart rate and dysrhythmias, both dose-related.[11] Dopamine crosses the blood-brain barrier and can evoke nausea and vomiting in conscious, awake patients. Intense vasoconstriction by dopamine can result in ischemia of digits and organ systems. Subcutaneous infiltration at the intravenous site can elicit pain and local ischemic changes, partially reversible with local injections of phentolamine. Dopamine has been noted to depress minute ventilation in patients with HF.[62]

OTHER ADRENERGIC AGENTS

These agents are indicated in a variety of clinical settings. Although often categorized as "positive inotropes," these agents are rarely used as primary positive inotropic drugs because of their predominant vascular effects.

Isoproterenol

This drug is perhaps the most selective β-adrenergic receptor agonist (β1 and β2) available for clinical use. However, its positive inotropic properties are largely overwhelmed by its powerful vasodilatory and positive chronotropic effects (Table 1 and Figure 2). Its clinical application is somewhat restricted, namely, to serve as a means to increase heart rate in the short-term, until recovery occurs or definitive intervention (e.g., pacemaker) is applied in patients with problematic bradycardia. This is particularly applicable in clinical situations where intravenous atropine is contraindicated, inadequate, or ineffective. In view of other, generally safer vasodilating agents (e.g., milrinone and nitrates), isoproterenol is rarely employed as a primary vasodilator. Adverse effects during isoproterenol administration include flushing, anxiety, tremors, hypotension, tachycardia, and dysrhythmias.

Epinephrine

This is another endogenous catecholamine, which acts by stimulating β1-, β2-, and α1-adrenergic receptors. Epinephrine differs from dobutamine in that its β2 and α1 effects are more intense than those of dobutamine, and its administration is modulated by neuronal uptake. In cardiovascular medicine, epinephrine is most often used during cardiopulmonary resuscitation or employed as a general hemodynamic support drug during withdrawal from cardiopulmonary bypass and

during immediate recovery from cardiac surgery. Undesirable effects include most of those described above for dobutamine, dopamine, and isoproterenol.

Norepinephrine and Phenylephrine

Again, these agents are often placed under the "positive inotrope" category, but they are predominant α1-adrenergic stimulants with mild β-receptor agonism, and thus, they are also best categorized and viewed as vasopressors (Table 1 and Figure 2). As such, these compounds are clinically applied for vasoconstriction to augment and stabilize systemic blood pressure in conditions of marked hypotension and shock (vasodilatory and cardiogenic forms).[55,63]

The results of a sizable multicenter trial (1,679 patients), conducted in Europe, on the management of shock-states demonstrated little difference in overall mortality at 28 days (primary endpoint) between norepinephrine and dopamine, when used to secure blood pressure and clinical status.[55] However, dopamine appeared to be more chronotropic and arrhythmogenic for comparable blood pressure responses. In a *post hoc* analysis, the 28-day survival-outcome in the cardiogenic subgroup of 280 patients favored norepinephrine as the optimal stabilizing vassopressor[55] (Figure 6).

Norepinephrine infusions in hypotension and shock generally range from 0.02 to 0.80 μg/kg/min. In addition to the undesirable effects described for dopamine, norepinephrine can, if not

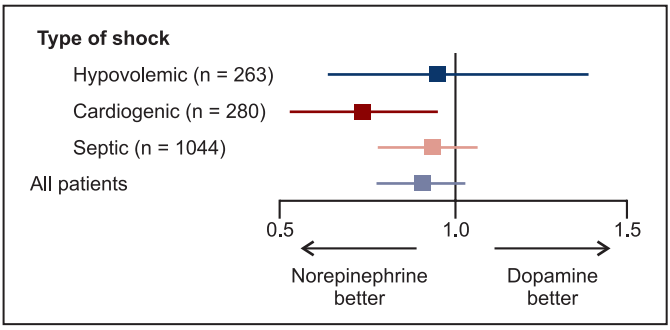

FIGURE 6. A forest plot showing the hazard ratio (+95% confidence intervals) of dopamine vs. norepinephrine support during shock management of the 3 major shock subgroups studied. There were no statistical differences between the 2 interventions for all shock patients combined or for the septic and hypovolemic subgroups. The hazard ratio for the cardiogenic shock subgroup favored norepinephrine over dopamine based on dysrhythmic events during treatment and on mortality at 28 days following the shock episode. *Adapted from* De Backer D, Biston P, Devriendt J, Madl C, Chochrad D, Aldecoa C, et al. Comparison of dopamine and norepinephrine in the treatment of shock. *N Engl J Med*. 2010;362(9):779-89, *with permission*.

carefully monitored, evoke dose-related systemic hypertension and consequent bradycardia.

More intense vasoconstriction with little-to-no positive inotropic effect is delivered by the intravenous administration of phenylephrine.

PHOSPHODIESTERASE INHIBITORS

These drugs are often referred to as "inodilators," because vasodilation is a major part of their pharmacology. In fact, amrinone, studied initially in this general group, is predominantly a vasodilator with little enhancement of ventricular contraction beyond its vasodilating-unloading effects on the left ventricle.[64-66] Thrombocytopenia and arrhythmogenesis during prolonged oral administration of amrinone tempered both oral and intravenous application.[65,66] Amrinone has been replaced by milrinone as a therapeutic modality.

Milrinone

Although milrinone can enhance some positive inotropy through other cellular mechanisms (e.g., activation of calcium-release channel on the sarcoplasma reticulum), its cardiovascular properties are principally caused by inhibition of phosphodiesterase III (PDE III) with subsequent delayed breakdown-metabolism of cAMP[67] (Figure 1).

Pharmacologic and Clinical Effects and Clinical Indications

In contrast to dobutamine, a positive inotropic agent with mild vasodilating properties, milrinone is primarily a vasodilator with mild positive inotropic effects. Therefore, for any matched level of enhanced inotropy-contractility, milrinone elicits a greater decrease in pulmonary and systemic vascular resistances, pulmonary artery pressure, systemic blood pressure, and biventricular filling pressures[68-78] (Figures 7 and 8). As a vasodilator, proper dosing of milrinone can augment hemodynamics with little-to-

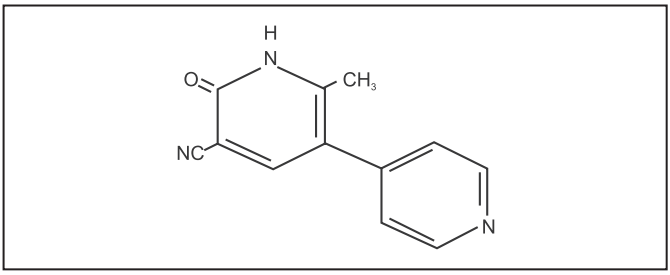

FIGURE 7. Molecular structure of milrinone.

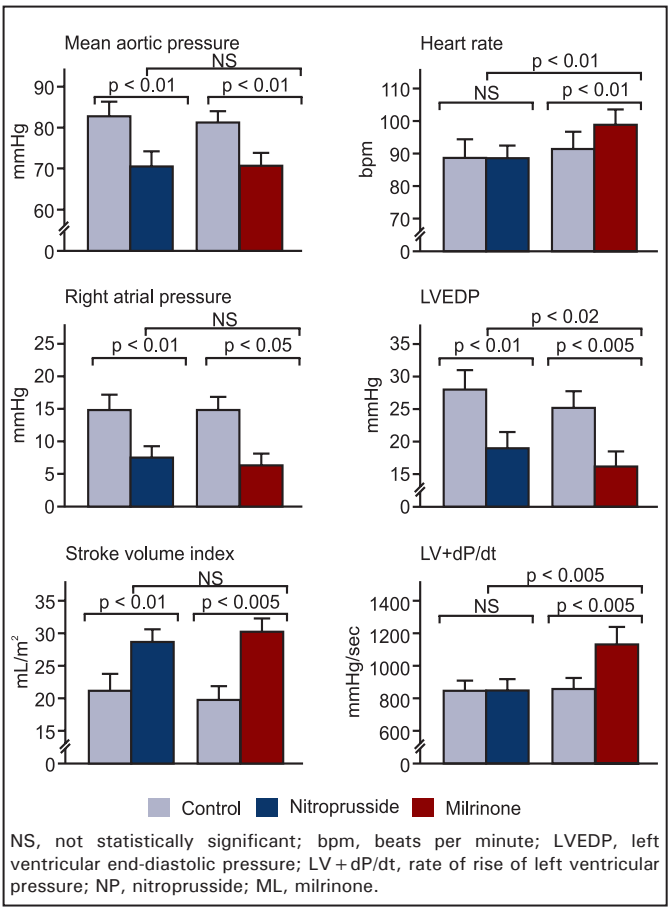

FIGURE 8. A comparison of the hemodynamic effects of milrinone at the maximal dose administered and nitroprusside at the dose selected to match the reduction in mean aortic pressure by milrinone. For comparable ventricular unloading, milrinone elicited positive inotropy (increased +dP/dt = change in LV developed systolic pressure over change in time) and positive chronotropy via a direct milrinone effect and perhaps an increase in reflex sympathetic tone from vasodilatory-hypotension. *Adapted from* Jaski BE, Fifer MA, Wright RF, Braunwald E, Colucci WS. Positive inotropic and vasodilator actions of milrinone in patients with severe congestive heart failure. Dose-response relationships and comparison to nitroprusside. *J Clin Invest*. 1985;75(2):643-9, *with permission*.

no increase in myocardial energetics-oxygen consumption.[73,74] Its ability to reduce pulmonary vascular resistance and pulmonary artery pressure makes it a favorable agent for augmentation of central hemodynamics in patients with high pulmonary artery pressures.[71,72]

Bolus milrinone is one of the vasodilating agents used to determine reversibility of elevated pulmonary artery pressures in patients with more severe HF under evaluation for cardiac transplantation.[75,76]

In patients with severe, low-output congestive HF, milrinone enhances the hemodynamic responses to dobutamine and vice versa. It is not unusual to employ the dobutamine-milrinone combination in patients with severely compromised hemodynamics, generally in the setting of end-stage HF, and often as a "pharmacologic bridge" to insertion of a ventricular assist device or cardiac transplantation. Parenthetically, without these major interventions (ventricular assist device and cardiac transplantation), the requirement for the dobutamine-milrinone combination to clinically support and stabilize the HF patient, portends a poor outlook.

Since milrinone acts distal to the activation of adrenergic receptors (Figure 1), it can enhance hemodynamics in patients on β-adrenergic antagonists (β-blockers). This is particularly important for patients treated with nonselective β-blockers (e.g., carvedilol), which competitively interfere at the β-receptor site with low-dose dobutamine.[77]

2009 Guidelines for the Diagnosis and Management of Heart Failure in Adults

Since milrinone is also placed under the heading of "positive inotropes," the guidelines for recommended use are generally considered similar to those of dobutamine, even though the drugs are pharmacologically and therapeutically quite different.

Administration and Dosing

Milrinone is generally started at 0.10–0.30 μg/kg/min and advanced gradually as needed to arrive at the intended hemodynamic and clinical end-points but short of evoking hypotension, tachycardia, and dysrhythmias. Milrinone has an elimination half-life of 1–3 hours,[79,80] and, thus, the onset of action, equilibration, and offset are not as prompt as that seen with the catechol-type of inotropes. Although rarely required, an initial intravenous bolus dose of 20–80 μg/kg delivered over 10–15 minutes accelerates the onset of action in conditions where a more rapid response is needed.[81] The relatively long elimination half-life (1–3 hours) results in a delayed recovery from undesirable effects after milrinone is discontinued; not an ideal pharmacokinetic profile for intensive or critical care medicine. Some pharmacodynamic tolerance can occur during prolonged infusions.

Adverse Effects and Undesirable Responses

While vasodilatation is a favorable effect of milrinone, when administered properly to the appropriate patient, vasodilatation

also offers its limitations. This drug is generally not used in patients with systemic systolic blood pressure below 90 mmHg and, therefore, milrinone is not a first-line agent used for low output hypotension or shock. Hypotension from extensive vasodilatation and myocyte inhibition of PDE III can elicit positive chronotropy and provoke dysrhythmias.[78] Some patients can experience flushing and generalized warmth at moderate-to-high infusion doses or during bolus administration. Fluid-volume retention is not uncommon during prolonged infusions.[78]

OTHER INTRAVENOUSLY ADMINISTERED POSITIVE INOTROPIC INTERVENTIONS

A number of additional agents are known to enhance positive inotropy and myocardial contractility.

Calcium Sensitizers

Calcium sensitizers (e.g., levosimendan) augment positive inotropy by "modulating" intracardiomyocyte mechanisms of contraction at the same levels of intracellular calcium (Figure 1).

Levosimendan

Although some of its positive inotropic response is likely through phosphodiesterase inhibition, levosimendan's ability to increase myocardial contractility is believed to be via sensitization of the contractile apparatus to available intracellular calcium by augmenting and/or securing calcium binding to troponin C[82,83] (Figure 1).

Levosimendan also behaves as an "inodilator" in human HF. As such, it lowers vascular resistances and ventricular filling pressures, and by vasodilatory unloading the left ventricle and perhaps some positive inotropy, levosimendan increases stroke volume and cardiac output.[84-87] Levosimendan predictably causes a greater drop in systemic blood pressure and B-type natriuretic peptide during infusions compared to dobutamine, but with the same all-cause mortality and comparable secondary clinical end-points, 180 days postinfusion.[86] Levosimendan, as an agent with vasodilating properties, theoretically, should have a favorable effect on myocardial energetics–oxygen balance, although this consideration has not been adequately investigated in human HF. For patients treated with nonselective adrenergic blockers (e.g., carvedilol), levosimendan can elicit its hemodynamic effects with mechanisms located beyond the adrenergic receptors with no need to compete for adrenergic receptor sites.[88] Because of its vasodilating properties, levosimendan should not be employed as a first-line intervention for low output hypotension or shock.

The levosimendan molecule has an elimination half-life of 1–2 hours, but a primary active metabolite (OR-1896) has an elimination half-life of over 75 hours. A sustained hemodynamic effect is seen long after the infusion is discontinued and may be favorable in some instances, but when this is accompanied by hypotension, tachycardia, dysrhythmias, or other undesirable effects, this prolonged and some what unpredictable drug clearance is a major limitation, particularly in intensive-critical care medicine.

Levosimendan is approved for clinical use in some countries of Europe, South America, and Asia.

Additional Intravenously Administered Positive Inotropes

Initial studies of istaroxime, an inhibitor of sarcolemmal sodium/potassium adenosine triphosphatase (Na^+/K^+ ATPase) and activator of calcium ATPase of sarcoplasmic reticulum, demonstrated some promise as an agent to augment systolic and diastolic performance of the heart.[89]

Intravenously delivered thyroxine or triiodothyronine can improve hemodynamics with a reasonably good safety margin, even in patients with end-stage HF and cardiogenic shock.[90,91]

Historically, intravenously administered glucagon has been used to augment myocardial contraction in patients with cardiogenic hypotension or shock refractory to or intolerant of adrenergic stimulation or in those treated with higher doses of β-blocking drugs.

ORALLY ADMINISTERED POSITIVE INOTROPIC AGENTS

While digitalis (now specifically digoxin) has been employed for over 200 years to treat the "dropsy" of HF, this coveted role has been curbed by the Digitalis Investigation Group (DIG) trial, published in 1997.[92] In general, newer oral inotropes have not fared well in clinical investigations over the past 2–3 decades as means of improving myocardial contractility and cardiac performance. Several nondigitalis, orally administered agents have been formulated over the past 3–4 decades to replace digoxin in the pharmacotherapeutics of HF. A few examples include amrinone, oral milrinone, pimobendan, vesnarinone, and butopamine. In general, all were determined to be ineffective, to evoke adverse effects or to adversely influence outcomes.

Digitalis-Digoxin

Pharmacologic and Clinical Effects

Much of the augmentation of myocardial contractility by digoxin appears to be generated by inhibiting the Na^+/K^+ ATPase pump of the cardiomyocyte sarcolemma (Figure 1). This blocking effect results in a rise of intracellular sodium, which elevates (via impairment of the sodium-calcium exchanger) the intracellular calcium available for contraction.[93] Digitalis may also bring calcium into the cardiomyocyte to augment contractility by modulating the voltage-sensitive sodium channels.[93]

Most of the clinical benefit of digitalis probably occurs through noninotropic mechanisms. Digitalis in human HF reduces sympathetic nervous system tone. HF increases sympathetic tone and decreases parasympathetic tone, resulting in several undesirable effects, including increased systemic vascular resistance, tachycardia, increased renin release, and reduced baroreceptor sensitivity. Most of these undesirable responses in HF are suppressed by chronic digitalis administration.[94-101] It is likely that the clinical and hemodynamic benefits noted with chronic digoxin therapy are attributable to a combination of the improvement of autonomic tone and the direct effect on the cardiomyocyte.

Intravenously delivered digoxin in HF evokes a modest-mild increase in mean stroke volume, cardiac output, and systemic blood pressure, while a modest-mild decrease in heart rate and ventricular filling pressures, and minimal change in vascular resistances. Although individual responses can vary widely, greater hemodynamic effects are noted in those who are more hemodynamically compromised.[100-103] The nonpredictable variability of clinical and hemodynamic responses, potential undesirable effects (e.g., dysrhythmias) for an agent with a relatively low therapeutic index (the difference between therapeutic effect and toxicity), and a rather long elimination half-life have limited the regular use of intravenous digoxin and its congeners.

Intravenously administered digoxin is, therefore, reserved as an option to slow a fast ventricular rate to rapidly conducting atrial flutter or fibrillation in patients with decompensated HF.

Over the years, the results of most noncontrolled or relatively small (few number of patients) studies have suggested that chronic, orally administered digoxin in human HF can favorably alter clinical status, enhance LV ejection fraction, increase exercise performance, and augment hemodynamics at rest and during

exercise.[104-111] Again, the clinical responses and hemodynamic effects are quite variable with improvement most noteworthy in HF patients with the most severe decompensation.[105-107,110]

Two studies looking at digoxin-withdrawal, both randomized, double-blind, and placebo-controlled, published around the same time (1993), provided reasonable evidence supporting the merits of chronic digoxin therapy in patients with mild-to-moderate HF (FC II-III) and sinus rhythm (it had always been assumed that HF patients in atrial fibrillation generally benefit from long-term digoxin).[111,112] The PROVED (Prospective Randomized Study of Ventricular Failure and the Efficacy of Digoxin) trial[111] was performed in HF patients treated with diuretics and digoxin chronically and the RADIANCE (Randomized Assessment of the effect of Digoxin in Inhibitors of the Angiotensin Converting Enzyme) trial[112] in HF patients chronically treated with ACEIs, diuretics, and digoxin. In both studies, compared to those randomized to continued digoxin therapy, the patients randomized to withdrawal of digoxin (to placebo therapy) experienced a fall in LV ejection fraction, impairment of clinical status, diminished functional capacity, and a documented decrease in exercise performance with an increase in heart rate and body weight over the 3-month study period. Again, this deterioration was greatest in patients with more severe HF, but also noteworthy in patients with a milder course.[113,114] It is important to remember that both trials were performed in an era before standard β-adrenergic blocker therapy (i.e., prior to background β-blockers).

Studies investigating either the intravenous or the chronic oral administration of digoxin in patients with LV dysfunction following acute myocardial infarction demonstrated minimal-to-no benefit with a high potential for adverse effects and undesirable outcomes.[115-121]

All prior studies regarding the use of long-term digitalis in patients with HF and sinus rhythm have now been somewhat overshadowed by the DIG trial.[92] This trial has now guided current digoxin use in this clinical setting (systolic HF in sinus rhythm). A total of 6,800 patients with the clinical features of HF LV ejection fraction <0.45 and in sinus rhythm were randomized 1:1 to digoxin or placebo. The median daily dose of digoxin for the patients randomized to this therapy was 0.25 mg. The average follow-up was 37 months. About 95% of the overall study population was chronically receiving an ACEI, 82% on a diuretic, and 78% taking both agents. Patients with HF and relatively preserved ejection fraction (>0.45) were enrolled in a parallel ancillary study.[122]

Long-term digoxin therapy in the DIG trial did not affect total all-cause mortality. Digoxin tended to lower mortality ($p = 0.06$) attributable to HF, and also statistically lowered the combined end-points of HF mortality or HF hospitalization (largely driven by the reduced rate of hospitalization).[92] This benefit appeared to be greatest in patients with worse clinical status and lower ejection fractions.

The findings for patients with an LV ejection fraction >0.45 demonstrated no effect of digoxin on overall mortality and perhaps a minimal to no benefit in combined death or hospitalization reduction from HF.[92,122,123]

The DIG trial has since undergone extensive scrutiny, *post hoc* analysis, and re-analysis. The trial has major limitations, including excessively high dosing of digoxin and consequent high serum levels, based on current standards and practices, and performance in the pre-β-blocker era.

Two percent of patients on long-term digoxin were hospitalized for suspected digoxin toxicity compared to 0.9% in the placebo group ($p < 0.001$). Higher serum levels of digoxin (>1.2 ng/mL) were associated with increased mortality.[124] But importantly, improvement in HF mortality or hospitalization rates were present at lower digoxin concentrations (<1.0 ng/mL).[124-126]

The initial concern for worse outcomes (specifically higher mortality) for women[127] on chronic digoxin was also found to be linked to higher serum digoxin concentrations. Clinical outcomes improved at levels <1.0 ng/mL and a progressive increase in mortality and morbidity was noted at digoxin concentrations >1.2 ng/mL.[128]

Again, the DIG trial was performed before β-blocker therapy was used routinely in HF.[92] The results of 2 retrospective studies on relatively small populations (compared to that of the DIG trial) suggest that chronic digoxin administration in HF patients (in sinus rhythm) may be of little benefit when added on top of currently available, optimal management, including β-adrenergic blockade, ACE inhibition or angiotensin receptor blockade, a diuretic, spironolactone, and biventricular pacing for LV resynchronization.[129,130]

Clinical Indications and Guidelines

For the overall HF population, chronic digoxin therapy has a class IIa indication (level of evidence: B) from the 2009 American College of Cardiology/American Heart Association Task Force, which states that "digitalis can be beneficial in patients with current or prior symptoms of HF and reduced LV ejection fraction

to decrease hospitalizations in HF."[26] Long-term oral digoxin therapy remains an option to control rapid ventricular rate in the HF patient with atrial fibrillation, although this consideration has also been challenged in the β-blocker era.[131]

Administration and Dosing

The initial and maintenance oral dose generally ranges from 0.0625 to 0.25 mg/day. The 0.25 mg/day dose, considered for decades to be the standard daily dose, has largely been replaced by the 0.125 mg/day dose as the daily maintenance dose; because at the lower dose (0.125 mg), serum digoxin levels (drawn >8 hours after dosing) typically remain <1.0 ng/mL in HF patients with normal kidney function. Fifty to eighty percent of orally administered digoxin is absorbed by the gastrointestinal tract with an elimination half-life of 36–48 hours in large part by renal excretion. Drug discontinuation or dose reduction becomes important in patients with renal dysfunction and impaired digoxin clearance or during concomitant administration of medications known, via a number of different mechanisms, to elevate digoxin concentrations (Table 3).

TABLE 3

Agents Known to Alter Serum Digoxin Concentrations	
Reduced levels	
▪ Cholestyramine	▪ Salbutamol
▪ Sucralfate	▪ Rifampicin
▪ Kaolin-pectin	▪ Thyroxine
▪ Antacids	
Increased levels	
Antiarrhythmics	
▪ Amiodarone	▪ Quinidine
▪ Propafenone	
Calcium channel blockers	
▪ Verapamil	▪ Dihydropyridines (e.g., nifedipine)
▪ Diltiazem	
Potassium-sparing diuretics	
▪ Spironolactone	▪ Amiloride
▪ Triamterene	
Antimicrobials	
▪ Macrolides	▪ Itraconazole
▪ Tetracycline	
Others	
▪ Captopril	▪ Indomethacin
▪ Carvedilol	▪ Omeprazole
▪ Cyclosporine	▪ St. John's wort

With the exception of blocking atrioventricular (AV) nodal conduction in atrial fibrillation or flutter, thereby, lowering a rapid ventricular rate in patients for whom other AV nodal blocking agents (e.g., β-adrenergic blockers and calcium-channel blockers) may be problematic (e.g., asthma and hypotension), there is rarely a need for high-dose digoxin administration (historically termed "digitalization").

Adverse Effects

The direct effect of digoxin on sinoatrial and AV nodal cells and its autonomic modulating properties (lowering sympathetic tone and augmenting parasympathetic tone) account for many of the manifestations of digoxin toxicity, including sinus bradycardia and AV nodal blockade, generally at serum levels >2.0 ng/mL. Other digoxin-induced or -toxic dysrhythmias include atrial tachycardia with AV nodal block ("paroxysmal atrial tachycardia with block"), other atrial tachydysrhythmias, ventricular ectopic beats, ventricular tachycardia and fibrillation, and accelerated conduction over accessory bypass tracts. Nausea, vomiting, mental disturbances, and visual aberrations are some of the systemic manifestations of digoxin toxicity. Digitalis is a sterol molecule with hormonal effects and, as such, is a common cause of gynecomastia and painful breasts in men receiving this agent chronically. To suppress some of the digoxin-induced dysrhythmias, the intravenous administration of atropine, potassium, and/or magnesium can be employed, when appropriate, until serum digoxin levels fall to acceptable concentrations and the undesirable effects become less problematic. Severe life-threatening toxicity generally requires the administration of antidigoxin fragment antigen binding immunotherapy.[132,133]

Other Orally Administered Positive Inotropic Agents

In human HF, it has been demonstrated that hydralazine has positive inotropic properties, in addition to its known vasodilating, ventricular-unloading effects.[12,26,134] These positive inotropic and hemodynamic effects of hydralazine are used to wean dobutamine from HF patients who appear to be clinically and hemodynamically dependent on this intravenous positive inotrope.[27]

Absolute and relative hypothyroidism can play a significant role in the clinical course of human HF.[135-140] Thyroid hormone replacement augments myocardial contractility through several mechanisms and is of clinical importance in these specific

patient groups. Whether thyroid hormone therapy merits consideration beyond hypothyroidism, as a way of enhancing cardiac contractility and performance and clinical outcomes in human HF, remains unanswered.

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3 CHAPTER

Antihypertensive Drugs

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PHYSIOLOGY AND PATHOPHYSIOLOGY OF BLOOD PRESSURE REGULATION

Blood pressure, specifically systemic arterial pressure is the pressure of blood exerted against the walls of the arteries within the vessel. This pressure is generated by left ventricular systolic contraction, which produces forward blood flow against the resistance of the arterioles and arteries. The maximum blood pressure (systolic) occurs during systolic contraction of the left ventricle, and lowest blood pressure (diastolic) occurs during relaxation of the left ventricle. Normal blood pressure is determined by the cardiac output (CO) and the total peripheral resistance (TPR), (blood pressure = CO x TPR). Normal blood pressure depends on the heart, blood vessels, extracellular fluid volume, the central and peripheral nervous system, kidneys, and circulating humoral factors.

CO is a complex function dependent on heart rate and stroke volume (L/min). Stroke volume depends on intravascular volume, which in turn is regulated by the kidneys as well as myocardial contraction. Stroke volume also depends on preload, afterload, and contractility. Decreased preload decreases stroke volume and lowers blood pressure. Decreased afterload and increased contractility increase stroke volume and blood pressure. Myocardial contraction is a complex process and depends on the intrinsic cardiac conduction system, membrane transport, and cellular events, including influx of calcium, effects of humoral substances, such as catecholamines and thyroxine, and sympathetic and parasympathetic regulation of heart rate.

The TPR is a complex integrated function, which depends on a number of factors, including neurohumoral substances, baroreflexes and the sympathetic nervous system, endothelial factors, electrolytes (sodium, potassium, calcium, etc.), volume, and intracellular events mediated by receptors and signal transduction. Two major nervous system reflex arcs are recognized: (i) low-pressure cardiopulmonary baroreceptors are present in

cardiac ventricles and atria and (ii) high-pressure baroreceptors in the carotid sinus and aortic arch. These baroreceptors react to filling pressures (low pressure receptors) and to stretch (high pressure receptors). For example, if systemic blood pressure increases, high pressure baroreceptors increase tonic inhibition of sympathetic outflow (efferent pathways) resulting in a decrease in vascular resistance and heart rate. On the other hand, decrease in blood pressure leads to less tonic inhibition of sympathetic outflow and heart rate, and peripheral vascular resistance and systemic blood pressure increases.

Elevated blood pressure or hypertension can occur when CO or TPR are elevated. CO may be elevated in young people or in certain medical conditions, such as hyperthyroidism. In most cases, hypertension is due to increased TPR, which in turn is caused by dysregulation of one or a number of other factors discussed above. Hypertension is classified as either primary (essential), or secondary. In primary (essential) hypertension, a uniform mechanism cannot be found. Primary hypertension likely involves the interaction of genetic factors, environment, known regulatory systems (hormonal, neural, renal, vascular, and cardiac), and possibly factors yet undiscovered. In secondary hypertension, a cause can be identified and often the mechanism too can be traced. Some causes for secondary hypertension include chronic kidney disease (CKD) (volume expansion, increased activity of the renin-angiotensin-aldosterone system (RAAS), and overactive sympathetic nervous system), renal artery stenosis (increased activity of RAAS), endocrine disorders (hyperaldosteronism from adrenal adenomas or hyperplasia, pheochromoctyoma (increased catecholamines)), Cushing's syndrome (excess cortisol), hyperthyroidism, hypothyroidism, hyperparathyroidism (hypercalcemia), acromegaly (increased growth hormone), coarctation of aorta, drug-induced, sleep apnea (sympathetic activation), obesity (sympathetic overactivity, possibly adipokines, and others), and pregnancy (placental stimulus). About 90–95% of cases of hypertension are of primary (essential) hypertension, and 5–10% are of secondary hypertension.

In this chapter, evidence-based drug therapy of essential hypertension is discussed.

DEFINITIONS AND CLASSIFICATIONS OF HYPERTENSION

For appropriate treatment of hypertension, adequate classification and definitions are necessary.

The 7th Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure[1]

The 7th report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure (the JNC 7 report) was published in 2003 (Table 1). Major differences from JNC 6 (1997) included a new category of prehypertension and elimination of stage 3 hypertension as a separate category (Table 2).

Guidelines for JNC 8 are expected for review and comment in 2012.

The European Society of Hypertension and the European Society of Cardiology Guidelines for the Management of Arterial Hypertension (2007)[2]

The recommendations by the European Society of Hypertension (ESH) and by the European Society of Cardiology (ESC) 2007 are summarized in table 3.

There is ample evidence to suggest that adequate treatment of hypertension is associated with a substantial reduction in the risks of adverse cardiovascular events. The risks of stroke, myocardial infarction (MI), and heart failure decline with adequate treatment of hypertension as illustrated in table 4.

TABLE 1

Blood Pressure Classification (JNC 7)	
Normal	<120 and <80 mmHg
Prehypertension	120–139 or 80–89 mmHg
Stage 1 hypertension	140–159 or 90–99 mmHg
Stage 2 hypertension	≥160 or ≥100 mmHg

TABLE 2

Blood Pressure Classification: Comparison Between JNC 6 and 7		
SBP/DBP mmHg	*JNC 7 category*	*JNC 6 category*
<120/80	Normal	Optimal
120–129/80–84	Prehypertension	Normal
130–139/85–89	Prehypertension	Borderline
≥140/90	Hypertension	Hypertension
140–159/90–99	Stage 1	Stage 1
160–179/100–109	Stage 2	Stage 2
≥180/110	Stage 2	Stage 3

SBP, systolic blood pressure; DBP, diastolic blood pressure.

TABLE 3

Blood Pressure Thresholds for Defining Hypertension with Different Types of Measurements (ESH/ESC)		
	Systolic blood pressure (mmHg)	*Diastolic blood pressure (mmHg)*
Office or clinic	140	90
24-hour	125–130	80
Day	130–135	85
Night	120	70
Home	130–135	85

TABLE 4

Benefits of Treating Hypertension (JNC 7)	
Cardiovascular events	*Average reduction (%)*
Stroke incidence	35–40
MI	20–25
Heart failure	50

MI, myocardial infarction.

RECOMMENDATIONS FOR TREATMENT OF HYPERTENSION

Several recommendations for the diagnosis and management of hypertension are available. It should be noted, however, that no uniform approach for recognition and management of hypertension is available. In the following sections current approach for selecting antihypertensive drugs are outlined.

Current Approach for Selecting Antihypertensive Medication

There is no "single approach". Hypertension experts in the United States, Europe, and other areas of the world offer recommendations based on clinical trials, pharmacology of the various drugs, and personal experience. The clinical trials, however, do not show uniformly consistent results, and experts in hypertension do not have a single approach. However, there is a general agreement that lifestyle modifications should be encouraged for every patient. There are also general priciples that are recommended for management of hypertension (Table 5). Each patient needs to have a comprehensive evaluation for lifestyle modifications and the principles listed in table 5. An algorithm representing treatment of hypertension is outlined in figure 1.

At present, lifestyle management includes treatment of obesity/overweight, restriction of excessive salt intake, smoking

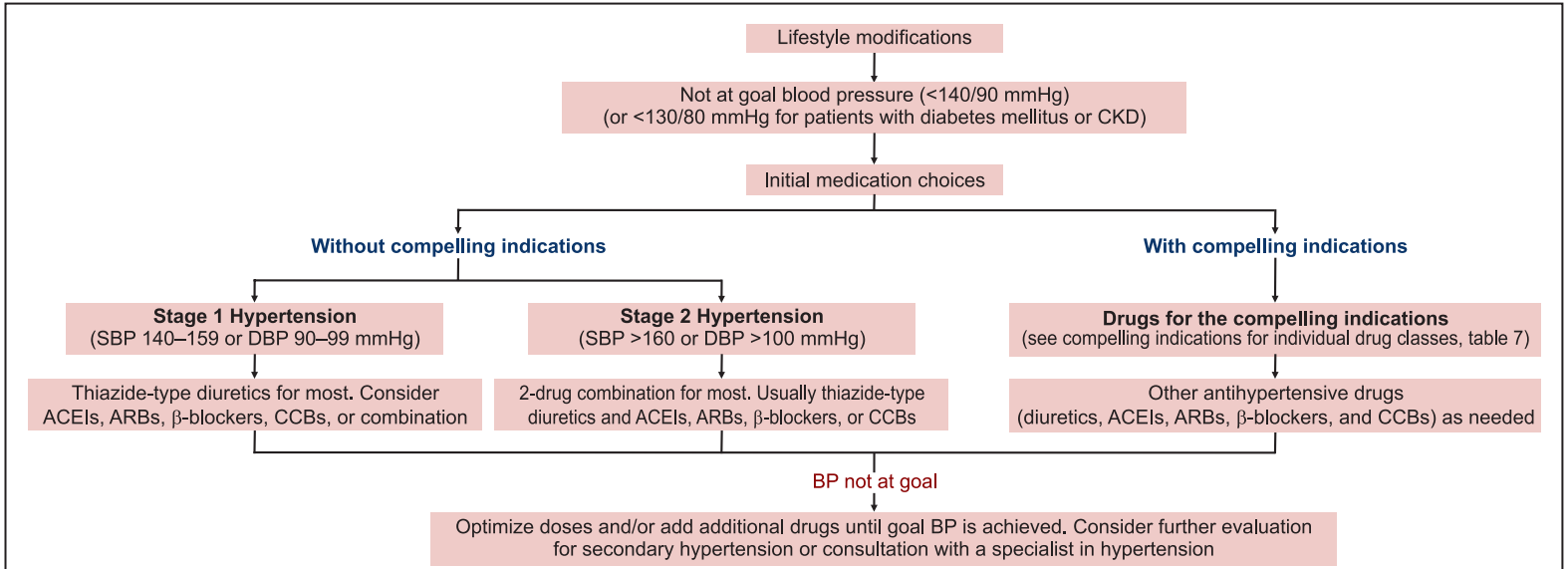
TABLE 5

Principles for Hypertension Treatment
▪ Evaluate for medical issues before considering the choice of antihypertensive drug therapy: – Cardiovascular risks and disease – Cerebrovascular risks and disease – Glucose metabolism/diabetes mellitus – Lipid profile – Liver functions – Renal functions – Peripheral vascular disease – Psychological factors and cognitive functions: evaluation for compliance – Weight – Other diseases and medical concerns.
▪ Other factors to evaluate: – Lifestyle (diet, especially sodium and caloric intake, occupation, recreation and exercise, use of other medications, cigarette smoking, alcohol, use of illicit drugs, and sexual practices) – Socioeconomic factors (including ability to pay for medication, religious beliefs, family support, etc.) – Race and ethnicity – Age – Gender
▪ Start with a small dose of an antihypertensive drug: once a day dosage preferred
▪ Increase dose until goal blood pressure is achieved: to minimize side effects, we may not increase single drug to maximum dose, or add another drug from a different class
▪ May need to add multiple drugs with different modes of action to achieve goal blood pressure. When possible, use combination therapy to improve compliance
▪ If two or more drugs are required to reach target blood pressure, reassess for secondary hypertension.

cessation, and alcohol abuse. Regular exercise of moderate intensity is encouraged. Correction of electrolyte imbalance and avoidance of use of drugs, which can increase blood pressure, such as steroidal and non-steroidal anti-inflammatory agents should be recommended. Drugs containing catecholamines, such as some nasal anticongestion drops and recreational drugs like metamphetamine and cocaine can increase blood pressure, and use of these agents should be discouraged.

Obesity is a risk factor not only for hypertension but also for diabetes, coronary artery disease (CAD), and heart failure. Reduction in body weight can be associated with a significant reduction in blood pressure.

Regular isotonic exercise, such as brisk walking is associated with decreased sympathetic tone and lower blood pressure.



CKD, chronic kidney disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; CCBs, calcium channel blockers.

FIGURE 1. Algorithm for the treatment of hypertension (JNC 7).

TABLE 6

Lifestyle Modifications (JNC 7)
▪ Optimize body weight, body mass index: 18.5–24.9 kg/m^2 (most effective, approximately 5–20 mmHg reduction in BP for every 10 kg weight loss)
▪ Reduce sodium intake: not more than 100 mEq/day (2.4 g sodium or 6 g sodium chloride) (approximately 2–8 mmHg reduction in BP)
▪ Moderate alcohol intake: limit to 2 drinks/day for men and 1 drink/day for women (approximately 2–4 mmHg reduction in BP)
▪ Manage stress: counseling if needed
▪ Stop smoking: to reduce cardiovascular risk
▪ Graduated exercise program: aerobic activity (e.g., brisk walking) at least 30 min/day, most days of the week (approximately 4–9 mmHg reduction in BP)
▪ Additional dietary management: dash diet (dietary approaches to stop hypertension): advise diet rich in vegetables, fruits (ample potassium intake), low-fat dairy products, reduced total fat, saturated fat, and no trans-fat (approximately 8–14 mmHg reduction in BP).

Isometric exercise, such as weight lifting, increases systemic resistance and blood pressure. Thus, isometric exercie should be avoided.

Excessive alcohol intake may increase blood volume and contribute to hypertension. The benefits of lifestyle modifications are summarized in table 6.

There are certain compelling indications for control of hypertension. There are different classes of antihypertensive drugs, and all are not suitable for all the special clinical circumstances. In patients with systolic heart failure (SHF), β-blockers, angiotensin inhibitors and aldosterone antagonists are appropriate. In SHF, calcium channel blockers (CCBs) should be avoided. In patients with high-risk cardiovascular complications, β-blockers, angiotensin inhibitors, and CCBs should be considered. In patients with recent MI, β-blockers, angiotensin inhibitors, and aldosterone antagonists are preferable. In diabetics, all classes of antihypertensive drugs can be used. For renal protection in patients with CKD, angiotensin inhibitors are preferable. For prevention of recurrent strokes, thiazide diuretics and angiotensin converting enzyme inhibitors (ACEIs) are recommended. The appropriate antihypertensive drugs for special clinical circumstances are summarized in table 7.

The rationale for lowering of blood pressure is to reduce the risks of adverse cardiovascular complications. Blood pressure should be reduced to at least 140/90 mmHg. It is preferable to lower the blood pressure further, if possible. In patients with

TABLE 7

Compelling Indications for Individual Drug Classes (JNC 7)	
Indications	*Drug Classes*
Heart failure	Thiazides, β-blockers, ACEIs, ARBs, ALDO antagonists
Post-MI	β-blockers, ACEIs, ALDO antagonists
High cardiovascular risk	Thiazides, β-blockers, ACEIs, CCBs
Diabetes mellitus	Thiazides, β-blockers, ACEIs, ARBs, CCBs
CKD	ACEIs, ARBs
Recurrent stroke prevention	Thiazides, ACEIs

ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; CCBs, calcium channel blockers; ALDO, aldosterone; MI, myocardial infarction; CKD, chronic kidney disease.

TABLE 8

ESH and ESC Guidelines 2007 to Reduce the Risks of Complications of Hypertension
Position statement: goals of treatment
▪ In hypertensive patients, the primary goal of treatment is to achieve maximum reduction in the long-term total risk of cardiovascular disease
▪ This requires treatment of the raised blood pressure *per se* as well as of all associated reversible risk factors
▪ Blood pressure should be reduced to be at least below 140/90 mmHg (systolic/diastolic), and to lower values, if tolerated, in all hypertensive patients
▪ Target blood pressure should be at least <130/80 mmHg in diabetics and in high- or very high-risk patients, such as those with associated clinical conditions (stroke, MI, renal dysfunction, and proteinuria)
▪ Despite the use of combination treatment, reducing SBP to <140 mmHg may be difficult and more so if the target is a reduction to <130 mmHg. Additional difficulties should be expected in elderly and diabetic patients and, in general, in patients with cardiovascular damage
▪ In order to achieve goal blood pressure more easily, anti-hypertensive treatment should be initiated before significant cardiovascular damage develops.

SBP, systolic blood pressure; MI, myocardial infarction.

diabetes, it is recommended to lower the blood pressure even further to at least 130/80 mmHg. To reduce the risk of complications of hypertension, antihypertensive treatment should be initiated early (Table 8).

All hypertensive patients are not at the same risk to develop complications. Patients with blood pressure of 180/110 mmHg or higher, systolic blood pressure >160 mmHg with low diastolic

pressure (<70 mmHg) are at higher risks of developing complications. Metabolic syndrome, dyslipidemia, and smoking are also high risks. Presence of overt or subclinical target organ damage, such as left ventricular hypertrophy (LVH) abnormal carotid artery wall thickening, and low estimated glomerular filtration rate and creatinine clearance, and established cardiovascular or renal disease constitute high risks for developing cardiovascular complications. The definition of high- and very high-risk subjects are summarized in table 9.

CHOICE OF MEDICATION FOR ESSENTIAL HYPERTENSION

There are several classes of antihypertensive drugs available for treatment of hypertension. For initiation of treatment, frequently one class of drugs are used. These drugs are known as first-line agents. Guidelines recommend thiazide diuretics as the initial agent. The other class of drugs can also be used as first-line agents (Table 10). It should be appreciated that frequently the use of combination of several classes of antihypertensive drugs are required to obtain adequate control of hypertension. The recommendation of monotherapy vs multiple drugs combinations are outlined in table 11.

Choice of Therapy in Essential Hypertension (Monotherapy and Combination Therapy)[3]

The AHA and ESH/ESC guidelines on the management of hypertension and meta-analyses in 2008 and 2009 concluded that the major factor for reduction in cardiovascular risk was not the choice of antihypertensive drug but the magnitude of blood pressure reduction. The conclusion applied to those individuals who were at increased cardiovascular risk as seen in the Antihypertensive and Lipid Lowering Treatment to prevent Heart Attack Trial (ALLHAT)[4], Comparison of Amlodipine vs. Enalapril to Limit Occurrences of Thrombosis (CAMELOT)[5], and Valsartan Antihypertensive Long-term Use Evaluation (VALUE)[6] clinical trials. Combination therapy, however, may be different. In Avoiding Cardiovascular events through COmbination therapy in patients LIving with Systolic Hypertension (ACCOMPLISH)[7] trial, amlodipine plus benazepril was associated with a 20% lower rate of cardiovascular events compared to hydrochlorothiazide plus benazepril. The 24-hour blood pressure was slightly higher in the patients treated with amlodipine plus benazepril).

The following recommendations do not apply to patients with underlying conditions for which particular antihypertensive

TABLE 9

Definition of High- and Very High-risk Subjects

- SBP ≥ 180 mmHg and/or DBP ≥ 110 mmHg
- SBP > 160 mmHg with DBP < 70 mmHg
- Diabetes mellitus
- Metabolic syndrome: According to AHA and NHLBI, metabolic syndrome is present if 3 or more of the following signs are present:
  - Blood pressure ≥ 130/85 mmHg
  - Fasting blood glucose ≥ 100 mg/dL (5.6 mmol/L)
  - Large waist circumference: Men ≥ 40 inches (102 cm), Women ≥ 35 inches (88 cm)
  - Low HDL: Men < 40 mg/dL, Women < 50 mg/dL
  - Triglycerides ≥ 150 mg/dL
- More than 3 cardiovascular risk factors: Cigarette smoking, high blood pressure, serum total cholesterol > 190 mg/dL (5.0 mmol/L) and LDL > 115 mg/dL (3.0 mmol/L), low HDL, advancing age (men > 55 years and women > 65 years), obesity, diabetes mellitus, and family history of premature heart disease
- One or more of the following subclinical organ damages:
  - Electrocardiographic LVH (Sokolow-Lyon > 38 mm; Cornell > 2440 mm*ms) or
  - Echocardiographic LVH* (LVMI: men ≥ 125 g/m^2, women ≥ 110 g/m^2)
  - Carotid wall thickening (IMT > 0.9 mm) or plaque
  - Carotid-femoral pulse wave velocity > 12 m/s
  - Ankle/brachial blood pressure index < 0.9
  - Slight increase in plasma creatinine: Men 115–133 μmol/L (1.3–1.5 mg/dL), Women: 107–124 μmol/L (1.2–1.4 mg/dL)
  - Low estimated glomerular filtration rate** (< 60 mL/min/1.73 m^2) or creatinine clearance*** (< 60 mL/min)
- Established cardiovascular or renal disease
  - Cerebrovascular disease: ischemic stroke cerebral hemorrhage, transient ischemic attack
  - Heart disease: MI, angina, coronary revascularization, heart failure
  - Renal disease: diabetic nephropathy, renal impairment (serum creatinine: men > 133 μmol/L (1.5 mg/dL); women > 124 μmol/L (1.4 mg/dL)); proteinuria (> 300 mg/day)
  - Peripheral artery disease
  - Advanced retinopathy: hemorrhages or exudates, papilledema.

*Risk maximal for concentric LVH (left ventricular hypertrophy): increased LVMI with a wall thickness/radius ratio > 0.42.
**MDRD formula.
***Cockcroft-Gault formula.

SBP, systolic blood pressure; DBP, diastolic blood pressure; AHA, American Heart Association; NHLBI, National Heart, Lung, and Blood Institute; HDL, high-density lipoproteins; LDL, low-density lipoproteins; LVH, left ventricular hypotrophy; LVMI, left ventricular mass index; IMT, Intima media thickness; MI, myocardial infarction.

TABLE 10

Drugs Which May be Used as "First Line" Agents
▪ ACEIs (long-acting)
▪ ARBs
▪ β-blockers (by ESH/ESC Guidelines; controversial—removed from UK Guidelines; not recommended as first-line in US unless compelling indications)
▪ CCBs (long-acting dihydropyridines, diltiazem, verapamil)
▪ Diuretics (multiple).

ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; CCBs, calcium channel blockers.

TABLE 11

Position Statement: Monotherapy vs. Combination Antihypertensive Therapy (ESH and ESC 2007)
▪ Regardless of the drug employed, monotherapy allows achievement of blood pressure target in only a limited number of hypertensive patients
▪ Use of more than one agent is necessary to achieve target blood pressure in the majority of patients. A vast array of effective and well-tolerated combinations are available
▪ During initial treatment, one can use monotherapy or combination of two drugs at low doses with a subsequent increase in drug doses or number, if needed
▪ Monotherapy could be the initial treatment for a mild blood pressure elevation with a low or moderate total cardiovascular risk. A combination of 2 drugs at low doses should be preferred as first step of treatment when initial blood pressure is in grade 2 or 3 range or total cardiovascular risk is high or very high (Figure 2)
▪ Fixed combinations of 2 drugs can simplify treatment schedule and favor compliance. The possible and preferred combinations of antihypertensive drugs have been outlined in figure 3
▪ If blood pressure control is not achieved by two drugs, a combination of 3 of more drugs is required
▪ In uncomplicated hypertensives and in the elderly, antihypertensive therapy should normally be initiated gradually. In higher-risk hypertensives, goal blood pressure should be achieved more promptly, which favors initial combination therapy and quicker adjustment of doses.

medications might be of benefit apart from blood pressure control.

Monotherapy

- In the absence of a compelling indication for the use of a specific antihypertensive medication, the major classes that have been used for monotherapy are: (a) low-dose thiazide diuretic, (b) long-acting ACEIs or angiotensin II receptor blockers (ARBs), or (c) long-acting dihydropyridine CCBs

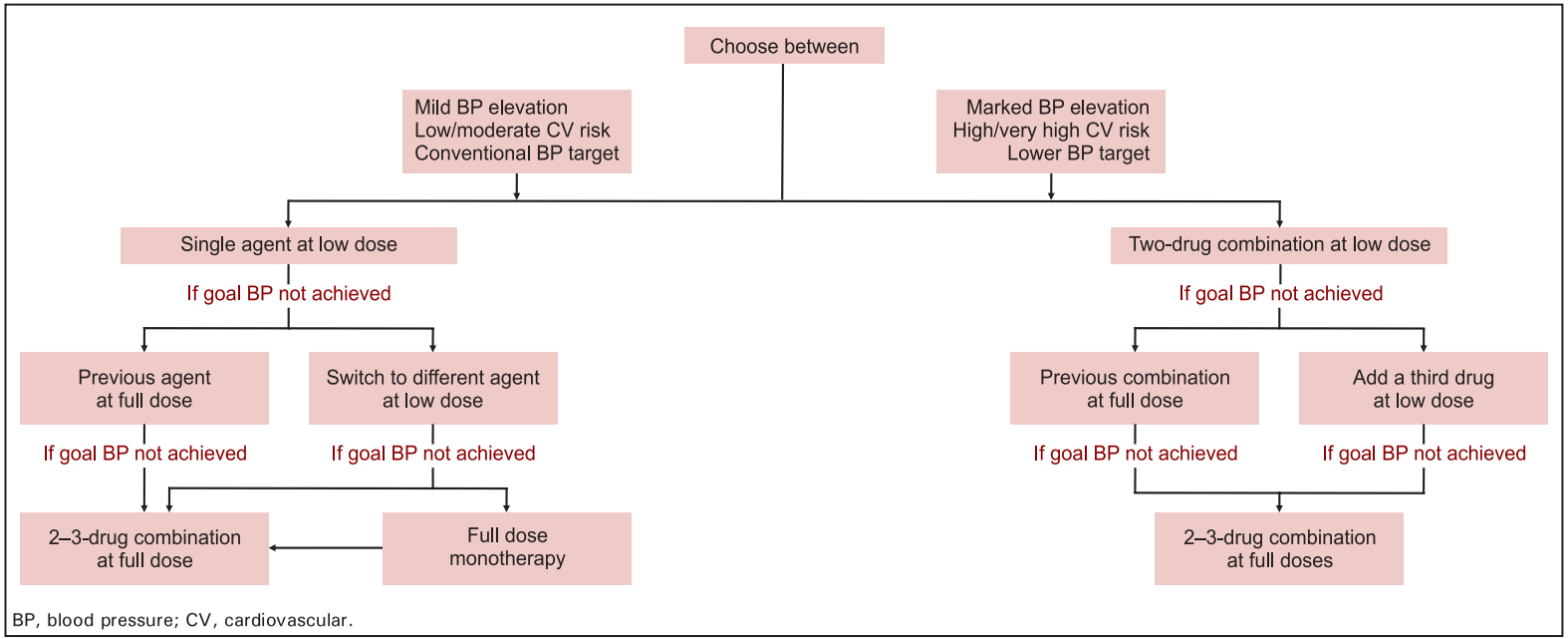


FIGURE 2. Monotherapy vs. combination therapy strategy (ESH and ESC 2007)

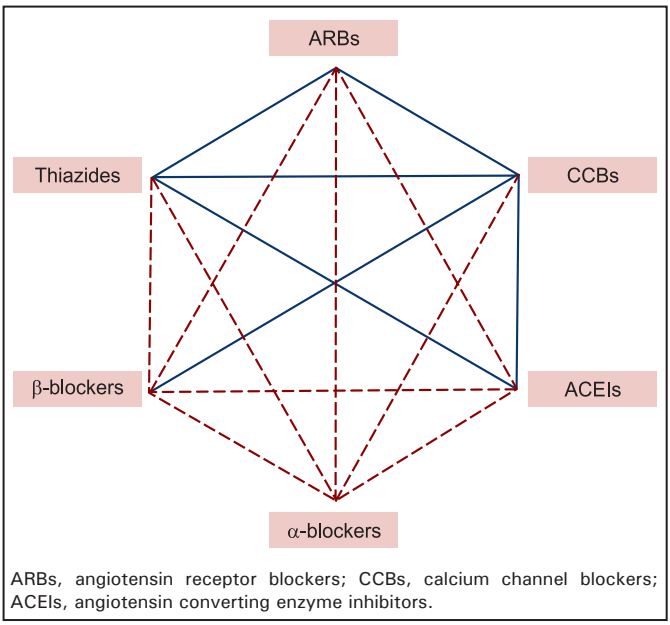


FIGURE 3. Possible combination between some classes of antihypertensive drugs (ESH and ESC 2007). The preferred combinations in the general hypertensive population are represented as solid blur lines. The frames indicate classes of agents proven to be beneficial in controlled intervention trials.

- From the ACCOMPLISH trial, if combination therapy is required, amlodipine plus benazepril were preferred. Therefore, an ACEI/ARB or a dihydropyridine CCB is suggested for initial monotherapy. If this rationale is chosen, younger patients may find an ACEI/ARB more effective, and elderly and black patients may do better with a dihydropyridine CCB
- If a thiazide-type diuretic is used as an initial antihypertensive drug, chlorthalidone rather than hydrochlorothiazide (HCTZ) is suggested. Chlorthalidone may be more likely to induce hypokalemia at the same dose than HTCZ. [Chlorthalidone produced hypokalemia in 7–8% of patients in ALLHAT and Systolic Hypertension in the Elderly Program (SHEP)[8] clinical trials]. Serum potassium needs to be monitored with both chlorthalidone and HCTZ
- If the response to the initial antihypertensive drug is minimal, treatment with sequential monotherapy is recommended
- β-blockers are not recommended for first-line therapy unless underlying medical conditions warrant their use. These conditions include: post-acute MI, stable heart failure, asymptomatic left ventricular dysfunction, rate control in atrial fibrillation, control of angina pectoris, migraine headaches, and other disorders. Two meta-analyses concluded, in older

patients, β-blockers showed an association with a higher risk of composite end-points and strokes[9,10]

- α-blockers are not advised for initial monotherapy, based on the ALLHAT trial in which the doxazosin arm was stopped early due to a significantly increased risk for heart failure when compared to chlorthalidone.

Combination Therapy

- If patients have blood pressure >20/10 mmHg above goal before treatment with antihypertensive drugs, therapy with a combination of a long-acting ACEI/ARB and a long-acting dihydropyridine CCB is recommended
- If patients are at goal blood pressure during treatment with an ACEI/ARB and a thiazide-type diuretic, it is recommended to stop thiazide and replace it with a long-acting dihydropyridine CCB. If patients are well controlled on combination drugs other than an ACEI/ARB plus a thiazide diuretic, do not change the therapy
- If patients are not at goal blood pressure while taking a thiazide diuretics as monotherapy, it is recommended to stop the thiazide diuretic and switch to a long-acting ACEI/ARB plus a long-acting dihydropyridine CCB.

Bedtime vs. Morning Dosing

Instead of taking all antihypertensive drugs in the morning, it is recommended to take at least one medication (but not the diuretic) at bedtime. This may be especially important in patients who do not have the usual 15% decrease in blood pressure during sleep (these patients, in whom blood pressure does not decrease by at least 10% are termed "nondippers". Nondippers are at increased risk for cardiovascular events.) (Caution: avoid excessive hypotension during sleep which will increase the risk for anterior ischemic optic neuropathy (AION)).

SOME NEW STUDIES, REVIEWS, AND GUIDELINES FOR THE TREATMENT OF HYPERTENSION (2009–2011)[11]

- *2009 Cochrane database of systematic reviews*: The trial done by Arguedas et al.[12] found no evidence that lowering of blood pressure to targets <140–160/90–100 mmHg were beneficial. Seven trials with 22,089 patients were included in the review. The Cochrane review is consistent with current guidelines, recommending a blood pressure target of <140/90 mmHg for the patient without increased cardiovascular risk. Currently recommended lower blood pressure target goals are for

high-risk patients rather than for hypertensive patients in the general population, based on clinical trials for high-risk patients [2003 meta-analysis from the ACE Inhibition in Progressive Renal Insufficiency (AIPRI),[13] Modification of Diet in Renal Disease (MDRD),[14] African American Study of Kidney disease and hypertension (AASK),[15] Ramipril Efficacy in Neuropathy-2 (REIN-2),[16] normotensive Appropriate Blood Pressure Control in Diabetes (ABCD),[17] Action to Control Cardiovascular Risk in Diabetes (ACCORD),[18] Stop Atherosclerosis in Native Diabetics Study (SANDS),[19] UK Prospective Diabetes Study (UKPDS),[20] Hypertension Optimal Trial (HOT),[21] and Action in Diabetes and VAscular disease: preterax and diamicron MR Controlled Evaluation (ADVANCE)[22]]. A concern arises when blood pressure during treatment is <120/70 mmHg (HOT)

- *2009 update ESH/ESC*:[23] ESH/ESC advised that double renin-angiotensin system blockade with an ACEI and ARB is useful in CKD patients with insufficient reduction of proteinuria with either an ACEI or ARB alone. [cited in combination treatment of angiotensin II receptor blockers and angiotensin converting enzyme inhibitor in nondiabetic renal disease (COOPERATE) trial,[24] but this trial is considered unreliable by American experts and was later retracted from the *Lancet*. Also, worse renal outcomes were seen with this combination in the Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) study][25]
- *2010 Meta-analysis*: 2010 meta-analysis in very elderly patients (>80 years) by Bejan-Angoulvant et al.[26] supported drug treatment for hypertension to decrease stroke, cardiovascular events, and heart failure. Also, SBP target of 150 mmHg may be reasonable
- *2010 ACCORD study*:[18] It addresses higher treatment SBP goal of 140 mmHg vs. SBP goal of 120 mmHg. The study randomized 4,733 high-risk diabetic patients. Achieved SBP; mean 119 mmHg and 133 mmHg. At the end of one year and thereafter, primary outcome was reduced nonsignificantly by 12% (cardiovascular death, nonfatal MI, and/or nonfatal stroke). Strokes were significantly less in the lower SBP group (0.32%/year in lower SBP group vs. 0.53%/year in the higher SBP group). End-stage kidney disease was equal between the groups. In diabetics, ACCORD suggests a SBP goal of mid-low 130s as reasonable
- *2010 ACCOMPLISH study*:[7] It addresses treatment with a combination of benazepril plus hydrochlorothiazide vs. benazepril plus amlodipine. The study enrolled 11,500 high-risk

patients. Outcomes were significantly better in the benazepril plus amlodipine group with 21% lower cardiovascular outcomes. Also, the benazepril plus amlodipine group showed slowing of the progression of nephropathy compared to the benazepril plus hydrochlorothiazide group. The latter point, however, is controversial

- *2011 guidelines update American College of Cardiology (ACC)*:[27] When measuring blood pressure for elderly patients (>64 years), blood pressure should be measured after standing for 1–3 minutes to assess the orthostatic hypotension. Suggested goal blood pressure: <140/90 mmHg (expert opinion)
- *2011 guidelines update National Institute for Health and Clinical Excellence (NICE) (UK) clinical guideline 127*:[28] If clinic blood pressure is >140/90 mmHg offer monitoring of ambulatory blood pressure to confirm the diagnosis of hypertension. (Decision to recommend ambulatory blood pressure monitoring in all newly diagnosed patients with hypertension has not been recommended in the United States).

PREFERRED ANTIHYPERTENSIVE DRUGS

The preferred antihypertensive drugs according to the class and compelling indications are discussed in tables 12–15. The preferred antihypertensive drugs for other morbid conditions are discussed in table 16. β-adrenergic receptor antagonists (β-blockers) have been used for many years for control of hypertension. Some β-blockers are selective. They only inhibit β1 receptors. Other β-blockers are nonselective and inhibit both β1 and β2 adrenoreceptors. Some β-blockers also possess α-adrenergic blocking property. Some β-blockers possess intrinsic sympathomimetic properties. Many β-blockers have local anesthetic effects. Table 17 summarizes the clinical uses of various β-blockers.

HYPERTENSION IN SPECIAL GROUPS

Resistant Hypertension

Despite multiple drugs therapy, some patients become resistant to drugs, and hypertension is poorly controlled. In patients who become resistant to drugs, proper investigation is necessary to identify the cause. In table 18 the potential causes of resistant hypertension are outlined.

Hypertensive Emergencies

Although infrequent, hypertensive emergencies (ESH and ESC) are still encountered in clinical practice. As these complications

TABLE 12

Preferred Antihypertensive Drugs by Class (ESH/ESC)			
Drug class	*Conditions favoring use*	*Compelling contraindications*	*Possible contraindications*
Thiazide diuretics	Isolated systolic hypertension (elderly), HF, hypertension in Blacks	Gout	MS, glucose intolerance, pregnancy
Diuretics (antialdosterone)	HF, post-MI	Renal failure, hyperkalemia	—
Loop diuretics	CKD (GFR <30 mL/min), end-stage renal disease, HF	—	—
β-blockers	Angina pectoris, post-MI, HF, tachyarrhythmias, glaucoma, pregnancy	Asthma, AV block (grade 2 or 3)	Peripheral arterial disease, MS, glucose intolerance, athletes and physically active patients, COPD
Calcium antagonists (dihydropyridines)	Isolated systolic hypertension (elderly), angina pectoris, LVH, carotid/coronary atherosclerosis, pregnancy, hypertension in Blacks	—	Tachyarrhythmias, HF
Calcium antagonists (verapamil, diltiazem)	Angina pectoris, carotid atherosclerosis, supraventricular tachycardia	AV block (grade 2 or 3), HF	—
ACEIs	HF, left ventricular dysfunction, post-MI, diabetic nephropathy, LVH, carotid atherosclerosis, proteinuria/ microalbuminuria, atrial fibrillation, MS	Pregnancy, angioneurotic edema, hyperkalemia, bilateral renal artery stenosis	—
ARBs	HF, post-MI, diabetic nephropathy, proteinuria, LVH, atrial fibrillation, MS, ACEIs-induced cough	Pregnancy, hyperkalemia, bilateral renal artery stenosis	—

COPD, chronic obstructive pulmonary disease; ACEIs, angiotensin converting enzyme inhibitors; LV, left ventricle; GFR, glomerular filtration rate; AV block, atrioventricular block; ARBs, antiotensin II receptor blockers; MI, myocardial infarction; LVH, left ventricular hypertrophy; ARBs, angiotensin II receptor blockers; HF, heart failure; MS, metabolic syndrome.

TABLE 13

Preferred Antihypertensive Agents by Compelling Indications (ESH/ESC 2007)	
For subclinical organ damage	
LVH	ACEIs, CCBs, ARBs
Asymptomatic atherosclerosis	CCBs, ACEIs
Microalbuminuria	ACEIs, ARBs
Renal dysfunction	ACEIs, ARBs
Clinical event	
Previous stroke	Any blood pressure lowering agents
Previous MI	β-blockers, ACEIs, ARBs
Angina pectoris	β-blockers, CCBs
Heart failure	Diuretics, β-blockers, ACEIs, ARBs, ALDO antagonists
Atrial fibrillation	
Recurrent	ARBs, ACEIs
Permanent	β-blockers, nondihydropyridine CCBs
ESRD/proteinuria	ACEIs, ARBs, loop diuretics
Peripheral artery disease	CCBs
Condition	
ISH (elderly)	Diuretics, CCBs
Metabolic syndrome	ACEIs, ARBs, CCBs
Diabetes mellitus	ACEIs, ARBs
Pregnancy	CCBs, methyldopa, β-blockers
Blacks	Diuretics, CCBs

LVH, left ventricular hypertrophy; ESRD, end-stage renal disease or renal failure; ACEIs, angiotensin converting enzyne inhibitors; ARBs, angiotensin II receptor blockers; CCBs, calcium channel blockers; ALDO, aldosterone; ISH, isolated systolic hypertension.

are life threatening, their early recognition is mandatory for adequate and appropriate management. The causes of hypertensive emergencies are summarized below:

- Hypertensive encephalopathy
- Hypertensive left ventricular failure
- Hypertension with MI and/or unstable angina
- Hypertension and dissection of the aorta
- Severe hypertension associated with subarachnoid hemorrhage or cerebrovascular accident
- Crisis associated with pheochromocytoma
- Use of recreational drugs, such as amphetamines, lysergic acid diethylamide (LSD), cocaine or ecstasy
- Perioperative hypertension
- Severe preeclampsia or eclampsia.

TABLE 14

Clinical Trial and Guideline Basis for Compelling Indications for Individual Drug Classes (JNC 7)

*High-risk conditions with compelling indications**	*Recommended drugs*						*Clinical trial basis***
	Diuretics	*β-blockers*	*ACEIs*	*ARBs*	*CCBs*	*ALDO antagonists*	
Heart failure	+	+	+	+		+	ACC/AHA Heart Failure Guideline, MERIT-HF,[29] COPERNICUS,[30] CIBIS,[31] SOLVD,[32] AIRE,[33] TRACE,[34] ValHEFT,[35] RALES,[36] CHARM[37]
Post-MI		+	+	+		+	ACC/AHA Post-MI Guideline, BHAT,[38] SAVE,[39] CAPRICORN,[40] EPHESUS[41]
High coronary disease risk	+	+	+		+		ALLHAT,[4] HOPE,[42] ANBP2,[43] LIFE,[44] CONVINCE,[45] EUROPA,[46] INVEST[47]
Diabetes mellitus	+	+	+	+	+		NKF-ADA Guideline, UKPDS,[20] ALLHAT[4]
CKD			+	+			NKF Guideline, Captopril trial, RENAAL,[48] IDNT,[49] REIN,[50] AASK[15]

(continued)

Table 14 *(continued)*

*High-risk conditions with compelling indications**	*Recommended drugs*						*Clinical trial basis***
	Diuretics	*β-blockers*	*ACEIs*	*ARBs*	*CCBs*	*ALDO antagonists*	
Recurrent stroke prevention	+		+				PROGRESS[51]

*Compelling indications for antihypertensive drugs are based on benefits from outcome studies or existing clinical guidelines; the compelling indication is managed in parallel with the blood pressure.
**Conditions for which clinical trials demonstrate the benefit of specific classes of antihypertensive drugs used as part of an antihypertensive regimen to achieve blood pressure goal to test.

AASK, African American Study of Kidney Disease and Hypertension; ACC/AHA, American College of Cardiology/American Heart Association; ACEIs, angiotensin converting enzyme inhibitors; AIRE, Acute Infarction Ramipril Efficacy; ALDO, aldosterone; ALLHAT, Antihypertensive and Lipid-Lowering Treatment to prevent Heart Attack Trial; ANBP2, 2nd Australian National Blood Pressure study; ARBs, angiotensin II receptor blockers; BHAT, β-Blocker Heart Attack Trial; CAPRICORN, CArvedilol Post-infarct survival control in left ventricular dysfunction; CCBs, calcium channel blockers; MI, myocardial infarction; CHARM, Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity; CIBIS, Cardiac Insufficiency BIsoprolol Study; CONVINCE, Controlled ONset Verapamil INvestigation of Cardiovascular Endpoints; COPERNICUS, Carvedilol Prospective Randomized Cumulative Survival Study; EPHESUS, Eplerenone Post-AMI Heart failure Efficacy and SUrvival Study; EUROPA, EUropean trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease; HOPE, Heart Outcomes Prevention Evaluation study; IDNT, Irbesartan Diabetic Nephropathy Trial; INVEST, the INternational VErapamil SR-trandolapril STudy; LIFE, Losartan Intervention For Endpoint reduction in hypertension study; MERIT-HF, Metoprolol CR/XL Randomized Intervention Trial in congestive Heart Failure; NKF-ADA, National Kidney Foundation-American Diabetes Association; PROGRESS, Perindopril pROtection aGainst REcurrent Stroke Study; RALES, Randomized ALdactone Evaluation Study; REIN, Ramipril Efficacy In Nephropathy study; RENAAL, Reduction of Endpoints in Non-insulin dependent diabetes mellitus with the Angiotensin II Antagonist Losartan study; SAVE, Survival And Ventricular Enlargement study; SOLVD, Studies Of Left Ventricular Dysfunction; TRACE, TRAndolapril Cardiac Evaluation study; UKPDS, United Kingdom Prospective Diabetes Study; ValHEFT, Valsartan HEart Failure Trial.

TABLE 15

Antihypertensive Drugs by Compelling Indications or Contraindications[3]	
Indication	*Antihypertensive drugs*
Compelling indication (major improvement in outcome independent of blood pressure)	
SHF	ACEIs or ARBs, β-blockers, diuretics, ALDO antagonist*
Post-MI	ACEIs, β-blockers, ALDO antagonists
Proteinuric chronic renal failure	ACEIs and/or ARBs
High coronary disease risk	Diuretics (ALLHAT), perhaps ACEIs (HOPE)
Diabetes mellitus (no proteinuria)	Diuretics (ALLHAT), perhaps ACEIs (HOPE)
Angina pectoris	β-blockers, CCBs
Atrial fibrillation, atrial flutter	β-blockers, nondihydropyridine CCBs
Likely to have a favorable effect on symptoms in comorbid conditions	
Benign prostatic hypertrophy	α-blockers
Essential tremor	β-blockers (noncardioselectives)
Hyperthyroidism	β-blockers
Migraine	β-blockers, CCBs
Osteoporosis	Thiazide diuretics
Perioperative hypertension	β-blockers
Raynaud's syndrome	Dihydropyridine CCBs
Contraindications	
Angioedema	ACEIs
Bronchospastic disease	β-blockers
Depression	Reserpine
Liver disease	Methyldopa
Pregnancy	ACEIs, ARBs (includes women likely to become pregnant)
Second or third degree heart block	β-blockers, nondihydropyridine CCBs
May have adverse effect on comorbid conditions	
Depression	β-blockers, central α-agonists
Gout	Diuretics
Hyperkalemia	ALDO antagonists, ACEIs, ARBs
Hyponatremia	Thiazide diuretics
Renovascular disease	ACEIs or ARBs

*A survival benefit from an ALDO antagonist has only been demonstrated in patients with advanced heart failure; in patients with less severe disease, an ALDO antagonist is primarily given for hypokalemia.

CCBs, calcium channel blockers; ALDO, aldosterone; ALLHAT, Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial; HOPE, Heart Outcomes Prevention Evaluation study; ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; MI, myocardial infarction.

Adapted from The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High blood pressure, *JAMA* 2003; 289:2560.

TABLE 16

Preferred Antihypertensive Drugs in Other Morbid Conditions and Cautions for the Usage

Condition	*Preferred drugs*	*Avoid or use with caution*
Asthma, COPD	Diuretics, CCBs (dihydropyridines and diltiazem, possibly not verapamil), central sympatholytic agents (clonidine, guanabenz), direct vasodialators (hydralazine), ACEIs (may produce cough and infrequently bronchospasm), ARBs, α-adrenergic blockers (prazosin, terazosin, doxazosin, not as single agent or first-line drug)	β-blockers, especially nonselectives (such as nadolol, propranolol, timolol, and others); in a patient without bronchospasm, may try β1 cardioselectives, β-blockers at low dose (such as metoprolol, atenolol, acebutolol, and others)
Atrial fibrillation/ atrial flutter	▪ Control of ventricular heart rate: β-adrenergic blockers (superior: atenolol (cardioselective) and nadolol and pindolol (nonselectives)), nondihyropyridine CCBs (verapamil, diltiazem) ▪ Prevention of relapse back into atrial fibrillation after cardioversion: β-adrenergic blockers [metoprolol, bisoprolol (cardioselectives) and carvedilol (nonselective β- and α-blockers)]	Control of ventricular heart rate, labetalol no better than placebo
BPH	α-adrenergic blockers (doxazosin, prazosin, terazosin) (α-blockers used primarily for BPH—tamsulosin, silodosin, alfuzosin)	Diuretics, α-blockers may cause orthostatic hypotension, especially in elderly
Children and adolescents[52,53]	▪ Diagnostic evaluation for secondary hypertension is important in infants and school age children ▪ New pediatric labeling since the Food and Drug Administration Modernization Act (FDAMA): amlodipine, benazepril, enalapril, fenoldopam, fosinopril, irbesartan, losartan, lisinopril, metoprolol, valsartan	▪ Nonpharmacologic treatment to be tried first and continued if drug therapy is needed ▪ Cautions for various classes of antihypertensive drugs are the same as those for adults

(continued)

Table 16 *(continued)*

Condition	*Preferred drugs*	*Avoid or use with caution*
Children and adolescents[52,53]	▪ Prior pediatric labeling: captopril, chlorothiazide, diazoxide, furosemide, hydralazine, hydrochlorothiazide, methyldopa, minoxidil, propranol, spironolactone ▪ Strongest evidence for use in pediatrics (Limited data compared to adults): ACEIs, ARBs, CCBs	
CKD[54]	Varies with medical condition ▪ CKD and proteinuria in nondiabetics or diabetics: ACEIs/ARBs, ALDO antagonists, then diuretics (loop diuretics for GFR <30 mL/min), then nondihydropyridine CCBs or β-adrenergic blockers (β-blockers not excreted primarily by kidneys—propranolol, metoprolol, timolol), may try dihydropyridines, although improvement in proteinuria is not predictable. ▪ CKD in nondiabetics with normal urinary protein excretion: Diuretics (especially if edema, loop diuretics for GFR <30 mL/min), then ACEIs or ARBs, then nondihydropyridine or dihydropyridine ▪ CCBs, or β-adrenergic blockers (β-blockers not excreted primarily by kidneys—propranolol, metoprolol, timolol) ▪ CKD in kidney transplant patients: CCBs-first-line drug (dihydropyridines might be favored over verapamil and diltiazem), diuretics, or β-adrenergic blockers (β-blockers not excreted primarily by kidneys—propranolol, metoprolol, timolol)	▪ K^+ sparing diuretics, β-blockers excreted by kidneys: Nadolol, atenolol, pindolol. ACEIs and ARBs may cause hyperkalemia, decrease GFR, and increase serum creatinine ▪ An increase in serum creatinine by of 30–35% is considered acceptable and associated with long-term stabilization, or slower decline, in renal function. ALDO antagonists may cause hyperkalemia
Chronic liver disease	Diuretics, CCBs, vasodilators, ACEIs, clonidine, guanabenz, α-adrenergic blockers (not as monotherapy or first-line drug)	β-blockers which depend on hepatic metabolism (major liver metabolism: metoprolol, nebivolol, oxprenolol, propranolol

(continued)

Table 16 *(continued)*

Condition	*Preferred drugs*	*Avoid or use with caution*
Chronic liver disease		hepatic and renal metabolism: acebutolol, betaxolol, bisoprolol, penbutolol, pindolol, timolol), methyldopa, labetalol; CCBs (caution with severe hepatic impairment)
CAD[55]	▪ Varies with medical condition: angina pectoris: (RE: morning peak in ischemia within 3 hours after awakening) β-blockers (avoid ISA), ACEIs, ARBs, CCBs ▪ Post-MI: β-blockers (mortality reduced with: atenolol, carvedilol, metoprolol, propranolol, timolol, acebutolol, pindolol), ACEIs, ARBs, ALDO antagonists ▪ High coronary risk: thiazide diuretics, β-blockers (atenolol, carvedilol, metoprolol, propranolol, timolol, acebutolol, and pindolol), ACEIs, CCBs (long-acting dihydropyridines, diltiazem, verapamil)	▪ Angina pectoris: hydralazine, minoxidil (unless adequately β-blocked), β-blockers with ISA activity (e.g. carteolol, pindolol, acebutolol, and others), guanethidine, guanadrel ▪ Post-MI: hydralazine, minoxidil (unless adequately β-blocked), postganglionic blockers (guanethidine, guanadrel)
Diabetes mellitus[56]	ACEIs and ARBs (with caution for increased K^+ and BUN), CCBs, thiazide diuretics, central sympatholytic agents, β1-selective blockers and those with ISA (may still blunt tachycardia response to hypoglycemia)	▪ If peripheral neuropathy: avoid agents leading to orthostatic hypotension (guanethidine, guanadrel, α-adrenergic receptor antagonists), avoid nonselective β-blockers (hypoglycemia) ▪ If K^+ increased: avoid nonselective β-blockers, K^+ sparing diuretics
Elderly and isolated systolic hypertension (ISH)	Diuretics (start low doses), CCBs, ACEIs and ARBs tend to be less effective	Drugs that cause orthostatic hypotension (guanabenz, guanfacine, guanadrel guanethidine) or CNS side effects (clonidine, methyldopa, reserpine)
Emergencies (hypertensive)[57]	Parenteral drugs generally given by intravenous infusion: nitroprusside (most effective), nitroglycerin, dihydropyridine CCBs (clevidipine, nicardipine), fenoldopam, β1 adrenergic blockers (labetalol	▪ Enalaprilat response is variable and not predictable ▪ Nitroprusside—monitor for cyanide toxicity (risk increases at doses >2–4 μg/kg/min), avoid in pregnancy

(continued)

Table 16 *(continued)*

Condition	*Preferred drugs*	*Avoid or use with caution*
Emergencies (hypertensive)[57]	as infusion or bolus) esmolol (useful during anesthesia), hydralazine (intravenous bolus-primarily used in pregnancy), phentolamine (limited to increased catecholamines (e.g., pheochromocytoma), tyramine ingestion in individual receiving MAOIs)	▪ Nitroglycerin: headache, tachycardia ▪ Labetalol: avoid—asthma, chronic obstructive lung disease, heart failure, bradycardia, >first-degree heart block ▪ Additional side effects listed under individual drugs
Erectile dysfunction	ACEIs (<1%), ARBs (<1%), CCBs (<1–3%), α-adrenergic blockers (not as monotherapy or first-line drug) (<1–4%), thiazide diuretics (3–9%)	β-blockers (6–15%), methyldopa (7–19%), clonidine (11–24%), guanabenz, guanadrel (20–30%), guanethidine (54%)
Essential tremor	β-adrenergic blockers (noncardioselectives > cardioselective β1 blockers)	Direct vasodilators (hydralazine, minoxidil), β-adrenergic blockers with ISA
Exercise	CCBs, β-blockers with ISA, central α2 agonists, ACEIs or ARBs (if volume repleted)	▪ Diuretics or ACEIs or ARBs in hot weather or during excessive sweating ▪ β-blockers without ISA ▪ Drugs that cause orthostatic hypotension (α1 antagonists: guanabenz, guanfacine, guanadrel guanethidine)
Glaucoma	β-blockers (timolol, betaxolol and others—for specific glaucoma therapy, use topically), clonidine (use topically)	Avoid systemic hypotension with all antihypertensives
Gout	No recommendation	Thiazide diuretics may precipitate attack of gout
Heart block (second and third degrees)	Diuretics, ACEIs, ARBs, hydralazine/nitrates	β-blockers, CCBs (verapamil, diltiazem)
Heart failure[58]	Diuretics, ACEIs, ARBs, β-blockers (metoprolol, bisoprolol carvedilol), ALDO antagonists, hydralazine/nitrates	▪ Other β-blockers: bucindolol (did not reduce mortality), nebivolol (approved for heart failure in 71 countries

(continued)

Table 16 *(continued)*

Condition	*Preferred drugs*	*Avoid or use with caution*
Heart failure[58]		▪ but not approved by USFDA. Results not as robust for decreasing mortality as the other three β-blockers listed); all β-blockers in uncontrolled heart failure ▪ CCBs especially verapamil or diltiazem, direct vasodilators (minoxidil), central acting sympatholytic agents, α-adrenergic antagonists (contraindicated in aortic stenosis)
Hyperthyroidism	β-adrenergic blockers (propranolol high dose, >160 mg/day), alprenolol (noncardioselecive), atenolol, and metroprolol (cardioselective) decrease T3 levels), CCBs if β-blockers are contraindicated (nondihydropyridines)	Nadolol does not decrease T3 levels
LVH	ACEIs, ARBs, ALDO antagonists (spironolactone, eplerenone), CCBs (diltiazem, verapamil, long-acting dihydropyridines), β-adrenergic blockers with α1 antagonist properties (carvedilol, labetalol), thiazide diuretics (used as additional drug), traditional β-adrenergic blockers	Direct vasodilators (hydralazine, minoxidil), β-adrenergic blockers with ISA
Menopausal symptoms	Clonidine, guanzabenz, methyldopa	Vasodilators
Metabolic syndrome	ACEI (lisinopril), ARBs, CCBs, β-blockers-vasodilating (carvedilol, nebivolol)	β-adrenergic blockers (without vadodilating properties), thiazide diuretics
Migraine headaches (prevention)	CCBs (verapamil, diltiazem, amlodipine, nicardipine), ACEI (lisinopril), ARB (candesartan), hydrochlorothiazide, β-blockers without ISA (atenolol, metoprolol, nadolol, propranolol, timolol) (not recommended as initial drug in patients >60 years due to increased rate of strokes)	Some CCBs are not effective (nifedipine, nimodipine), vasodilators

(continued)

Table 16 *(continued)*

Condition	*Preferred drugs*	*Avoid or use with caution*
Peptic ulcer disease	ACEIs, ARBs, β-blockers, CCBs, diuretics, central sympatholytic agents	Spironolactone, reserpine, postganglionic blockers (guanethidine, guanadrel)
Peripheral vascular disease	CCBs, ACEIs, ARBs, α-adrenergic blockers (not as monotherapy or first-line drugs—prazosin, terazosin, doxazosin), hydralazine (usually used with diuretics and β-blockers)	Avoid nonselective β-blockers (such as nadolol, propranolol, timolol, and others). If compelling indications for a β-blocker, use β1-cardioselective β-blocker at low dose (such as metoprolol, atenolol, acebutolol, and others)
Pheochromocytoma; clonidine, guanabenz, or guanfacine rebound (with abrupt withdrawal); crisis in patient taking MAOIs	α-adrenergic blockers [phenoxybenzamine-irreversible α-blockers, preferred over prazosin, terazosin, or doxazosin], β-blockers after α-blocker is effective (e.g. propranolol, atenolol, metoprolol), preoperative treatment requires both α- and β-blockers, CCBs (e.g., nicardipine, amlodipine, diltiazem and others), α-methylparatyrosine (metyrosine), adequate/generous salt intake	Do not use β-blockers without adequate α-blockers first. Intravenous labetalol has been used successfully in patients with pheochromocytoma, but a small number of other patients have had a paradoxical hypertensive response, with MAOIs avoid methyldopa
Pregnancy[59]	▪ Varies with type of hypertension during pregnancy: chronic hypertension: preferred methyldopa, second-line agents (labetalol, hydralazine, β-adrenergic blockers, hydrochlorothiazide, clonidine, CCBs (nifedipine: avoid in 1st trimester, may be used in 2nd and 3rd trimesters)) ▪ Mild preeclampsia: methyldopa, labetalol, other β-adrenergic blockers, CCBs ▪ Severe hypertension in preeclampsia: usually requires intravenous hydralazine or labetalol, or peroral nifedipine, rarely sodium nitroprusside	▪ ACEIs and ARBs (increase fetal mortality, renal agenesis, cardiac defects, oligohydramnios) ▪ No antihypertensive drugs are proven to be safe during the first trimetester ((β-blockers may lead to intrauterine growth retardation (labetalol, atenolol), diuretics-not first-line, CCBs-limited data beyond nifedipine)) may inhibit labor. Sympatholytic agents with hydralazine may lead to neonatal thrombocytopenia ▪ Severe hypertension in preeclampsia: nifedipine can cause a marked drop in blood pressure if used with magnesium

(continued)

Table 16 *(continued)*

Condition	*Preferred drugs*	*Avoid or use with caution*
	▪ Eclampsia: after control of seizures and hypertension with magnesium sulfate, control hypertension with intravenous hydralazine or labetalol	▪ sulfate; sodium nitroprusside may lead to fetal cyanide poisoning ▪ Eclampsia: avoid diuretics
Psychiatric comorbidity[60]	▪ Varies with psychiatric condition: depression: CCBs, ACEIs, ARBs, diuretics ▪ Panic disorder, anxiety: β-adrenergic blockers ▪ Schizophrenia, other major psychiatric disorders (little data), suggested drugs that have little entry into CNS: ACEIs, ARBs, CCBs (verapamil-mania), possibly diuretics	▪ Depression: β-blockers (lipid soluble, fewer side effects with hydrophilic β-blockers (see table 12 under β-blockers above)), central α2 agonists (clonidine, guanabenz, methyldopa and others), reserpine ▪ Caution: interaction between vasodilating β-blockers (nebivolol, labetalol, and others) and SSRIs (increased blood pressure lowering effect) ▪ Panic disorder (anxiety): α-adrenergic blockers, possibly direct vasodilators ▪ Schizophrenia, other major psychiatric disorders: caution with diuretics if patients are compulsive water drinkers
Race: African-Americans, ancestry-black Africans	Diuretics, CCBs (often 3 drugs are required): Add an ACEI or ARB or β-blocker for compelling indications or vasodilating β-blocker (carvedilol–cardioprotective in African-Americans)	β-blockers may be less effective and require higher doses. Note: in the ALLHAT study, African-Americans randomized to the ACEI group had a 40% increased risk of stroke and a 32% increased risk of heart failure compared to patients randomized to the diuretic group. These differences disappeared when the ACEI was combined with a diuretic
Raynaud's phenomenon	CCB (long-acting dihydropyridines, diltiazem), ARB (losartan), α-adrenergic blockers, methyldopa, nitroglycerin cream	β-blockers

(continued)

Table 16 *(continued)*

Condition	*Preferred drugs*	*Avoid or use with caution*
Renovascular disease (renal artery stenosis)	If choice is for medical therapy: ACEIs, ARBs, CCBs (often with ACEIs or ARBs), diuretic added to ACEIs or ARBs (chlorthalidone, loop diuretic for GFR < 30 mL/min), β-adrenergic blockers	ACEIs and ARBs may lead to rise in BUN and creatinine, especially with bilateral renal artery stenosis, or renal artery stenosis in solitary kidney, renal dysfunction may be worsened by diuretics, need to monitor renal function
Resistant hypertension (AHA 2008 definitions: ▪ Blood pressure above goal despite 3 antihypertensive drugs of different classes, including one diuretic. ▪ Blood pressure requiring 4 different drugs for control)[61]	▪ Three or more drugs are required, including a diuretic. Chlorthalidone recommended, plus ACEIs or ARBs and CCBs (long-acting dihydropyridine), then add ALDO antagonist (eplerenone or spironolactone). If still hypertensive: may add, one at a time—vasodilating β-blocker (carvedilol, labetalol, nebivolol), centrally acting sympatholytic agents (clonidine, guanfacine), or direct vasodilator (minoxidil or hydralazine) ▪ Experimental invasive treatments: – Radiofrequency ablation of renal sympathetic nerves (symplicity-HTN-2 trial) – Electrical activation of carotid sinus baroreceptors.	▪ Evaluate and treat secondary hypertension (if present) ▪ Include nonpharmacologic treatment as part of regimen ▪ Standard β-blockers may be less effective than vasodilating β-blockers ▪ Monitor patients for orthostatic hypotension
Stroke[62-63]	Varies with medical condition ▪ Risk of stroke: primary prevention—diuretics (hydrochlorothiazide, indapamide, chlorthalidone, bendrofluazide), amlodipine (exact place in therapy controversial) ▪ Recurrent stroke prevention: thiazide diuretics, thiazide diuretics plus ACEI combined (ACEI alone not as effective), possibly ARB (nimodipine for subarachnoid hemorrhage)	▪ Avoid drugs which produce an abrupt drop or orthostatic decrease in blood pressure—direct vasodilators ▪ Risk of stroke – Primary prevention—β-adrenergic blockers are not as effective for primary prevention of stroke as other drugs (risk of storke is higher in patients >60 years) ▪ Caution: large artery stenosis (e.g., carotid artery stenosis)

(continued)

Table 16 *(continued)*

Condition	*Preferred drugs*	*Avoid or use with caution*
Stroke[62-63]	▪ Hypertension control in acute stroke: candidates for fibrinolysis: blood pressure >185/110 mmHg labetalol intravenously or nitropaste or nicardipine infusion ▪ Noncandidates for fibrinolysis: blood pressure >220/120 mmHg labetalol intravenously or nicardipine infusion	▪ Recurrent stroke prevention: β-adrenergic blockers not recommended unless compelling indication ▪ Caution: large artery stenosis (e.g., carotid artery stenosis) ▪ Avoid volume depletion with diuretics ▪ Hypertension control in acute stroke.*

*Additional information: Jauch EC, et al. based on ACLS Guidelines, 2005 and American Stroke Association Scientific Statement, 2007.

COPD, chronic obstructive pulmonary disease; CCBs, calcium channel blockers; ACEIs, angiotensin converting enzyne inhibitors; ARBs, angiotensin II receptor blockers; BPH, benign prostatic hypertrophy; CKD, chronic kidney disease; GFR, glomerular filtration rate; ISA, intrinsis sympathomimetic activity; BUN, blood urea nitrogen; MAOIs, monoamine oxidase inhibitors; SSRIs, selective serotonin reuptake inhibitors; MI, myocardial infarction; CAD, coronary artery disease; LVH, left ventricular hypertrophy.

TABLE 17

Clinical Uses of β-adrenoceptor Blockers[64]

Class/Drug	*Clinical uses*					*Comments*
	Hypertension	*Angina*	*Arrhythmia*	*MI*	*CHF*	
Nonselective β1/β2						
Carteolol	✓	x	x	x	x	ISA, long acting, also used for glaucoma
Carvedilol	✓	x	x	x	✓	α-blocking activity
Labetalol	✓	✓	x	x	x	ISA, α-blocking activity
Nadolol	✓	✓	✓	✓	x	Long acting
Penbutolol	✓	✓	x	x	x	ISA

(continued)

Table 17 *(continued)*

Class/Drug	*Clinical uses*					*Comments*
	Hypertension	*Angina*	*Arrhythmia*	*MI*	*CHF*	
Pindolol	✓	✓	x	x	x	ISA, MSA
Propranolol	✓	✓	✓	✓	x	MSA, prototypical β-blocker
Sotalol	x	x	✓	x	x	Several other significant mechanisms
Timolol	✓	✓	✓	✓	x	Primarily used for glaucoma
β1-selective						
Acebutolol	✓	✓	✓	x	x	ISA
Atenolol	✓	✓	✓	✓	x	—
Betaxolol	✓	✓	✓	x	x	MSA
Bisoprolol	✓	✓	✓	x	x	—
Esmolol	✓		✓	x	x	Ultrashort acting, intra- or postoperative hypertension
Metoprolol	✓	✓	✓	✓	✓	MSA
Nebivolol	✓	x	x	x	x	Relatively selective in most patients, vasodilating (NO release)

MI, myocardial infarction; CHF, congestive heart failure; ISA, intrinsic sympathomimetic activity; MSA, membrane stabilizing activity; NO, nitric oxide.

Adapted from Klabunde RE. Cardiovascular Pharmacology Concepts: Beta-Adrenoceptor Antagonists (Beta-Blockers). Available from: http://www.cvpharmacology.com/cardioinhibitory/beta-blockers.htm. Feb 2010, *with permission*.

TABLE 18

Causes of Resistant Hypertension (JNC 7 AND ESH/ESC)
▪ Volume overload
– Excess sodium intake
– Volume retention from kidney disease
– Inadequate diuretic therapy
▪ Drug-related, drug-induced or other causes
– Nonadherence
– Inadequate doses
– Inappropriate combinations
– Nonsteroidal anti-inflammatory drugs, cyclooxygenase 2 inhibitors
– Cocaine, amphetamines, other illicit drugs
– Sympathomimetics (decongestants, anorectics)
– Oral contraceptive hormones
– Adrenal steroid hormones
– Cyclosporine and tacrolimus
– Erythropoietin
– Licorice (including some chewing tobacco)
– Selected over-the-counter dietary supplements and medicines (e.g., ephedra, ma huang, bitter orange)
– Unsuspected secondary hypertension, including obstructive sleep apnea
▪ Associated conditions
– Obesity
– Excess alcohol intake
▪ Causes of spurious resistant hypertension
– Isolated office (white-coat) hypertension
– Failure to use large cuff on large arm (improper measurement)
– Pseudohypertension.

End-organ damage may occur in some hypertensive patients. Cerebrovascular, and cardiovascular complications have been discussed. Renal dysfunction is another complication that may occur in hypertensive patients. Proteinuria and albuminuria is a manifestation of renal dysfunction. In table 19, definitions of proteinuria and albuminuria are summarized.

Hypertension in Children and Adolescents

Hypertension is recognized in children and adolescents too. It is more frequently observed in children and adolescents with hypertensive parents. There are other risk factors, such as obesity, culture, environment, and family history for development of hypertension in children and adolescents. It is highly desirable to recognize those at risk of developing hypertension.

TABLE 19

Definitions of Proteinuria and Albuminuria[65]

	Urine collection	*Normal*	*Microalbuminuria*	*Albuminuria or proteinuria*
Total protein	24-hour excretion	<300 mg/day	—	>300 mg/day
	"Spot" urine dipstick	<30 mg/dL	—	>30 mg/dL
	"Spot" or random urine protein-to-creatinine ratio	<200 mg/g	—	>200 mg/g
Albumin	24-hour excretion	<30 mg/day	30–300 mg/day	>300 mg/day
	"Spot" urine dipstick (albumin-specific dipstick)	<3 mg/dL	>3 mg/dL	—
	"Spot" or random urine albumin-to-creatinine ratio	<17 mg/g (men) <25 mg/g (women)	17–250 mg/g (men) 25–355 mg/g (women) or 30–299 mg/g	>250 mg/g (men) >355 mg/g (women)

TABLE 20

Blood Pressure Values* Requiring Further Evaluation According to Age and Gender in Children and Adolescents[53]

Age (years)	*Blood pressure values (mmHg)*			
	Male		*Female*	
	Systolic	*Diastolic*	*Systolic*	*Diastolic*
3	100	59	100	61
4	102	62	101	64
5	104	65	103	66
6	105	68	104	68
7	106	70	106	69
8	107	71	108	71
9	109	72	110	72
10	111	73	112	73
11	113	74	114	74
12	115	74	116	75
13	117	75	117	76
14	120	75	119	77
15	120	76	120	78
16	120	78	120	78
17	120	80	120	78
≥18	120	80	120	80

*These values represent the lower limits for abnormal blood pressure ranges, according to age and gender. Any blood pressure readings equal to or greater than these values represent blood pressures in the prehypertensive, stage 1 hypertensive, or stage 2 hypertensive range and should be further evaluated by a physician.

In table 20, the blood pressure values in children and adolescents that require further evaluation are summarized.

Dyslipidemia

Dyslipidemia has been recognized as a potential side effect of antihypertensive therapy for several years. However, not all antihypertensive agents exert similar effects on lipid profile. Some agents can produce deleterious effects and others have beneficial effects. The effects of antihypertensive drugs on serum lipids are summarized in table 21.

ANTIHYPERTENSIVE DRUGS AND DOSING RECOMMENDATIONS

Dosing recommendations for various classes of antihypertensive drugs are summarized in tables 22–24 and 26–34. The actions

of β-adrenergic receptors on various organs are summarized in table 25. Dosing recommendations of various combinations of antihypertensive drugs are summarized in table 35–45.

ANTIHYPERTENSIVE DRUG: SIDE EFFECTS AND CAUTIONS[67-72]

Antihypertensive drugs are prone to produce minor or serious adverse effects. The serious side effects are important causes of noncompliance. Some side effects are common. The major and minor side effects are summarized in the tables 46–49, 51–54, and 56–60. The lipid solubility of some β-blockers is summarized in table 50. Effects of various calcium channel blockers on selected cardiac and vascular functions are summarized in table 55.

TABLE 21

Antihypertensive Drugs and Their Effects on Serum Lipids[66]

- Favorable effects
  - α1-adrenergic receptor blockers: lower total cholesterol (3–5%) and triglycerides (3–4%) and raise HDL (mild effect)
  - CCBs: may increase HDL and decrease triglycerides (mild effect), or have no effect on lipids (diltiazem may have the most favorable effects compared to verapamil and dihydropyridines)
- Unfavorable effects (may be mild)
  - Thiazide diuretics: may raise LDL (5–10%) and increase triglycerides. This may occur with short-term use and may not be present after a year
  - β-adrenergic receptor blockers (nonselective and β1-selective):
    Without ISA: may lower HDL (10%) and raise triglycerides (20–40%)
    With ISA: less effect to lower HDL or raise triglycerides, or changes in lipids non-significant
- No effect (or mild beneficial effect)
  - Central sympatholytic action (α2 adrenergic agonists)—methyldopa, clonidine, guanabenz, guanfacine: lipid (neutral), guanabenz, small decreases in total cholesterol and triglycerides and reduction in HDL
  - β-blockers with vasodilating properties: generally lipid neutral, nebivolol may increase triglycerides and decrease HDL
  - ACEIs and ARBs: lipid neutral, or mild effect to increase HDL, decrease LDL and triglycerides
  - Vasodilators (hydralazine, minoxidil): lipid neutral or mild effect to increase HDL and decrease LDL, no effect on triglycerides
  - Potassium channel openers: lipid neutral or mild effect to decrease LDL and triglycerides and increase HDL

HDL, high-density lipoproteins; LDL, low-density lipoproteins; ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; ISA, intrinsic sympathomimetic activity; CCBs, calcium channel blockers.

TABLE 22

Dosing Recommendations for Diuretics[67-72]			
Drugs	*Starting adult daily dose [oral unless specified]*	*Daily dose range*	*Frequency/day*
Thiazides (benzothiadiazine derivatives) (Ineffective in patients with GFR <30 mL/min, serum creatinine >2.5 mg/dL [221 μmol/L])			
Bendroflumethiazide (only in combination tablet)	1.25–2.5 mg	1.25–20 mg	1
Benzthiazide	50 mg	50–200 mg	1–2
Butizide or buthiazide	2.5 or 5 mg	2.5–15 mg	1–2
Chlorothiazide	500 mg	500–1000 mg	1–2
Clopamide	10–40 mg	Initial: 10–40 mg, maintenance: 5–20 mg daily or every other day	1 or for maintenance: once every other day
Cyclopenthiazide	0.25 mg	0.25–1.5 mg	1
Cyclothiazide	2 mg	2–6 mg	1–3
HCTZ	12.5 or 25 mg	12.5–50 mg (up to 100 mg)	1–2
Hydroflumethiazide	12.5–25 mg	12.5–50 mg	1–2
Mefruside	10 mg	10–50 mg	1–2 (maintenance: daily or every other day)

(continued)

Table 22 *(continued)*

Drugs	*Starting adult daily dose [oral unless specified]*	*Daily dose range*	*Frequency/day*
Methyclothiazide	2.5 mg	2.5–5 mg	1
Meticrane	150 mg	150–300 mg	1
Polythiazide	1.0 mg	1–4 mg	1
Trichlormethiazide	1–2 mg	1–4 mg	1
Xipamide	20 or 40 mg	10–80 mg (for maintenance, may decrease to 10–20 mg)	1
Diazoxide (nondiuretic/nonsaluretic thiazide)	Intravenous use only for malignant hypertension	1–2 mg/kg (maximum dose/bolus = 150 mg)	May repeat every 5–15 minutes until diastolic pressure <100
Phthalimidine derivatives			
Chlorthalidone	12.5 or 25 mg 15 mg	12.5–50 mg 15–45 mg	1
Quinazoline derivatives			
Metolazone	2.5 mg	2.5–10 mg (20 mg CKD)	1
Metolazone (bioavail)	0.5 mg	0.5–1.0 mg	1
Quinethazone	25 mg	25–100 mg	1–2
Indoline derivatives			
Indapamide	1.25–2.5 mg	1.25–5 mg	1

(continued)

Table 22 *(continued)*

Drugs	*Starting adult daily dose [oral unless specified]*	*Daily dose range*	*Frequency/day*
Metipamide	1.25–2.5 mg	1.25–5 mg	1 (for maintenance: once/day or every other day)
Tripamide	15 mg	15–30 mg	1–2
Loop diuretics [Diuretics of choice in patients with GFR <30 mL/min or serum creatinine 2.5 mg/dL (221 μmol/L)]			
Azosemide (similar - furosemide; may also act in proximal tubule)	30–60 mg (azosemide 30 mg = furosemide 20 mg)	30 or 60 mg (maximum dose not established)	1
Bumetanide	0.5 mg	0.5–10 mg	1–2
Ethacrynic acid	25 mg	25–100 mg (max: 200 or 400 mg)	1–2
Etozolin	200 mg	200–400 mg	1
Furosemide	20–40 mg	Oral: 40–480 mg (max: 600 mg), intravenous 0.05 mg/kg/hour and titrate or 20 to 40 mg intravenous over 1 to 2 minutes, may repeat in 2 hours (usually for edema)	1, 2, or more
Piretanide	6 mg (piretanide 6 mg = furosemide 40 mg)	6–12 mg	1

(continued)

Table 22 *(continued)*

Drugs	*Starting adult daily dose [oral unless specified]*	*Daily dose range*	*Frequency/day*
Torsemide	5 mg	5–200 mg	1, 2, or more
Potassium sparing diuretics			
Amiloride	5 mg	5–20 mg	1–2
Triamterene	50–100 mg	50–300 mg	1 or 2 or every other day
ALDO antagonists			
Canrenone (major metabolite of spironolactone)	50 mg	50–300 mg	1
Eplerenone	25–50 mg	25–100 mg	1–2
Potassium canrenoate (prodrug for canrenone)	100 mg	100–400 mg (in one or two divided doses)	1–2
Spironolactone	25 mg	25–100 mg (maximum 400 mg)	1–2

CKD, chronic kidney disease; GFR, glomerular filtration rate; ALDO, aldosterone; HCTZ, hydrochlorothiazide.

TABLE 23

Dosing Recommendations for Central Sympatholytic Agents, Imidazoline Receptor Antagonist[67-72]			
Drugs	*Starting adult daily dose [oral unless specified]*	*Daily dose range*	*Frequency/day*
Central sympatholytic agents (α2 adrenergic agonists)			
Clonidine Oral tablets Transdermal patch (TTS)	 0.1 mg TTS-1 (1 patch/week = 0.1 mg/day)	 0.1– 0.6 mg (max 1.2 mg) One TTS-1 to two TTS-3	 1–2 (up to 4) 1 patch/week
Guanabenz	4 mg	4–32 mg	2
Guanfacine	1 mg	1–3 mg	1 (HS)
Methyldopa	250 mg	250–3000 mg	2–3 (or 4)
	(Intravenous use: 250–500 mg QID, infuse slowly over 1/2–1 hour, maximum 1 g QID)		
Central depleting agents of catecholamines and 5-hydroxytryptophan (Rauwolfia alkaloids)			
Reserpine 0.1 mg; 0.25 mg	0.05–0.1 mg	0.05–0.25 mg	1
Central imidazoline receptor agonists (α2-adrenergic agonists)			
Moxonidine	0.1–0.2 mg	0.1–0.6 mg	1 (or 2)
Rilmenidine	1 mg	1–2 mg	1 (or 2)

TABLE 24

Dosing Recommendations for Ganglionic and Post-ganglionic Blockers[67-72]			
Drugs	*Starting adult daily dose [oral unless specified]*	*Daily dose range*	*Frequency of dose/day*
Ganglionic blockers			
Trimethaphan	Continuous intravenous only, 1 g/L (1 mg/mL), titrated, start 0.5–1 mg/min, range: 0.5–6 mg/min (used for malignant hypertension, acute aortic dissection)		
Mecamylamine	2.5 mg	2.5–25 mg	2 (or 3 or 4)
Postganglionic blockers			
Bethanidine	5 or 10 mg	15 mg or 30–200 mg	3
Debrisoquine	10 mg	10 mg or 20–120 mg	1–2
Guanadrel	5 mg	10–75 mg	2 (or 3 or 4)
Guanethidine	10 mg	10–100 mg	1–2
Parglyline (monoamine oxidase inhibitor)	10 mg	10–25 mg	1

TABLE 25

Actions of β-adrenergic Receptors

- β1-receptors
  - Heart
    - Increase heart rate via SA node
    - Increase conduction velocity via AV node
    - Increase contractility via atria and ventricles
    - Increase conduction velocity and automaticity of cardioventricular pacemakers via ventricles
  - Kidneys
    - Increase renin
  - Posterior pituitary
    - Increase vasopressin (ADH)
  - Parathyroid gland
    - Increase parathormone secretion
  - Stomach
    - Increase ghrelin
- β2-receptors
  - Heart
    - β2-receptors are also present on heart with similar functions to β1-receptors
  - Lungs
    - Relax bronchiolar smooth muscle
  - Blood vessels
    - Relax smooth muscles (arterioles, veins)
  - Intestines
    - Decrease motility
  - Stomach
    - Decrease motility
  - Skeletal muscle
    - Increase contractility, K^+ uptake
  - Liver
    - Increase glycogenolysis and gluconeogenesis
  - Fat cells
    - Lipolysis (also, β3-receptors)
  - Pancreas
    - Stimulate insulin secretion
  - Urinary bladder
    - Detrusor relaxation
  - Uterus
    - Relaxation
  - Thyroid
    - Promote conversion of T4 to T3.

SA, sinoatrial; AV, atrioventricular; ADH, antidiuretic hormone; K^+, potassium; T3, tri-iodothyronine; T4, thyroxine.

TABLE 26A

Dosing Recommendations for Adrenergic Receptor Blocking Drugs

Drugs	*Half-life (hours)*	*Starting adult daily dose*	*Daily dose range*	*Frequency of dose/day*
β-blockers				
Nonselective (β1- and β2-receptor antagonists)				
Alprenolol	2–3	25 mg BD	50–800 mg	2
Bopindolol* (prodrug for pindolol)	4–6	0.5–1.0 mg	0.5–2 mg (has been used up to 8 mg)	1
Bupranolol (similar to propranolol)	2–4	50 mg BD	50 mg BD to100 mg QID	2–4
Carteolol*	5–6	2.5 mg	2.5–60 mg	1
Indenolol*	7	60 mg	60–120 mg	1
Mepindolol* (analog of pindolol)	3–4.5	5 mg	5–15 mg	1
Nadolol	20–24	20–40 mg	20–320 mg	1
Oxprenolol*	2	160 mg	160–480 mg	4
Penbutolol*	5–6	10 mg	10–20 mg	1
Pindolol*	3–4	5 mg BD	10–60 mg	2
Propranolol				
Regular preparation	4	20–40 mg BD	40–480 mg (maximum 640 mg)	2–4
Long-acting preparation	8–11	80 mg	80–480 mg (maximum 640 mg)	1
Extended-release preparation		80 mg at bedtime	80–120 mg	1

(continued)

Table 26A *(continued)*

Drugs	*Half-life (hours)*	*Starting adult daily dose*	*Daily dose range*	*Frequency of dose/day*
Propranolol (intravenous use)		(Intravenous: 1 mg/min; total 1-3; electrocardiographic monitoring		
Tertatolol	3–9	5 mg	5–10 mg	1
Timolol	4–5	10 mg BD	20–60 mg	2
Cardioselective (β1-selective antagonists)				
Acebutolol*	3–4	200 mg BD	200–1200 mg	Usually 2 (or 1)
Atenolol	6–7	25 mg	25–100 mg	1
Betaxolol	14–22	5 mg	5–20 mg (or 40 mg)	1
Bisoprolol	9–12	2.5 mg	2.5–20 mg	1
Celiprolol*	5.1–5.8	200 mg	200–400 mg (or 600 mg)	1
Esatenolol (isomer of atenolol)	6–7	25 mg	25–100 mg	1
Metoprolol (tartrate)	3–7	50–100 mg	50–450 mg	1–2
Metoprolol (succinate) extended release	3–7	25–100 mg	50–400 mg	1
Talinolol	12	50–100 mg in morning and 50 mg in evening	100–300 mg	2
Esmolol (intravenous use)	Approximately 9 minutes	Intravenous load: 500 μg/kg over 1 min followed by 25 μg/kg/min; increase by 25–50 μg/kg/min every 5 minutes. Usual maintenance: 100 μg/kg/min; maximum: 200 μg/kg/min.		

(continued)

Table 26A *(continued)*

Drugs	*Half-life (hours)*	*Starting adult daily dose*	*Daily dose range*	*Frequency of dose/day*
β-blockers with vasodilating properties				
Amosulalol (β-nonselective, α-antagonist)	5	10 mg BD	20–60 mg (effective dose range in clinical studies)	2
Arotinolol* (β-nonselective, α-antagonist)	10–11.2	10 mg BD	20–40 mg in 2 divided doses, or 30 mg OD	1–2
Bevantolol (β1-selective, α1-selective antagonist)	1–2	75 mg BD	150–400 mg in 2 divided doses	2
Bucindolol (β-nonselective, very weak α1-selective antagonist)	4–12	10–50 mg TID	50–200 mg TID (optimal dose not established)	3
Carvedilol (β-nonselective, α1-selective antagonist)	7–10	6.25 mg BD	12.5–50 mg	2
Labetalol* (β-nonselective, α1-selective antagonist)	6–8	100 mg BD peroral	200–1200 mg (maximum 2400 mg)	2
		Intravenous use: start bolus 20 mg; then 20–80 mg every 10 minutes to maximum of 300 mg or infusion: start 0.5 to 2 mg/min to total 30 mg		
Nebivolol (β1-selective plus vasodilator through nitric oxide pathway)	12–19	5 mg	5–40 mg	1
Tilisolol (β-nonselctive, vasodilator properties, possibly K^+ channel opener)	12	10 mg	10–30 mg	1

*Intrinsic sympathomimetic activity.

OD, once a day; BD, twice a day; TID, thrice a day; QID, four times a day.

TABLE 26B

Dosing Recommendations for Adrenergic Receptor Antagonists

Drugs	*Starting adult daily dose [oral unless specified]*	*Daily dose range*	*Frequency/day*
α-adrenergic receptor antagonists			
Bunazosin (competitive α1 antagonists)	Start 6 mg at bedtime; then 6 mg every morning	6–12 mg	1
Doxazosin (competitive α1 antagonists) Regular preparation Extended-release preparation (GITS)	 Start 1 mg Start 4 mg	 1–16 mg 4–8 mg	1
Indoramin (competitive α1 antagonists)	25 mg BD	50–200 mg/day	2
Prazosin (competitive α1 antagonists)	Start 1 mg at bedtime, then 1 mg every morning	2–30 mg	2–3
Terazosin (competitive α1 antagonists)	Start 1 mg at bedtime, then 1 mg every morning	1–20 mg (maximum 40 mg)	1–2
Tolazoline (competitive α1 antagonists) (for pulmonary hypertension)	Intravenous: 10–50 mg QID	40–200 mg	4
Phenoxybenzamine (noncompetitive α1 and 2 antagonists)	10 mg BD	20–40 mg	2–3
Phentolamine (competitive α1 and 2 antagonists)	Intramuscular: 5–10 mg, intravenous: 5–10 mg, bolus: may repeat every 5 minutes to 20–30 mg, infusion: 0.1–100 μg/kg/min		

GITS, gastrointestinal therapeutic system; OD, once a day; BD, twice a day; TID, thrice a day; QID, four times a day.

TABLE 27A

Dosing Recommendations for Direct Vasodilators (Oral Acting)

Drugs	*Starting adult daily dose [oral unless specified]*	*Daily dose range*	*Frequency of dose/day*
Cadralazine	10 mg	10–30 mg	1
Dihydralazine	12.5 mg BD	25–100 mg (maximum 150 mg)	2–3
Endralazine	10 mg	10–40 mg	1–2
Hydralazine	10 mg BD to QID	50–300 mg	2–4
	(Intravenous or intramuscular use: start 10 mg, may use to 40 mg every 4–6 hours		
Minoxodil (also listed under K^+ channel openers)	2.5–5 mg	2.5–100 mg	1–2
Todralazine	20 mg BD	40–120 mg	2–4

BD, twice a day; QID, four times a day, K^+, potassium.

TABLE 27B

Dosing Recommendations for Direct Vasodilators (Intravenous Use of Hypertensive Emergencies)

Drugs	*Dose*
Sodium nitroprusside	Continuous intravenous infusion (in dextrose 5% in water only): 0.3–10.0 μg/kg/min, average dose: 3 μg/kg/min. Risk of cyanide toxicity increased at >2–4 μg/kg/min
Diazoxide (also listed under K^+ channel openers)	Intravenous bolus injection: 1–3 mg/kg (max: 150 mg); bolus repeated every 5–15 minutes as needed

K^+, potassium.

TABLE 28

Dosing Recommendations for Inhibitors of the Renin-angiotensin System				
Drugs	*Half-life (hours)*	*Starting adult daily dose*	*Daily dose range*	*Frequency of dose/day*
ACEIs				
Alacepril (converted to captopril)	1.9	12.5 mg	12.5–100 mg	1
Benazepril	10	5 or 10 mg	5–80 mg	1 (or 2)
Captopril	<3	12.5–25 mg BD or TID	12.5–450 mg	2–3
Cilazapril	30–50	2.5 mg	2.5–10 mg	1
Delapril	1/2	15 mg BD	30–120 mg in 2 divided doses	2
Enalapril	11	2.5 or 5 mg	2.5–40 mg	1 (or 2)
Enalaprilat	11	Intravenous use: 0.625 mg or 1.25 mg every 6 hours, given over a 5 minute period. Maximum dose: 5 mg QID		
Fosinopril	11.5–12	10 mg	10–80 mg	1 (or 2)
Imidapril	1.1–2.5	5 mg	10 mg	1
Lisinopril	12	5 or 10 mg	5–80 mg	1
Moexipril	9.8	7.5 mg	7.5–60 mg	1 (or 2)
Perindopril	20–120	4 mg	4–16 mg	1 (or 2)
Quinapril	25	10–20 mg	10–80 mg	1 (or 2)
Ramipril	13–17	2.5 mg	2.5–20 mg	1 (or 2)
Spirapril	30–35	6 mg	6 mg	1

(continued)

Table 28 *(continued)*

Drugs	*Half-life (hours)*	*Starting adult daily dose*	*Daily dose range*	*Frequency of dose/day*
Temocapril	1.6	1 mg	1–4 mg	1
Trandolapril	10	1 mg (non-Blacks) 2 mg (Blacks)	1–8 mg	1 (or 2)
Zofenopril	5	15 mg	15–60 mg	1
ARBs				
Azilsartan	11	40–80 mg	40–80 mg	1
Candesartan	9	8 mg	8–32 mg	1 (or 2)
Eprosartan	20	400–600 mg	400–800 mg	1 (or 2)
Irbesartan	11–15	75–150 mg	75–300 mg	1
Losartan	6-9	25 or 50 mg	25–100 mg	1 (or 2)
Olmesartan	12–18	20 mg	20–40 mg	1
Telmisartan	24	20–40 mg	20–80 mg	1
Valsartan	6–9	80 mg	80–320 mg	1
DRIs				
Aliskiren*	40	150 mg	150–300 mg	1

*As of December 20, 2011, The randomized ALTITUDE study with aliskiren has been terminated due to increased adverse events among high-risk patients taking aliskiren in addition to conventional antihypertensive drugs (ACEIs or ARBs). Patients had type 2 diabetes mellitus and CKD.

Historical note: Teprotide is a nonapeptide isolated from venom of the snake *Bothrops jararaca*. It was the first ACEI observed by Sergio Ferreira in 1965 and required intravenous use. Saralasin is a competitive angiotensin II inhibitor used intravenously as a test for renin-dependent hypertension. It was discontinued in 1984.

ACEIs, angiotensin converting enzymes inhibitors; ARBs, angiotensin II receptor blockers; DRIs, direct renin inhibitors; BD, twice a day; TID, thrice a day; QID; four times a day.

TABLE 29

Dosing Recommendations for Calcium Channel Blockers			
Drugs	*Starting adult daily dose*	*Daily dose range*	*Frequency of dose/day*
Benzothiazepines (block L-type channels)			
Diltiazem	30 mg QID	120–360 mg	3–4
Diltiazem injectable	Intravenous use: 0.25 mg/kg over 2 minutes. After 15 minutes, repeat 0.35 mg/kg over 2 minutes, or intravenous infusion 5–10 mg (up to 15 mg/hr)		
Diltiazem sustained-release	60–120 mg BD	120–360 mg	2
Diltiazem extended-release capsule	120–240 mg	120–480 mg*	1
Diltiazem extended-release tablet	120–240 mg	120–540 mg	1
Dihdropyridines (block l-type channels)			
1st Generation: may suppress myocardial contractility or suppress SA node			
Nifedipine immediate-release	10 mg TID For angina pectoris, not recommended for hypertension treatment	30–180 mg	3–4
Nifedipine slow-release	30–60 mg 30 mg	30–120 mg 30–90 mg	1 1
2nd Generation dihydropyridines			
Benidipine	2 mg	2–4 mg (8 mg)	1
Felodipine	2.5 or 5 mg	2.5–10 mg	1

(continued)

Table 29 *(continued)*

Drugs	*Starting adult daily dose*	*Daily dose range*	*Frequency of dose/day*
Isradipine			2
Capsule	2.5 mg BD	5–20 mg	1
Tablet	5 mg	5–20 mg	
Nicardipine immediate-release	20 mg TID	60–120 mg	3
Nicardipine slow-release	30 mg BD	60–120 mg	2
Nisoldipine			
Hydrogel tablet	17 mg	17–34 mg	1
Coatcore tablet	20 mg	20 –60 mg	1
Nitrendipine	5–10 mg	10–40 mg	1–2
Nimodipine	60 mg six times a day	360 mg/day	6
	(USFDA approved for subarachnoid hemorrhage (SAH) from ruptured intracranial aneurysm. Begin within 96 hours after SAH and continue for 21 days)		
3rd Generation dihydropyridines			
Amlodipine	2.5 mg or 5 mg	2.5–10 mg	1
Aranidipine	5 mg	5–20 mg	1
Azelnidipine	8 mg	8–16 mg	1
Barnidipine	5–10 mg	5–20 mg	1
Cilnidipine	5 mg	5–20 mg	1
Efonidipine	10 mg BD	20–40 mg	(1)–2
Lacidipine	2–4 mg	2–6 mg (8 mg)	1
Lercanidipine	10 mg	10–30 mg	1
Manidipine	10 mg	10–20 mg	1

(continued)

Table 29 *(continued)*

Drugs	*Starting adult daily dose*	*Daily dose range*	*Frequency of dose/day*
Nilvadipine	8 mg	8–16 mg	1
Pranidipine	1 mg	1–4 mg	1
Clevidipine	Intravenous use: 1–2 mg/hour. May double dose every 90 seconds, increase of 1–2 mg/hour decreases systolic blood pressure by 2–4 mmHg. Maximum dose: 21 mg/hour		
Phenylalkylamines (block L-type channels)			
Gallopamil	50 mg BD	50–200 mg	2–4
Verapamil (immediate-release)	80 mg TID	240–480 mg	3
Verapamil (sustained-release)	(120 mg or) 180 mg	(120 mg or) 180–480 mg	1 (or 2)
Verapamil (extended-release at bedtime)	200 mg	200–400 mg	1
Verapamil (intravenous)	Intravenous use: 5–10 mg over 2–3 minutes; repeat in 30 minutes if necessary. Used for PSVT		
Diarylaminopropylamine ester			
Bepridil (USFDA approved for angina pectoris)	200 mg	200–400 mg	1

*The daily dose can go up to 540 mg depending on the preparation of the drug.

BD, twice a day; TID, thrice a day; QID, four times a day; PSVT, paroxysmal supraventricular tachycardia.

TABLE 30

Dosing Recommendations for Nitrates

Drugs	*Starting adult daily dose*	*Daily dose range*	*Frequency of dose/day*
Nitroglycerin (intravenous)		5–100 μg/min	
Nicorandil (used for angina pectoris; also is a K^+ channel opener activator—see table 32)	10 mg BD	20–80 mg	2

BD, twice a day; K^+, potassium.

TABLE 31

Dosing Recommendations for Catecholamine Synthesis Inhibitor (Tyrosine Hydroxylase Blocker) (for Pheochromocytoma only)			
Drugs	*Starting adult daily dose*	*Daily dose range*	*Frequency of dose/day*
Metyrosine	250 mg QID	1000–4000 mg (decrease catecholamines by 35–80%)	4

QID, four times a day.

TABLE 32

Dosing Recommendations for Potassium Channel Openers or Activators			
Drugs	*Starting adult daily dose*	*Daily dose range*	*Frequency of dose/day*
Cromakalim, Levcromakalim and others	Under investigation		
Minoxodil	2.5–5 mg	2.5-100 mg	1–2
Nicorandil (used for angina pectoris, also has nitrate-like actions—see table 30)	10 mg BD	20–80 mg	2
Pinacidil (sustained-release)	12.5 mg BD	25–150 mg (200 mg) (preliminary)	2
Diazoxide	Intravenous bolus injection: 1–3 mg/kg (max: 150 mg) Bolus repeated every 5–15 minutes as needed		

BD, twice a day.

TABLE 33

Dosing Recommendations for Serotonin Receptor Agents			
Drugs	*Starting adult daily dose*	*Daily dose range*	*Frequency of dose/day*
Ketanserin (antagonizes serotonin S2 receptor in peripheral vasculature and α1 adrenergic receptors)	20 mg BD	40–80 mg	2
	Intravenous dose for hypertensive emergencies: (a) 5–30 mg infused at 3 mg/min, or (b) repeated injections of 5 mg every few minutes, or (c) 5 mg bolus doses every 10 minutes followed by infusion of 5–10 mg/hour		
Urapidil (stimulates central serotonin 1A receptors and antagonizes peripheral α1 adrenergic receptors)	30 mg OD or BD	30–180 mg (above 30 mg, use BD)	1–2
	Intravenous dose for hypertensive emergencies: 25 mg over 20 seconds. May repeat 25 mg after 5 minutes and 50 mg after another 5 minutes, then continuous infusion 9–30 mg/hour		

OD, once a day; BD, twice a day.

TABLE 34

Dosing Recommendations for Dopamine Agonists (peripheral D1 receptor)			
Drugs	*Starting adult daily dose*	*Daily dose range*	*Frequency of dose/day*
Fenoldopam mesylate (severe hypertension)	Intravenous use: 0.03–0.1 μg/kg/min	Usual effective dose: 0.1–1.6 μg/kg/min	Increase or decrease by 0.05–0.1 μg/kg/min no sooner than every 15 minutes, use up to 48 hours

TABLE 35

Dosing Recommendations for Combinations with Two Diuretics

Drugs (Dose in mg)	*Starting adult daily dose*	*Daily dose range*	*Frequency of dose/day*
Altizide/spironolactone (15/25)	1/2–1 tab	1/2–2 mg	1
Bemetizide/triamterene (10/20, 25/50)	10/20 mg	10/20–25/50 mg	1
Butizide/spironolactone (2.5/25)	2 tab	2–4 tab (max: 8 tab/day)	1
Cyclopenthiazide/amiloride (0.25/2.5)	1 tab	1–2 mg	1
Epitizide/triamterene (4/50)	1 mg tab	1–4 mg	1
HCTZ/amiloride (50/5)	1/2 tab	1/2–2 tab	1
HCTZ/triamterene (25/37.5)	1 cap	1–2 cap	1–2
HCTZ/triamterene (50/75)	1/2 tab	1/2–1 tab	1

(continued)

Table 35 *(continued)*

Drugs (Dose in mg)	*Starting adult daily dose*	*Daily dose range*	*Frequency of dose/day*
(25/37.5)	1 tab	1–2 tab	1
HCTZ/spironolactone (25/25) (50/50)	 1 tab 1 tab	 1–4 tab 1–2 tab	 1–2 1–2

HCTZ, hydrochlorothiazide; tab, tablet(s); cap, capsule(s).

TABLE 36

Dosing Recommendations for Combinations of β-blockers with Diuretics

Drugs (Dose in mg)	*Starting adult daily dose*	*Daily dose range*	*Frequency of dose/day*
Atenolol/chlorthalidone (50/25, 100/25)	50/25 mg	Start 1 tab Increase to 100/25 mg	1 1
Bisoprolol/HCTZ (2.5/6.25, 5/6.25, 10/6.25)	2.5/6.25 mg	2.5/6.25–20/12.5 mg	1
Mepindolol/HCTZ (5/12.5)	1 tab	1–3 tab	1
Metoprolol/HCTZ (50/25, 100/25, 100/50)	50/25 mg 100/25 mg 100/50 mg	1 or 2 tab 1 or 2 tab 1 tab	1–2 1–2 1

(continued)

Table 36 *(continued)*

Drugs (Dose in mg)	*Starting adult daily dose*	*Daily dose range*	*Frequency of dose/day*
Nadolol/bendroflumethazide (40/5, 80/5)	40/5 mg	Start 1 tab Increase to 80/5 mg	1 1
Pindolol/clopamide (10/5)	1/2–1 tab	Start 1/2 or 1 tab Increase to BD (maximum TID)	1
Propranolol/HCTZ (40/25, 80/25)	40/25 mg	Start BD Increase to 80/25 mg BD	2
Propranolol (extended-release)/HCTZ (80/50, 120/50, 160/50)	80/50 mg 120/50 mg 160/50 mg	Start OD Increase OD Increase OD	1 1 1
Timolol/HCTZ (10/25)	1 tab	1 tab BD or 2 tab OD	1–2

HCTZ, hydrochlorothiazide; tab, tablet(s); OD, once a day; BD, twice a day; TID, thrice a day.

TABLE 37

Dosing Recommendations for Combinations of Angiotensin Converting Enzyme Inhibitors with Diuretics

Drugs (Dose in mg)	*Starting adult daily dose (mg)*	*Daily dose range (mg)*	*Frequency of dose/day*
Benazepril/HCTZ (5/6.25, 10/12.5, 20/12.5, 20/25)	5/6.25 10/12.5	Start with 5/6.25 Titrate to maximum of each: benazepril 80, HCTZ 50	1 1
Captopril/HCTZ (25/15, 25/25, 50/15, 50/25)	25/15	Start OD Titrate to maximum 150/50	1 1 or 2
Enalapril/HCTZ (5/12.5, 10/25)	5/12.5 10/25	Start OD Titrate to maximum 20/50	1 1 (or 2)
Fosinopril/HCTZ (10/12.5, 20/12.5)	10/12.5	Start with 10/12.5 Maximum dose: fosinopril 80, HCTZ 50	1
Lisinopril/HCTZ (10/12.5, 20/12.5, 20/25)	10/12.5 20/12.5	Start OD Titrate to maximum 80/50	1 1
Moexipril/HCTZ (7.5/12.5, 15/12.5, 15/25)	7.5/12.5	3.75/6.25 (1/2 tab) or 7.5/12.5 to start, titrate to maximum 30/50	1 (or 2)
Quinapril/HCTZ (10/12.5, 20/12.5, 20/25)	10/12.5	Start with 20/12.5, titrate to maximum dose: quinapril 80, HCTZ 50	1 (or 2)

HCTZ, hydrochlorothiazide; OD, once a day.

TABLE 38

Dosing Recommendations for Combinations of Angiotensin II Receptor Blockers with Diuretics

Drugs (Dose in mg)	*Starting adult daily dose (mg)*	*Daily dose range (mg)*	*Frequency of dose/day*
Candesartan/HCTZ (16/12.5, 32/12.5, 32/25)	16/12.5	16/12.5–32/25	1
Azilsartan/chlorthalidine (40/12.5, 40/25)	40/12.5	40/12.5–40/25	1
Eprosartan/HCTZ (600/12.5, 600/25)	600/12.5	600/12.5–600/25	1
Irbesartan/HCTZ (150/12.5, 300/12.5, 300/25)	150/12.5	150/12.5–300/25	1
Losartan/HCTZ (50/12.5, 100/12.5, 100/25)	50/12.5	50/12.5–100/25	1
Olmesartan/HCTZ (20/12.5, 40/12.5, 40/25)	20/12.5	20/12.5–40/25	1
Telmisartan/HCTZ (40/12.5, 80/12.5, 80/25)	40/12.5	40/12.5–80/25	1
Valsartan/HCTZ (80/12.5, 160/12.5)	80/12.5 or 160/12.5	80/12.5–320/25	1

HCTZ, hydrochlorothiazide.

TABLE 39

Dosing Recommendations for Combinations of Direct Renin Inhibitors with Other Antihypertensives			
Drugs (Dose in mg)	*Starting adult daily dose (mg)*	*Daily dose range (mg)*	*Frequency of dose/day*
Aliskiren/amlodipine (150/5, 150/10, 300/5, 300/10)	150/5	150/5–300/10	1
Aliskiren/HCTZ (150/12.5, 150/25, 300/12.5, 300/25)	150/12.5	150/12.5–300/25	1
Aliskiren/valsartan (150/160, 300/320)	150/160	150/160–300/320	1

HCTZ, hydrochlorothiazide.

TABLE 40

Dosing Recommendations for Combinations of Calcium Channel Blockers and Angiotensin Converting Enzymes Inhibitors			
Drugs (Dose in mg)	*Starting adult daily dose*	*Daily dose range*	*Frequency of dose/day*
Amlodipine/benazepril (2.5/10, 5/10, 5/20, 5/40, 10/20, 10/40)	2.5/10 mg	2.5/10–10/40 mg	1
Diltiazem/enalapril (180/5)	1 tab	1–2 tab	1

(continued)

Table 40 *(continued)*

Drugs (Dose in mg)	*Starting adult daily dose*	*Daily dose range*	*Frequency of dose/day*
Felodipine extended-release/enalapril (2.5/5, 5/5)	2.5/5 mg or 5/5 mg	Increase to10/10 mg	1 1
Verapamil extended-release/trandolapril (180/2, 240/1, 240/2, 240/4)	180/2 mg or 240/1 mg	Increase to maximum for each: Verapmail 480 mg, trandolapril 4 mg	1–2

tab, tablet(s).

TABLE 41

Dosing Recommendations for Combinations of Calcium Channel Blockers and Angiotensin II Receptor Blockers

Drugs (Dose in mg)	*Starting adult daily dose (mg)*	*Daily dose range (mg)*	*Frequency of dose/day*
Amlodipine/olmesartan (5/20, 5/40, 10/20, 10/40)	5/20	5/20–10/40	1
Amlodipine/telmisartan (5/40, 5/80, 10/40, 10/80)	5/40	5/40–10/80	1
Amlodipine/valsartan (5/160, 5/320, 10/160, 10/320)	5/160	5/160–10/320	1

TABLE 42

Dosing Recommendations for Combinations of Rauwolfia Alkaloids and Other Antihypertensive Agents

Drugs (Dose in mg)	*Starting adult daily dose*	*Daily dose range*	*Frequency of dose/day*
Chlorthalidone/reserpine			
(50/0.25)	50/0.25 mg	1 tab	1
(25/0.125)	25/0.125 mg	1–2 tab	1
Chlorothiazide/reserpine			
(250/0.125)	1 tab OD	1 or 2 tab OD or BD	1–2
(500/0.125)	1 tab OD	1 tab OD or BD (avoid chronic reserpine dose above 0.25 mg/day)	1–2
Hydrochlorothiazide/reserpine			
(25/0.125)	1 tab	1–2 tab	1
(50/0.125)	1 tab	1 tab	1
Methyclothiazide/deserpidine			
(5/0.25)	1/2 or 1 tab	1/2 to 2 tab	1
(5/0.5)	1/2 or 1 tab	1/2 to 2 tab	1
Polythiazide and reserpine	1/2 or 1 tab	1/2–2 tab (avoid chronic reserpine dose above 0.25 mg/day)	1

OD, once a day; BD, twice a day; tab, tablet(s).

TABLE 43

Dosing Recommendations for Other Combinations of Two Antihypertensive Drugs

Drugs (Dose in mg)	*Starting adult daily dose*	*Daily dose range*	*Frequency of dose/day*
Clonidine/chlorthalidone (0.1/15, 0.2/15, 0.3/15)	0.1/15 mg OD	0.1/15 mg OD to maximum 0.3/15 mg BD	1–2
Guanethidine/HCTZ (10/25)	1 tab	1–2 tab (average dose for guanethidine is 25–50 mg/day and HCTZ dose usual maximum 50 mg/day)	1–2
Hydralazine/HCTZ (25/25, 50/50, 100/50)	25/25 mg BD	Increase to maximum for each: hydralazine 300 mg, HCTZ 50 mg (100 mg)	2
Methyldopa/HCTZ (250/15, 500/30, 500/50)	250/15 mg BD (or TID)	Increase to maximum HCTZ dose of 50 mg	2–3
Prazosin/polythiazide (1/0.5, 2/0.5, 5/0.5)	1/0.5 mg BD (or TID)	Increase daily dose to maximum: prazosin 20 mg and/or polythiazide 4 mg	2–3

HCTZ, hydrochlorothiazide; OD, once a day; BD, twice a day; TID, thrice a day; tab, tablet(s).

TABLE 44

Dosing Recommendations for Combinations of Three Antihypertensive Drugs

Drugs (Dose in mg)	*Starting adult daily dose*	*Daily dose range*	*Frequency of dose/day*
Amlodipine and olmesartan and HCTZ 5/20/12.5, 5/40/12.5, 5/40/25, 10/40/12.5, 10/40/25	5/20/12.5 mg	5/20/12.5 mg, titrate to maximum 10/40/25 mg	1
Amlodipine and valsartan and HCTZ 5/160/12.5, 10/160/12.5, 5/160/25, 10/160/25, 10/320/25	5/160/12.5 mg	5/160/12.5 mg, titrate to maximum 10/320/25 mg	1
Aliskiren and amlodipine and HCTZ 150/5/12.5, 300/5/12.5, 300/5/25, 300/10/12.5, 300/10/25	150/5/12.5 mg	150/5/12.5 mg, titrate to maxium 300/10/25 mg	1
Hydralazine and HCTZ and reserpine 25/15/0.1	1 tab	1 or 2 tab (avoid chronic reserpine dose above 0.25 mg/day)	1

HCTZ, hydrochlorothiazide; tab, tablet(s).

TABLE 45

Dosing Recommendations for Combinations which Include Antihypertensive Drugs

Drugs (Dose in mg)	*Starting adult daily dose*	*Daily dose range*	*Frequency of dose/day*
Amlodipine and atorvastatin 2.5/10, 2.5/20, 2.5/40, 5/10, 5/20, 5/40, 5/80, 10/10, 10/20, 10/40, 10/80	2.5/10 or 5/10 mg	2.5/10 mg, increase to maximum 10/80 mg	1
Hydralazine and isosorbide dinitrate 37.5/20	37.5/20 mg TID	1/2 tab up to 2 tab TID	3

TID, thrice a day; tab, tablet(s).

TABLE 46

Diuretics—Side Effects and Cautions

Drugs	*Frequent or severe side effects*	*Caution*
Thiazides (multiple) chlorthalidone	Decreases serum K^+, Mg^{2+}, Na^+, HDL. Increases glucose, serum uric acid, Ca^{2+}, triglycerides, LDL. Pancreatitis, erectile dysfunction.	Digitalis and hypokalemia (arrhythmias), gout, renal insufficiency (may not be effective at GFR <30 mL/min), pancreatitis, hyponatremia, lithium (decreased excretion), sulfa allergy*
Loop-furosemide, ethacrynic acid, bumetanide, torsemide	Decreases serum K^+, Mg^{2+}, Ca^{2+}, HDL. Increases glucose, serum uric acid, triglycerides, LDL. Volume depletion, metabolic alkalosis	Digitalis and hypokalemia (arrhythmias), gout, excessive diuresis, ototoxicity (ethacrynic acid worse than furosemide, torsemide and bumetanide), hyponatremia, lithium (decreased excretion), effect blunted by NSAIDs, sulfa allergy*

(continued)

Table 46 *(continued)*

Drugs	*Frequent or severe side effects*	*Caution*
Potassium sparing diuretics spironolactone, eplerenone	Increases serum K^+, gynecomastia (men), hair growth (women) (less with eplerenone). Decreases HDL, triglycerides (modest effect). Libido, gastrointestinal symptoms (gastric hemorrhage-spironolactone), impotence, menstrual irregularities, agranulocytosis, tumorigenic in rats	Hyperkalemia, CKD (GFR <50 mL/min), use with CYP3A4 inhibitors (multiple drugs), ACEIs, ARBs, renin inhibitors, other K^+ sparing diuretics, lithium, NSAIDs, type 2 diabetes mellitus. Safety in pregnancy (teratogenic in animal studies), peptic ulcer disease (upper gastrointestinal bleeding)
Trimaterene	Increases serum K^+, nausea	Nephrolithiasis, hyperkalemia, CKD (GFR <50 mL/min), ACEIs, ARBs, renin inhibitors, other K^+ sparing diuretics, lithium, NSAIDs, cyclosporine, black licorice
Amiloride	Increases serum K^+	Hyperkalemia, CKD (GFR <50 mL/min), ACEIs, ARBs, renin inhibitors, other K^+ sparing diuretics, lithium, NSAIDs, cyclosporine, tacrolimus, black licorice

*If sulfa allergy is present, may use: amiloride, eplerenone, ethacrynic acid, spironolactone, triamterene.

NSAIDs, nonsteroidal anti-inflammatory drugs; GFR, glomerular filtration rate; ACEIs, angiotensin converting enzyme inhibitors; HDL, high-density lipoproteins; LDL, low-density lipoproteins; ARBs, angiotensin II receptor blockers; CKD, chronic kidney disease; K^+, potassium; Mg^{2+}, magnesium; Na^+, sodium; Ca^{2+}, calcium.

TABLE 47

Central Sympatholytic Agents and Central Depleting Agents of Catecholamines and 5-Hydroxytryptophan—Side Effects and Cautions

Drugs	*Frequent or severe side effects*	*Caution*
Central sympatholytic action (α2 adrenergic agonists)		
Clonidine*	Dry mouth, somnolence, sedation, drowsiness, fatigue, dizziness, constipation, AV block, lipid (neutral) with patches—contact dermatitis (5–47%), erythema (26%)	Rebound hypertension and arrythmias with abrupt withdrawal, use with other depressants
Guanabenz Guanfacine	Dry mouth, somnolence, sedation, weakness, dizziness, arrhythmias, orthostatic hypotension, impotence, small decrease in total cholesterol and triglycerides, similar to clonidine, reduction in HDL with guanabenz	Rebound hypertension with abrupt withdrawal
Methyldopa	Drowsiness, fatigue, dizziness, dry mouth, fever, edema, hepatotoxicity, bone marrow depression, red cell aplasia, abnormal cardiac conduction, parkinsonism, impotence, reduces HDL	Hepatic disease, hemolytic anemia (Coombs' positive), fever
Central depleting agents of catecholamines and 5-hydroxytryptophan (rauwolfia alkaloids)		
Reserpine	Depression (6–30%), nasal congestion, lethargy, hematemesis, nausea, vomiting, dry mouth, atrial fibrillation, arrhythmias, orthostatic hypotension, wheezing	Mental depression, peptic ulcer disease, asthma

*Except clonidine, centrally acting sympatholytic drugs are not used for treatment of hypertension.

AV, atrioventricular; HDL, high-density lipoproteins.

TABLE 48

Central Imidazoline Receptor Agonists—Side Effects and Cautions		
Drugs	*Frequent or severe side effects*	*Caution*
Moxonidine Rilmenidine	Dry mouth, somnolence, headache, dizziness, vertigo, edema, nervousness, diuresis	Severe coronary insufficiency, SA and AV conduction defects, CKD (especially serum creatinine >1.8 mg/dL and GFR <30 mL/min), angioedema, claudication, Raynaud's syndrome, Parkinson's disease, depression

SA, sinoatrio; AV, atrioventricular; CKD, chronic kidney disease; GFR, glomerular filtration rate.

TABLE 49

Ganglionic and Postganglionic Blockers—Side Effects and Cautions		
Drugs	*Frequent or severe side effects*	*Caution*
Ganglionic blockers*		
Trimethaphan (intravenous) Mecamylamine (oral tablet)	Intravenous use emergencies (e.g., acute aortic dissection), postural hypotension, syncope, paralytic ileus, constipation, nausea, vomiting, dry mouth, angina pectoris, urinary retention, blurred vision (mydriasis, diplopia), respiratory depression (fatal respiratory arrest with dose >5 mg/min), asthma, impaired cognition, weakness	CAD, heart failure, CKD, cerebral vascular disease, chronic lung disease, bladder outlet obstruction, gastrointestinal obstruction, abrupt withdrawal (rebound hypertension)
Postganglionic blockers*		
Guanethidine	Postural hypotension, dizziness, weakness, drowsiness, fluid retention, diarrhea, leg cramps, inhibition of ejaculation, impotence, blurred vision, nasal congestion	Heart failure, CKD, CAD, bradycardia, cerebral vascular disease, peptic ulcer disease, anesthesia (stop guanethidine 48–72 hours before), asthma, patients with pheochromocytoma

(continued)

Table 49 *(continued)*

Drugs	*Frequent or severe side effects*	*Caution*
Bethanidine	As with guanethidine	As with guanethidine
Debrisoquine	As with guanethidine	As with guanethidine
Guanadrel	Shorter-acting than guanethidine	As with guanethidine
MAOIs	Rarely used. CNS disturbances—dizziness, headache, blurred vision, vertigo, insomnia. Postural hypotension, vomiting, muscle twitching, fever	Foods with tryamine produce increased blood pressure (extensive list includes most cheese, alcohol, chocolate, and foods that are pickled, aged, fermented, or smoked), never use with methyldopa

*Presently ganglionic and postganglionic blockers are seldom used for long-term treatment of hypertension because of their side effects.

MAOIs, monoamine oxidase inhibitors; CNS, central nervous system; CKD, chronic kidney disease; CAD, coronary artery disease.

TABLE 50

Lipid Solubility of β-adrenergic Receptors			
Low lipid solubillity/hydrophilic			
Atenolol	Labetalol*	Carteolol*	Nadolol
Esmolol	Sotalol		
Lipophilic			
Acebutolol*	Betaxolol	Bisoprolol	Bucindolol*
Carvedilol	Celiprolol, metoprolol	Penbutolol*	Pindolol*
Propranolol	Timolol		

*Intrinsic sympathomimetic activity.

TABLE 51

Adrenergic Receptor Blockers—Side Effects and Cautions		
Drugs	*Frequent or severe side effects*	*Caution*
β-blockers		
Nonselective (β1 and β2 receptor antagonists: tend to be lipophilic and metabolized by the liver)		
Nadolol	Similar to propranolol but hydrophilic and low CNS concentration with less CNS side effects, longer half-life	Similar to propranolol, acute kidney injury, CKD
Carteolol, penbutolol, pindolol and other nonselective β-blockers with ISA	Similar to propranolol but has ISA, less bradycardia, less effect on lipids, may not be cardioprotective after MI	Similar to propranolol, carteolol—renal insufficiency, penbutolol—hepatic dysfunction
Propranolol, timolol, and other nonselective β-blockers without ISA	Bradycardia, anorexia, fatigue, sleep disturbance, dizziness, depression, first-degree AV block, bronchospasm, hypoglycemia, hypotension, reduces exercise tolerance, raises or does not affect total cholesterol and LDL, lowers HDL, increases triglycerides, cardioprotective after MI, timolol—less CNS effect (propranolol and timolol are lipophilic and CNS concentrations are higher compared to hydrophilic β-blockers)	Heart failure, second- or third-degree heart block, ventricular dysrhythmias, COPD, asthma, peripheral vascular disease, insulin dependent diabetics (may mask hypoglycemia), hyperkalemia (K^+ translocation into cells is mediated in part by β2 receptors), avoid abrupt withdrawal especially in CAD
Cardioselective (β1 selective: tend to be hydrophilic and removed by the kidneys)		
Acebutolol and other cardioselective β-blockers with ISA	Relatively selective β1 blocker once a day, similar to atenolol but has ISA, less bradycardia, overall fewer side effects than atenolol, less effect on lipids, may not be cardioprotective after MI	Similar to atenolol, avoid abrupt withdrawal especially in CAD

(continued)

Table 51 *(continued)*

Drugs	*Frequent or severe side effects*	*Caution*
Atenolol, metoprol, betaxolol, bisoprolol, and other cardio-selective β-blockers without ISA	Relatively selective β1 blocker at lower doses. Bradycardia, somnolence, dizziness, depression (less than propranolol), cold extremities, bronchospasm, hypoglycemia, hypotension, reduced exercise tolerance. Raises or does not affect total cholesterol and LDL, lowers HDL, increases triglycerides. Cardioprotective after MI. Atenolol preferred in hepatic insufficiency. Metoprolol preferred in CKD	COPD, asthma, peripheral vascular disease (at low doses, less effect on bronchial and vascular smooth muscle than nonselective β-blockers), heart failure, second- or third-degree heart block, ventricular dysrhythmias, insulin dependent diabetics (may mask hypoglycemia), hyperkalemia, atenolol with GFR <35 mL/min. Avoid abrupt withdrawal, especially in CAD
β-blockers with vasodilating properties		
Labetalol (with ISA), carvedilol, and other β-blockers with vasodilating properties	From nonselective β-blockade: dizziness, somnolence, GI (nausea 14%), hypotension, postural hypotension (5%), wheezing, bronchospasm. From α-blockade: nasal stuffiness, sexual dysfunction, urinary retention, lipid neutral, may not be cardioprotective after MI	Similar to propranolol. Concommitant diuretics and high doses produce dizziness. Heart failure, second- or third-degree heart block, COPD, asthma, insulin dependent diabetics (may mask hypoglycemia), hepatic impairment, hyperkalemia. Peripheral vascular disease. Avoid abrupt withdrawal, especially in CAD
Nebivolol	Similar to labetalol, increases triglycerides, decreases HDL	Similar to labetalol, peripheral vascular disease. Avoid concomitant use with other β-blockers, verapamil, diltiazem, clonidine. Avoid use with CYP2D6 inhibitors which raise nebivolol levels)Strong inhibitors: fluoxetine, paroxetine (SSRIs), bupropion (non-SSRI antidepressant), quinidine (class I antiarrhythmic agent), cinacalcet (calcimimetic), ritonavir (antiretroviral). Moderate inhibitors: sertraline (SSRI), duloxetine, terbinafine, and others)

(continued)

Table 51 *(continued)*

Drugs	*Frequent or severe side effects*	*Caution*
α-adrenergic receptor antagaonists		
Prazosin, terazosin, doxazosin, and other α-blockers	"1st dose phenomenon" (syncope within 30–90 minutes of first dose due to excessive postural hypotension), postural hypotension, dizziness, asthenia, somnolence, palpitations, tachycardia, fluid retention. Nasal congestion, vasculitis, intraoperative floppy iris syndrome. Reduces total cholesterol, triglycerides, LDL and elevates HDL	Avoid use as first-line treatment and single agent treatment (excessive risk of heart failure shown with doxazosin (ALLHAT clinical trial). 1st dose syncope, increased potential for hypotension when used with other antihypertensives (β-blockers and diuretics). Cataract surgery (intraoperative floppy iris syndrome, especially with α-blockers used for BPH (tamsulosin, silodosin))
Phentolamine, phenoxybenzamine	Similar to prazosin; postural hypotension, tachycardia (used in pheochromocytoma or clonidine rebound)	Cerebral or coronary atherosclerosis, angina pectoris, MI, exercise, volume depletion

ISA, intrinsic sympathomimetic activity; CNS, central nervous system; AV, atrioventricular; HDL, high-density lipoproteins; LDL, low-density lipoproteins; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; ALLHAT, antihypertensive and lipid-lowering treatment to prevent heart attack trial; SSRIs, selective serotonin reuptake inhibitors; CKD, chronic kidney disease; BPH, benign prostatic hypertrophy; MI, myocardial infarction; CAD, coronary artery disease; GI, gastrointestinal.

TABLE 52

Direct Vasodilators—Side Effects and Cautions		
Drugs	*Frequent or severe side effects*	*Caution*
Oral acting		
Hydralazine and other direct vasodilators	Headaches, tachycardia, palpitations, angina pectoris, anorexia, nausea, hypotension (intravenous), SLE, fluid retention, peripheral neuritis, hepatitis. No effect on triglycerides. May increase HDL and decrease LDL	Contraindicated in aortic dissection Caution: history of CAD, cerebrovascular disease, SLE, systemic hypertension reported in pulmonary hypertension
Minoxidil	Tachycardia, palpitations, edema, hypertrichosis, hirsutism, hypotension, may be associated with pericardial effusion, pericardial tamponade (especially in CKD), thrombocytopenia, leukopenia. Effect on lipids same as hydralazine	Avoid: pheochromocytoma, use with guanethidine Caution: CAD, cerebrovascular disease, CHF, pericarditis, CKD hemodialysis
Intravenous use for hypertensive emergencies (vasodilators)		
Diazoxide	Hypotension, palpitaions, tachycardia, MI, dizziness, weakness, salt and water retention, hyperglycemia, ketoacidosis, nonketotic hyperosmolar coma, extrapyramidal signs, increased uric acid, hypertrichosis	Marked hypotension with other antihypertensives, concomitant use with coumarin anticoagulants (warfarin and others—increased risk of bleeding), CAD, gout, CKD
Sodium nitroprusside	Hypotension, nausea, vomiting, dizziness, somnolence, headache, palpitations, tachycardia	Cyanide toxicity (can be lethal)—monitor acidosis, thiocyanate toxicity, CHF with decreased peripheral vascular resisitance, rebound hypertension after cessation of drug, hypothyroidism

LDL, low-density lipoprotein; HDL, high-density lipoprotein; SLE, systemic lupus erythematosus; CKD, chronic kidney disease; CAD, coronary artery disease; CHF, congestive heart failure; MI, myocardial infarction.

TABLE 53

Inhibitors of Renin-angiotensin System*—Side Effects and Cautions		
Drugs	*Frequent or severe side effects*	*Caution*
ACEIs		
Captopril	Cough, bronchospasm, acute renal failure with bilateral renal artery stenosis, or unilateral renal artery stenosis in solitary kidney, worsening renal insufficiency, hypotension if volume depleted, dysgeusia, rash, SLE-like syndrome, bone marrow depression, hyperkalemia, angioedema, cholestatic jaundice. Effect on lipids: some studies, no effect; others, increased HDL and lowered LDL and triglycerides.	Avoid: Pregnancy, discontinue as soon as possible (causes fetal injury and increased fetal mortality), angioedema history Caution: Bilateral renal artery stenosis, volume depletion or severe CHF, CKD-reduce dose for GFR <50 mL/min, CKD and/or, collagen vascular disease (may lead to blood dyscrasia), hemodialysis with high-flux membranes [PAN (polyacrylonitrile)] may produce anaphylactoid reaction, aortic stenosis
Benazepril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril, and other ACEIs	Side effects are similar to captopril but may be less as enalapril and others lack S-H group. Enalapril: pancreatitis (half cases due to enalapril; others due to captopril, lisinopril: lisinopril is lysine analogue of enalapril), otherwise similar to captopril	Same as captopril, creatinine clearance <30–40 mL/min, may need to decrease dose
ARBs		
Azilsartan, candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan	Headache, dizziness, asthenia, fatigue, dysgeusia, acute renal failure with bilateral renal artery stenosis, or unilateral renal artery stenosis in solitary kidney, worsening renal insufficiency, hypotension if volume depleted, cough and	Avoid: pregnancy, discontinue as soon as possible (causes fetal injury and increased fetal mortality) May increase serum K^+, BUN, creatinine (especially in CKD, bilateral renal artery stenosis), orthostatic hypotension if

(continued)

Table 53 *(continued)*

Drugs	*Frequent or severe side effects*	*Caution*
	angioedema are significantly less than ACEIs. Losartan uniquely lowers serum uric acid. Effect on lipids: some studies, no effect; others, increases HDL and lowers LDL and triglycerides	volume depleted, severe CHF, angioedema history. Losartan use with rifampin or fluconazole
DRI		
Aliskiren	Dizziness, headache, hyperkalemia (especially in CKD), hypotension (especially with volume depletion or other anti-hypertensive drugs), increased BUN and creatinine (minor), acute renal failure (similar to ACEIs and ARBs), rash, diarrhea, angioedema (rare), less cough than ACEIs	Avoid: pregnancy, discontinue as soon as possible (causes fetal injury and increased fetal mortality); avoid with ACEIs, cyclosporine, itraconazole Caution: volume depletion

*Renin-angiotensin inhibitors are valuable armamentarium for management of hypertension. Sometimes combination of ACEIs and ARBs are also used. Addition of direct renin inhibitors may produce undesirable side effects.

SLE, systemic lupus erythematosus; CKD, chronic kidney disease; LDL, low-density lipoproteins; HDL, high-density lipoproteins; BUN, blood urea nitrogen; ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; GFR, glomerular filtration rate; CHF, congestive heart failure; DRI, direct renin inhibitor.

TABLE 54

Calcium Channel Blockers*—Side Effects and Cautions		
Drugs	*Frequent or severe side effects*	*Caution*
Benzothiazepines (block L-type channels)		
Diltiazem	Bradyarrhthmia, cardiac conduction defect, hypotension, gingival hyperplasia (21%), edema (4.6–8%), dizziness, headache, asthenia, agranulocytosis, SLE, cognitive decline, acute renal failure (rare). Lipids (neutral) or may increase HDL and decrease triglycerides	General comments: (i) cimetidine (and drugs that decrease hepatic blood flow) may increase drug levels, (ii) CCBs may increase digoxin levels. Contraindicated: acute MI with pulmonary congestion, atrial fibrillation or flutter with accessory bypass tract (Wolff-Parkinsons-White), cardiogenic shock, second or third degree heart block, ventricular tachycardia, aortic stenosis. Caution: CKD, use with β-blockers, impaired hepatic function, cyclosporine (levels increased), (many drug-drug interactions) (grape-fruit juice does not increase plasma levels of diltiazem)
Dihydropyridines** (block L-type channels)		
Dihydropyridines: amlodipine, felodipine, isradipine, nicardipine, nifedipine, nisoldipine and others	Peripheral edema (7–29%), reflex tachycardia (most likely with 1st generation nifedipine), palpitations, hypotension (5%, especially with β-blockers), dizziness (4–10%), flushing (4%), headache (19–23%), increased angina pectoris, acute	Contraindications: cardiogenic shock, flecainide (increased flecainide side effects), concomitant use of strong CYP3A4 inducers (carbamazepine, phenytoin, oxcarbazepine, barbiturates, St John's wort, rifampicin, rifabutin, efavirenz, nevirapine,

(continued)

Table 54 *(continued)*

Drugs	*Frequent or severe side effects*	*Caution*
Note: side effects are mainly due to powerful vasodilation. Short-acting nifedipine has the highest frequency of side effects, which are less with sustained-release nifedipine and newer longer-acting dihydropyridines. In general, the minimal influence on cardiac conduction and decreased heart contractility are less in 2nd and 3rd generation dihydropyridines compared to 1st generation	MI, CHF (tight aortic stenosis, with β-blockers), asthenia (4–12%), nausea (10%), gastrointestinal obstruction (bezoar), gingival hyperplasia [especially nifedipine, nicardipine, felodipine (40%)], increased BUN and creatinine (in CKD), Parkinson-like syndrome, tremor (8%), agranulocytosis (rare, fatal cases). Nicardipine may cross the blood-brain barrier and produce cerebral vasodilation. Lipids (neutral) or increase HDL	pioglitazone, troglitazone, glucocorticoids, modafinil, and others). Caution: aortic stenosis, heart failure, surgery with high dose fentanyl anesthesia, abrupt withdrawal (may lead to rebound hypertension), hepatic impairment. Some drug-drug interactions: cyclosporine levels increased with amlodipine, felodipine, and nicardipine, but not with isradipine or nifedipine, grape-fruit juice increases plasma levels
Nimodipine USFDA indication: subarachnoid hemorrhage, from ruptured intracranial berry aneurysms (Hunt and Hess grades I–V)	Greater effect to dilate cerebral vessels compared to coronary or peripheral vessels (crosses blood-brain barrier), excess bleeding during elective heart valve surgery, rarely thrombocytopenia, hypotension, similar to nifedipine, both tachycardia and bradycardia	Warning: do not give intravenously or parenterally (deaths reported). Do not use perioperatively Caution: hepatic impairment, similar to nifedipine
Phenylalkylamines (block L-type channels)		
Verapamil	Negative inotropic effect, CHF, decreased SA node discharge and AV conduction, bradyarrhythmias, ventricular tachycardia, hypotension, cardiogenic shock, atrial fibrillation (especially with paroxysmal atrial fibrillation), dizziness (3–5.9%), headache	Contraindications: atrial fibrillation or flutter with accessory bypass tract (Wolff-Parkinsons-White), left ventricular dysfuntion (left venricular ejection fraction <30%), CHF; 2nd or 3rd degrees heart block, sick sinus syndrome

(continued)

Table 54 *(continued)*

Drugs	*Frequent or severe side effects*	*Caution*
	(2.2–12.1%), constipation (8.8–42%), nausea, gingival hyperplasia (20%), dyspnea, cough. Lipids (neutral) or increase HDL	Caution: hepatic impairment, abrupt withdrawal—increased angina pectoris in some, hypertrophic cardiomyopathy. Drug-drug interactions: quinidine produces hypotension and ventricular arrhythmias, decreased clearance of digoxin, β-blockers—left ventricular dysfunction and possible heart failure, cyclosporine levels increased (and many others). Grape-fruit juice increases plasma levels
Diarylaminopropylamine ester		
Bepridil (blocks slow calcium channel and fast sodium channel)	Proarrhythmic, including ventricular tachycardia (torsade de pointe) or fibrillation, prolongation QTc interval, death, lengthening of QRS, decreased left ventricular function, flushing, gingival hyperplasia, nausea, nervousness, dizziness (15%), asthenia (10%), headache (7%), tremor	Contraindications: heart block, sick sinus, serious ventricular arrhythmias, QT prolongation, uncompensated cardiac insufficiency Caution: CHF, MI, hepatic and renal impairment, hypokalemia, sinus bradycardia, left bundle branch block

*CCBs are important antihypertensive drugs and are frequently used in clinical practice. These agents are also used for treatment of angina. Nondihydropyridine CCBs are also used for treatment of supraventricular tachycardias. In general, CCBs are contraindicated in patients with SHF.
**Dihydropyridines which cross the blood-brain barrier: Amlodipine, azelnidipine, clevidipine, clinidipine, felodipine, isradipine, nicardipine, nifedipine, nimodipine.

CCBs, calcium channel blockers; SLE, systemic lupus erythematosus; HDL, high-density lipoproteins; BUN, blood urea nitrogen; CKD, chronic kidney disease; SA, sinoatrial; AV, atrioventricular; CHF congestive heart failure; SHF, systolic heart failure; MI, myocardial infarction.

TABLE 55

Effects of Various Calcium Channel Blockers on Selected Cardiac and Vascular Functions

Drugs	*Coronary vasodilation*	*Suppression*		*Negative inotropic effect*	*Vascular vasodilation*	*Side effects*	*Frequency of dose/day*
		SA node	*AV node*				
Dihydropyridines							
Nifedipine*	5	0–1	0	1	3	3	1
Nimodipine*	5	0–1	0	0	3 (cerebral)	3	6
Nicardipine**	5	0–1	0	0	3	3	3
Nisoldipine**	5	0–1	0	0	3	3	1
Isradipine**	5	0	0	0	3	3	2
Felodipine**	5	0	0	0	3	3	1
Amlodipine***	5	0	0	0–1	3	3	1
Diltiazem*	3	5	4	2	2	1	1
Verapamil*	4	5	5	4	2	2	1

*, first generation; **, second generation; ***, third generation; numbers 0–5 indicate relative values of the effect: e.g., 0–1 = least effect; 4–5 = greatest effect.

TABLE 56

Nitrates—Side Effects and Caution		
Drugs	*Frequent or severe side effects*	*Caution*
Nitroglycerin (intravenous)*	Headache (>60%), hypotension and sever orthostatic hypotension, increased angina pectoris, paradoxical bradyarrhythmia, fatal ventricular tachycardia (torsades de pointes)	Contraindications: concomitant use of phosphodiesterase-5 inhibitors (sildenafil, tadalafil, vardenafil), other nitrates, constrictive pericarditis, pericardial tamponade, restrictive cardiomyopathy, early MI, increased intracranial pressure Caution: Volume depletion, CAD

*Intravenous nitroglycerin is occasionally used to control hypertension. It is more frequently used as an adjunctive treatment for acute coronary syndromes.

PDE-5i, phosphodiesterase-5 inhibitors; CAD, coronary artery disease; MI, myocardial infarction.

TABLE 57

Catecholamine Synthesis Inhibitor (Tyrosine Hydroxylase Blocker) (for Pheochromocytoma only)—Side Effects and Cautions		
Drugs	*Frequent or severe side effects*	*Caution*
Metyrosine	Diarrhea (10%), nausea, extrapyramidal symptoms (10%) (drooling, tremor, speech difficulty), lethargy, metyrosine crystalluria (needles or rods), slight gynecomastia, galactorrhea (infrequent)	Increased sedation with ethanol, CNS depressants, need for liberal fluid intake (>2 L) (to minimize crystalluria), rebound insomnia when discontinued

CNS, central nervous system.

TABLE 58

Potassium Channel Openers or Activators—Side Effects and Cautions		
Drugs	*Frequent or severe side effects*	*Caution*
Minoxidil*	See vasodilators (oral acting) (Table 52)	
Nicorandil (also has nitrate-like actions—see table 56)	Headache (22–48%), postural hypotension, palpitations, aphthous ulcers of the mouth (and infrequent ulcers in other parts of gastrointestinal tract), dizziness, fatigue, angioneurotic edema (rare), lipid (neutral)	Recent MI, hypotension, AV or intraventricular conduction disturbance, severe liver impairment, cerebral hemorrhage, recent head trauma, concomitant treatment with nitrates
Pinacidil	Peripheral edema (23.5–45.2%), reflex tachycardia, palpitations, headache, dizziness, somnolence, chest pain, depression. Effect on lipids: decreased LDL, and triglycerides, increased HDL	CAD, acutely after MI, cerebrovascular accidents, severe renal impairment
Diazoxide	See intravenous use for hypertensive emergencies (vasodilators) (Table 52)	

*Direct acting vasodilator minoxidil is used in patients with severe hypertension. Hair growth limits its use. It can also produce pericardial effusion. Potassium channel opener, such as nicorandil has been used in patients with angina. It is seldom used for treatment of hypertension.

AV, atrioventricular; LDL, low-density lipoproteins; HDL, high-density lipoproteins; MI, myocardial infarction; CAD, coronary artery disease.

TABLE 59

Serotonin Receptor Agents—Side Effects and Cautions		
Drugs	*Frequent or severe side effects*	*Caution*
Ketanserin	Sedation, fatigue, light-headedness, dizziness, headache, dry mouth, gastrointestinal disturbance, edema (better tolerated in the elderly compared to younger patients)	Contraindication: second and third degrees atrioventricular heart block Caution: if QT is prolonged, ventricular arrhythmias (including torsades de pointes), liver cirrhosis Concomitant drugs: diuretic use—avoid hypokalemia, β-blockers (may produce profound hypotension), other antiarrhythmic drugs
Urapidil	Dizziness, headache, fatigue, nausea, enuresis, palpitations (no tachycardia), edema, orthostatic hypotension, sleep disturbance, increased liver function tests, lipid (neutral)	Contraindication: aortic stenosis Caution: liver disease, moderate-to-severe renal impairment, head trauma (increased intracranial pressure), elderly Concomitant drugs: cimetidine (need to reduce dose of urapidil)

*Serotonin receptor agents are seldom used for treatment of hypertension. They are prone to produce undesirable side effects.

TABLE 60

Dopamine Agonsits* (Peripheral D1 Receptors)—Side Effects and Cautions		
Drugs	*Frequent or severe side effects*	*Caution*
Fenoldopam mesylate	Headache (10–54.5%), hypotension (5–18.2%), tachycardia (18.2%), atrial fibrillation, angina pectoris, MI, ECG changes (~12.9%) (ST-T changes, T-wave inversion), CHF, peripheral edema, hypokalemia, nausea (10%), vomiting (~18.2%), dizziness (~7.1%), flushing (~27.3%), increased IOP, backache (~18.2%), oliguria (~5%), increased serum creatinine (6.5%), reaction at injection site (3.8–18.2%), increased blood sugar (~5%)	Contraindication: sensitivity to sulfites Caution: glaucoma, hypotension, hypokalemia, tachycardia, liver disease Concomitant drugs: β-blockers (may cause severe hypotension)

*Dopamine agonists are used only acutely to control severe hypertension. Activation of dopamine 1 receptors induce peripheral vasodilatation and reduction in blood pressure.

ECG, electrocardiography; MI, myocardial infarction; IOP, intraocular pressure.

CONCLUSION

Hypertension is a common disorder and is frequently asymptomatic. It is a risk factor for CAD, stroke and peripheral vascular disease CKD. Adequate control of hypertension is associated with a reduction in the incidence of MI, stroke and congestive heart failure and renal failure. The desirable level of blood pressure varies according to comorbidity. For example in diabetics, blood pressure should be reduced to a lower level than in nondiabetics.

Several classes of antihypertensive drugs are available for treatment of hypertension. Frequently combination of several classes of antihypertensive agents need to be used for adequate control of hypertension. All classes of antihypertensive drugs can produce side effects. Some side effects are unique to a particular class of antihypertensive drugs. The dosing regimens of different drugs in the same class are variable. Constant vigilance is necessary to avoid side effects.

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*For drugs not available in the US and not available in references 67–72, internet websites were carefully searched. Every effort has been taken to assure the accuracy of information. However, practitioners should check current information from medication inserts, local pharmacies and appropriate texts and websites before prescribing.

4 CHAPTER

Diuretics

Michael E Ernst

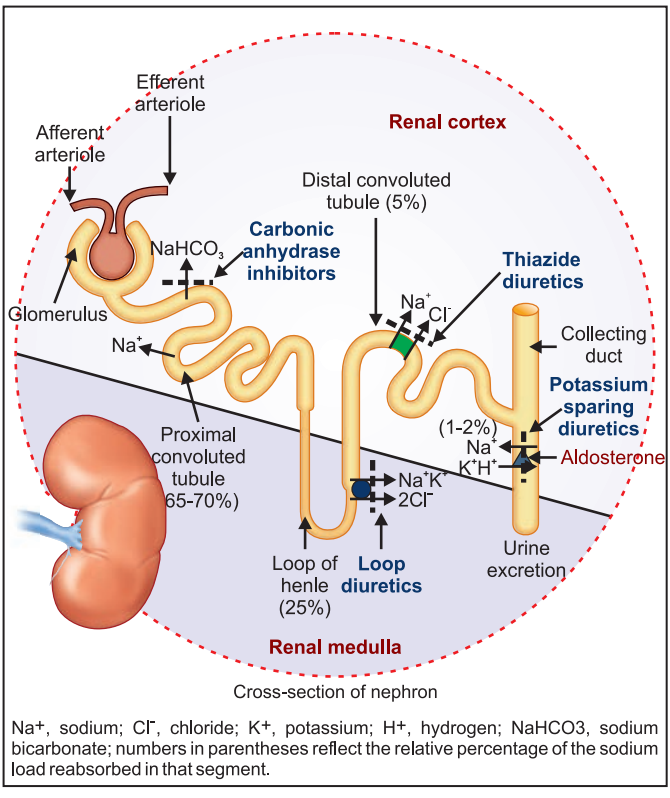
INTRODUCTION

Diuretic compounds promote the fractional excretion of sodium leading to an increased rate and extent of urine formation and a change in long-term sodium balance. They are fundamental therapies in the management of several cardiac and edematous disorders, including congestive heart failure, hypertension, and renal disease. The selection of an individual diuretic agent is based on several key features, including its site of action in the nephron, pharmacokinetic and pharmacodynamic properties, and adverse effect profile.

DIURETIC CLASSIFICATION AND OVERVIEW OF USE

Modern diuretic compounds are grouped into the following categories on the basis of their primary site of action in the nephron (Figure 1).

- *Carbonic anhydrase inhibitors (e.g., acetazolamide):* They interfere with carbonic anhydrase activity in the proximal tubule brush border and inside the epithelial cells, leading to impaired sodium, bicarbonate, and water reabsorption. The resulting alkaline diuresis is of limited therapeutic value, because sodium rejected proximally continues downstream where it is reabsorbed in the thick ascending limb of the loop of Henle. Acetazolamide is the prototype in the class but is rarely used, because of its minimal diuretic capability as well as the development of metabolic acidosis occurring with long-term use. Acetazolamide use is now primarily for noncardiac conditions, such as in decreasing intraocular pressure in patients with glaucoma and in the prophylaxis of acute mountain sickness.
- *Loop or high-ceiling diuretics (e.g., furosemide and torsemide):* They bind to the Na^+–K^+–$2Cl^-$ cotransporter and found within the apical membrane of epithelial cells of the thick ascending



Na+, sodium; Cl-, chloride; K+, potassium; H+, hydrogen; NaHCO3, sodium bicarbonate; numbers in parentheses reflect the relative percentage of the sodium load reabsorbed in that segment.

FIGURE 1. Diuretic sites of action in the nephron. *Adapted from* Ernst ME. Diuretics. In: Chatterjee K (editor). Cardiology: An Illustrated Textbook. New Delhi: Jaypee Brothers Medical Publishers; 2012. p.54.

limb of the loop of Henle. This transporter passively carries sodium, potassium, and chloride ions into the cell based on the electrochemical Na^+ gradient generated by the Na^+–K^+-adenosine triphosphatase (ATPase) pump of the basolateral membrane. Inhibition of this transporter by loop-acting agents causes a diuresis of Na^+Cl^- and K^+Cl^-. Loop diuretics are also referred to as "high-ceiling" diuretics due to the substantial diuresis they induce, resulting from their ability to block nearly all sodium reabsorption (~25%) occurring in the loop of Henle. These are the preferred diuretics for relieving edematous states, such as in congestive heart failure and nephrotic syndrome.

- *Thiazide and thiazide-like diuretics (e.g., hydrochlorothiazide and chlorthalidone):* They inhibit sodium reabsorption from the luminal side in the early segments of the distal tubule by interfering with the electroneutral Na^+Cl^- symporter located in the apical membrane. The increased delivery of sodium to the collecting duct results in a modest diuresis, but it is prolonged at a low level and alters cardiovascular hemodynamics over the long-term.[1] The reduction in total peripheral resistance shifts

blood pressure downward, making thiazides and thiazide-like agents the optimal diuretics for the chronic management of hypertension.

- *Potassium-sparing diuretics:* They act primarily at the cortical part of the collecting duct and, to a lesser extent, in the final segment of the distal convoluted tubule and connecting tubule. They are further subdivided into those acting as direct antagonists of cytoplasmic mineralocorticoid receptors (e.g., spironolactone) and those acting independent of mineralocorticoids (e.g., triamterene). The latter exert their action via blocking of the epithelial sodium channels in the luminal membrane. Since only a small amount of sodium is reabsorbed here, these agents provide only limited natriuresis (excluding states of mineralocorticoid excess). Their primary clinical utility resides in their ability to prevent potassium wasting from thiazides and loops.
- *Osmotic agents (e.g., mannitol):* They interfere with sodium reabsorption throughout all segments of the nephron by creating an osmotic force throughout the length of the renal tubule. The prevailing diuresis resembles the glucose-mediated osmotic polyuria observed in patients with uncontrolled diabetes.[2] The use of mannitol is limited to neurosurgical procedures, head trauma, and in other conditions of increased intracranial pressure. It has also been used as a preventive measure against kidney injury in patients receiving iodinated contrast agents. As its main use is not in cardiac disorders, it will not be discussed further.

LOOP DIURETICS

Loop diuretics were developed in the 1960s while developing more tolerable and effective replacements to organic mercurials. Furosemide, the most commonly used loop diuretic in the United States, was the first to be developed, followed by bumetanide and torsemide (Table 1).

Mechanism of Action

All loop diuretics bind to the Na^+–K^+–$2Cl^-$ cotransporter in the thick ascending limb of the loop of Henle. This segment is responsible for concentrating urine, and solute removal from this area generates the hypertonic medullary interstitium that serves as the osmotic force, driving water reabsorption across the collecting duct. Inhibition of this reabsorptive process by loop diuretics impairs the ability of the kidney to generate concentrated urine causing sodium chloride and potassium ions to remain intraluminally and be lost in the urine.

TABLE 1

High-ceiling or Loop Diuretics[1,2]

Agent	*Oral bioavailability (%)*	*V_d (L/kg)*	*Protein binding (%)*	*Fate*	*Normal $t_{1/2}$ (hour)*	*Duration of natriuresis (hour)*
Furosemide	10–100	0.15	91–99	R (50%), 50% conjugated in kidneys	1.5*	6
Bumetanide	80–100	0.15	90–99	R (60%) M (40%)	1.5*	3–6
Torsemide	80–100	0.2	99	R (20%) M (80%)	3–4*	8–12
Ethacrynic acid**	100	—	90	R (67%) M (33%)	1	4–8

*Prolonged in renal insufficiency.
**Higher risk of ototoxicity; reserve for patients with documented allergy to other loops diuretics.
V_d, volume of distribution; $t_{1/2}$, elimination half-life; R, renal excretion as intact drug; M, hepatically metabolized; —, insufficient data.

Pharmacology

Pharmacokinetics

All loop diuretics are extensively bound to serum albumin (>95%).[3] Consequently, to obtain access to their site of action, they must be actively secreted into the tubular lumen through probenecid-sensitive organic anion transporters located in the proximal tubule. This process may be slowed by elevated levels of endogenous organic acids, such as in chronic kidney disease, as well as some commonly prescribed drugs that share the same transporter, including salicylates and nonsteroidal anti-inflammatory drugs (NSAIDs).

Bioavailability, half-life, and routes of metabolism differ among the available loop diuretics. Furosemide is the most widely used, but it does not possess the most favorable pharmacokinetic profile within the class; absorption is erratic and ranges from 10–100%.[4] Coadministration with food can further decrease the bioavailability. The absorption of bumetanide and torsemide are more predictable, ranging from 80–100%.[5]

The duration of action and frequency of dosing for loop diuretics are determined by their half-lives. Furosemide and bumetanide act rapidly with very short half-lives (~1.5 hours). Therapeutic response occurs within minutes after intravenous administration, while peak response from oral administration occurs in about 30–90 minutes. With both routes of administration, diuretic effects continue for approximately 2–3 hours, lasting up to 6 hours.[2] Due to their brief action, loop diuretics are subject to a significant antinatriuretic period after the dose falls below the threshold necessary to trigger diuresis. This postdose rebound sodium retention can offset their therapeutic benefit such that furosemide and bumetanide must be given multiple times per day to ensure that adequate amounts of drug are maintained at the site of action. Torsemide has a longer plasma half-life and duration of action and can be dosed less frequently.

Furosemide is excreted both unchanged in the urine (approximately 50% of the dose), with the remainder conjugated to glucuronic acid in the kidney.[6] Bumetanide and torsemide are primarily hepatically metabolized.[7] In hepatic disease, the plasma half-lives of bumetanide and torsemide are prolonged, and their therapeutic effects may be paradoxically enhanced.[8] Similarly, renal insufficiency alters the pharmacokinetics of furosemide by prolonging both the plasma half-life and duration of action due to decreased urinary excretion and renal conjugation.

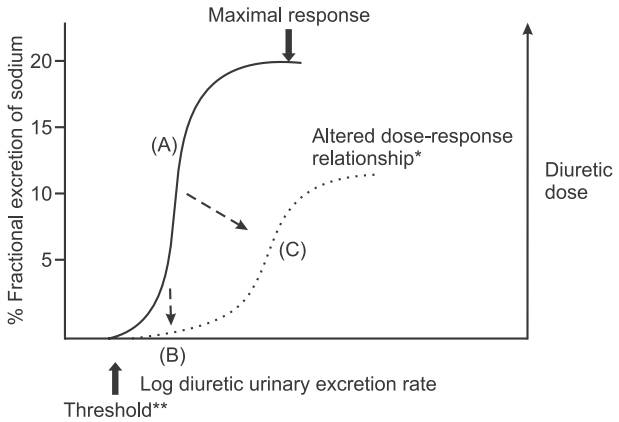
Pharmacodynamics

Specific hemodynamic changes in both systemic and renal microcirculations occur subsequently after the administration of a loop diuretic. Initially, intravenous administration stimulates the renin-angiotensin-aldosterone system (RAAS) at the macula densa, causing vasoconstriction, increased afterload, and decreased renal blood flow.[9] This may account for lack of response to a bolus dose. This action is temporary; however, a second-phase response occurs within 5–15 minutes. The second phase is characterized by an increase in renal release of vasodilating prostaglandins, leading to venodilation, and decreased preload and ventricular filling pressures.[10] The latter effects may explain the nearly immediate symptomatic improvement often noted in patients with acute pulmonary edema, which may precede the onset of actual diuresis.[2] With prolonged use, a compensatory activation of the sympathetic nervous system occurs and can lead to chronic adaptations known as the "braking" effect. These changes are natural compensations intended to protect intravascular volume. Their net result is to stabilize volume losses, leading to tolerance of the diuretic effect. Diuretic tolerance should be distinguished clinically from diuretic resistance states; the latter more appropriately refer to what is observed in conjunction with pathophysiologic conditions, such as renal failure, nephrotic syndrome, congestive heart failure, and cirrhosis.[3]

Dosage

Diuresis is dependent upon achieving a diuretic threshold specific within the individual patient. Once the threshold is met, there is an optimal rate of drug delivery leading to maximal response (Figure 2). Because diuretic response is not linearly related to dose, once the dose and rate of delivery leading to maximal response is determined, additional diuretic administration will not increase diuresis. To identify the point of maximal response, it is best to start first with small doses then titrate upward according to response. This can be achieved by sequentially doubling the dose until response is observed or a ceiling dose is reached (Table 2).

Intravenous furosemide is usually started with a 40 mg loading dose, followed by a repeated dose an hour later or a continuous infusion. The wide degree of variability in absorption of furosemide makes it difficult to reliably predict response; thus, one must try different doses before the drug is determined to be ineffective.[2] With its short duration of action (4–6 hours), oral dosing must be twice a day, usually early morning and mid-afternoon, to avoid nocturia. Given the wide bioavailability range



*Nephrotic syndrome, congestive heart failure, cirrhosis
**Determinants of diuretic threshold and efficacy include: dose, bioavailability, tubular secretory capacity, rate of absorption, and time course of delivery. After identifying the threshold dose to achieve effect, a higher diuretic concentration (A) leads to significant natriuresis. When severe sodium retention occurs or sodium intake is reduced, the curve shifts to the right and the previous diuretic serum concentration achieved by the dose in (A) is no longer effective (B). The dose of the diuretic must be increased to achieve clinically effective natriuresis (C) Increasing the frequency of doses has no effect on sodium excretion as long as each dose is below the threshold.

FIGURE 2. Relationship betwen loop diuretic dose and response. *Adapted from* Ernst ME. Diuretics. In: Chatterjee K (editor). Cardiology: An Illustrated Textbook. New Delhi: Jaypee Brothers Medical Publishers; 2012. p.56.

for furosemide, if one assumes an average absorption of 50%, the oral dose should be approximately twice the intravenous dose when switching routes of administration. Because absorption of bumetanide and torsemide is more reliable, the dose is approximately the same when switching from intravenous to oral dosing.

Larger doses of all loops may be necessary in the presence of renal disease to effectively reach the site of action since they compete with accumulated endogenous organic acids for delivery into the tubular lumen.

Indications and Clinical Evidence

Loops are the most effective agents when strictly evaluated according to the level of diuresis they produce. They are agents of choice for symptomatic relief in patients with edematous disorders, such as congestive heart failure, cirrhosis, and nephrotic syndrome.

General Therapeutic Considerations

The removal of excess extracellular fluid volume with loop diuretics should generally be gradual to minimize electrolyte

TABLE 2

Intravenous and Oral Dosing of Loop Diuretics[3,13]					
		Furosemide IV (mg)	*Furosemide PO (mg)*	*Bumetanide IV and PO (mg)*	*Torsemide IV and PO (mg)*
Continuous infusion (mg/hour)					
Loading dose		40	—	1	20
CrCl <25 mL/min		20 then 40	—	1 then 2	10 then 20
CrCl 25–75 mL/min		10 then 20	—	0.5 then 1	5 then 10
CrCl >75 mL/min		10	—	0.5	5
Single-dose ceilings (mg)					
Renal insufficiency Moderate	CrCl 20–50 mL/min	80–160	160	2–3	20–50
Renal insufficiency Severe	CrCl <20 mL/min	160–200	400	8–10	50–100
Congestive heart failure		40–80	80–160	1–2	20–40
Cirrhosis		40	80	1	10–20
Nephrotic syndrome		80–120	240	2–3	40–60

IV, intravenous; PO, per oral; CrCl, creatinine clearance.

imbalances as well as avoid reductions in blood volume that may impair adequate perfusion to the kidneys and other vital tissues and organs. Initial losses in response to diuretic administration occur from the plasma volume. The rate at which vascular space is refilled by fluid mobilized from the interstitium is variable, and this will direct the maximal rate of diuresis that can be tolerated.[11] For generalized edema, interstitial fluid is rapidly mobilized and a diuresis of 1–2 L/day can be safely achieved.[11] Mobilization is much slower, and diuresis must, therefore, be approached more gradually for edema that is sequestered as ascites or in the pleural space.

The short half-lives of loop diuretics limits their effectiveness as a treatment for hypertension, unless there is impaired renal function [glomerular filtration rate (GFR) <40 mL/min/1.73 m^2], where thiazides may lose efficacy (see the heading "Thiazide Diuretics").

Renal Disease

Renal disease impairs the ability of the diuretic to reach its site of action, so there is a need to administer larger doses to attain adequate amounts to reach the threshold for diuresis (Figure 2).[12] This is accomplished by giving gradually, increasing the doses of loop diuretic until an effective dose is identified or a specific ceiling dose is achieved (Table 2). Once the effective dose is identified, it should be given as frequently as necessary to maintain response, which will be influenced by the duration of action of the drug in the particular patient as well as the degree of sodium restriction employed.[3] Continuous infusions can be tried, if intermittent doses are not sufficient. However, before using a continuous infusion, a loading dose should be given first to reduce the time necessary to achieve a steady state therapeutic drug concentration. The rate of the continuous infusion is then determined based on renal function.[3]

Patients with inadequate natriuresis, despite the use of maximal doses of loop diuretics, may benefit from using a combination of diuretic agents—a strategy commonly referred to as "sequential nephron blockade" (Table 3).[13] Addition of a distally acting diuretic, such as a thiazide, to the loop agent is the most common strategy. Several mechanisms contribute to the enhanced response with combination use in refractory states. First, the longer half-life of distally acting agents may decrease the effect of the postdose sodium retention observed with the shorter-acting loops. Secondly, chronic administration of loop diuretics can induce hypertrophy of distal tubule cells, enhancing reabsorption of sodium at this site and blunting the response to loop diuretics.[13]

TABLE 3

Clinical Considerations with Diuretic use in Renal Disease[12]	
Consideration (cause)	*Solution*
Diuretic resistance	
Renal disease (impaired delivery of diuretic to site of action)	▪ Use larger doses; increase frequency or use continuous infusion ▪ Try sequential nephron blockade (i.e., addition of distally-acting agent such as thiazide)
Nephrotic syndrome (diminished nephron response and increased binding of diuretic to urinary albumin—reduced delivery of drug to site of action)	Need to obtain sufficiently high dose to reach diuretic threshold—increase the frequency of effective dose; coadministration with albumin
Proteinuria despite maximized renin-angiotensin-aldosterone blockade	Add spironolactone
Hypertension in chronic kidney disease	Loop diuretic (usually twice a day unless torsemide is used) preferred when GFR $\leq$40 mL/min/1.73 m^2

GFR, glomerular filtration rate.

Congestive Heart Failure

Several factors influence responsiveness to oral loop diuretics in patients with heart failure, including the extent of gastrointestinal absorption and rate of tubular secretion. The absolute bioavailability of the diuretic is usually unchanged, but the rate of absorption is slowed, such that the peak response may not be observed for several hours after the dose is administered.[3] Torsemide has a higher bioavailability than furosemide, and evidence exists for less fatigue and readmittance for decompensated heart failure in patients receiving torsemide compared to furosemide.[14]

As long as normal renal function is intact, delivery of diuretic into the tubular fluid remains normal in heart failure. However, renal responsiveness to loops as measured by the natriuretic response to maximally effective doses can be one-third to one-fourth with those of healthy individuals.[15] Larger doses will, therefore, not overcome this diminished response, unless renal insufficiency is present. Rather, the natriuretic response may be increased by giving moderate doses more frequently.[3] In this manner, intravenous therapy is often appropriate in patients with severe heart failure or acute pulmonary edema. In addition to avoiding troughs in drug concentration that can lead to intermittent periods of positive sodium balance, it also has the added advantage of bypassing the delayed gut absorption of

the diuretic. A loading dose followed by a continuous infusion (Table 2) is preferred, as they seem to provide greater natriuresis with a lower incidence of toxicity than intermittent bolus injections.[16]

THIAZIDE DIURETICS

While developing more potent inhibitors of carbonic anhydrase, researchers serendipitously discovered chlorothiazide.[1] Rather than the usual alkaline diuresis expected from a carbonic anhydrase inhibitor, an unanticipated finding with chlorothiazide was that it increased chloride excretion. Chlorothiazide was quickly made available for clinical use in 1957, marking the beginning of the modern era of effective oral diuretic therapy.

Mechanism of Action

Thiazide and the thiazide-like diuretics (Table 4) are also referred to as benzothiadiazines, as most compounds are analogues of 1,2,4-benzothiadiazine-1,1-dioxide.

The primary mechanism of action of thiazides is by interfering with the electroneutral Na^+Cl^- symporter located in the apical membrane in the early segments of the distal tubule. The increased delivery of sodium to the collecting duct also increases the exchange with potassium, leading to potassium depletion. Magnesium excretion is also increased as a result of thiazide administration. As the normal Na^+Cl^- reabsorption in the distal tubule contributes to tubular fluid dilution, thiazides impair the diluting capacity of the kidney but preserve urinary concentrating mechanisms.

There is significant heterogeneity within the class in their structure-activity relationships, and thiazides can be further designated as thiazide-type or thiazide-like; however, the general designation of thiazide diuretic is considered inclusive of all diuretics with a primary action in the distal tubule.[1] Although all thiazides retain an unsubstituted sulfonamide group in common with the carbonic anhydrase inhibitors and retain varying degrees of potency against carbonic anhydrase, this activity is not believed to contribute to their diuretic effect.[1]

Pharmacology

Pharmacokinetics

All thiazides are orally absorbed, have volumes of distribution equal to or greater than equivalent body weight, and are extensively bound to plasma proteins.[1] As with loop agents, thiazides must

TABLE 4

Thiazide and Thiazide-like Diuretics[1,2]

Agent	*Daily dosage (mg) (dosing schedule)*	*Oral bioavailability (%)*	*V_d (L/kg)*	*Protein binding (%)*	*Fate (%)*	*Normal $t_{1/2}$ (hours)*	*Normal duration of natriuresis (hours)*
Chlorothiazide	125–500 OD or BD	15–30	1	70	R (100)	1.5–2.5	6–12
Hydrochlorothiazide	12.5–50 OD	60–70	2.5	40	R (100)	3–10	6–12
Bendroflumethiazide	2.5–5 OD	90	1–1.5	94	R (30) M (70)	2–5	18–24
Chlorthalidone*	12.5–25 OD	65	3–13	99	R (65)	50–60	24–72
Metolazone*	2.5–10 OD	65	113 (total)	95	R (80)	8–14	12–24
Indapamide*	1.25–5 OD	71–79	25 (total)	75	M (70) R (5)	14	24–36

*Considered thiazide-like.

BD, twice a day; OD, once a day; $t_{1/2}$, elimination half-life; R, renal excretion as intact drug; M, hepatically metabolized; V_d, volume of distribution.

be actively secreted into the proximal tubule to access their site of action, because they are highly protein bound and subject to limited glomerular filtration.

The average onset of action for thiazides is approximately 2–3 hours, peaking at 3–6 hours, with progressively diminishing natriuretic effect occurring beyond 6 hours for most agents, except chlorthalidone.[1] There is significant variation in the metabolism, bioavailability, and plasma half-lives of the thiazides (Table 4). Hydrochlorothiazide, the most commonly used thiazide, is well absorbed (approximately 60–70%).[17] Coadministration with food slightly enhances absorption, most likely through interference with gastric emptying.

Several thiazides undergo hepatic metabolism (e.g., bendroflumethiazide, polythiazide, methyclothiazide, and indapamide), while others are excreted nearly completely intact in urine (e.g., chlorothiazide and hydrochlorothiazide). Metabolism of chlorthalidone and metolazone are mixed, primarily renal (50–80%) with minor biliary excretion (10%).[17] Other than a 50% reduction in hydrochlorothiazide absorption noted in patients with heart failure, the influence of disease on the pharmacokinetics of thiazides is not well described.[17]

Since the distal tubule is responsible for reabsorbing only about 5% of the filtered sodium load, the potential for appreciable volume removal with thiazides in edematous disorders is limited. However, relative to loops and other diuretics, an advantage of the thiazide diuretics is their long duration of action (minimum of 8–12 hours). This property is the major determinant in their usefulness as antihypertensive agents. Chlorthalidone distinguishes itself from other thiazide diuretics as a naturally long-acting agent, as it possesses a significantly longer elimination half-life, averaging 50–60 hours with chronic dosing.[18] It has a larger volume of distribution than other thiazide diuretics, with ≥99% of drug sequestered within erythrocyte carbonic anhydrase. In effect, this functions as a storage reservoir and enables a constant backflow of drug into the plasma, which may sustain a more constant, low-level diuresis, and minimize the postdose antinatriuretic period.[1]

Pharmacodynamics

The dose-response curve of thiazides is much shallower than that of loops, such that there is little difference in efficacy between the lowest and maximally effective doses. Although the various analogues differ by potency in the dose required to produce their therapeutic effects, there are minimal differences between individual agents with respect to their optimal therapeutic or maximal responses when equipotent doses are employed.

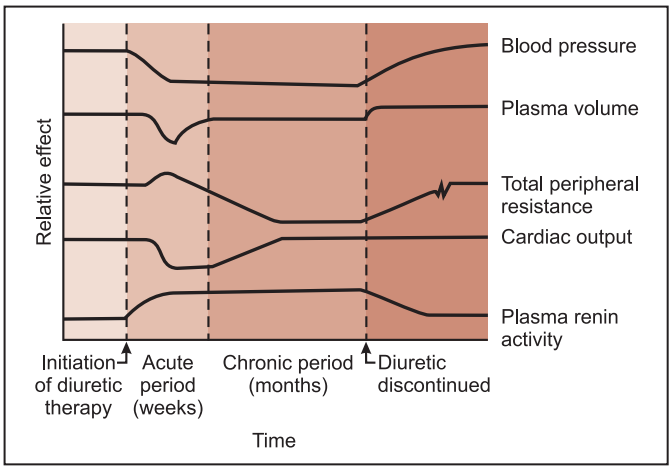


FIGURE 3. Time course of hemodynamic responses to thiazides. *Adapted from* Ernst ME. Diuretics. In: Chatterjee K (editor). Cardiology: An Illustrated Textbook. New Delhi: Jaypee Brothers Medical Publishers; 2012. p.61.

The antihypertensive efficacy of thiazides does not directly stem from strict diuresis, but rather, from the long-term hemodynamic changes, which accompany their administration. These hemodynamic changes are induced by a protracted low level of diuresis and allow the duration of antihypertensive effect to exceed that of their diuretic effect. Hemodynamic effects of thiazides can be separated into acute (1–2 weeks) and chronic (several months) periods (Figure 3).[19] In the acute period, blood–pressure lowering is initially attributed to extracellular fluid contraction and reduction in plasma volume.[20] The accompanying decrease in venous return depresses cardiac preload and output, thereby, reducing blood pressure. With chronic use, effects on plasma volume and cardiac output dissipate, and these parameters return to near-normal levels, suggesting other reasons for sustained antihypertensive efficacy.[21] The most likely explanation for the long-term effects of thiazides in lowering blood pressure is an overall reduction in total peripheral resistance induced by a modest but protracted state of volume contraction.[1]

Dosage

Originally, it was believed that thiazide efficacy depended explicitly on the amount of renal sodium excretion and reduction in plasma volume that could be obtained; thus, larger doses were assumed to provide greater reductions in blood pressure.[22] A more thorough understanding of the dose-response relationship of thiazides has since led to use of significantly lower doses, generally 12.5–25 mg/day of hydrochlorothiazide or its equivalent.[1]

Approximately 50% of patients will respond initially, even to these small doses. Increasing the dose of hydrochlorothiazide to 25 mg/day may add approximately 20% to the responders, while at 50 mg/day, 80–90% of possible responders should experience measurable blood pressure decreases.[23] A dose of 50 mg/day will result in significant hypokalemia (50% or higher) for most patients and may require potassium supplementation or coadministration with a potassium-sparing diuretic. Thus, many clinicians do not routinely exceed 25 mg/day, although increasing the dose to 50 mg/day should be considered for certain patients with resistant hypertension or in those who exhibit signs of volume expansion despite being on a low-dose diuretic (often see in obesity and in blacks). The risk of excessive potassium-wasting can be lessened when diuretics are coadministered with RAAS blockers such as angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), and when patients restrict their dietary sodium intake.[24]

Indications and Clinical Evidence

For many years, diuretic-based therapy has been an essential part for the treatment of hypertension. Thiazides are the preferred agents for chronic therapy in most hypertensive patients where a diuretic is indicated.[1]

General Therapeutic Considerations

Randomized, placebo-controlled trials over the last 40 years involving nearly 50,000 hypertensive patients demonstrated that lowering of blood pressure with diuretic-based regimens leads to a reduction in cardiovascular events. Combined meta-analyses and systematic reviews suggest that thiazide-based regimens reduce relative rates of heart failure by 41–49%, stroke by approximately 29–38%, coronary heart disease by 14–21%, and overall mortality by 10–11% compared to placebo.[1] Effect sizes are consistent when examined by gender, age, and presence of diabetes.[25-27] The results of these studies have collectively formed the basis for national treatment recommendations, advocating thiazides as a foundation of therapy for most patients.

The efficacy of thiazides in reducing hypertension-related cardiovascular events has typically been considered a class effect, although there are no direct comparative studies within the class.[1] On the basis that it has reduced cardiovascular events in every study where used, chlorthalidone is often recommended, since other thiazide regimens (particularly hydrochlorothiazide-based) have resulted in less consistent benefit in clinical trials.[1]

The few trials of hydrochlorothiazide in which it has successfully lowered cardiovascular disease events have typically used higher doses (≥25–50 mg/day) than commonly used today, while lower-dose regimens in clinical use today have been found inferior to comparator regimens.[28,29] The reason for these differences is unexplained but could relate to differences in potency between the two drugs at the low doses commonly employed today. It is now becoming more widely appreciated that chlorthalidone is 1.5–2 times more potent than hydrochlorothiazide, when evaluated with respect to doses required to achieve similar levels of blood pressure reduction.[30-32] Like chlorthalidone, indapamide is another thiazide-like diuretic that is not widely used but has favorable clinical trial outcome data. In the Hypertension in the Very Elderly Trial (HYVET), indapamide-based regimen resulted in significant reductions; 39% in rate of death from stroke, 21% in death from any cause, and 64% in heart failure rates.[33]

Hypertension

Thiazide administration typically results in a 10–15/5–10 mmHg placebo-adjusted reduction in blood pressure.[1] Thiazide responders are often referred to as having low-renin or salt-sensitive hypertension, reflecting the large dependence of blood pressure on volume and sodium in these individuals. These patients typically include the elderly, blacks, and high cardiac output states, such as obesity. Although they are more likely to respond to thiazides, thiazides can be effectively combined with nearly any antihypertensive to achieve an antihypertensive effect that is usually additive of the two individual components.[1] Racial differences observed in the monotherapy response to ACEIs or ARBs (blacks often do not respond as well to monotherapy with these agents) are minimized with the addition of a thiazide.

Thiazides are generally considered ineffective when GFR falls below 40 mL/min/1.73 m^2, since less drug is delivered to the site of action in the distal tubule, and the distal tubule is only responsible for a small portion of sodium reabsorption even under normal circumstances.[12] However, the exact level of GFR at which point the efficacy of each thiazide compound is obliterated has not been thoroughly investigated. Larger doses of thiazides have been shown to induce diuresis in patients with chronic kidney disease,[34,35] but increasing the doses of thiazides is often impractical given the risk of metabolic and electrolyte side effects. Thus, in patients with chronic kidney disease, a loop diuretic is preferred, and usually dosed 2 or 3 times a day to maintain efficacy. Metolazone, a thiazide-like agent, is an exception among thiazides, as it retains efficacy in patients

with renal insufficiency and other diuretic-resistance states. It has slow and erratic absorption, so the more predictable bioavailability of other thiazides makes them better suited for chronic therapy of hypertension. Metolazone is reserved in combination with loop diuretics in volume-overloaded patients undergoing close monitoring of fluid and electrolyte balance. It is usually administered daily for a short period (3–5 days) to achieve euvolemia, and then reduced to approximately three times weekly.[13]

POTASSIUM-SPARING DIURETICS

Potassium-sparing diuretics (Table 5) can be classified into 2 groups—epithelial sodium channel blockers and mineralocorticoid receptor antagonists. Generally, both groups are only modestly effective in lowering blood pressure and, with minimal exception, are primarily used in the general hypertensive population to offset potassium and magnesium losses in patients receiving a loop or thiazide diuretic.

Mechanism of Action

Sodium reabsorption in the distal tubule and collection ducts is mediated through an aldosterone-sensitive sodium channel and by activation of an ATP-dependent sodium-potassium pump. To preserve electroneutrality, potassium and hydrogen are concurrently secreted into the lumen.[1] Spironolactone and eplerenone (Table 5) are competitive antagonists of aldosterone, and interfere with the aldosterone-mediated exchange of sodium for potassium and hydrogen. Amiloride and triamterene are pteridine derivatives. They block epithelial sodium channels in the luminal membrane, which causes the electrical potential across the tubular epithelium to fall and reduces the driving force for secretion of potassium into the lumen.[2]

Pharmacology

Pharmacokinetics/Pharmacodynamics

Spironolactone is the prototypical mineralocorticoid receptor antagonist. It is orally absorbed (~65%) and highly protein bound (90%). It has a short half-life of only 1.5 hours but undergoes extensive metabolism in the liver into several active metabolites.[2] The two most well characterized metabolites are 7-α-thiomethylspirolactone and canrenone. Both have half-lives of about 15–20 hours and are responsible for the majority of spironolactone's therapeutic effect. Eplerenone is very similar to spironolactone, with the exception that its activity is not due

TABLE 5

Potassium-sparing Diuretics[1,2]							
Agent	*Daily dosage (mg) (dosing schedule)*	*Oral bioavailability (%)*	*V_d (L/kg)*	*Protein binding (%)*	*Fate*	*Normal $t_{1/2}$ (hours)*	*Normal duration of natriuresis (hours)*
Amiloride	5–10 OD	15–25	350 (total)	0	R (50%) 50% fecal	17–26*	24
Triamterene	50–150 OD	50	—	55–67	M (80%) R (10%)	3	7–9
Spironolactone	12.5–50 (up to 200 for ascites) OD	65	—	90	M (extent unknown)	1.5 (15 hours for active metabolite, canrenone)	16–24
Eplerenone	25–100 OD	69	43–90 (total)	50	M (extent unknown)	5	24

*$t_{1/2}$, 100 hours in end-stage renal disease.

V_d, volume of distribution; $t_{1/2}$, elimination half-life; OD, once a day; R, renal excretion as intact drug; M, hepatically metabolized; —, insufficient data.

to active metabolites, and it has lower affinity for androgen and progesterone receptors to the tune of 100 folds or even more. Spironolactone retains efficacy in renal impairment, since it is not dependent on glomerular filtration to reach its site of action.

Triamterene and amiloride are also orally absorbed (~50%). Triamterene has a short half-life (3–6 hours) and duration of action.[3] Both renal and liver diseases significantly affect the disposition of triamterene, since it is conjugated in the liver and the metabolite then secreted into the proximal tubular fluid.[3] Triamterene should be used carefully with other potential nephrotoxins, as it is associated with formation of crystals, nephrolithiasis, interstitial nephritis, and acute renal failure.

Amiloride has a much longer half-life (17–26 hours) than triamterene, achieving steady state in approximately 2 days.[2] It is preferred in patients with liver disease, since it is not metabolically activated. However, it is extensively renally cleared, and accumulates rapidly when administered in patients with chronic kidney disease. In these situations, the dose and/or dosing frequency of amiloride should be reduced to avoid the potential for hyperkalemia.

Dosage

The active metabolites of spironolactone have half-lives which are sufficiently long enough to allow spironolactone to be dosed once a day. Since time must be allowed to accumulate these active metabolites, spironolactone has a characteristically slow onset, taking up to 48 hours before becoming maximally effective.[2] Usual dosing is to begin with 12.5 mg/day, titrating up to 50 mg/day (Table 5). Side effects, such as gynecomastia and hyperkalemia are dose-related, and doses above 50 mg/day are generally reserved for cirrhotic patients with ascites. Eplerenone is naturally long-acting and can be dosed once a day, usually 25–100 mg.

Triamterene should ideally be dosed multiple times per day, however, since it is rarely prescribed alone (most commonly used in a fixed-dose combination with hydrochlorothiazide), once a day dosing is usually employed. The use of lower doses of thiazides, with less electrolyte disturbances has led to lower overall use of triamterene. Amiloride can be dosed once or twice a day due to its long half-life. Amiloride is also usually given as part of a fixed-dose combination with hydrochlorothiazide.

Indications and Clinical Evidence

In the absence of states of mineralocorticoid excess or certain rare genetic conditions, the primary role of potassium-sparing

diuretics in treatment of hypertension is that of an ancillary to help offset the potassium and magnesium wasting induced by thiazides.

Hypertension

Spironolactone and eplerenone are indicated for treating low-renin forms of hypertension. They are particularly effective in combination with a thiazide-type diuretic. Spironolactone has shown significant additive hypotensive effects in patients resistant to treatment regardless of ethnicity or baseline aldosterone level.[36] In doses of ≤50 mg/day, spironolactone is effective and well tolerated. Direct antihypertensive efficacy comparisons between spironolactone and eplerenone in patients with resistant hypertension are lacking. Amiloride, an epithelial sodium channel blocker, has demonstrated greater efficacy than spironolactone in blacks resistant to treatment.[37]

It is generally assumed that angiotensin blockade will secondarily suppress aldosterone. However, "aldosterone escape" (unsuppressed aldosterone levels while on an ACEIs or ARB) may be an important contributor of disease progression in patients with chronic kidney disease, as evidence by the finding that many hypertensive patients with chronic kidney disease and proteinuria do not have resolution of proteinuria despite treatment with ACEIs or ARBs. Several studies have indicated that the addition of spironolactone to an ACEI or ARB can reduce proteinuria and progression of chronic kidney disease, independent of additional blood pressure-lowering effects induced.[38,39] Aldosterone is profibrotic, including to kidney, and animal models have shown that unopposed aldosterone increases glomerulosclerosis.[38]

Other Conditions

The addition of spironolactone 25 mg/day to the standard regimen of an ACEI and loop diuretic in patients with severe heart failure (ejection fraction <35%) reduced death by 30% and hospitalizations by 35% in a pivotal trial.[40] Similarly, eplerenone has also shown reductions in mortality in both mild and severe heart failure patients.[41,42]

Liddle's syndrome, a rare autosomal dominant disorder characterized by severe hypertension, hypokalemia, and hypo-aldosteronism, is treated with amiloride or triamterene. Mineralo-corticoid antagonist therapy in this condition is ineffective.

Side Effects

Several predictable side effects occur with diuretics (Table 6). The majority of these involve electrolyte and metabolic disturbances.

TABLE 6

Electrolyte and Metabolic Effects of Diuretics			
Category	*Thiazide diuretics*	*Loop diuretics*	*Potassium-sparing diuretics*
Electrolytes			
Potassium	↓	↓	↑
Magnesium	↓	↓	↑
Sodium	↓	↓	—
Metabolic			
Glucose	↑	↑	—
Lipids	↑	↑	—
Other			
Uric acid	↑	↑	—

↑, increased; ↓, decreased; —, minimal/no effect.

Their clinical impact can be lessened by using the lowest effective dose and insuring a regular monitoring schedule.

Electrolyte Disturbances

Thiazide and loop diuretics increase potassium and magnesium excretion in a dose-related manner. An average potassium fall of 0.2–0.4 mEq/L with typical dosing in monotherapy can be expected.[1] In the Antihypertensive and Lipid-Lowering to Prevent Heart Attack Trial (ALLHAT), the average potassium level for chlorthalidone-treated patients (12.5–25 mg/day) over 4 years went from 4.3 to 4.1 mEq/L.[43] Concurrent administration of an ACEI or ARB can reduce incident hypokalemia with thiazides. If hypokalemia should occur, it can be managed by coadministering a potassium-sparing diuretic, or oral potassium supplements. Potassium-sparing diuretics are preferred, since they correct the underlying etiology and have the additional effect of correcting hypomagnesemia, which itself must be normalized before hypokalemia can be effectively remedied. Dietary sodium restriction should also be recommended for those on a diuretic, as it can help reduce the loss of potassium occurring with diuretics.[24] It should be noted that in the Systolic Hypertension in the Elderly Program (SHEP), the benefit of the diuretic in reducing coronary events was nullified in those patients experiencing potassium levels of <3.5 mEq/L.[44] Thus, maintenance of normokalemia should be a priority in patients treated with diuretics.

Amiloride, triamterene, spironolactone, and eplerenone can all cause hyperkalemia. Caution is advised when they are coadministered with ACEIs, ARBs, or other potentially nephrotoxic agents (e.g., NSAIDs), or in the presence of preexisting renal disease.

Hyponatremia is often asymptomatic, but careful monitoring of serum sodium should occur and patients should be advised to avoid excessive free-water intake while on a diuretic. Thiazides are more frequently implicated than loops, but both are equally capable of causing hyponatremia.[45] Thiazide-induced hyponatremia usually manifests within the first 2 weeks of therapy, while loops can occur after a longer interval. Risk factors for diuretic-induced hyponatremia include older age, female gender, psychogenic polydipsia, and concurrent antidepressant use (in particular, selective serotonin reuptake inhibitors).[45]

Metabolic Disturbances

Diuretics can increase plasma glucose levels, and data suggest that receipt of thiazides in the treatment of hypertension over several years may lead to an excess of 3–4% in new diabetes cases compared to other antihypertensives.[46] These data must be interpreted cautiously, since the diagnosis of diabetes is a dichotomous end-point—a change from 124 to 27 mg/dL would establish a new diagnosis of diabetes, despite being an absolute glucose change of only 3 mg/dL. The etiology for incident diabetes with diuretics may lie in reduced insulin release secondary to hypokalemia, but definitive studies have not been performed.[46]

The clinical significance of glucose changes with diuretics has been the subject of intense debate. New cases of diabetes are recognized over time in many hypertensive patients, regardless of which class of antihypertensive is used. For example, in ALLHAT, new-onset diabetes occurred in 11.6% of chlorthalidone-treated patients but occurred in 9.8 and 8.1% of amlodipine and lisinopril-treated patients, respectively.[47] To date, analyses from several different studies indicate that diabetics treated with diuretics, and individuals who develop diabetes while on a diuretic, experience a great or greater decrease in cardiovascular events than nondiabetics.[47,48]

Diuretics can cause atherogenic changes in blood lipids, namely, by increasing total cholesterol and low-density lipoproteins. Estimates are approximately 5–7% in the first 3–12 months of therapy.[49] However, these changes are short lived, as evidenced from long-term follow-up in clinical trials. A low-fat diet and regular monitoring are advised.

Hyperuricemia

Thiazides compete with uric acid for secretion into the proximal tubule by the organic acid secretory system; therefore, this leads to reduced uric acid excretion and can precipitate gout in predisposed individuals. If a patient experiences gout while taking a diuretic, the diuretic should be discontinued, if possible. Uric

acid can be rechecked after resolution of the attack and the need for prophylaxis or alternate antihypertensive therapy assessed. If the diuretic remains necessary to control blood pressure and the serum urate rises >10 mg/dL, allopurinol may be used.

Drug Interactions

Diuretics are relatively free of significant drug–drug interactions. Most drug interactions are pharmacodynamic in nature, relating to antagonism of effect or synergistic adverse effects, rather than in specific pharmacokinetic interferences. NSAIDs and steroids can antagonize the therapeutic effects of diuretics by causing sodium retention. They also lessen the renal response to loop diuretics, probably by decreasing the formation of vasodilatory prostaglandins. Coadministration of NSAIDs increases the risk of hyperkalemia when used with potassium-sparing diuretics, because they decrease secretion of renin and aldosterone. Lithium clearance can be decreased by thiazides (but not loops). Cotherapy with certain antibiotics such as aminoglycosides can potentiate nephrotoxicity.

Other

A number of other side effects of diuretics are described, including hypovolemia, ototoxicity (particularly with high-dose loop therapy), urinary frequency, and erectile dysfunction. Thiazide diuretics retain calcium through an increase in proximal tubular reabsorption. This is not generally harmful but, in fact, may be protective in fractures.[50] However, hyperparathyroid patients may be at risk for hypercalcemia. Lastly, there appears to be no specific cross-sensitivity between sulfa antibiotic allergy and other nonantibiotics that have a sulfa moiety, such as thiazides.[51]

CONCLUSION

Over 50 years since first introduced into mainstream clinical use, diuretics remain valuable drugs for managing sodium and fluid balance in the treatment of several cardiac diseases, including hypertension, and congestive heart failure and related edematous disorders. Heterogeneity between-class in their mechanisms of action, pharmacokinetic, and pharmacodynamic properties dictates their primary therapeutic roles (e.g., thiazide diuretics for hypertension, loop diuretics for congestive heart failure, and renal disease). Importantly, their within-class heterogeneity further allows individualization of treatment which can help insure a successful therapeutic outcome. Prescribers of diuretics for use in cardiac disorders should equally appreciate both their powerful thearpeutic capabilities, while also respecting their

potential adverse effects through proper selection of dosing and appropriate monitoring.

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5 CHAPTER

Drugs for Dyslipidemias

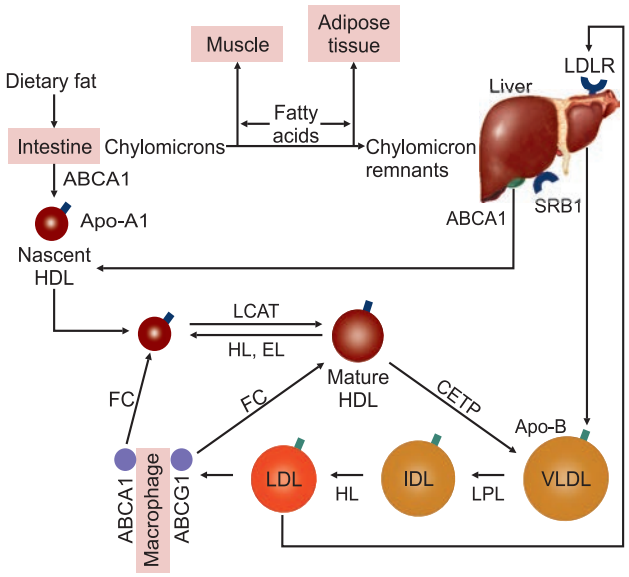
Byron Vandenberg

INTRODUCTION

The treatment of lipid disorders is directed at preventing progression and promoting regression of atherosclerosis. Atherosclerosis is primarily a lipid storage disease involving the retention of apolipoprotein-B (apo-B) containing lipoproteins which subsequently induce chronic inflammation, cell death, and thrombosis resulting in heart disease and stroke. Clinical studies have demonstrated that elevated levels of the apo-B lipoprotein, low-density lipoprotein (LDL), promotes human atherosclerosis.[1] Cardiovascular (CV) morbidity and mortality vary directly with the level of total cholesterol and LDL, although the association is not linear, as risk rises mores steeply with increasing LDL concentrations.[2] LDL is one of the lipoprotein complexes involved in cholesterol and triglyceride transport (Figure 1).[3] The lipoprotein complexes include LDL, high-density lipoprotein (HDL), very low-density lipoprotein (VLDL), and intermediate density lipoprotein (IDL).

The recommended goals for LDL reduction are based on risk level (i.e., very high, high, moderately high, moderate, or low), which is determined by risk factors (presented in figure 2 for women and figure 3 for men) and Framingham risk scoring (Table 1).[1,2] Risk factors include cigarette smoking, hypertension (blood pressure >140/90 mmHg or on antihypertensive medication), low HDL (<40 mg/dL), family history of premature coronary heart disease (CHD) (i.e., CHD in male first-degree relative <55 years of age or in female first-degree relative <65 years of age), and age (i.e., men >45 years; women >55 years).[1,2] Factors that favor a decision to reduce LDL levels to <70 mg/dL are those that place patients in the very high-risk category.[2] The efficacy and safety of more intensive lowering of LDL has been reviewed by Cholesterol Treatment Trialists' Collaboration.[4]

After the LDL goal has been achieved, and if the triglyceride level is still >200 mg/dL, non-HDL cholesterol (i.e., total minus HDL cholesterol) becomes a secondary target of therapy.[1]



ABCA1, ATP binding cassette A1; SRB1, scavenger receptor B1; LCAT, lecithin cholesterol acyltransferase; HL, hepatic lipase; EL, endothelial lipase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LDLR, LDL-receptor; IDL, intermediate density lipoprotein; LPL, lipoprotein lipase; VLDL, very low-density lipoprotein; CETP, cholesteryl ester transfer protein; ABCG1, ATP binding cassette G1; Apo-A1, apolipoprotein-A1; Apo-B, apolipoprotein-B.

FIGURE 1. Schematic diagram of lipoprotein metabolism. The intestine absorbs dietary fat and packages it into chylomicrons (large triglyceride-rich lipoproteins), which are transported to peripheral tissues through the blood. In muscle and adipose tissues, the enzyme LPL breaks down chylomicrons, and fatty acids enter these tissues. The chylomicron remnants are subsequently taken up by the liver. The liver loads lipids onto apo-B and secretes VLDL, which undergoes lipolysis by LPL and HL to form LDL. LDL is then taken up by the liver through binding to the LDLR, as well as through other pathways. By contrast, HDL is generated by the intestine and the liver through the secretion of lipid-free apo-A1. Apo-A1 then recruits cholesterol from these organs through the ABCA1 transporter, forming nascent HDL, and this protects apo-A1 from being rapidly degraded in the kidneys. In the peripheral tissues, nascent HDL promotes the efflux of cholesterol from tissues, including from macrophages, through the actions of ABCA1. Mature HDL also promotes this efflux but through the actions of ABCG1. The free (unesterified) cholesterol in nascent HDL is esterified to cholesteryl ester by the enzyme LCAT, creating mature HDL. The cholesterol in HDL is returned to the liver both directly through uptake by the SRB1, and indirectly, by transfer to LDL and VLDL through the CETP. The lipid content of HDL is also altered by the enzymes HL and EL.

Non-HDL cholesterol represents the concentration of all atherogenic lipoproteins, including LDL, IDL, and VLDL; and goals are set 30 mg/dL higher than LDL goals for each risk category. Elevated non-HDL cholesterol may be related to the atherogenic triad of elevated triglycerides, low HDL, and small LDL particle

Total cholesterol					
mg/dL	*Age (years)*				
	20–39 (points)	*40–49 (points)*	*50–59 (points)*	*60–69 (points)*	*70–79 (points)*
<160	0	0	0	0	0
160–199	4	3	2	1	1
200–239	8	6	4	2	1
240–279	11	8	5	3	2
≥280	13	10	7	4	2

Smoking status					
	Age (years)				
	20–39 (points)	*40–49 (points)*	*50–59 (points)*	*60–69 (points)*	*70–79 (points)*
Nonsmoker	0	0	0	0	0
Smoker	9	7	4	2	1

Systolic blood pressure		
mmHg	*If untreated (points)*	*If treated (points)*
<120	0	0
120–129	1	3
130–139	2	4
140–159	3	5
≥160	4	6

Age	
Years	*Points*
20–34	–7
35–39	–3
40–44	0
45–49	3
50–54	6
55–59	8
60–64	10
65–69	12
70–74	14
75–79	16

Risk of heart disease					
Total points	*10-year risk (%)*	*Total points*	*10-year risk (%)*	*Total points*	*10-year risk (%)*
<9	<1	14	2	20	11
9	1	15	3	21	14
10	1	16	4	22	17
11	1	17	5	23	22
12	1	18	6	24	27
13	2	19	8	≥25	≥30

HDL	
mg/dL	*Points*
≥60	–1
50–59	0
40–49	1
<40	2

HDL, high-density lipoprotein.

FIGURE 2. Estimating 10-year risk for women. Risk assessment for determining the 10-year risk for developing coronary heart disease is carried out using Framingham risk scoring. The risk factors included in the Framingham calculation of 10-year risk are age, total cholesterol, high density lipoprotein, systolic blood pressure, treatment for hypertension, and cigarette smoking. The total risk score sums the points for each risk factor. The 10-year risk for myocardial infarction and coronary death is estimated from the total points and the person is categorized according to absolute 10-year risk.

Total cholesterol					
mg/dL	*Age (years)*				
	20–39 (points)	*40–49 (points)*	*50–59 (points)*	*60–69 (points)*	*70–79 (points)*
<160	0	0	0	0	0
160–199	4	3	2	1	0
200–239	7	5	3	1	0
240–279	9	6	4	2	1
≥280	11	8	5	3	1

Smoking status					
	Age (years)				
	20–39 (points)	*40–49 (points)*	*50–59 (points)*	*60–69 (points)*	*70–79 (points)*
Nonsmoker	0	0	0	0	0
Smoker	8	5	3	1	1

Systolic blood pressure		
mmHg	*If untreated (points)*	*If treated (points)*
<120	0	0
120–129	0	1
130–139	1	2
140–159	1	2
≥160	2	3

Age	
Years	*Points*
20–34	–9
35–39	–4
40–44	0
45–49	3
50–54	6
55–59	8
60–64	10
65–69	11
70–74	12
75–79	13

Risk of heart disease					
Total points	*10-year risk (%)*	*Total points*	*10-year risk (%)*	*Total points*	*10-year risk (%)*
<0	<1	6	2	13	12
0	1	7	3	14	16
1	1	8	4	15	20
2	1	9	5	16	25
3	1	10	6	≥17	≥30
4	1	11	8		
5	2	12	10		

HDL	
mg/dL	*Points*
≥60	–1
50–59	0
40–49	1
<40	2

HDL, high-density lipoprotein.

FIGURE 3. Estimating 10-year risk for men. Risk assessment for determining the 10-year risk for developing coronary heart disease is carried out using Framingham risk scoring. The risk factors included in the Framingham calculation of 10-year risk are age, total cholesterol, high density lipoprotein, systolic blood pressure, treatment for hypertension, and cigarette smoking. The total risk score sums the points for each risk factor. The 10-year risk for myocardial infarction and coronary death is estimated from the total points and the person is categorized according to absolute 10-year risk.

TABLE 1

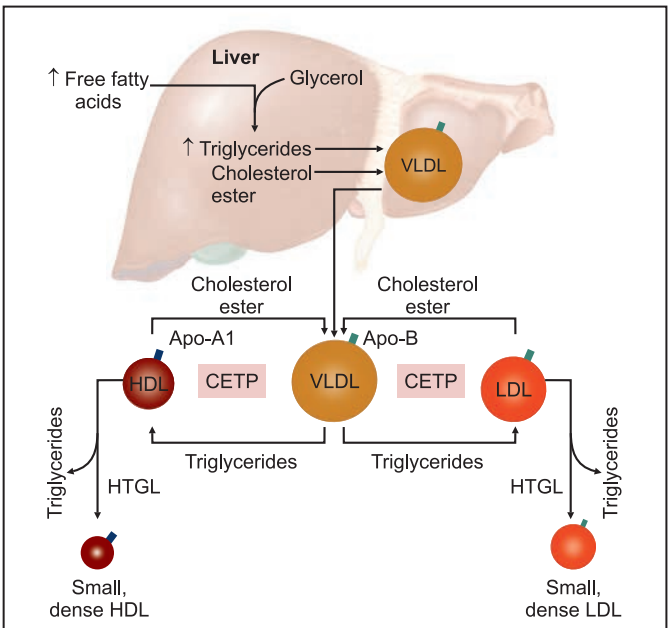
Recommendation for LDL Goal is Based on Assessment of Risk Factors and Framingham Risk[2]

Risk category	*Risk factors, Framingham risk*	*LDL goal (mg/dL)*	*LDL level at which to initiate therapeutic lifestyle changes (mg/dL)*	*LDL level at which to consider drug therapy (mg/dL)*
Very high	*	<70	>70	>70
High	CHD or CHD risk equivalents**	<100	≥100	≥100 (<100 is optional)
Moderately high	2+ risk factors, 10-year risk 10–20%	<130 <100 is optional	≥130	≥130 (100–129 is optional)
Moderate	2+ risk factors, 10-year risk <10%	<130	≥130	≥160
Low	0–1 risk factor	<160	≥160	≥190 (160–189 is optional)

*Presence of established cardiovascular disease plus (i) multiple major risk factors (especially diabetes), (ii) severe and poorly controlled risk factors (especially continued cigarette smoking), (iii) multiple risk factors of the metabolic syndrome (especially high triglycerides ≥200 mg/dL plus non-HCL-C ≥130 mg/dL with low HDL <40 mg/dL), and (iv) patients with acute coronary syndromes.

**CHD: history of MI, unstable angina, stable angina, coronary artery procedures (e.g., angioplasty or bypass surgery), or evidence of clinically significant myocardial ischemia. CHD risk equivalent: clinical manifestation of noncoronary forms of atherosclerotic disease [e.g., peripheral arterial disease, abdominal aortic aneurysm, and carotid disease (transient ischemic attacks or stroke of carotid origin or >50% obstruction of a carotid artery)], diabetes, or 2+ risk factors with 10-year risk for hard CHD >20%.

LDL, low-density lipoprotein; CHD, coronary heart disease.



Apo-A1, apolipoprotein-A1; Apo-B, apolipoprotein-B100; HDL, high-density lipoprotein; HTGL, hepatic triglyceride lipase; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein; CETP, cholesteryl ester transfer protein.

FIGURE 4. Metabolic consequences of hypertriglyceridemia and the metabolic syndrome. In the setting of insulin resistance and mixed dyslipidemia, there is increased free fatty acid flux to the liver and increased VLDL secretion. Higher VLDL output activates CETP that results in enrichment of LDL and HDL. The triglyceride content within these particles is hydrolyzed by hepatic triglyceride lipase which results in small, dense LDL and HDL particles.

size (Figure 4); frequently, part of metabolic syndrome which is associated with a 2-fold increase in CV outcomes.[5]

Plasma triglyceride levels have not consistently been shown to be an independent risk factor for CHD.[6] The National Cholesterol Education Program/Adult Treatment Panel III (NCEP/ATP III) guidelines did not set a specific goal of therapy for patients with triglyceride levels in the range of 200–499 mg/dL and suggested that the best way to reduce risk is to normalize non-HDL cholesterol, a surrogate measure of apo-B.[1] The American Diabetes Association (ADA) recommends a triglyceride goal of <150 mg/dL for diabetics.[7]

For patients presenting with baseline triglycerides >500 mg/dL, the goal of therapy is a reduction in the risk of pancreatitis and not CV risk.[1] When fasting triglycerides are >1 g/dL, there is usually a secondary cause of hypertriglyceridemia (e.g., diabetes mellitus, hypothyroidism, or medications known to increase triglycerides, such as β-blockers or thiazide diuretics) occurring in individuals with one or more common genetic hyper-

triglyceridemia disorders, such as familial hypertriglyceridemia or familial combined hyperlipidemia. Excess body weight and alcohol intake may be important factors in hypertriglyceridemia and should be addressed prior to therapy.[1]

CV morbidity and mortality varies inversely with the level of HDL. The NCEP/ATP III guidelines define HDL <40 mg/dL as an independent CV risk and encourage the use of nondrug and drug therapies to raise HDL but stop short of an HDL treatment goal.[1] However, the ADA recommends that raising HDL to >40 mg/dL in men and >50 mg/dL in women should be considered in patients with diabetes mellitus.[7]

STATINS

Introduction

Inhibitors of the 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, also known as the statins, are considered first line therapy for lowering LDL.[1,8] The beneficial effect of statins on clinical events may also involve non-lipid or pleiotropic-related mechanisms that modify endothelial function, inflammatory responses, plaque stability, and thrombus formation. Primary and secondary prevention trials demonstrate that statin use is associated with improved survival and significant reductions in the risk of CV events.[9-15]

Drugs under the Category

The currently available statins are atorvastatin,[9] fluvastatin,[10] lovastatin,[11] pitavastatin,[12] pravastatin,[13] rosuvastatin,[14] and simvastatin.[15]

Mechanism of Action

Statins are competitive inhibitors of HMG-CoA reductase that is responsible for the conversion of HMG-CoA to mevalonate, a precursor of sterols, including cholesterol. The inhibition in the cholesterol biosynthesis pathway reduces the cholesterol in hepatic cells, which further stimulates the synthesis of LDL receptors thereby increasing LDL uptake. The pleiotropic effects are probably related to a decrease in protein prenylation in peripheral cells with a subsequent decrease in activation and release of growth factors and a decrease in platelet aggregation/activation[16] (Figure 5).

Pharmacology

Statins mimic the HMG moiety substrate of HMG-CoA reductase and competitively bind to the enzyme, although the binding site

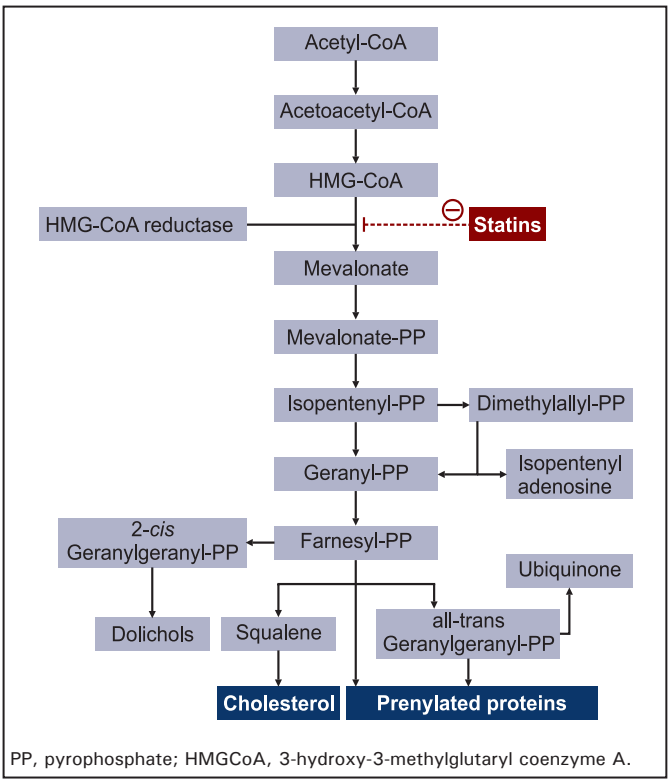


FIGURE 5. The mevalonate pathway and the beneficial effects of statins. The inhibition of HMG-CoA reductase results in a decrease in cholesterol and upregulation of LDL receptors. Mevalonic acid is the product of the effect of HMG-CoA reductase on HMG-CoA and is the precursor of numerous metabolites. The inhibition of HMG-CoA reductase has the potential to inhibit signaling pathways that require prenylated proteins resulting in decreased cell growth, an example of the pleiotropic effects of statins. In addition, isoprenoids such as isopentenyl adenosine, dolichols and ubiquinone are vital for diverse cellular functions.

residues are different between statins and this affects their relative potency. The lipophilicity also varies and may influence side effects, such as an increase in the risk for muscle related adverse effects (Table 2).[9-15,17]

All statins are absorbed rapidly with time to peak absorption within 4 hours.[18,19] However, their elimination half-lives vary considerably. Since atorvastatin and rosuvastatin have longer elimination half-lives, their cholesterol lowering efficacy is similar throughout the day.[19]

All statins, with the exception of pravastatin, are highly plasma protein bound and these statins are more likely to displace albumin-bound drugs, such as warfarin. For example, rosuvastatin or simvastatin coadministration can result in an increased prothrombin time.[14,15]

TABLE 2

Pharmacology of Statins[9-15,17]

	Atorvastatin	*Fluvastatin*	*Lovastatin*	*Pitavastatin*	*Pravastatin*	*Rosuvastatin*	*Simvastatin*
Lipophilicity Log P	Lipophilic 1.11	Lipophilic 1.27	Lipophilic 1.70	Lipophilic 1.49	Hydrophilic −0.84	Hydrophilic −0.33	Lipophilic 1.60
Metabolizing CYP enzymes	3A4	2C9 (75%) 2C8 (~5%) 3A4 (~20%)	3A4	Minimal (2C9 > 2C8)	—	2C9	3A4
$t_{½}$ (hours)	14	0.5–2.3	2.9	12	1.3–2.8	19	1.9–3
Renal excretion (%)	<2	5	10	15	20	10	13
Protein binding (%)	>98	98	>95	>99	50	88	95

CYP, cytochrome P450.

The cytochrome P450 (CYP) enzymes in the gastrointestinal (GI) tract and liver are responsible for statin metabolism, although some statins are more dependent on these enzymes for their metabolism than other statins. Interactions between statins and other drugs occur because of the interference with the CYP isoenzymes by either induction or inhibition of the CYP enzymes. Induction of these enzymes may lead to a reduced bioavailability and therapeutic effect of the statin. In contrast, CYP enzyme inhibitors may raise the plasma concentration of statins and increase the risk of adverse effects, such as myopathy.[19]

Indications

Statins are indicated to:

- Lower LDL in patients with mixed (combined) dyslipidemias or familial hypercholesterolemia
- Lower triglyceride levels in patients with mixed (combined) dyslipidemias or primary dysbetalipoproteinemia
- Raise HDL in patients with mixed (combined) dyslipidemias.

In addition, some of the statins are indicated for the reduction in the risk of total mortality by reducing CHD deaths and to reduce the risk of nonfatal myocardial infarction (MI), stroke, and the need for revascularization procedures in patients at high risk of coronary events.[9,13,15]

Dosage

Pravastatin

The recommended starting dose for pravastatin is 40 mg once a day. If this dose does not achieve desired cholesterol levels, 80 mg once a day can be used. However, a starting dose of 10 mg daily is recommended in patients with significant renal impairment.

Pravastatin can be administered as a single dose at any time of the day, irrespective of meal timings. Since the maximal effect of a given dose is seen within 4 weeks, periodic lipid determination should be performed at this time and dosage adjusted according to the patient's response to therapy and established guidelines.[13]

The dose of pravastatin should not exceed 20 mg/day when administered along with cyclosporine and not exceed 40 mg/day when administered along with clarithromycin. Pravastatin should be avoided on patients taking gemfibrozil and used with caution on patients taking other fibrates or colchicine. A dose reduction should be considered in patients on niacin.[13]

Lovastatin

The usual recommended starting dose is 20 mg once a day given with the evening meal. The dose range is 10–80 mg/day in a single or two divided doses. A starting dose of 10 mg may be considered for patients requiring <20% reduction in LDL. Dose adjustments should be made at intervals of 4 weeks or more. In patients with severe renal insufficiency [i.e., glomerular filtration rate (GFR) <30 mL/min/1.73 m^2], dosage above 20 mg/day should be implemented with caution.[11]

The use of lovastatin with strong inhibitors of CYP3A4 is contraindicated (see the heading "Contraindications"). The concomitant use of gemfibrozil or cyclosporine should be avoided. The lovastatin dose should not exceed 20 mg/day when administered along with danazol, diltiazem, or verapamil and should not exceed 40 mg/day when administered with amiodarone.[11]

Simvastatin

The usual dosage range is 5–40 mg/day. The recommended starting dose is 10 or 20 mg once a day in the evening. However, for patients at high risk of a CHD event (e.g., patient with existing CHD, diabetes mellitus, peripheral vessel disease, history of stroke, or other cerebrovascular disease), the recommended starting dose is 40 mg/day. Due to the increased risk of myopathy, including rhabdomyolysis, particularly during the first year of treatment, use of 80 mg dose should be restricted to patients who have been taking the dose for 12 months or more without evidence of muscle toxicity. Patients receiving 80 mg dosing who need to be initiated on a drug with potential interaction that is contraindicated or associated with a dose maximum for simvastatin should be switched to an alternative statin with a lower potential for drug-drug interaction. Patients unable to achieve their LDL goal utilizing 40 mg dose should not be titrated to 80 mg dose, but should be placed on alternative LDL lowering therapy.[15]

The combined use of simvastatin with strong CYP3A4 inhibitors, gemfibrozil, cyclosporine, or danazol is contraindicated (see the heading "Contraindications"). The daily dose should not exceed 10 mg/day when taken with verapamil or diltiazem and should not exceed 20 mg/day when taken with amiodarone, amlodipine, or ranolazine.[15]

Caution should be used when treating Chinese patients with simvastatin in doses exceeding 20 mg/day, coadministered with lipid modifying doses of niacin because of the increased risk of myopathy. It is not known if the increased risk applies to other Asian patients.[15]

Atorvastatin

The recommended starting dose is 10 or 20 mg once a day. Patients who require >45% reduction in LDL levels may be directly started on 40 mg once a day. The dosage range is 10–80 mg once a day. Atorvastatin can be administered as a single dose at any time of the day, irrespective of meal timings. Lipid levels should be analyzed within 2–4 weeks and dose should be adjusted as required. Renal disease does not affect the plasma concentration of atorvastatin, so dose adjustment in patients with renal dysfunction is not necessary.[9]

Atorvastatin should be avoided in patients taking cyclosporine, the human immunodeficiency virus (HIV) protease inhibitor combination, tipranavir plus ritonavir, or the hepatitis C protease inhibitor, telaprevir. Caution (and the lowest dose necessary) should be taken when prescribing atorvastatin in combination with the HIV protease inhibitor combination, lopinavir plus ritonavir. The atorvastatin dose should be limited to 20 mg/day when used with clarithromycin, itraconazole, or in patients with HIV taking a combination of saquinavir plus ritonavir, darunavir plus ritonavir, fosamprenavir, or fosamprenavir plus ritonavir. In HIV patients taking nelfinavir, atorvastatin dosage should not exceed 40 mg/day.[9]

Atorvastatin is a substrate of the organic anion transport polypeptide transporter, OATP1B1. Therefore, inhibitors of OATP1B1 (e.g., cyclosporine) can increase the bioavailability of atorvastatin.[9]

Fluvastatin

For patients requiring LDL reduction to a goal of >25%, the recommended starting dose is 40 mg in the evening, 80 mg as one extended-release (XR) tablet administered as a single dose at any time of the day, or 80 mg in divided doses of the 40 mg capsule given twice a day. The XR tablets should not be crushed or broken. For patients requiring LDL reduction to a goal of <25%, a starting dose of 20 mg may be used. The recommended dosing range is 20–80 mg/day.[10]

The fluvastatin dose should be limited to 20 mg twice a day for those patients who are also receiving cyclosporine or fluconazole. Fluvastatin should be cautiously used when patients are also taking fibrates, niacin, glibenclamide, phenytoin, or coumarin anticoagulants.[10]

Fluvastatin has not been studied at doses greater than 40 mg in patients with severe renal impairment, so caution should be exercised when treating such patients at higher doses. Fluvastatin

may be taken without regard to meals. The maximal reduction in LDL is seen within 4 weeks.[10]

Since fluvastatin is eliminated via the biliary route, there is the potential for drug accumulation in patients with hepatic insufficiency.

Rosuvastatin

The dose range is 5–40 mg once a day. The recommended starting dose of rosuvastatin is 10–20 mg once a day administered at any time of the day, with or without food. For patients with marked hyperlipidemia (e.g., LDL >190 mg/dL) and aggressive lipid targets, a 20 mg starting dose may be considered. After initiation or upon titration of rosuvastatin, lipid levels should be analyzed within 2–4 weeks and the dosage adjusted accordingly. The 40 mg dose should be used only for those patients who have not achieved their LDL goal utilizing the 20 mg dose. Initiation of rosuvastatin therapy with 5 mg once a day should be considered for Asian patients.[14]

The use of rosuvastatin with gemfibrozil should be avoided and the dose limited to 10 mg/day if used. The dose of rosuvastatin should not exceed 5 mg/day when used with cyclosporine. Caution should be exercised when coadministering rosuvastatin with protease inhibitors in combination with ritonavir. The rosuvastatin dose should be limited to 10 mg/day when given with combination therapy of ritonavir plus lopinavir or ritonavir plus atazanavir. Caution should also be exercised with dosing when patients are also taking niacin, fenofibrate, or coumarin anticoagulants.[14]

In patients with severe renal impairment (i.e., GFR <30 mL/min/1.73 m^2) and not on hemodialysis, rosuvastatin should be started at 5 mg once a day and not to exceed 10 mg once a day. In patients on hemodialysis, plasma concentrations were approximately 50% greater compared with healthy volunteers. Dose reduction should be considered in patients on rosuvastatin with unexplained proteinuria or hematuria.[14]

Pitavastatin

The dose range for pitavastatin is 1–4 mg once a day irrespective of meals. The recommended starting dose is 2 mg once a day. After initiation or titration, lipid levels should be analyzed at 4 weeks and the dose adjusted accordingly. Patients with moderate and severe renal impairment (i.e., GFR 30–59 mL/min/1.73 m^2 and 15–29 mL/min/1.73 m^2, respectively) as well as end-stage renal disease receiving hemodialysis, should receive a starting dose of 1 mg once a day, and a maximum dose of 2 mg once a day.[12]

Pitavastatin is contraindicated in patients simultaneously receiving cyclosporine (see the heading "Contraindications"). The dose should not exceed 1 mg/day in patients receiving erythromycin and not exceed 2 mg/day in patients on rifampicin. Pitavastatin should be used with caution in patients on fibrates and a dose reduction should be considered in patients on niacin.[12]

Contraindications

Statins are contraindicated in:[9-15]

- Women who are or may become pregnant because of the potential hazard to the fetus. They are also contraindicated in nursing mothers because of the potential for serious adverse effects in nursing infants. Statins are pregnancy category X drugs
- Patients with active liver disease or unexplained persistent elevation in hepatic transaminase elevations
- Patients with hypersensitivity to any component of the medication.

Simvastatin and lovastatin are contraindicated for co-administration with strong CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, posaconazole, HIV protease inhibitors, boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin, or nefazodone). Simvastatin is contraindicated in patients also taking gemfibrozil, cyclosporine, or danazol. Pitavastatin is contraindicated during concomitant administration of cyclosporine.[11,12,15]

Adverse Effects

Statins may cause myopathy (i.e., muscle ache or weakness) in conjunction with increases in creatine phosphokinase (CPK) >10 times the upper limit of normal (ULN), although rare (i.e., <4 events/10,000 patient years[19]). Myopathy may take the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria. The use of statins with CYP inhibitors increases the risk of myopathy and rhabdomyolysis and they should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.[19] Statin dose adjustment is recommended when taking gemfibrozil, cyclosporine, or drugs that inhibit the CYP3A4 or 2C9 pathways (Table 3). Large quantities of grape juice should be avoided while taking statins that are metabolized by CYP3A4 pathway (i.e., avoid >964 mL daily while taking simvastatin or lovastatin or >1.2 L while taking atorvastatin).[9,11,15]

TABLE 3

Statin Interactions: Maximum Recommended Statin Doses (mg) and Cautions[9-15]

	Simvastatin	*Lovastatin*	*Pravastatin*	*Atorvastatin*	*Rosuvastatin*	*Fluvastatin*	*Pitavastatin*
Itraconazole	0[h]	0[h]	—[i]	20 mg[a]	—[i]	—[i]	—[i]
Ketoconazole	0[h]	0[h]	—[i]	[b]	—[i]	—[i]	—[i]
Posaconazole	0[h]	0[h]	—[i]	[b]	—[i]	—[i]	—[i]
Fluconazole	—[i]	—[i]	—[i]	[b]	—[i]	20 mg BD	—[i]
Erythromycin	0[h]	0[h]	—[i]	[b]	—[i]	—[i]	1 mg
Clarithromycin	0[h]	0[h]	40 mg	20 mg[a]	—[i]	—[i]	—[i]
Telithromycin	0[h]	0[h]	—[i]	—[i]	—[i]	—[i]	—[i]
HIV protease inhibitors	0[h]	0[h]	—[i]	0–40 mg[c]	10 mg[c,d]	—[i]	—[i]
Telaprevir	0[h]	0[h]	—[i]	Avoid	—[i]	—[i]	—[i]
Boceprevir	0[h]	0[h]	—[i]	—[i]	—[i]	—[i]	—[i]
Nefazodone	0[h]	0[h]	—[i]	—[i]	—[i]	—[i]	—[i]
Gemfibrozil	0[h]	Avoid	Avoid	[b,d]	Avoid or 10 mg	[d]	[d]
Other fibrates	[d]	20 mg	[d]	[b,d]	[d]	[d]	[d]
> 1 g niacin/day	[b,d]	20 mg	[b]	[b]	[d]	[b]	[b]
Cyclosporine	0[h]	Avoid	20 mg	Avoid	5 mg	20 mg BD	0[h]
Danazol	0[h]	20 mg	—[i]	[d]	—[i]	—[i]	—[i]
Amiodarone	10 mg	40 mg	—[i]	—[i]	—[i]	—[i]	—[i]

(continued)

Table 3 *(continued)*

	Simvastatin	*Lovastatin*	*Pravastatin*	*Atorvastatin*	*Rosuvastatin*	*Fluvastatin*	*Pitavastatin*
Verapamil	10 mg	20 mg	—[i]	—[i]	—[i]	—[i]	—[i]
Diltiazem	10 mg	20 mg	—[i]	—[i]	—[i]	—[i]	—[i]
Amlodipine	20 mg	—[i]	—[i]	—[i]	—[i]	—[i]	—[i]
Ranolazine	20 mg	—[i]	—[i]	—[i]	—[i]	—[i]	—[i]
Digoxin	—[i]	—[i]	—[i]	[e]	—[i]	—[i]	—[i]
Warfarin	[f]	[f]	—[i]	—[i]	[d]	[f]	[f]
Rifampicin	—[i]	—[i]	—[i]	[g]	—[i]	—[i]	2
Phenytoin	—[i]	—[i]	—[i]	—[i]	—[i]	[d]	—[i]
Colchicine	[d]	—[i]	[d]	—[i]	—[i]	—[i]	—[i]

[a]Caution should be used at doses above this dose (lowest dose necessary should be used).
[b]Consider statin dose reduction when coadministering this drug.
[c]Refer to the section "Statin Dosage".
[d]Coadminister with caution.
[e]Coadministration of atorvastatin and digoxin can increase digoxin level by 20%, these patients should be monitored appropriately.
[f]Monitor INR when statin started.
[g]Administration of atorvastatin with inducers of CYP 450 3A4 (e.g., rifampicin and efavirenz) can lead to variable reduction in plasma concentration of atorvastatin. Thus, atorvastatin should be administered simultaneously with drugs that are 3A4 inducers since delaying the statin administration can result in reduced statin plasma concentration.
[h]Not to be used in this particular combination.
[i]No specific USFDA recommendation.

HIV, human immunodeficiency virus; CYP, cytochrome P450; INR, International Normalized Ratio; BD, twice a day.

Statins should be temporarily withheld or discontinued during an acute, serious condition, suggesting myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis (e.g., severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures). Statins should be prescribed with caution in patients with predisposing factors for myopathy: age >65 years, female gender, undertreated hypothyroidism, or renal impairment. The risk of myopathy is dose-related. About 5–10% of patients may report myalgias without CPK elevation during statin therapy. These symptoms typically resolve within 2 months of statin discontinuation.[20]

Statins have been associated with biochemical abnormalities of liver function with alanine aminotransferase (ALT) elevations in <1.2%, although increasing to 2.3% with higher doses. Liver enzyme changes generally occur in the first 3 months of therapy (possibly related to changes in the lipid components of the hepatocyte membrane, leading to an increase in permeability).[21] ALT and aspartate aminotransferase (AST) should be checked prior to the initiation of therapy and when clinically indicated. Serious liver injury with statins is rare and unpredictable in patients. Routine periodic monitoring of liver enzymes does not appear to be effective in detecting or preventing serious liver injury. However, if liver injury occurs and an alternative etiology is not found, statin therapy should not be restarted.[22]

Patients who develop increased transaminase levels should be monitored until the abnormalities resolve. Nearly 70% of cases resolve spontaneously.[21] Statins should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease.

Strategies to improve statin tolerance include decreasing the statin dose, intermittent dosing of long-acting statins (e.g., atorvastatin and rosuvastatin), or alternative LDL-lowering agents [e.g., niacin, bile acid sequestrants (BASs), or ezetimibe].[20]

Memory loss and confusion have been reported with statin use; however, these symptoms are not common, generally not serious, do not leads to cognitive decline, and resolve when the statin is discontinued. The time to onset is highly variable, ranging from one day to years after exposure. The reported cases do not appear to be associated with dementia, such as Alzheimer's disease.[22]

Statin therapy has been associated with a 9–13% increased risk of diabetes mellitus. However, the USFDA believes that the CV benefits of statins outweigh the small increased risk associated with an elevation in glucose levels.[22]

Clinical Evidence

In general, the reduction in LDL increases with statin dose and for most statins equivalent doses can achieve the targeted levels of LDL (Table 4). For example, fluvastatin XR 80 mg, lovastatin 40 mg, pravastatin 20–40 mg, simvastatin 20 mg, atorvastatin 10 mg, and pitavastatin 1–2 mg are equivalent in decreasing LDL by 30–40%. Greater than 40% reduction is expected with atorvastatin >20 mg, rosuvastatin >5 mg, and pitavastatin 4 mg. The HDL elevating and triglyceride lowering effects are similar among different statins of equivalent dose.[23]

Secondary prevention trials have demonstrated that statin therapy reduce coronary morbidity and mortality as well as overall mortality (Table 5).[9,10,13,15,24] Primary prevention trials have expanded the populations shown to benefit from statins to include patients without CHD.[9,11,13,14,24] Generic pricing has ameliorated concerns over cost effectiveness. In a metaanalysis of 10 primary prevention trials, statin therapy was associated with a significant 12% relative risk reduction (RRR) in all-cause mortality, a 30% RRR in major coronary events and a 19% RRR in major cerebrovascular events. Moreover, statin use was not associated with an increased risk of cancer.[25]

Choice of Therapy/Guidelines

In patients with elevated LDL and needing pharmacologic therapy, statins are considered first-line drug therapy.[1] For primary prevention, goal LDL targets are established by determining risk category. Secondary prevention guidelines recommend that an adequate dose of statin therapy should be used to achieve an LDL <100 mg/dL and at least a 30% lowering of LDL. A goal of LDL <70 mg/dL is reasonable in patients who are in the very high risk category. For patients with triglyceride levels >200 mg/dL, non-HDL values should be used as a guide to therapy.[8]

FIBRATES

Introduction

Fibrates reduce triglycerides and increase HDL. They are considered first-line therapy for severe hypertriglyceridemia and as a therapeutic option for mixed dyslipidemia, usually in combination with a statin.[26] Fibrates decrease triglyceride levels by 20–50%, with a more significant effect when baseline levels are higher.[27] HDL increases in the range of 10–20%, and is also related to the severity of the baseline abnormality. LDL may decrease by 5–20%, but LDL may increase if high triglycerides are present.[1]

TABLE 4

Changes in Lipoprotein Levels with Statin Therapy[9-15]

Statin	*Dose (mg)*	*Low-density lipoprotein cholesterol (% change)*	*High-density lipoprotein cholesterol (% change)*	*Triglycerides (% change)*
Lovastatin				
—	10	−21	5	−10
	20	−27	6	9
	40	−31	5	−8
Fluvastatin				
Baseline triglycerides ≤ 200	20	−22	3	−12
	40	−25	4	−14
	40 BD	−36	6	−18
	80 XR	−35	7	−19
Baseline triglycerides > 200	20	−22	6	−17
	40	−24	7	−20
	40 BD	−35	9	−23
	80 XR	−33	11	−25
Rosuvastatin				
Baseline triglycerides ≤ 250	5	−45	13	−35
	10	−52	14	−10
	20	−55	8	−23
	40	−63	10	−28

(continued)

Table 4 *(continued)*

Statin	*Dose (mg)*	*Low-density lipoprotein cholesterol (% change)*	*High-density lipoprotein cholesterol (% change)*	*Triglycerides (% change)*
Baseline triglycerides > 250	5	−28	3	−21
	10	−45	8	−37
	20	−31	22	−37
	40	−43	17	−43
Pravastatin				
Baseline triglycerides ≤ 200	10	−22	7	−15
	20	−32	2	−11
	40	−34	12	−24
	80	−37	3	−19
Baseline triglycerides > 200	40	−32	7	−21
Dysbetalipoproteinemia	40	−30 to −41	5 to 6	−12 to −24
Pitavastatin				
—	1	−32	8	−15
	2	−36	7	−19
	4	−43	5	−18
Atorvastatin				
Baseline triglycerides ≤ 250	10	−39	6	−19
	20	−43	9	−26
	40	−50	6	−29
	80	−60	5	−37

(continued)

Table 4 *(continued)*

Statin	*Dose (mg)*	*Low-density lipoprotein cholesterol (% change)*	*High-density lipoprotein cholesterol (% change)*	*Triglycerides (% change)*
Baseline triglycerides >250	10	−26	14	−41
	20	−30	11	−39
	80	−40	8	−52
Dysbetalipoproteinemia	10	—	—	−39
	80	—	—	−53
Simvastatin				
—	5	−26	10	−12
	10	−30	12	−15
	20	−38	8	−19
	40	−41	9	−18
	80	−47	8	−24
Baseline triglycerides elevated (median¸ 404)	40	−28	11	−29
	80	−37	15	−34
Dysbetalipoproteinemia	40		7	−41
	80		7	−38

BD, twice a day; XR extended release.

TABLE 5

Statin Prevention Trials							
Statin	*Trial (Year)*	*Dose (mg)*	*Population (Number of patients)*	*Baseline LDL*	*Duration (Years)*	*End-points*	*Relative risk reduction (p value)*
Primary prevention							
Pravastatin	West of Scotland (1995)[13]	40	LDL >155 (6,595 men)	272	4.8	CHD death, non-fatal MI	31% (p = 0.0001)
Atorvastatin	ASCOT (2003)[9]	10	Hypertensive and >3 other risk factors [10,305 (81% men)]	132	3.3	Fatal and non-fatal CHD	36% (p = 0.0005)
Atorvastatin	CARDS (2004)[9]	10	Diabetes mellitus + >1 additional risk factor [2,838 (68% men)]	117	3.9	MI, CHD death, unstable angina, coronary revascularization, and stroke	37% (p = 0.001)
Rosuvastatin	JUPITER (2008)[14]	20	LDL <130, hs-CRP >2 mg/dL (17,802)	108	2	CV death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina or arterial revascularization	44% (p < 0.001)
Lovastatin	AFCAPS/ TexCAPS (1998)[11]	20–40	LDL 130–190; 63% with >1 risk factor (6,605)	150	5.1	MI, unstable angina, and sudden cardiac death	37% (p < 0.001)
Secondary prevention							
Fluvastatin	LIPS (2002)[10]	40 BD vs. placebo	CAD after PCI (1,677)	131	3.9	Recurrent cardiac events	22% (p = 0.013)

(continued)

Table 5 *(continued)*

Statin	*Trial (Year)*	*Dose (mg)*	*Population (Number of patients)*	*Baseline LDL*	*Duration (Years)*	*End-points*	*Relative risk reduction (p value)*
Pravastatin	LIPID (1998)[13]	40 OD vs. placebo	CAD (MI or unstable angina) (7,498 men, 1,516 women)	150	5.6	CHD death	24% (p = 0.0004)
Pravastatin	CARE (1996)[13]	40 OD vs. placebo	Previous MI (3,583 men, 576 women)	139	4.9	CHD death and non-fatal MI	24% (p = 0.003)
Atorvastatin	TNT (2005)[9]	80 vs. 10 OD	CAD and LDL <130 mg/dL (on atorvastatin 10) [10,001 (81% men)]	<130	4.9	CHD death, non-fatal MI, resuscitated cardiac arrest, and fatal/non-fatal stroke	22% (p = 0.0002)
Simvastatin	4S (1994)[15]	20 [could titrate to 10 (n = 2) or 40 (37%)]	CAD [4,444 (81% men)]	188	5.4	Overall mortality	30% (p = 0.0003)
Simvastatin	HPS (2002)[15]	40	CAD, occlusive non-CAD arterial diease, or DM [20,536 (75% men)]	132	5	Overall mortality and CHD mortality	13% (p = 0.0003) 18% (p = 0.0005)

ASCOT, Anglo-Scandinavian Cardiac Outcomes Trial; CARDS, Collaborative Atorvastatin Diabetes Study; JUPITER, Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; AFCAPS/TexCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study; LIPS, Lescol Intervention Prevention Study; LIPID, Long-Term Intervention with Pravastatin in Ischemic Disease; CARE, Cholesterol and Recurrent Events; TNT, Treating to New Target; 4S, Scandinavian Simvastatin Survival Study; HPS, Heart Protection Study; LDL, low-density lipoprotein cholesterol; MI, myocardial infarction; CV, cardiovascular; CHD, coronary heart disease; CAD, coronary artery disease; hs-CRP, high-sensitivity C-reactive protein; PCI, percutaneous coronary intervention; DM, diabetes mellitus, BD, twice a day; OD, once a day.

Fibrates reduce small, dense LDL by promoting a shift to larger, more buoyant particles, which are less susceptible to oxidation and possess higher binding affinity for the LDL receptor.[28,29]

Fibrates are agonists for the peroxisome proliferator receptor-α (PPAR-α) group of nuclear receptors, which control expression of genes that play important roles in lipid cholesterol transport and metabolism. The PPAR-α receptors are located in liver, kidney, heart, and skeletal muscle cells where higher amounts of fatty acids are metabolized.[29] Fibrates also have pleiotropic effects on endothelial function, vascular inflammation, and coagulation/fibrinolytic pathways.[26]

Drugs under the Category

Fenofibrate, fenofibric acid, gemfibrozil, and bezafibrate are the currently available fibrates. There are many available dosing formulations of fenofibrate for patients with and without renal dysfunction. The differences among strengths are in part related to bioavailability, which varies with particle size (i.e., micronized formulations have lower dose strengths because of improved bioavailability of the smaller particles).

Mechanism of Action

Multiple mechanisms are involved through which fibrates lower plasma triglycerides levels.[29,30]

- Suppression of fatty acid synthesis
- Increase in fatty acid catabolism by stimulation of mitochondrial uptake and β-oxidation of fatty acids
- Decrease in production of triglycerides by inhibition of diacylglycerol acyl transferase 2 (DGAT2), an enzyme that catalyzes formation of triglyceride from diglyceride.
- Increase in triglyceride hydrolysis of VLDL (and chylomicrons) by stimulation of lipoprotein lipase (LPL) expression. LPL action is also potentiated by the decreased expression of hepatic apoprotein-C3, a lipoprotein that attenuates LPL activity.

As VLDL level is reduced, plasma CETP activity is attenuated. This results in a shift of smaller to larger, more buoyant, LDL particles and diminished triglyceride content in HDL particles with increased cholesterol ester content. The formation of LDL particles with a higher affinity for the LDL receptor increases their removal and large HDL is less vulnerable to renal excretion.[31]

Fibrates promote reverse cholesterol transport (RCT) and increase HDL in part through an increase in tissue production of

apo-A1 and apo-A2. Apo-1 is a structural protein for HDL and an activator of lecithin cholesterol acyl transferase. Apo-2 is also a structural protein for HDL and an activator of hepatic lipase. The HDL particle profile then shifts from a predominance of small, protein-rich, lipid-poor HDL^3 to large, cholesterol ester rich HDL^2 particles. Fibrates may upregulate adenosine triphosphate (ATP) binding cassette A1 (ABC A1) on the surface of macrophages (which promotes conversion of unstable nascent HDL to stable spherical particles) and scavenger receptor B1 (SRB1) on the surface of hepatocytes.[29-31]

Nonlipid changes with fibrates may help account for the decreased risk of CV disease with their use. For example, fibrates reduce the inflammatory and prothrombotic markers, including C-reactive protein and lipoprotein-associated phospholipase A2.[29]

Fibrate therapy appears to have a synergistic effect with niacin on HDL, since their mechanisms of action are complementary. Fibrates stimulate hepatic production of apo-A1 while niacin inhibits its catabolism.[31]

The decreased uric acid levels seen in the fenofibrate trials are related to an increase in the urinary excretion of uric acid.

Pharmacology

Gemfibrozil is completely absorbed after oral administration, reaching peak plasma concentration 1–2 hours after dosing. Both the rate and extent of absorption of the drug are increased when administered 0.5 hour before meals, so dosing is recommended before meals. Approximately 70% of an administered dose is excreted in the urine, mostly as the glucuronide conjugate, while <2% is excreted as unchanged gemfibrozil. Gemfibrozil is highly bound to plasma proteins and there is a potential for displacement interactions with other drugs. The elimination half-life is approximately 1.1 hours.[29,32]

Fenofibrate is a prodrug of the active moiety, fenofibric acid. Fenofibrate is converted by ester hydrolysis to fenofibric acid. Protein binding is approximately 99%. Fenofibric acid is metabolized by conjugation with glucuronic acid and primarily excreted in the urine (60%) in the form of fenofibric acid and fenofibric acid glucuronide. Approximately 25% is excreted in the feces. Neither fenofibrate nor fenofibric acid undergo oxidative metabolism by CYP P450 to a significant extent. The elimination half-life is approximately 20 hours.[29,33-35]

Bezafibrate has an elimination half-life of 1–2 hours and protein binding of 94–96%. Excretion is almost exclusively renal, with 95% recovered in the urine.[36]

Indications

Fibrates are indicated as adjunctive therapy to diet for treatment of adult patients with severe hypertriglyceridemia.[32-36]

Fibrates are also indicated to reduce elevated LDL, total cholesterol, triglycerides, and apo-B and to increase HDL in adult patients with primary hypercholesterolemia or mixed dyslipidemia.[33-36] However, as noted above, fibrates have a variable effect on LDL and may increase LDL in patients with atherogenic dyslipidemia (i.e., elevated triglycerides and low HDL). Therefore, the potential benefit of a fibrate in treating patients with elevation of LDL only is not likely to outweigh the risk of potential side effects. Fibrates are not indicated for the treatment of patients with isolated low HDL as their only lipid abnormality.[32] Fenofibric acid is the only fibrate approved by the USFDA for use with a statin.[35]

Dosage

Fenofibrate

The recommended dose of fenofibrate will vary on the product used. In the USA, the initial dose is 120–160 mg once a day, depending on the trade name. The recommended initial dose of fenofibric acid is 135 mg once a day.[35]

For severe hypertriglyceridemia, the initial recommended dosing is between the low and high dose, "individualized according to patient response."[33-36]

For patients with impaired renal function, the initial dose of fenofibrate should be lowered. Low dose fenofibrate is recommended when GFR is <60 mL/min/1.73 m^2 and may be given without regard to meals.[33,34]

Gemfibrozil

The recommended dose of gemfibrozil is 600 mg twice a day, given 30 minutes before the morning and evening meals.[32] Dose adjustment is recommended according to GFR with a dose decrease to 600 mg once a day when GFR is <60 mL/min/1.73 m^2. However, since half-life is independent of renal function, dose adjustment may not be necessary in patients with renal transplant or chronic renal disease.[37,38] Fibrate use is not recommended in patients who undergo long-term dialysis, because of the narrow margin between effective and toxic doses.[37]

Bezafibrate

The recommended dosage of bezafibrate is 200 mg twice or thrice a day (or 400 mg modified release formula daily), with a dose adjustment according to renal function. The sustained release form is contraindicated if GFR is <60 mL/min/1.73 m^2.[36]

Since BAS may bind other drugs given concurrently, patients should take fibrates at least 1-hour before or 4–6 hours after a BAS to avoid impeding its absorption.

Fibrate therapy should be withdrawn in patients who do not have an adequate response after 2 months of treatment with the maximum dose.

Contraindications

Contraindications include hypersensitivity reactions to the medication or history of active liver disease (including those with primary biliary cirrhosis) and unexplained persistent liver function abnormalities, severe renal dysfunction (including patients receiving dialysis), or gallbladder disease.

Fibrates are pregnancy category C drugs and should be used during pregnancy only if the benefit justifies the potential risk to the fetus. Fibrates are contraindicated in nursing mothers because of the tumorigenicity seen in animal studies.[32-36]

Adverse Effects

Myopathy and rhabdomyolysis have been reported with fibrate use and the risk is increased when fibrates are coadministered with a statin, particularly in elderly patients and in patients with diabetes mellitus, renal failure, or hypothyroidism.[27,32-36] Approximately 1% of patients in fibrate trials withdrew because of muscle discomfort.[31] The risk of rhabdomyolysis is increased when fibrates, in particular gemfibrozil, are coadministered with a statin. The rate of myopathy for gemfibrozil with a statin is estimated to be 33 times more that that of a statin with fenofibrate.[37] The combination should be avoided unless the benefit of further alterations in lipid levels is likely to outweigh the increased risk of this drug combination. The increased risk associated with the gemfibrozil-statin combination is likely related to the inhibition of statin glucuronidation by gemfibrozil. If gemfibrozil is necessary, fluvastatin may be an appropriate option, since there is no significant effect of gemfibrozil on its concentration.[27,31,37]

In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial, there were no cases of rhabdomyolysis reported in approximately 1,000 patients taking combination

fenofibrate-statin therapy.[39] In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, 40% of participants reported muscle symptoms during the trial, but the number reporting such symptoms was essentially identical in both the fenofibrate/statin and placebo/statin groups.[40] In addition, such complaints were rarely associated with an elevation in CPK >10 times ULN (0.4% in fenofibrate and 0.3% in placebo).[40,41]

Fenofibrate at doses of 96–145 mg/day has been associated with increases in serum hepatic transaminases. In a pooled analysis of 10 placebo-controlled trials, increases to >3 times the ULN occurred in 5.3% of patients taking fenofibrate (compared to 1.1% on placebo).[33,34] The incidence of increases in transaminases related to fenofibrate therapy appears to be dose related. When transaminase determinations were followed either after discontinuation of treatment or during continued treatment, a return to normal was usually observed. Liver function tests, including ALT, should be periodically monitored during therapy and therapy discontinued if enzyme levels persist >3 times the ULN.[33,34]

Fenofibrate can reversibly increase serum creatinine levels by 10–20%,[38] so renal function should be monitored periodically in patients with renal impairment. Etiology of the reversible increase in creatinine is uncertain, although fibrates may increase creatinine production with no attenuation of GFR.[37] Fenofibrate and bezafibrate are more likely than gemfibrozil to increase creatinine.[29] In the ACCORD trial, the study drug was discontinued by 2.4% in fenofibrate and 1.1% in the placebo group because of a decrease in the estimated GFR. This effect of fenofibrate was also seen in the FIELD trial. A serum creatinine should be checked before initiating fibrate therapy, and routine creatinine monitoring is recommended in patients with preexisting chronic kidney disease.[37]

Fibrates alter biliary composition, reducing bile acid content and increasing cholesterol content. Increased biliary secretion of cholesterol may be a major mechanism for cholesterol removal from the body, but it increases lithogenicity of bile.[27,37] While an early clinical trial with clofibrate demonstrated that cholecystectomies occurred 2–3 times more often than in placebo-treated patient, the association with gemfibrozil and fenofibrate is less clear. A recent meta-analysis demonstrated no increased risk of gallbladder disease.[42] However, fibrate therapy should be discontinued if gallstones are found and are not recommended in the presence of preexisting gallbladder disease.[31]

Pancreatitis has been reported in patients on fenofibrate or gemfibrozil. This may represent a failure of efficacy in patients

with severe hypertriglyceridemia, a direct drug effect, or a secondary phenomenon, mediated by biliary tract stone or sludge formation with common bile duct obstruction.[32-36]

Pulmonary embolism occurred in 1% of the fenofibrate group, compared to 0.7% in the placebo group (p = 0.022) in the FIELD trial.[39] Treatment with fibrates and fenofibrate, in particular, is known to increase homocysteine levels, an effect which may be mediated by a direct PPAR-α action.[37] However, gemfibrozil does not appear to raise homocysteine and no change in thromboembolic events were reported in the Helsinki Heart Study (HHS) or Veterans Administration HDL Intervention Trial (VA-HIT).[27,43,44] The dosage of coumarin anticoagulants may need to be adjusted during fibrate therapy to prevent bleeding complications.[37]

Clinical Evidence

Lipid effects of fibrates are generally additive to those of statin monotherapy,[45,46] especially with respect to improvements in triglycerides and HDL, making the combination a useful option to manage patients with combined dyslipidemia and metabolic syndrome (Table 6).[27,30] However, the addition of gemfibrozil rather than fenofibrate (or fenofibric acid) to a statin is associated with an increased risk of rhabdomyolysis (see the heading "Adverse Effects").

Angiographic trials have shown that fibrates retard progression of atherosclerotic coronary artery disease (CAD).[31] Results from clinical trials have not been consistent in their finding of impact on CV events and mortality. While fibrate therapy is associated with a clinically important decrease in nonfatal MI,

TABLE 6

Changes in Lipoprotein Levels with Fenofibrate (or Fenofibric Acid) as Monotherapy and in Combination with Statin Therapy

Trials	*LDL (% change)*	*HDL (% change)*	*Triglycerides (% change)*
SAFARI (2005)[45]			
Simvastatin 20 mg	−26	10	−20
Simvastatin 20 mg + Fenofibrate 160 mg/day	−31*	19*	−43*
Goldberg et al. (2009)[46]			
Atorvastatin 20 mg	−37	6	−16
Atorvastatin 20 mg + Fenofibric acid 135 mg/day	−34	14**	−46*

*p < 0.001 vs. statin.
**p = 0.005 vs. statin.
LDL, low-density lipoprotein; HDL, high-density lipoprotein; SAFARI, simvastatin plus fenofibrate for combined hyperlipidemia.

they have little effect, if any, on all-cause mortality.[42,47] However, subgroup analyses have demonstrated that in patients with atherogenic dyslipidemia (i.e., high triglyceride levels and low HDL), fibrates may exert a greater cardioprotective effect than in the general populations studied (Table 7).[26,39-41,43,44,48-50] A meta-analysis of the 5 major fibrate trials found that fibrate-treated patients with atherogenic dyslipidemia had a 30% RRR of major CV events.[51]

Fibrate therapy is associated with a reduction in microvascular complications of diabetes mellitus, including progression of albuminuria and diabetic retinopathy.[42] The reduced risk of progression of diabetic retinopathy appears to be mainly restricted to patients with baseline retinopathy.[26]

Choice of Therapy/Guidelines

Treatment of elevated triglyceride levels depends on the cause and severity of elevation. In patients with triglycerides >500 mg/dL, fibrate therapy should be started to prevent pancreatitis.[1,8] Onlyafter triglycerides are <500 mg/dL, attention should be turned to LDL lowering in order to reduce the risk of CHD.[1]

In patients with mixed dyslipidemia, after achieving goal LDL, non-HDL becomes the secondary target when triglycerides are 200–499 mg/dL. Aside from weight reduction and increased physical activity, drug therapy with fibrates (or nicotinic acid) can be added to statin therapy to achieve the non-HDL goal.[1,8] When combination therapy is necessary to achieve non-HDL goal, a consensus guideline preferred the combination of statin and niacin over statin and fibrate because of better evidence for the former in reducing CV risk and the potential for myopathy with combination statin and fibrate therapy (especially if the fibrate is gemfibrozil).[52]

Subgroup and *post hoc* analyses imply mortality benefits for treating patients with elevated triglycerides and low HDL. However, there are no studies that prospectively examine a patient population with the metabolic syndrome and, therefore, the true mortality benefit of fibrates remains to be determined.[31] The combination of statin and fibrate should be reserved for high-risk patients, only after optimal control of LDL has been achieved with statin therapy.[53]

BILE ACID SEQUESTRANTS

Introduction

BASs are large polymers that bind the negatively charged bile acids and bile salts in the small intestine. As bile acids decrease, hepatic

TABLE 7

Fibrate Clinical Trials

Trial (Year)/ Duration (Years)	*Fibrate (Dose)*	*Patients (Number)*	*Population*	*Primary outcome*	*LDL (% change)*	*HDL (% change)*	*TG (% change)*	*Outcomes*		
								RRR in primary end-point: entire cohort (p value)	*Lipid subgroup criterion*	*RRR in primary end-point: subgroup (p value)*
HHS (1987, 1992)[43,48]/5	Gemfibrozil (600 mg BD)	4,081 M (1° prevention)	Non-HDL ≥200 + No CAD	Fatal or nonfatal MI, cardiac death	−11	11	−35	−34% (0.02)	TG ≥204, HDL <42, BMI >26 kg/m^2	−78% (0.005)
VA-HIT (1999)[44]/5.1	Gemfibrozil (600 mg BD)	2,531 M (2° prevention)	HDL ≤40 + LDL ≤140 + CAD	Nonfatal MI, death from CHD	0	6	−31	−22% (0.006)	HDL <31.5 TG ≥151	−30% (0.003)* −27 (0.01)*
BIP (2000)[49]/6.2	Bezafibrate (400 mg/day)	3,090 (91% M) (2° prevention)	HDL ≤45 + LDL ≤180 + TG ≤300 + CAD	Fatal or non-fatal MI or sudden death	−6	18	−21	−7.3% (0.24)	TG ≥200 + HDL <35	−42% (0.02)

(continued)

Table 7 *(continued)*

Trial (Year)/ Duration (Years)	*Fibrate (Dose)*	*Patients (Number)*	*Population*	*Primary outcome*	*LDL (% change)*	*HDL (% change)*	*TG (% change)*	*Outcomes*		
								RRR in primary end-point: entire cohort (p value)	*Lipid subgroup criterion*	*RRR in primary end-point: subgroup (p value)*
FIELD (2005, 2009)[39,50]/5	Fenofibrate (200 mg/day)	9,795 (63% M) (1° + 2° prevention)	Diabetic + TC 116–251 + TC/HDL >4 or TG 87–443	Nonfatal MI or CHD death	−12	5	−29	−11% (0.16)	TG ≥204 + HDL <42	−27% (0.005)
ACCORD (2010)[40]/4.7	Fenofibrate (160 mg/day)	5,518 (69% M) (1° + 2° prevention)	Diabetic on statin + LDL 60–180 + HDL< 50–55 + TG <400	Nonfatal MI, nonfatal stroke, or cardiac death	−11	6	−21	−8% (0.32)	TG ≥204 + HDL ≤34	−31% (0.057)

*Includes confirmed stroke.

HHS, Helsinki Heart Study; VA-HIT, Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial; BIP, Bezafibrate Infarction Prevention; FIELD; Fenofibrate Intervention and Event Lowering in Diabetes; ACCORD; Action to Control Cardiovascular Risk in Diabetes, BD, twice a day; HDL, high-density lipoprotein; LDL, low-density lipoprotein; CAD, coronary artery disease; TG, triglyceride; MI, myocardial infarction; BMI, body mass index; RRR, relative risk reduction; TC, total cholesterol; M, men.

cholesterol is converted to bile acid and there is a compensatory increase in LDL receptors. Monotherapy with BAS lowers LDL by 5–30% in a dose-dependent manner.[54]

Cholestyramine and colestipol were initially available as water-insoluble powder, but colestipol was subsequently developed as a tablet form to improve palatability and compliance.[55] Colesevelam was developed with a unique polymer structure accounting for its gelatinous structure (in contrast to the sandy consistency of cholestyramine and colestipol) and is a high-capacity bile acid binding molecule.

Mechanism of Action

During normal digestion, bile acids are secreted in the bile from the liver and gallbladder into the intestine. Bile acids emulsify the fat and lipid material present in food, facilitating dietary fat and lipid-soluble vitamin absorption. A major portion of the secreted bile acid is reabsorbed from the intestines and returned to the liver via the portal circulation, thus, forming the enterohepatic cycle.[56] However, about 5% escape absorption and additional bile acids are synthesized from cholesterol by the liver.

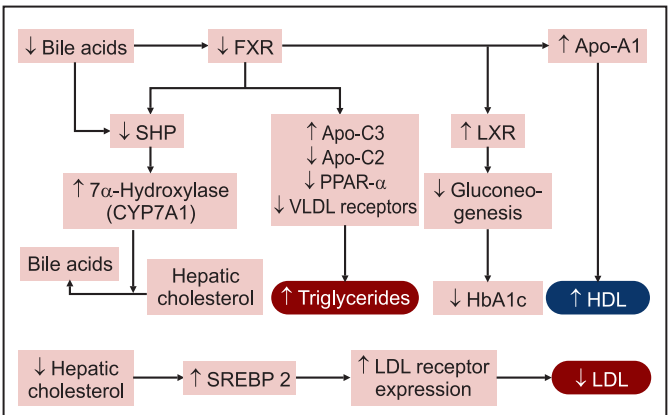
Bile acids are ligands for the nuclear receptor farnesoid X receptor (FXR), and as bile acid levels and FXR activity decrease during BAS therapy, there is increased conversion of cholesterol into bile acids by increased 7α-hydroxylase activity (which is regulated by the nuclear receptor Sterol Heterodimer Partner)[55,56] (Figure 6). The resulting decrease in hepatocyte cholesterol content promotes an increase in LDL receptors and increased clearance of LDL from the circulation.[56]

BAS increases HDL by increasing synthesis of apo-A1 (the major lipoprotein of HDL),[55,56] ABCA1, and hepatic lipase (an enzyme involved in the catabolism of HDL). While the expression of SRB1 and CETP activity may be increased with the potential to decrease HDL, the net effect of BAS is a modest increase in HDL.[55,57]

The likely mechanism for improvement in glucose levels during BAS therapy is deactivation of FXR and increased liver X receptor activity, which may increase insulin secretion from the pancreas and improve adipose tissue functionality.[55]

Pharmacology

BASs are not absorbed (<0.2% is excreted in the urine) or metabolized, and there is no interference with systemic drug metabolizing enzymes.[54,58,59]



SHP, sterol heterodimer partner; SREBP2, sterol regulatory element binding protein 2; LDL, low-density lipoprotein; FXR, farnesoid X receptor; LXR, liver X receptor; PPAR-α, peroxisome proliferator receptor-α; Apo, apolipoprotein; HDL, high-density lipoprotein.

FIGURE 6. Mechanism of action of bile acid sequestrants (BASs). The reduction in bile acids by BASs reduces activity of the FXR. LDL levels are reduced due to increased clearance by receptors which compensates for the reduced hepatic cholesterol (due to conversion to bile acids). HDL increases with increased expression of apolipoprotein-A1. Triglycerides increase due to reduced expression of PPAR-α and changes in the cofactors apo-C2 and C3 activity. Improvement in glucose levels is related to increased expression of the LXR.

Indication

BASs are indicated to reduce elevated LDL as monotherapy or in combination with a statin. BASs improve glycemic control in adults with type 2 diabetes mellitus, and colesevelam is approved for use as an adjunct to diet and exercise; however, it has not been studied as monotherapy or in combination with a dipeptidyl peptidase-4 inhibitor and has not been extensively studied in combination with thiazolidinediones.[58]

In addition to combining statins with BAS, the combination of niacin and BAS may achieve greater LDL reduction than BAS alone.[54]

Dosage

Cholestyramine

The recommended starting dose is 4 g (i.e., one 4 g packet or scoop of the bulk form) once or twice a day. The recommended maintenance daily dose is 8–16 g, divided into 2 doses. Dose increments should be gradual with periodic assessment of lipid levels at intervals of 4 weeks. The maximum recommended daily dose is 24 g. The suggested time of administration is mealtime but may be modified to avoid absorption of other medications.

Although the recommended dosing schedule is twice a day, cholestyramine may be administered in 1–6 divided doses during the day.[60]

Colestipol

The starting doses should be 5 g (i.e., approximately 1 teaspoon) of granules once or twice a day, or two 1 g tablets once or twice a day. Dosage increases of one 5 g dose/day of granules, or 2 g/day of tablets should occur every 1–2 months. The dose is 5–30 g/day of granules or 2–16 g/day of tablets given once or in divided doses.[59]

Colesevelam

The dosage is six 625 mg tablets once a day or divided in two doses. The medication should be taken with a meal and liquid. It can be dosed at the same time as a statin or the two drugs can be dosed apart. Colesevelam has greater bile acid-binding capacity and affinity than that of cholestyramine or colestipol, so it can be used at lower doses. After initiation, lipids should be checked in 4–6 weeks. No specific recommendation or dosage adjustments are recommended when colesevelam is administered to patients with hepatic impairment.[58]

The decline in LDL is usually evident within 2 weeks with colesevelam and by 1 month with colestipol and cholestyramine.[58-60]

Contraindications

BASs are contraindicated in patients with a history of bowel obstruction, complete biliary obstruction, elevated triglycerides >500 mg/dL, and a history of triglyceride-induced pancreatitis or hypersensitivity.

Cholestyramine and colestipol are pregnancy category C drugs. Their use during pregnancy or lactation, or by women of childbearing age requires that potential benefit be weighed against hazard to mother or child.[59,60]

Colesevelam is a pregnancy category B drug and should be used during pregnancy only if clearly needed. It is not expected to be excreted in human milk because it is not absorbed systemically from the GI tract.[58]

The effect of BAS on the absorption of fat-soluble vitamins has not been studied in pregnant women.[58-60]

Adverse Effects

BAS may produce or worsen preexisting constipation. To minimize GI side effects with BAS, low initial doses are suggested.

For constipation, increased fluid and dietary fiber intake are recommended and stool softeners may be added as needed. Less frequent adverse effects include abdominal discomfort and/or pain, flatulence, nausea, and vomiting. BASs are not recommended in patients with gastroparesis, other gastrointestinal motility disorders, in those who have had major gastrointestinal motility tract surgery or who may be at risk of bowel obstruction and those with complete biliary tract obstruction. Because of tablet size, colesevelam and colestipol should be used with caution in patient with dysphagia or swallowing disorders, since they may cause dysphagia or esophageal obstruction.[58-60]

BAS can increase triglycerides. For example, colesevelam may increase triglycerides by 5% in patients with primary hyperlipidemia; however, median increases in triglycerides of 18–22% have been reported in clinical studies treating patients with type 2 diabetes mellitus.[58] Decreased FXR activity decreases apo-C2 activity (which is an activator of LPL) and increases apo-C3 activity (which is an inhibitor of LPL). The net effect of BAS on these cofactors is to decrease LPL and, therefore, the lipolysis of triglyceride rich particles, such as VLDL and chylomicrons. A decrease in PPAR-α activity also results in decreased fatty acid oxidation.[56]

Chronic use of BAS may be associated with increased bleeding tendency due to hypoprothrombinemia and vitamin K deficiency. In addition, a reduction of serum or red cell folate has been reported with chronic use of cholestyramine and colestipol.[59,60]

Prolonged use of cholestyramine or colestipol may produce hyperchloremic acidosis, since they are chloride forms of an anion exchange resin. The chloride anion of the resin can be replaced by other anions, usually those with greater affinity for the resin than chloride. Caution should be exercised in patients with renal insufficiency, volume depletion, and on spironolactone therapy.[59,60]

BAS may decrease absorption of fat-soluble vitamins.[58-60] Patients on vitamin therapy should take vitamins at least 4 hours before the BAS. If a patient is taking other medications in addition to cholestyramine or colestipol, the other medications should be taken 1 hour before or 4 hours after the BAS. Colesevelam is a more specific BAS, but may reduce GI absorption of some drugs. Drugs with a known interaction that should be taken at least 4 hours prior to a colesevelam dose are: cyclosporine, glyburide, l-thyroxine, oral contraceptive containing ethinyl estradiol and norethindrone, and phenytoin.[58]

Clinical Evidence

Randomized controlled trials using coronary arteriography have demonstrated that BAS as monotherapy or in combination with niacin or lovastatin slows progression and promotes regression of atherosclerotic lesions in the coronary arteries of patients with CHD[55,59,60] (Table 8).

The most significant outcome trial was the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT), which demonstrated a 19% decrease in risk of combined CHD death and nonfatal MI in men with elevated cholesterol treated with 24 g/day of cholestyramine.[61] The effect of colesevelam on CV morbidity and mortality has not been determined.[58]

In combination trials, the addition of colesevelam to a statin resulted in an additional 10–16% reduction in LDL above that seen by the statin alone (Table 9). Advantages of the statin-BAS combination are that both drug classes have been shown to improve LDL and outcomes (although not studied with colesevelam) and there may be reduced blood glucose in diabetics with the addition of a BAS. Disadvantages are the need to avoid absorption interference of statins if taken simultaneously with colestipol and cholestyramine.[58]

Colesevelam in combination with ezetimibe reduces LDL by 32% with nonsignificant increases in HDL and triglyceride levels.[55]

Choice of Therapy/Guidelines

If treatment with a statin does not achieve the LDL goal selected for a patient, intensification of LDL lowering drug therapy with a BAS is reasonable.[8] In addition, BAS provides an alternative to statins as initial drug therapy for LDL-lowering.[1] Recommendations for limiting use in patients with elevated triglycerides vary from restricting use in patients with triglycerides >200 to >300 mg/dL.[8,58] They are contraindicated when triglycerides are >500 mg/dL.[8]

The combination of BAS and ezetimibe can have additive effects on LDL lowering, and is useful for patients who do not tolerate a statin or for whom statins are contraindicated.[54]

NIACIN

Introduction

Niacin reduces apo-B-containing particles, including LDL, VLDL, triglycerides, and lipoprotein(a) but is most commonly clinically utilized because it is currently the most effective available

TABLE 8

Clinical Studies of Bile Acid Sequestrants

Study (Year)	*Type of study*	*Number of patients*	*Heart disease*	*Duration (Years)*	*Study drug*	*LDL (% change)*	*HDL (% change)*	*Results*
LRC-CPPT (1984)	Outcome	3,806 men	Without CHD	7.4	Cholest 24 g/day	−20.3	1.6	19% reduction in fatal and nonfatal MI in treated group
NHLBI (1984)	Angiography	116 men + women	CHD	5	Cholest 24 g/day	−26	8	Significant decreased progression in coronary artery lesions >50% stenosis at baseline
CLAS 1 (1987)	Angiography	162 men	CABG	2	Colest 30 g/day + niacin 4.3 g/day	−43	37	Significant increased regression and decreased progression in treated group than placebo group
CLAS 2 (1990)	Angiography	103 men	CABG	4	Colest 30 g/day + niacin 4.2 g/day	−40	37	Significant increased regression and decreased progression in treated group than placebo group
FATS (1990)	Angiography	38 men	CAD + FH of CVD	2.5	Colest 30 g/day + lovastatin 40 mg/day	−46	15	Significant increased regression, decreased progression, and decreased CHD events compared with conventional therapy

(continued)

Table 8 *(continued)*

Study (Year)	*Type of study*	*Number of patients*	*Heart disease*	*Duration (Years)*	*Study drug*	*LDL (% change)*	*HDL (% change)*	*Results*
FATS (1990)	Angiography	36 men	CAD + FH of CVD	2.5	Colest 30 g/day + niacin 4 g/day	−32	43	Significant increased regression, decreased progression, and decreased CHD events compared with conventional therapy
UCSF-SCOR (1990)	Angiography	72 men + women	Type IIa	2	Colest, niacin ± lovastatin	−39	26	Mean within-patient change in percent area of stenosis was significantly greater in diet than drug intervention group with the treatment group demonstrating mean regression and the diet group demonstrating mean progression
STARS (1992)	Angiography	90 men	CHD	3	Cholest 16 g/day	−35.7	4	Greater increase in coronary diameter with cholest + diet than diet alone

Colest, colestipol; cholest, cholestyramine; FH, family history; CHD, coronary heart disease; type IIa, familial hypercholesterolemia; LRC-CPPT, Lipid Research Clinics Coronary Primary Prevention Trial; NHLBI, National Heart, Lung and Blood Institute; CLAS, Cholesterol Lowering Atherosclerosis Study; CABG, coronary artery bypass graft; FATS, Familial Atherosclerosis Treatment Study; UCSF-SCOR, University of California, San Francisco Specialized Center of Research; STARS, St Thomas Atherosclerosis Regression Study.

Adapted from: Bays HE, Goldberg RB. The 'forgotten' bile acid sequestrants: is now a good time to remember? *Am J Ther.* 2007;14(6):567-80, *with permission*.

TABLE 9

Changes in Lipoprotein Levels with Bile Acid Sequestrant Therapy[58]

Therapy	*LDL (% change)*	*HDL (% change)*	*Triglycerides (% change)*
Monotherapy			
Colesevelam 3.8 g/day	−15	3	10
Combination therapy			
Simvastatin 10 mg/day	−26	3	−17
Simvastatin 10 mg/day + colesevelam 3.8 g/day	−42	10	−12
Atorvastatin 10 mg/day	−38	8	−24
Atorvastatin 10 mg/day + colesevelam 3.8 g/day	−48	11	−1

LDL, low-density lipoprotein; HDL, high-density lipoprotein.

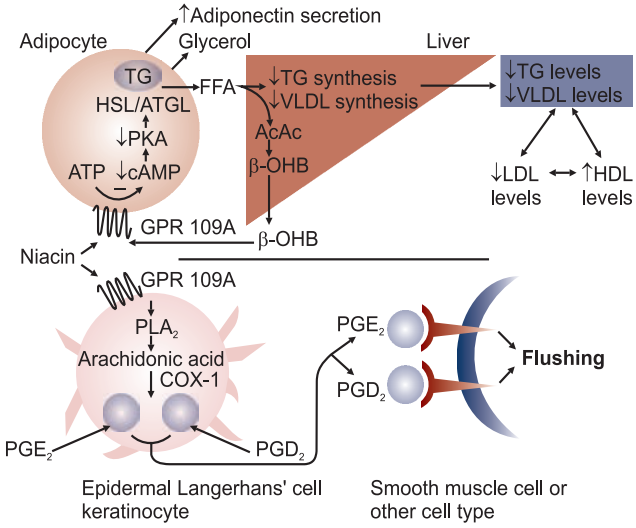
medication for raising HDL.[62-64] Niacin may also exert beneficial pleiotropic effects independent of changes in lipid levels, such as improving endothelial function and attenuating vascular inflammation.[62,65]

Drugs under the Category

Two prescription niacin products are available in the USA; namely, immediate release (IR) and extended release (ER) formulations. A third prescription product involves the addition of laropiprant, a prostaglandin receptor antagonist (to reduce flushing), to a moderate-release formulation of niacin and has been launched in Europe but not in the USA. Niacin products are also available as over-the-counter dietary supplements, and include intermediate-release, sustained release, and "no-flush" formulations. However, "no flush" niacin preparations may contain several niacin compounds (e.g., inositol hexanicotinate) that neither contain nor metabolize to nicotinic acid.

Mechanism of Action

Niacin acts via the G protein-coupled receptor (GPR 109A) in the adipocyte which inhibits the formation of intracellular cyclic adenosine monophosphate and down-regulates lipolysis (by reduced activation of lipases, such as hormone sensitive lipase) and production of free fatty acids[62,65,66] (Figure 7). This leads to a reduction in the amount of free fatty acids released from the adipocyte that are available to the liver for triglycerides and VLDL production. Decreased levels of VLDL lead to diminished hepatic and peripheral production of IDL and LDL. Niacin also inhibits hepatocyte DGAT-2 and the reduction in intrahepatic



ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; PKA, protein kinase A; HSL, hormone sensitive lipase; ATGL, adipose triglyceride lipase; GPR, G protein-coupled receptor; TG, triglyceride; FFA, free fatty acid; VLDL, very low-density lipoprotein; AcAc, acetoacetate; β-OHB, β-hydroxybutyrate; LDL, low-density lipoprotein; HDL, high-density lipoprotein; PLA_2, phospholipase A_2; COX-1, cyclooxygenase-1; PGE_2, prostaglandin E_2; PGD_2, prostaglandin D_2.

FIGURE 7. Mechanism of action of niacin for causing changes in lipids and flushing. GPR109A is a receptor for endogenous (β-OHB) and exogenous (e.g., niacin) ligands. Activation of the GPR109A (top panel) in the adipocyte results in inhibition of adenylate cyclase activity and subsequent reduction in cAMP levels and PKA, and HSL/ATGL activity. This results in reduced hydrolysis of TG and subsequent suppression of FFA and glycerol release from the adipocyte. At the same time, adipocyte secretion of adiponectin is increased. The reduction of substrate availability to the liver limits TG and VLDL synthesis and subsequently reduces serum concentrations of TG and LDL and increases HDL. In epidermal Langerhans' cells and keratinocytes (bottom panel), GPR109A activation results in arachidonic acid-mediated prostaglandin synthesis which will initiate a flushing response. *From* Wanders D, Judd RL. Future of GPR 109A agonists in the treatment of dyslipidaemia. *Diabetes Obes Metab*. 2011;13(8):685-91, *with permission*.

triglyceride synthesis decreases the availability of triglycerides to be incorporated within VLDL.[29,62,65-67]

Although the precise mechanism by which niacin increases HDL is unclear, it is likely multifaceted. Niacin increases apo-A1 by decreasing its cellular uptake.[62] HDL may also interact with SRB1 which primarily acts as a docking station to allow downloading of cholesterol ester.[65] Niacin interferes with HDL holoparticle endocytosis by interfering with the β-chain of adenosine triphosphate synthase.[29,65-67] Niacin inhibits plasma hepatic lipase activity and promotes the formation of mature HDL.[2,63] The reduction in VLDL production that occurs with

niacin therapy limits the activity of plasma CETP to exchange triglycerides in VLDL (and LDL) particles for cholesterol esters in HDL particles. Thus, niacin therapy favors carriage of cholesterol esters in HDL particles.[67] Finally, niacin may improve RCT efficiency through GPR 109A activation and increased expression of ABCA1 and ABCG1 cholesterol transporters in macrophages (and ABCA1 transporters in adipocytes) resulting in cholesterol efflux to HDL.[62,64,66]

Pharmacology

The absorption (i.e., peak plasma concentration after ingestion) of IR formulation of niacin is at around 30–60 minutes and about 5 hours for the ER formulation. Approximately 60–76% of ER formulation of niacin (or its metabolites) and 88% of IR formulation is excreted in the urine. The plasma elimination half-life of IR formulation is 20–45 minutes.[68,69]

Niacin is metabolized in the liver by 2 independent, saturable pathways. One is a low-affinity, high-capacity conjugation (with glycine) pathway resulting in the production of nicotinuric acid. The other pathway is a high-affinity, low-capacity amidation pathway resulting in the production of nicotinamide, which does not have lipid lowering properties and may be associated with hepatotoxicity,[62] although there is controversy.[70] IR formulations provide a short lived bolus of niacin; overwhelming the high-affinity, low capacity pathway, resulting in more nicotinuric acid production via the conjugation pathway. Sustained release niacin formulations lengthen the dissolution of niacin and, therefore, provides substrate for the high affinity amidation pathway and may have higher rates of hepatotoxicity.[29,62,69]

Indications

Niacin is indicated to reduce elevated LDL and triglycerides, and to increase HDL in patients with primary hypercholesterolemia or mixed dyslipidemia. Niacin is an alternative to statin as first-line therapy for LDL lowering and in patients with triglycerides >200 mg/dL as adjunctive therapy to statins for lowering non-HDL after LDL is controlled.[1] Niacin is also indicated as adjunctive therapy to lower triglycerides in patients with hypertriglyceridemia who present a risk for pancreatitis.[68,69]

Dosage

Immediate Release Niacin

The usual dose range of IR niacin is 1–2 g twice or thrice a day. The starting dose of 250 mg as a single daily dose is given following

the evening meal. The frequency of dosing and total daily dose can be increased every 4–7 days until the desired LDL and/or triglyceride level is achieved or the dose of 1.5–2 g is achieved. If goals are not achieved after 2 months, the dose can be increased at 2–4 weeks interval to 1 g thrice a day.[68]

Extended Release Niacin

The usual dose range of ER niacin is 0.5–2 g once a day, taken at bedtime with a low-fat snack. Therapy should be initiated at 500 mg in order to reduce the incidence and severity of side effects which may occur during early therapy and should not be increased by more than 500 mg in any 4-week period. The maintenance dose range is 1–2 g once a day. When combined with a statin, the statin dose should not be the maximum allowed (e.g., limit the maximum daily doses of 40 mg simvastatin and 40 mg lovastatin).[69]

When switching a patient from IR to ER niacin, the equivalent doses should not be substituted; the ER should be started at a lower total daily dose. ER niacin should be used with caution in patients with renal impairment.[68,69]

Contraindications

Active liver disease or unexplained persistent elevation in hepatic transaminase levels are contraindications to niacin use. Active peptic ulcer disease and arterial bleeding are also contraindications.[68,69]

ER niacin is a pregnancy category C drug. The benefit of treatment of women with hypertriglyceridemia during pregnancy should be weighed against the risk of continued therapy. Since niacin is excreted into human milk, the potential for adverse reaction in nursing infants should be taken into account.[68,69]

Adverse Effects

The most common adverse reactions are flushing, diarrhea, nausea, vomiting, increased cough, and pruritus. Flushing has been reported in as many as 88% of patients in trials. Nicotinic acid produces flushing via binding to the GPR 109A receptor and mediates release of vasodilatory prostaglandins from the Langerhans' cells in the dermis.[63,64,70] Symptoms typically last for 30–60 minutes. Skin flushing may be reduced in frequency or severity by aspirin-pretreatment (up to the recommended dose of 325 mg) taken 30 minutes prior to the niacin administration. Tolerance to flushing develops rapidly over the course of several weeks. Fewer flushing episodes have been reported with ER niacin compared to IR niacin. Concomitant consumption of

alcoholic drinks, hot beverages, or spicy foods may increase the side effects of flushing and pruritus and should be avoided around the time of niacin.[63,68,69]

Niacin preparations have been associated with abnormal liver tests. In clinical studies, less than 1% discontinued therapy due to transaminase elevations >2 times ULN. In studies combining statin and niacin, 1% experienced reversible elevation in AST/ALT to >3 times ULN; however, no patients at a dose limit of 1 g niacin had an elevation >3 times ULN. Serum transaminase levels, including AST and ALT should be monitored before initiating the treatment, every 6–12 weeks for the first year, and periodically thereafter (e.g., at approximately 6-month intervals). The drug should be discontinued if the transaminase levels show evidence of progression, particularly if they rise to 3 times ULN and are persistent, or if they are associated with symptoms of nausea, fever, and/or malaise. Severe hepatic toxicity has occurred in patient substituting sustained-release niacin for IR niacin at equivalent doses. Niacin should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease.[68,69] Slow-release preparations may increase the risk for hepatotoxicity.[29,62]

The risk for myopathy and rhabdomyolysis are reported to be increased when a statin is coadministered with ER niacin, particularly in elderly patients and patients with diabetes, renal failure, or uncontrolled hypothyroidism. Caution has been recommended when prescribing niacin doses of >1 g/day with a statin. However, in the absence of niacin hepatotoxicity, there is little evidence that the addition of an appropriate formulation of a moderate dose of niacin to a statin increases the risk for muscle adverse experience compared with statin therapy alone.[68,69,71]

ER niacin can increase serum glucose and glycosylated hemoglobin (HbA1C) levels (but generally <5 and <0.3%, respectively). Glucose levels should be monitored in diabetic or potentially diabetic patients, particularly during the first few months of use or dose adjustment, since diabetic patients may experience a dose-related increase in glucose intolerance. The insulin resistance may be related to a rebound increase in free fatty acids when nicotinic acid blood levels fall.[62,65,67,71] The majority of the increases can be treated with adjustment in the antihyperglycemic regimen. Niacin at doses <2 g daily are considered safe for diabetic patients when the CV benefits outweigh the risks.[63]

Elevated uric acid levels may occur with niacin therapy and, therefore, it should be used with caution in patients predisposed to gout. Elevations as high as 11% in mean uric acid levels have

been reported.[68,69,71] The mechanism of the increase appears to be the competitive inhibition of the tubular secretion of uric acid by nicotinic acid.[71]

Nicotinic acid should be used with caution in patients with unstable angina or in the acute phase of an MI, particularly when such patients are also receiving vasoactive drugs since niacin may potentiate the effects of these drugs resulting in postural hypotension.[68,69]

The development or exacerbation of peptic ulcer has been described, usually in patients with high doses of regular niacin.[68,69,71]

Atrial fibrillation was more common in male patients with CAD studied in the Coronary Drug Project (CDP).[68,69] However, atrial fibrillation has not emerged as a significant adverse experience in numerous other smaller, randomized, controlled niacin trials, which mostly enrolled patients without CHD.[71]

Small decreases in phosphorous levels (i.e., 13%) have been reported with the use of 2 g niacin. Dose-related reductions in platelet counts of about 11% may occur and caution should, therefore, be observed when niacin is administered with anticoagulants; platelet counts should be monitored in such patients. In addition, a small (i.e., 4%) increase in protime has been associated with ER niacin use.[69] However, these changes have been regarded as clinically insignificant.[71]

Clinical Evidence

Nicotinic acid produces an average 10–20% reduction in LDL-C, 30–70% reduction in triglycerides, and an average 20–35% increase in HDL. The magnitude of individual lipid and lipoprotein responses may be influenced by the severity and type of underlying lipid abnormality.[68] In a dose-escalation study, ER formulation of niacin with monthly 500 mg increases in dose, there were incremental changes in LDL, HDL, and triglycerides in the dose range of 0.5–2 g daily[69] (Table 10). When niacin is added to a statin, there may be additional LDL lowering of 10–20% depending on the dose of niacin.[54]

Niacin has anti-inflammatory properties with decreases in C-reactive protein by 15% and lipoprotein-associated phospholipase A2 by 20%.[72]

The CDP, completed in 1975, was designed to assess the safety and efficacy of 3 g/day of IR niacin in men 30–64 years old with a history of MI. The incidence of nonfatal, recurrent MI was reduced from 12.2 to 8.9% (a 14% RRR), although there was no difference in mortality after 5 years. A follow-up analysis performed 15 years after completion of the trial demonstrated a significant overall 11% RRR in mortality (58.2 vs. 52.0%).[73]

TABLE 10

Changes in Lipoprotein Levels with Niacin Therapy[69]

Dose	*LDL (% change)*	*HDL (% change)*	*Triglycerides (% change)*
Extended release Niacin			
1 g	−7	14	−16
1.5 g	−13	19	−25
2 g	−16	22	−38
Lovastatin 40 mg	−32	6	−20
Extended release Niacin/Lovastatin			
1 g/20 mg	−30	20	−32
1 g/40 mg	−36	20	−39
1.5 g/40 mg	−37	27	−44
2 g/40 mg	−42	30	−44

LDL, low-density lipoprotein; HDL, high-density lipoprotein.

When combined with BAS, angiographic trials have demonstrated a decrease in progression of coronary lesions (see the heading "Clinical Evidence under BAS").

When combined with statins, several studies have used carotid intima-media thickness (CIMT) as a surrogate end-point. In the Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol Study (ARBITER 2), the addition of 1 g/day of niacin to baseline statin therapy prevented progression of atherosclerosis in patients with CHD and HDL <45 mg/dL.[74] In an extension trial, CIMT regressed and the change in CIMT was independently associated with changes in HDL but not LDL or triglycerides.[75] In the ARBITER-6 HDL and LDL Treatment Strategies in Atherosclerosis Trial (ARBITER-6 HALTS), the addition of 2 g ER niacin to stable statin therapy in patients with CHD or its equivalent (with LDL <100 mg/dL and HDL <50–55 mg/dL) was associated with regression by CIMT.[72,76,77]

Outcome trials demonstrating the benefit of adding niacin to statin are limited. In the HDL Atherosclerosis Treatment Study (HATS) trial, the combination of statin and niacin was compared to placebo.[78] An RRR of 90% in the composite end-point of nonfatal MI, revascularization, or CV death was demonstrated in the combination therapy group. In ARBITER 2, CV end-points were reduced in the statin and niacin group (3.8%) compared to statin alone (9.6%). However, the RRR of 60% was not significant ($p = 0.20$).[74] The addition of niacin therapy to patients with well controlled LDL has been shown to improve endothelial flow-mediated dilation of the brachial artery, especially in those with low baseline HDL.[72] However, improved outcomes have not been confirmed in controlled trials. For example, in the

Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides Impact on Global Health Outcomes (AIM-HIGH) trial, ER niacin or placebo was given to patients with CAD, high triglycerides, HDL <40–50 mg/dL, and LDL controlled to 40–80 mg/dL with simvastatin ± ezetimibe. In patients who achieved and maintained LDL <70 mg/dL while receiving intensive statin therapy treatment, ER niacin plus simvastatin did not decrease CV events over 36 months compared to patients treated with simvastatin alone.[79] The clinical efficacy of combining niacin and a BAS is discussed in the section on BAS.

Choice of Therapy/Guidelines

If treatment with a statin does not achieve the selected LDL goal, intensification of LDL lowering drug therapy with niacin is reasonable as an alternative or as adjunctive therapy.[1,8] However, dietary supplemental niacin should not be used as a substitute for prescription niacin.[8] In patients who have achieved goal LDL using statin therapy but have elevated triglycerides >200 mg/dL, niacin may be considered as adjunctive therapy to achieve the non-HDL cholesterol goal.[1,8] A specific HDL target goal has not been recommended except for diabetic patients (i.e., >40 mg/dL in men and >50 mg/dL in women).[1,7] While a recent meta-analysis suggests that simply increasing HDL does not reduce the risk of CHD events, CHD deaths, or total deaths.[79] There is controversy since studies with niacin alone were not included. Another meta-analysis of nicotinic acid alone or in combination demonstrated positive effects on CV events and atherosclerosis evolution.[80]

Niacin may be used in patients with severely elevated triglycerides >500 mg/dL in order to prevent pancreatitis.[1] However, whether drug therapy of an isolated elevation of triglycerides influences CV disease outcome remains to be established.[6] A goal of <150 mg/dL is recommended for patients with diabetes mellitus.[7]

OMEGA-3 FATTY ACIDS

Introduction

The omega-3 fatty acids (O3FAs) include the marine-derived long-chain fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). They may be used as monotherapy or as adjunctive therapy with fibrates and/or nicotinic acid to lower triglycerides in patients with severe hypertriglyceridemia.

LDL is unchanged or variably increased with O3FA therapy, and the degree of elevation is generally related to the

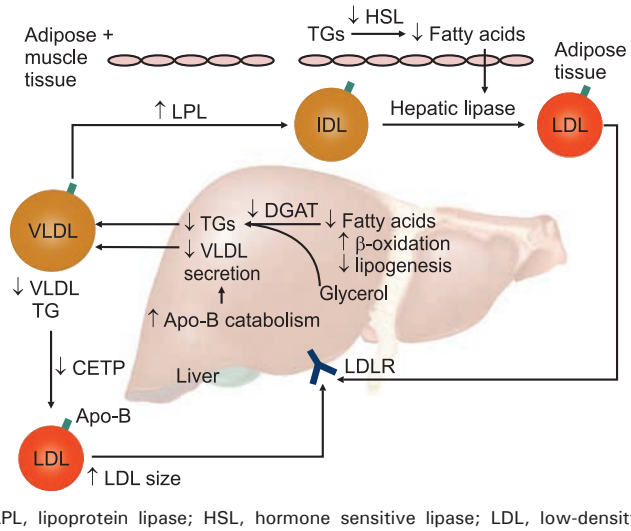
pretreatment triglyceride level. The elevation is related to increased conversion of VLDL to LDL particles with increased particle size. However, concurrent treatment with statins may reduce the increase in LDL.[81]

Drugs under the Category

Prescription O3FAs are available as a 1 g liquid-filled gel capsule containing at least 900 mg ethyl esters of O3FAs derived from fish oils. These are predominantly a combination of ethyl esters of EPA (approximately 465 mg) and DHA (approximately 375 mg).[82]

Mechanism of Action

The triglyceride lowering ability of O3FAs is likely mediated by their capacity to agonize and antagonize several of same nuclear transcription factors involved in the action of fibrates[30] (Figure 8). They compete with other fatty acids and prevent their entry into triglyceride synthesis. For example, lipogenesis is suppressed by increased mitochondrial β-oxidation, and triglyceride synthesis



LPL, lipoprotein lipase; HSL, hormone sensitive lipase; LDL, low-density lipoprotein; LDLR, LDL-receptor; HDL, high-density lipoprotein; CETP, cholesteryl ester transfer protein; DGAT, diacylglycerol acyltransferase; IDL, intermediate-density lipoprotein; TGs, triglycerides.

FIGURE 8. Mechanism of action of omega-3 fatty acids (O3FA). O3FAs inhibit the biosynthesis of fatty acids, decrease DGAT expression and increase apolipoprotein-B catabolism resulting in decreased VLDL secretion. A decrease in hormone sensitive lipase leads to reduced adipocyte fatty acid mobilization and release. Reduced VLDL triglyceride content leads to decreased CETP activity. This results in an increase in LDL and HDL size. With the increase in LPL activity, there is augmentation of VLDL lipolysis and increased formation of LDL.

is decreased by the inhibition of DGAT, resulting in less substrate available for synthesis of VLDL. An increase in expression of LPL promotes the conversion of VLDL to LDL.[30,82,83]

The net effect on HDL is minimal since there are offsetting mechanisms of action. HDL is expected to increase with PPAR-α activation and enhanced RCT. However, FXR is activated, resulting in a decrease in HDL.[83]

Pharmacology

Prescription O3FA are manufactured by transesterification of fish triglycerides, which allows for the separation of individual fatty acids and selective concentrations of EPA and DHA ethyl esters while other fatty acids are discarded. After intestinal absorption and breakdown of the ethyl esters, the resulting EPA and DHA do not differ from the fatty acids produced in the body.[84]

O3FAs administered as ethyl esters induce significant, dose-dependent increases in serum phospholipid EPA content. However, the increases in DHA content are less marked and dose-dependent.[82]

Indications

For patients with mixed hyperlipidemia and LDL at target goal on statin monotherapy, non-HDL cholesterol is a secondary target in patients with triglyceride levels over 200 mg/dL. O3FA supplementation is a reasonable therapeutic option or alternative to fibrate or niacin therapy to achieve non-HDL target goals.[8]

For patients with very high triglyceride levels >500 mg/dL, the initial therapeutic goal is to lower triglyceride levels to prevent pancreatitis, and O3FAs are indicated as an adjunct to diet.[1]

Dosage

A daily dose of O3FA of 4 g/day is recommended for severe hypertriglyceridemia. The daily dose may be taken as a single 4 g dose or as two 2 g doses. The capsule should be swallowed whole and not broken open or chewed.[82] An approximate reduction of 5–10% in triglycerides is expected for each 1 g of O3FA consumed, although efficacy is greater in individuals with higher triglycerides before treatment with possibly a curvilinear relationship.[6]

Contraindications

O3FA contains ethyl esters of EPA and DHA obtained from the oil of several fish source. It is not known whether patients with

allergies to fish and/or shellfish are at increased risk of an allergic reaction and, therefore, should be used with caution in these patients.[82]

Prescription O3FAs are pregnancy category C drugs and should be used during pregnancy only if the potential benefit to the patient justifies the potential risk to the fetus. It is not known whether O3FAs are excreted in human milk, and caution should be exercised when O3FAs are administered to a nursing woman.[82]

Adverse Effects

Eructation, dyspepsia, and/or taste perversion have been reported in 3–4% of patients in clinical studies.[82] GI adverse effects, primarily eructation and taste can be minimized by highly purified, high potency formulations, that allow for much lower dosing.[85] Refrigeration of supplements and the addition of vitamin E may reduce fish oil oxidation and improve tolerance.[86]

Fasting glucose levels may rise slightly in patients with diabetes mellitus but without significant change in HbA1C.[87]

Some studies have demonstrated a prolongation of bleeding time, but the times reported have not exceeded normal limits and did not produce clinically significant bleeding episodes.[82] Clinical trials have demonstrated high-dose O3FA consumption to be safe when concurrently administered with other agents, such as aspirin and warfarin that may increase bleeding. However, patients receiving treatment with high dose O3FA and an anticoagulant or other drug affecting coagulation should be monitored periodically. In the setting of an acute bleeding illness, such as during and immediately after hemorrhagic stroke, or in patients at high risk of hemorrhagic stroke, it is prudent to discontinue high-dose fish oil consumption or supplementation. In addition, some clinicians consider discontinuing fish oil therapy 4–7 days prior to planned invasive procedures with a highest risk for bleeding complications.[86] In patients with hepatic impairment, ALT and AST levels should be monitored periodically.

In recommending the most appropriate form of fish oil to patients, clinicians should be aware of potential fish oil toxicities, and know which details of purification processes to minimize potential toxicities. This can present a challenge since no USFDA regulatory mechanisms are in place for dietary supplements. The manufacturers of dietary supplements are not required to provide excellence of efficacy, safety, or manufacturing standards before marketing products. The USFDA has determined that fish oil

dietary supplements should not exceed 2 g/day of EPA and DHA. A "USP-verified" mark indicates compliance with standards set by the United States Pharmacopeia.[86]

Finally, the combination of statins and O3FA has been shown to be safe and well-tolerated treatment for combined dyslipidemia.[85]

Clinical Evidence

In patients with severe hypertriglyceridemia (levels >500 mg/dL), 4 g prescription of O3FA decreased triglycerides by 45% and increased HDL by 9%. However, LDL increased by 44%. In patients treated with simvastatin 40 mg/day and having persistently elevated triglycerides in the range of 200–499 mg/dL, the addition of 4 g prescription O3FA resulted in reductions in triglyceride levels by 23% and increases in HDL of 4.6% and LDL of 3.5%.[82]

In the Japan EPA Lipid Intervention Study (JELIS), patients received a low dose statin plus either EPA (1.8 g) or placebo. Subgroup analysis of primary prevention patients with baseline triglyceride levels >150 mg/dL and HDL <40 mg/dL demonstrated that combination therapy reduced CV disease risk by 53% compared with statin monotherapy.[88] However, the risk reduction was associated with only an additional 5% triglyceride reduction compared to controlled clinical trials. The effect of prescription O3FA on CV mortality and morbidity in patients with elevated triglycerides has not been determined.[82]

Choice of Therapy/Guidelines

Prescription O3FA is indicated as initial treatment of patients with severe hypertriglyceridemia. For patients with LDL at target on statin monotherapy but with a non-HDL above the recommended goal, O3FA supplementation is a reasonable therapeutic option.[8]

EZETIMIBE: A CHOLESTEROL ABSORPTION INHIBITOR

Introduction

Ezetimibe is in a class of lipid-lowering compounds that selectively inhibits the absorption of cholesterol by the small intestine.[54]

Ezetimibe reduces LDL and triglycerides and increases HDL in patients with combined hyperlipidemia. The maximal response is generally achieved within 2 weeks and maintained during chronic therapy. The addition of ezetimibe to either a statin or fenofibrate is more effective in lipid lowering than with either agent alone.

However, the effect of ezetimibe as monotherapy or in addition to a statin or fenofibrate on CV morbidity and mortality has not been established.[89]

Mechanism of Action

Cholesterol entering the small intestine is derived from dietary sources or from biliary cholesterol and is emulsified by bile salts into micelles and transferred from the micelles to duodenal and jejunal enterocytes via a sterol transporter, identified as a member of the Niemann-Pick family of proteins (NPC1L1). The molecular target of ezetimibe is the NPC1L1 sterol transporter. The decrease in delivery of cholesterol to the liver causes a reduction of hepatic cholesterol stores and a compensatory increase in LDL receptors and, therefore, increased clearance of cholesterol from the blood.[89,90]

Pharmacology

Ezetimibe is primarily metabolized in the small intestine and liver via glucuronide conjugation with subsequent biliary and renal excretion. Both ezetimibe and its glucuronide metabolite have an elimination half-life of 22 hours. Excretion of the drug is 78% in feces and 11% in urine. Ezetimibe is highly (>90%) bound to plasma proteins. Ezetimibe is neither an inhibitor nor an inducer of the CYP P450 isoenzymes.[89]

Indications

Ezetimibe is indicated as monotherapy or in combination with statin therapy for the reduction of elevated LDL in patients with primary hyperlipidemia. It is also indicated for use in combination with fenofibrate for the reduction of elevated LDL and non-HDL cholesterol in patients with mixed hyperlipidemia. Ezetimibe may be administered at the same time as the statin or fenofibrate.[89]

Dosage

The recommended dose of ezetimibe is 10 mg once a day. Concomitant food administration has no effect on absorption, and ezetimibe can be administered with or without food. No dosage adjustment is necessary in patients with mild hepatic or renal impairment, or in geriatric patients. Caution should be exercised when using ezetimibe and cyclosporine concomitantly.[89]

Contraindications

Due to the unknown effects of increased exposure to ezetimibe in patients with moderate or severe hepatic impairment (i.e., Childs-

Pugh score >7), ezetimibe is not recommended in these patients. The combination of ezetimibe with a statin is contraindicated in patients with active liver disease or unexplained persistent elevations in hepatic transaminase levels.[89]

Ezetimibe is a pregnancy category C drugs. There are no adequate and well-controlled studies of ezetimibe in pregnant women.

Adverse Effects

The most commonly reported adverse reactions in ezetimibe + statin trials were nasopharyngitis (3.7%), myalgia (3.2%), and arthralgia (2.6%).

Ezetimibe monotherapy does not cause significant elevations of hepatic transaminases.[54] While the incidence of elevations of hepatic transaminase levels to ≥3 times the ULN was similar between ezetimibe and placebo, the incidence of increased transaminases is higher in patients receiving ezetimibe in combination with a statin (1.3%) compared to patients treated with a statin alone (0.4%).[89,91] The elevations are mild, transient, reversible, and without apparent clinical significance. The effect is considered to be due to statins and is dose related. A systematic review of randomized controlled trials demonstrated that compared to ezetimibe therapy alone, combination therapy with a statin did not result in significant absolute increases in the risk of transaminase elevations, myalgia, CPK increases, rhabdomyolysis, GI adverse events, or discontinuations because of adverse events.[92]

Safety monitoring for ezetimibe monotherapy is not required: however, when used with a statin, liver function tests should be performed at the initiation of therapy and according to the recommendations of the statin.[91]

Clinical Evidence

Ezetimibe produces LDL reductions of 14–25%.[54] Since ezetimibe monotherapy results in a decrease in hepatic cholesterol pool, there is a compensatory increase in cholesterol synthesis. However, in the presence of statin therapy, this increase in cholesterol synthesis is diminished (due to HMG-CoA reductase inhibition), resulting in the greater decrease in LDL (i.e., >20%) with the combination compared to ezetimibe monotherapy.[54,90] The advantage of the combination is the low incidence of side effects, but the disadvantage is the lack of clinical outcome data for ezetimibe.[54]

Ezetimibe monotherapy has not been associated with a decrease in high-sensitivity (hs)-CRP levels. However, the addition

of ezetimibe to statin therapy resulted in greater hs-CRP reduction than with statin therapy alone.[90]

The ability of ezetimibe to improve measures of subclinical atherosclerosis, including CIMT, has been mixed. In the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial, the addition of ezetimibe to statin therapy did not significantly change CIMT compared to statin monotherapy, despite a >50 mg/dL lowering of LDL in the combination therapy group.[93]

Choice of Therapy/Guidelines

If treatment with a statin, BAS and/or, niacin does not achieve the LDL goal selected for a patient, intensification of LDL lowering drug therapy with ezetimibe may be considered. In addition, for patients who continue to have an elevated non-HDL while on adequate statin therapy, niacin, fibrate, or O3FA therapy, ezetimibe may be reasonable.[8]

CONCLUSION

Drug therapy of dyslipidemia begins with the identification of risk category, which establishes target goals for LDL and non-HDL. Initial therapy for LDL reduction begins with a statin. However, the addition of niacin, a bile acid sequestrant, or the cholesterol absorption inhibitor, ezetimibe, maybe needed. When the LDL goal is reached, and if triglycerides are >200 mg/dL, attention is directed at the non-HDL goal. Therapy to reduce non-HDL may include the uptitration of a statin or the addition of niacin, a fibrate, or O3FAs. For patients with severe hypertriglyceridemia, fibrates are considered first line drug therapy. Niacin and/or O3FAs may also be used.

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6 CHAPTER

Drugs for Diabetes and Cardiodysmetabolic Syndrome

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CARDIODYSMETABOLIC SYNDROME, IMPAIRED GLUCOSE TOLERANCE, AND DIABETES MELLITUS

Introduction

It is estimated that as much as 30–40% of the adult population in the developed countries have cardiodysmetabolic syndrome/dysmetabolic syndrome. As currently understood, the epidemic of obesity is primarily responsible for preponderance of cases with cardiodysmetabolic syndrome and is an essential element in the definition of the syndrome. Obesity is associated with resistance to the effects of insulin in the muscle tissue and results in hyperinsulinemia, hyperglycemia, dyslipidemia, hypertension, and endothelial dysfunction. A similar profile is seen in individuals with type 2 diabetes mellitus.[1-4] In 2001, the National Cholesterol Education Program (NCEP) defined the metabolic syndrome with a focus on the cardiovascular risk posed by the syndrome.[5] The International Diabetes Foundation (IDF) revised the Adult Treatment Panel III (ATP III) criteria for metabolic syndrome to address disparities in waist circumference thresholds related to ethnic differences in different populations[6] (Table 1).

For the clinician, the phenotypic pattern can be recognized by a simple look at the patient and review of basic laboratory studies. In this regard, the mnemonic DROP, where D stands for Dyslipidemia, R for insulin Resistance, O for Obesity, and P for high blood Pressure helps in easier identification of the individual with this syndrome (Table 2).[7]

Prevalence

In the National Health and Nutrition Examination Survey (NHANES) 1999–2002 database, 34.5% of participants met ATP III criteria for the metabolic syndrome compared with 22% in NHANES III (1988–1994).[8,9] Ford reported a 39% prevalence in the USA, using data from NHANES 1999–2002 participants, with IDF criteria as compared to 34.5% prevalence using the ATP III criteria.[8]

TABLE 1

International Diabetes Foundation Definition of Cardiodysmetabolic Syndrome	
Metabolic parameter	*Measurement criteria*
Central obesity* (Waist circumference)	
South Asians	Men ≥90 cm; women ≥80 cm
Europids	Men ≥94 cm; women ≥80 cm
Chinese	Men ≥90 cm; women ≥80 cm
South and Central Americans	Men ≥90 cm; women ≥80 cm
Raised triglycerides	≥150 mg/dL
Reduced high-density lipoprotein	Men <40 mg/dL Women<50 mg/dL
Raised blood pressure	Systolic ≥130 mmHg
	Diastolic ≥85 mmHg
Raised fasting plasma glucose	≥100 mg/dL
	Previously diagnosed type 2 diabetes

*Central obesity according to the waist circumference plus any two of the other four risk factors.

TABLE 2

The Cardiometabolic Syndrome	
D	Dyslipidemia
	Fasting triglycerides >140 mg/dL or
	HDL <40 mg/dL or
	LDL particle size <260 Å
R	Insulin Resistance
	Fasting plasma glucose ≥110 mg/dL or
	Type 2 diabetes mellitus
O	Obesity
	Body mass index >25 kg/m^2 or
	Waist/hip ratio >0.85 or
	Waist circumference >100 cm
P	High Blood Pressure
	Systolic blood pressure ≥140 mmHg or
	Diastolic blood pressure ≥90 mmHg

Pathophysiology of Cardiodysmetabolic Syndrome

The cardiodysmetabolic syndrome results from a complex interplay of insulin resistance, adiposity, and endothelial dysfunction. Adipose tissue secretes many biologically active intermediaries that mediate insulin resistance (Figure 1). Typically, in disease states associated with insulin resistance, different tissues show

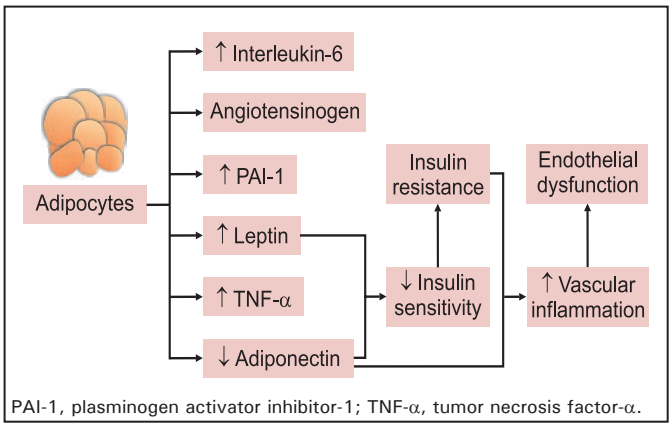

FIGURE 1. Adipocyte role in insulin resistance, metabolic syndrome, and CVD.

varying levels of insulin resistance. Thus, when plasma insulin levels increase to maintain euglycemia in the insulin resistant state, the mitogenic effects of insulin on cell growth and differentiation might become more pronounced leading to hypertriglyceridemia, hypertension, and hyperandrogenism.[10] Parallel insulin signaling pathways in metabolic and vascular tissues, cross-talk between inflammatory and insulin signaling, pathway-specific insulin resistance, coupling of blood flow with glucose metabolism, cross talk between metabolic and vascular tissues, and shared stressors lead to endothelial dysfunction.

Clinical Implications

There is controversy over whether cardiodysmetabolic syndrome confers incremental risk compared with risk related to the individual components of metabolic syndrome. The cardiovascular risk associated with the metabolic syndrome was found to be elevated in a recent meta-analysis of approximately a million patients from 87 prospective trials. NCEP and revised NCEP criteria in the general population were used to define the metabolic syndrome.[11] Overall, the metabolic syndrome was associated with a 2-fold increase in risk of cardiovascular disease (CVD), CVD mortality, and stroke; and a 1.5-fold increase in the risk of all-cause mortality. There was a 2-fold increase in the risk for myocardial infarction (MI) as well. Metabolic syndrome was associated with an increased risk for cardiovascular events even after exclusion of individuals with diabetes. The estimates of cardiovascular risk were consistently higher in women as compared to men. However, there is still the need for studies to firmly establish the risk associated with cardiodysmetabolic syndrome, independent of the risk of its individual components.

Therapy

Since visceral obesity is central to the pathophysiology of cardiodysmetabolic syndrome, therapy should be primarily directed towards this. Additionally, insulin resistance and endothelial dysfunction play an important role in the pathogenesis of the metabolic and cardiovascular perturbations as reflected by epidemiological data suggesting links between metabolic and cardiovascular disorders. Various pharmacological and nonpharmacological therapeutic interventions to treat the metabolic and cardiovascular abnormalities have been shown to improve insulin sensitivity and endothelial function. While most of the therapeutic interventions have been developed with the intention of metabolic and symptomatic control, improved long-term outcomes of any salubrious intervention appears to be predicated upon concurrent improvement in insulin sensitivity and endothelial dysfunction.

The therapeutic goals for management of metabolic syndrome have been outlined by the American Heart Association (AHA) and the Endocrine Society[12,13] (Table 3). They include reduction of abdominal obesity, increasing physical activity, dietary modification, and treatment of specific cardiovascular risk factors if present.

Lifestyle Modification

Current evidence suggests that the first step in the management of patients with cardiodysmetabolic syndrome should be focused on weight loss and increased physical activity. Lifestyle modifications, including diet, weight loss, and physical exercise, reduce insulin resistance, obesity, and improve endothelial function. The benefit of weight management in controlling cardiodysmetabolic syndrome is highlighted by the Coronary Artery Risk Development in Young Adults (CARDIA) study.[14] In this observational study for over 15 years, more than 5,000 young individuals between the ages of 18 and 30 years, increasing body mass index (BMI) was associated with progression of components of metabolic syndrome as opposed to those in whom BMI remained stable over the same period. Obese individuals can lose up to 0.5 kg/week by restricting calories to less than 500–1,000 kcal below daily requirements.[15] Combining calorie restriction with regular exercise can lead to a weight loss of 5–10% from baseline over a 6-month period. A realistic goal for weight reduction is a target of 7–10% over a 6–12-month period. Such reductions in body weight are associated with much greater loss of visceral adiposity (the central problem

TABLE 3

Therapeutic Goals and Clinical Recommendation for Management of Metabolic Syndrome		
Target	*Goal*	*Recommendation*
Abdominal obesity	10% weight loss in first year and continued weight loss thereafter	Diet control and increased physical activity
Physical inactivity	Regular moderate physical activity	30–60 minutes of exercise daily
Atherogenic diets	Reduced intake of saturated fats, trans-fats, and cholesterol	Total fats 25–35% of total calories, saturated fats <7% of calories
Smoking	Complete cessation	Complete cessation
High-LDL cholesterol	LDL cholesterol <100 mg/dL in moderate risk patients and <70 mg/dL in high-risk patients	Lifestyle changes and cholesterol lowering drugs to achieve targets
High triglycerides	Insufficient data. Possibly triglycerides <100 mg/dL in high-risk patients	Lifestyle changes and triglyceride lowering drugs (fenofibrate) to achieve targets
Low-HDL cholesterol	Insufficient data	Lifestyle changes and HDL-raising drugs (nicotinic acid, CETP inhibitors) to achieve targets
High blood pressure	Blood pressure <135/85 mmHg. In diabetes and chronic kidney disease <130/80 mmHg	Lifestyle therapy and antihypertensive drugs to achieve targets
Elevated glucose	Reduction and maintenance of fasting glucose <90 mg/dL. HbA1C <7.0% for diabetics	Lifestyle therapy and hypoglycemic drugs if required
Prothrombotic state	Reduction of prothrombotic state	Low-dose aspirin in all high- and moderate-risk patients. Consider clopidogrel if aspirin not tolerated
Proinflammatory state	Reduction of proinflammatory state	No specific therapies. Aspirin and/or statins are being evaluated

LDL, low-density lipoprotein; HDL, high-density lipoprotein; CETP, cholesterylester transfer protein.

in cardiodysmetabolic syndrome). This marginal weight loss results in improvement of many of the metabolic abnormalities.[16]

Diet Intervention

Several dietary approaches have been advocated for treatment of the metabolic syndrome. A Mediterranean diet which is high in fruits, vegetables, nuts, whole grains, and olive oil results in improved lipid profile and insulin resistance as compared to a low-fat diet.[17,18] Objective data on other weight reducing diets, such as high-protein, low-carbohydrate diet is limited. Foods with low glycemic index may be beneficial. In a cross-sectional analysis of carbohydrate-related dietary factors, insulin resistance, and prevalence of metabolic syndrome in nearly 3,000 subjects from the Framingham Offspring Study, dietary glycemic index was positively associated with prevalence of the metabolic syndrome.[19]

Exercise

Current guidelines recommend practical, regular, and moderate regimens for exercise. The standard exercise recommendation is a daily minimum of 30 minutes of moderate-intensity physical activity (e.g., brisk walking). The Diabetes Prevention Project (DPP) study demonstrated that multiple metabolic risk factors can be controlled and type 2 diabetes prevented or delayed by controlling weight with regular exercise. The study enrolled 3,234 normotensive subjects who were mostly obese and randomized them to intensive lifestyle modification, metformin, troglitazone, or placebo. The rate of development of diabetes/metabolic syndrome was least in the intensive lifestyle modification group, which consisted of low-fat diet and 150 minutes of walking/week.[20] Exercise may be beneficial beyond its effect on weight loss by more selectively removing abdominal fat at least in women.[21]

Pharmacological Options

Currently available pharmacologic alternatives include drugs that combat obesity and medications that address the individual components of the metabolic syndrome, including hyperglycemia, dyslipidemia, hypertension, and abnormal coagulation. No specific drug has been developed that can reverse or block the fundamental abnormalities underpinning the cardiodysmetabolic syndrome, namely, insulin resistance and endothelial dysfunction.

Antiobesity Drugs

There have been various medications that have been developed over the last few decades with the aim of achieving weight reductions. These medications have various mechanisms of

actions. However, most of the medications that have been developed so far have all been demonstrated to have significant side effects that have ultimately led to the withdrawal of most of these medications. Metabolic benefits associated with sibutramine-induced weight loss were reported by Krejs et al.[22] Orlistat has been shown in a few studies to improve individual components of metabolic syndrome in addition to promoting weight loss and mobilizing visceral fat.[23,24] The problem with these drugs continues to be a relatively high rate of side effects leading to poor compliance. Sibutramine was recently withdrawn from the market based on postmarketing data from the Sibutramine Cardiovascular and Outcome (SCOUT) trial showing a 16% increase in the incidence of nonfatal MI and nonfatal stroke.[25] Discovery of the endocannabinoid system led to the development of cannabinoid receptor type 1 inhibitors, such as rimonabant. While manufacturer sponsored clinical trials in overweight patients demonstrated clinical benefit, the drug was subsequently withdrawn due to significant psychiatric side effects.[26-28]

Lipid Management

The ATP III guidelines emphasize that low-density lipoprotein (LDL) reduction is the primary target in lipid management even in the metabolic syndrome, with low high-density lipoprotein (HDL) and triglycerides being secondary targets.[29] The more aggressive target of LDL <70 mg/dL is supported by the recent Treating to New Targets (TNT)-metabolic syndrome study showing greater reduction in coronary events in the group that achieved LDL levels of 70 mg/dL as opposed to the group that attained levels of <100 mg/dL.[30] While the efficacy of statins in reducing LDL cholesterol is well established, combination therapy has been suggested for achieving LDL targets, reducing triglycerides and apolipoprotein B, and increasing HDL cholesterol.

Antihypertensive Therapy

The value of angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) in hypertensive patients with the metabolic syndrome who do not have CVD or diabetes is not clear. Animal studies have shown improvement in insulin resistance, reduction of reactive oxygen species production, and increased mitochondrial biogenesis with enalapril and losartan.[31,32] Studies have also shown significant increase in adiponectin levels with inhibition of renin-angiotensin-aldosterone system, which is associated with improved insulin sensitivity.[33] ACEI and ARBs might increase

peroxisome proliferators-activated receptor (PPARγ) activity, which might promote adipogenesis, thus, improving metabolic perturbations.[34]

Sympathetic activation in obese hypertensive patients seems to be a contributory factor for the elevated blood pressure and cardiovascular and metabolic consequences of the metabolic syndrome. In theory, drugs inhibiting the sympathetic nervous system could be useful, but the evidence of efficacy of central imidazoline receptor binding agents and peripheral β-adrenergic blocking agents is not convincing. In fact, a diabetogenic effect has been unequivocally demonstrated with thiazide diuretics and older β-blockers, such as atenolol. Therefore, these drugs may not be suitable as first line therapy for hypertension in subjects with metabolic syndrome.

Antithrombotic Therapy

The cardiodysmetabolic syndrome is characterized by a procoagulant state with increased levels of fibrinogen, plasminogen activator inhibitor-1 (PAI-1), and other coagulation factors. It is also a proinflammatory state that is characterized by elevated cytokines, such as the tumor necrosis factor and interleukin-6, and acute phase reactants, such as C-reactive protein and fibrinogen. In patients with the cardiodysmetabolic syndrome and a high risk of future cardiovascular events, aspirin in a dose of 75–150 mg/day is an attractive therapeutic option for lowering the rate of cardiovascular events.[35] It is also important to note that inhibition of the renin-angiotensin system reduces PAI-1 levels and inflammatory cytokines and, thus, potentially reduces the risk of increased thrombotic events in patients with metabolic syndrome.[36]

PROGRESSION FROM METABOLIC SYNDROME TO DIABETES AND CARDIOVASCULAR DISEASE

The discussion, thus far, has been focused on the metabolic syndrome. Apart from the increased risk for CVD, the metabolic syndrome is also associated with increased risk of developing diabetes mellitus. Multiple prospective observational studies demonstrate a strong association between the metabolic syndrome and the risk for subsequent development of type 2 diabetes. The risk of diabetes appears to increase with increasing components of the metabolic syndrome.[37-39] Intuitively, it is not surprising that the risk of developing diabetes in the presence of the metabolic syndrome is higher since insulin resistance or surrogate markers of insulin resistance are generally incorporated

in the definition. As noted earlier, the metabolic syndrome is characterized by insulin resistance, involving the glycogen synthetic pathway, leading to hyperglycemia and diabetes. The increased incidence of cardiovascular complications associated with the diabetic state find their explanation in varying insulin sensitivities in different tissues. Differential insulin sensitivity leads to atherogenesis via mitogen-activated protein kinase pathway, which shows normal growth promoting response to insulin and hyperglycemia from insulin resistance in the PI-3 kinase metabolic pathway.

Prevention of Hyperglycemia, Impaired Glucose Tolerance, and Diabetes Mellitus

Approaching cardiodysmetabolic syndrome from the aspect of insulin resistance is conceptually reasonable. Practically, this translates into treatment of individuals with impaired fasting glucose or impaired glucose tolerance (IGT) before the development of overt hyperglycemia. Recent studies targeting individuals with IGT using aggressive lifestyle interventions or pharmacotherapy have shown reduced incidence of diabetes and the risk of cardiovascular disease. The Finnish Diabetes Prevention Study[40] and the USDPP[20,41,42] demonstrated that diet and exercise do have a significant effect on reducing the progression from IGT to type 2 diabetes. In the Finnish study and the DPP study, personalized recommendations about diet and exercise led to a reduction in the incidence of new onset diabetes by 58% compared to the group receiving usual instructions.

Pharmacologic approaches directed at reducing insulin resistance potentially can control hyperglycemia, dyslipidemia, abnormal coagulation, and possibly even hypertension. Metformin, which was first described in 1922, improves hyperglycemia primarily by suppression of hepatic glucose production. In addition, metformin increases insulin sensitivity, enhances peripheral glucose uptake, fatty acid oxidation, and decreases absorption of glucose from the gastrointestinal tract. Increased peripheral utilization of glucose may also be the result of improved insulin binding to insulin receptors. Metformin was included in one of the treatment arms along with lifestyle advice in DPP. While metformin was effective in reducing the incidence of diabetes as compared with placebo, it was not as effective as intensive lifestyle intervention.

Acarbose, an α-glucosidase inhibitor slows the digestion of carbohydrates in the intestine and reduces postprandial glucose levels. The Study to Prevent Non-Insulin Dependent Mellitus (STOP-NIDDM) was a randomized trial to evaluate whether

acarbose would prevent development of type 2 in subjects with IGT.[43] The acarbose group had significantly lower incidence of diabetes compared to placebo and also was likely to revert IGT to normal with concomitant decrease in cardiovascular events.

One of the first group of drugs to address all the abnormalities manifested in the insulin resistance state are the thiazolidinediones (TZDs). TZDs are insulin-sensitizing drugs that act via the nuclear PPARγ to change activation of a plethora of genes and the levels of various expressed proteins. Rosiglitazone and pioglitazone, the currently available TZDs have been shown to improve many of the metabolic abnormalities associated with the metabolic syndrome.[44,45] However, there is as yet no strong evidence that TZDs reduce CVD end-points, and, in particular, there are no data on such risk reduction for people with metabolic syndrome. Moreover, based on cumulative data pointing toward increased risk of CV events with rosiglitazone, FDA has withdrawn its approval for this particular drug.

Cardiovascular Control with Established Type 2 Diabetes

With established diabetes mellitus, all modifiable risk factors should be addressed. These include hypertension, hyperglycemia, obesity, dyslipidemia, dietary indiscretion, physical inactivity, and smoking. Intervention should start with dietary advice and advice regarding physical activity. Early initiation of a moderate exercise program may be the best strategy for reducing risk of later macrovascular complications. Dietary advice should include recommendations regarding optimal fat intake. It is recommended that intake of polyunsaturated fat should be limited to 10% of calorie intake, though there is lack of evidence to support this. Consumption of fish, high in omega-3 fatty acids (1–2 serving/week), reduced the risk of coronary death and total mortality in epidemiologic studies and randomized clinical trials, and this benefit seems to extend to the diabetic individual as well.[46] Several cohort studies have an association between dietary glycemic load and incidence of type 2 diabetes. Prospective cohort studies have also reported an inverse association between whole grain consumption and risk of diabetes and coronary heart disease (CHD). Moderate alcohol consumption (1–2 drinks or 10–20 g of alcohol per day) shows a benefit on CHD incidence in the general population. This benefit also extends to the diabetic population.

Individual interventions for CV risk factors in diabetic patients give a 15–30% risk reduction. The results of these studies

have been scrutinized in detail, leading to the establishment of treatment guidelines with specific targets regarding glycemic control, desirable blood pressure, and lipid levels (Table 4).

Management of Individual Risk Factors

In the following sections, recent advances in the therapeutic strategies for management of the individual risk factors associated with the diabetic state are discussed.

Hyperlipidemia

In the diabetic population, the prevalence of hypertriglyceridemia and low HDL levels is approximately twice as high and the prevalence of high LDL level is not different as compared to the nondiabetic population.[50] However, whatever the level of LDL in the diabetic individual, the LDL is atherogenic (type B small dense LDL) and, therefore, treatment with statins has been found to be highly effective in preventing macrovascular events. Initial data on benefits of statins in diabetic subjects were obtained from subgroup analyses of the major secondary intervention trials, such as the Scandinavian Simvastatin Survival Study (4S) and CARE trials.[51,52]

More recently, the benefits of high-dose statin-use were demonstrated in the TNT study which compared atorvastatin 10 mg to an 80 mg/day dose in patients with stable coronary artery disease (CAD).[53] A subanalysis demonstrated that major CV events were reduced by 25% in diabetic patients receiving high-dose atorvastatin, supporting the use of intensive lipid lowering regimens. Further *post hoc* analysis of the TNT study was done to investigate the effect of intensive lipid lowering on future CV events in patients with diabetes, with or without coexisting mild to moderate chronic kidney disease (CKD).[54] Compared with a 10 mg dose of atorvastatin, the 80 mg dose reduced the relative risk of major cardiovascular events by 35% in patients with diabetes and CKD and by 10% in patients with diabetes and normal epidermal growth factor receptor. The absolute risk reduction in patients with diabetes and CKD was substantial, yielding a number needed to treat of 14 to prevent 1 major cardiovascular event over 4.8 years. This result is very encouraging and stands in contrast to previous observations in patients with diabetes and end-stage renal disease.

These data from TNT analysis of diabetic cohort provide a strong support to the prevailing recommendations of reducing LDL to levels <70 mg/dL as recommended by various guidelines including American Diabetes Association (ADA). There is less evidence for interventions directed at the diabetic dyslipidemia

TABLE 4

Goals for Risk Factor Management in Diabetes

Risk factor	*Goal of therapy*	*Reference***
Cigarette smoking	Complete cessation	ADA, AHA
BP	<130/80 mmHg	JNC 7, ADA
BP with proteinuria	<125/75 mmHg	JNC 7, ADA
LDL cholesterol (measured annually)	<70 mg/dL for secondary prevention*	ATP III, ADA
For age >40 years	Without CVD but >1 risk factor, LDL goal is <100. If LDL is <100 at baseline, statin is based on additional risk factors	ATP III, ADA
For age <40 years	Without CVD, but estimated to have high risk of CVD, LDL goal is <100 mg/dL	ATP III, ADA
Triglycerides 200–499 mg/dL	Non-HDL cholesterol <130 mg/dL	ATP III, AHA
Triglycerides >500 mg/dL	Fibrate/niacin before LDL lowering Non-HDL <130 mg/dL	ATP III, AHA
	Target triglycerides <150	ADA
HDL cholesterol <40 mg/dL (<50 mg/dL in women)	Raise HDL	ATP III, ADA
Prothrombotic state	Low-dose aspirin therapy (patients with CHD and other high risk factors including age >40)	ADA, AHA
Glucose	HbA1C <7%	ADA, AHA
Overweight and obesity (BMI >25 kg/m^2)	Lose 5–7% of body weight	ADA, AHA
Physical inactivity	150 min moderate aerobic exercise or at least 90 min vigorous aerobic exercise/week (not more than 2 consecutive days without physical activity)	ADA, AHA
Adverse nutrition	Diets low in fat (<30%) and saturated fat <7%; lower glycemic index (when necessary with caloric restriction) 1.2–2 g sodium/day Alcohol up to 2 drinks/day (1 drink/day for women; 1 drink = 354.88 mL beer or 118.29 mL wine, or 44.36 mL distilled spirit)	ADA, AHA, ATP III, OEI, JNC 7

*NCEP.[5,29]

**ADA,[47] AHA,[47] JNC 7,[48] ATP III,[5] OEI.[49]

ADA, American Diabetes Association; AHA, American Heart Association; BP, blood pressure; JNC, Joint National Committee; ATP, Adult Treatment Panel; OEI, Obesity Education Initiative; NCEP, National Cholesterol Education Program; LDL, low-density lipoprotein; HDL, high-density lipoprotein; CVD, cardiovascular disease; CHD, coronary heart disease; HbA1C, glycosylated hemoglobin; BMI, body mass index.

(high triglyceride and low HDL). The Action to Control Cardiovascular Risk in Diabetes (ACCORD) lipid trial evaluated treatment with fenofibrate compared with placebo among patients with type 2 diabetes treated with an open-label statin medication.[55] Among 5,518 patients randomized into the study, the addition of fenofibrate to statin therapy was not superior to statin therapy alone. While fenofibrate reduced triglyceride levels, there was only a small difference in mean HDL and no difference in LDL between groups, which could help explain lack of benefit.

Hypertension

As regards management of hypertension, the ACCORD study demonstrated that decreasing systolic blood pressure (SBP) to a mean value of 119.3 mmHg was associated with decrease in all stroke and nonfatal stroke.[56] Results from the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) study are also instructive in the management of hypertension in the diabetic patient.[57] ADVANCE was a 2 × 2 factorial study, in which 11,140 patients were randomized to either intensive glucose control or standard glucose therapy, and fixed-dose combination of perindopril, and indapamide, or placebo. After a mean of 4.3 years of follow-up, those who received active therapy had a mean reduction in SBP of 5.6 mmHg (mean SBP of 134.7 active vs. 140.3 placebo) and diastolic blood pressure (DBP) of 2.2 mmHg (mean DBP 74.8 active vs. 77 placebo). The relative risk of death from CVD was reduced by 18% ($p = 0.03$) and death from any cause was reduced by 14% ($p = 0.03$) (Figure 2). This benefit was attributed mostly to reduction in microvascular events.

So, the natural question that arises is what should be the target blood pressure for therapy in the diabetic patient? Although guidelines have recommended target blood pressure <130/80 or 120/75 in those with CKD, this target had not been supported by prospective large scale randomized controlled trial specifically designed to evaluate the benefit of targeted therapy to a goal of blood pressure <130/80. The ACCORD blood pressure study is the first such trial, where treatment directed to a goal of <120/80 was prospectively evaluated against blood pressure goal of <140/80. Although the findings of the ACCORD trial have not yet been incorporated into guidelines, it seems reasonable in the meanwhile to consider that the target blood pressure for most diabetic patients should be <130/85.

In choosing an antihypertensive agent, it is important to realize that the degree of blood pressure reduction obtained is more important than the specific agent which might be

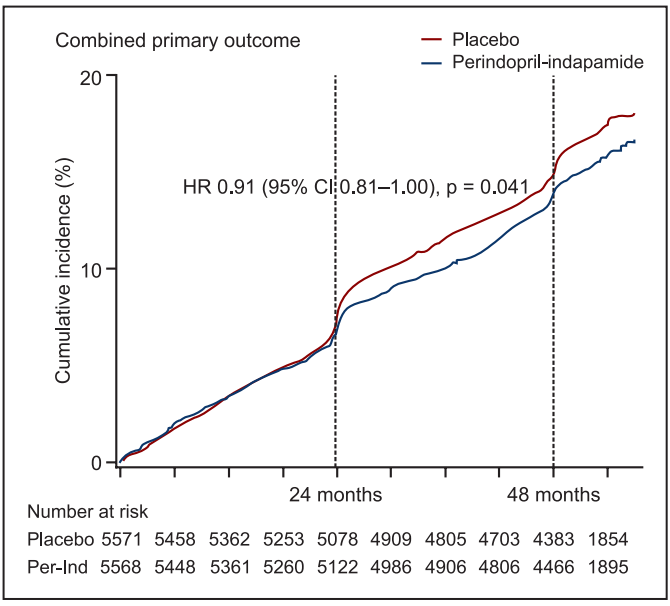

FIGURE 2. Impact of therapeutic strategies on combined macro- and microvascular events. *From* Patel A; ADVANCE Collaborative Group, MacMahon S, Chalmers J, Neal B, Woodward M, Billot L, et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. *Lancet*. 2007;370(9590):829-40, *with permission*.

selected for the purpose. Moreover, since therapy requires use of multiple antihypertensive medications at the outset, it is a moot point as to which should be the preferred initial drug. Nevertheless, ACEIs have been generally recommended as preferred initial drugs. There is persuasive data from the Heart Outcomes Prevention Evaluation (HOPE) study in support of the use of ACEIs.[58]

While ACEIs remain the cornerstone of therapy for patients with type 1 diabetes and nephropathy, the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan trial (RENAAL) and Irbesartan Type II Diabetic Nephropathy (IDNT) studies support initial therapy with angiotensin receptor blockers in type 2 diabetes. ARBs represent the only evidence-based treatment strategy for patients with type 2 diabetes mellitus and proteinuria and have been recommended as initial treatment of choice by the National Kidney Foundation.[59]

It is also important to remember that β-blockers are recommended and provide cardioprotection in patients with established CHD, and as such when additional therapy is needed, β-blockers should be considered in appropriate patients.

The role of calcium channel blocker therapy was clarified by the recently published Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension (ACCOMPLISH) trial.[60] The diabetic subgroups in this study involving 6,946 subjects were randomized to treatment with benazepril plus amlodipine or benazepril plus hydrochlorothiazide. A subgroup of 2,842 high-risk diabetic patients (previous cardiovascular or stroke events) was further analyzed. While the mean achieved blood pressure was similar in both treatment groups, there were clear benefits with benazepril plus amlodipine combination in cardiovascular end-points. The difference between the two treatment groups demonstrated that contemporary treatment with benazepril and amlodipine was better in higher risk groups, i.e., individuals with diabetes and high-risk diabetic individuals.

To conclude, pharmacologic therapy to block the renin-angiotensin-aldosterone system (RAAS) should be mandatory in patients with diabetic nephropathy (which includes patients with microalbuminuria). Since appropriate therapy of hypertension generally requires more than one agent, the initial therapy with RAAS blocking agents and amlodipine may be considered.

Hyperglycemia

While the benefit of glycemic control on delaying or preventing microvascular disease has been well documented, the relationship between hyperglycemia and macrovascular disease has been a subject of constant debate. United Kingdom Prospective Diabetes Study (UKPDS) is the largest study addressing this issue.[61,62] It was designed to answer the question as to whether intensive control of glucose compared to conventional treatment in newly diagnosed type 2 diabetics lowers the risk of complications. Over a mean follow-up duration of over 10 years in approximately 2,500 patients in each group, intensive therapy lead to a 12% reduction in any diabetes related end-point and a significant reduction in the microvascular end-points (25% reduction; $p = 0.0099$). A 16% reduction in MI ($p = 0.052$) and nonsignificant reduction in diabetes related and all-cause mortality was also seen in the intensively treated group. Nevertheless, the European Prospective Investigation into Cancer and Nutrition-Norfolk (EPIC-Norfolk) study found a continuous relationship between all-cause mortality and glycosylated hemoglobin (HbA1C) even for values in the nondiabetic range.[63] The increased risk of death among men with diabetes was largely explained by HbA1C concentration.

The threshold to which glycemic control needs to be pushed has probably been adequately answered by the recently published

data from the ACCORD trial.[64] The goal of the trial was to evaluate intensive glycemic control through currently available means (i.e., HbA1C <6%), compared with standard glycemic control (i.e., HbA1C 7.0–7.9%), among patients with type 2 diabetes mellitus with known CVD or with additional risk factors for CVD. At 1 year, HbA1C was 6.4 vs. 7.5%, respectively. The glycemic arm of the trial was stopped prematurely due to excess death that was reported in the intensive treatment group. While there was no identifiable cause for excess death in the intensively treated group in the ACCORD trial, a strategy of lowering HbA1C to a mean of <6.5% may not be advisable. These results were somewhat mirrored by the ADVANCE trial, which is the largest trial on diabetes treatments to date.[65] In this trial, a total of 11,140 patients with type 2 diabetes were randomly assigned to undergo either standard glucose control or intensive glucose control with gliclazide and other agents to achieve an HbA1C value of ≤6.5%. At the end of 5 years, the mean HbA1C was 6.5% in the intensive control arm vs. 7.3% in the standard therapy arm. The main finding of this study was that gradually implemented intensive glucose control, with a goal to achieve an HbA1C of ≤6.5%, was associated with a significant reduction in some microvascular complications of diabetes but not macrovascular complications. Intensive glucose control was also associated with a higher incidence of hospitalizations and severe hypoglycemia. A recent presentation by the ADVANCE group indicated that severe hypoglycemia was associated with significant increased risk of cardiovascular and all-cause mortality.

The choice of hypoglycemic therapy should be influenced by consideration of multiple factors, including BMI, renal function, comorbidities, financial issues, and patient preferences. In general, overweight individuals should preferably be initially started on metformin in the absence of contraindications. The use of TZDs noted earlier remains a topic of debate, and the decision to use them should be individualized. The 2008 ADA and the European Association for the Study of Diabetes consensus algorithm recommended against the use of rosiglitazone, owing to concern regarding safety and the availability of alternative therapies, including pioglitazone that do not have the same concerns.[66]

Recent publication of a 10-year follow-up of intensive glucose control in type 2 diabetes from the UKPDS study cohort has raised the concept of a "legacy effect".[67] In the UKPDS study, 4,209 patients with newly diagnosed type 2 diabetes were randomized to either conventional therapy (dietary restriction) or intensive therapy (either sulfonylurea, insulin, or metformin in overweight

patients). In post-trial monitoring, patients returned to community- or hospital-based care with no attempt to maintain their previously randomized therapies. The median follow-up was 17 years, with close to 9 years of post-trial follow-up. While between-group differences in HbA1C were lost within a year of cessation of assigned treatments, levels of HbA1C continued to fall in both groups over 5 years reflecting appropriate risk factor management. In the sulfonylurea/insulin group, reduction in risk persisted for microvascular disease and any diabetes-related outcome at 10 years. Additionally, reductions were also noted for diabetes-related death, MI, and death from any cause. Furthermore, in the group treated with metformin, significant risk reductions persisted for any diabetes related outcomes, MI, and death from any cause without any effect on microvascular disease. The persistence and emergence of benefits, despite early loss of within-trial differences, in HbA1C levels between the intensive-therapy group and the conventional-therapy group has been called the legacy effect.

To summarize, while glycemic control does significantly impact the incidence of microvascular complications, the effect on macrovascular cardiovascular outcomes is less obvious, especially in those with prolonged duration of diabetes or preexisting CV disease. Additionally, there appears to be a lower threshold value of glycemic control (HbA1C of 6.5%), below which the risk of therapy may outweigh the benefits. Moreover, the strategy and medications used for glycemic control may have an effect on outcomes. Based on the results of the recent trials as noted above, the American College of Cardiology (ACC), AHA, and ADA came up with a consensus statement recommending the maintenance of HbA1C levels at or <7% for most people with diabetes while recommending that a comprehensive risk factor reduction should be instituted for CV risk reduction in all diabetic patients.

Antithrombotic Therapy

Primary Prevention

The multiple biochemical and functional abnormalities in the platelet function in both type 1 and 2 diabetes lead to increased platelet aggregability and adhesiveness. The correction of this abnormality with antiplatelet agents, such as aspirin should logically reduce CV events in diabetics. A meta-analysis of the 6 large trials of aspirin for primary prevention in the general population found that aspirin reduced the risk of vascular events by 12%, with the largest reduction being for nonfatal MI.[68] There was little effect on total stroke or CHD death. Three of the trials

in the above meta-analysis focused on the effect of aspirin exclusively among patients with diabetes [the Early Treatment Diabetic Retinopathy Study (ETDRS) trial, the Prevention of Progression of Arterial Disease and Diabetes (POPADAD) trial, and the Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes (JPAD) trial].[69,70] None of the trials mentioned above provided definitive results.

Based on these and other studies, the US Preventive Services Task Force recently recommended encouraging aspirin use in men age 45–79 years and women age 55–79 years, but discouraging the use of aspirin in younger adults regardless of the presence or absence of diabetes.[71,72] Two ongoing studies with combined sample size of more than 15,000 individuals with diabetes will provide additional information on the role of low-dose aspirin for the prevention of cardiovascular events. Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes (ACCEPT-D) is an open-label Italian primary prevention trial comparing aspirin 100 mg once a day to no aspirin among adults over age 50 years with diabetes who are also on simvastatin.[73] The second trial, A Study of Cardiovascular Events in Diabetes (ASCEND), will also examine the effects of 100 mg aspirin daily vs. placebo for primary prevention among men and women over age 40 years with either type 1 or type 2 diabetes.[74]

In order to provide guidelines for management, the ADA, AHA, and ACC recently published an expert consensus document recommending low-dose aspirin (75–162 mg/day) as primary prevention for adults with diabetes who are at increased CVD risk (10-year risk of CVD events over 10%) and are not at increased risk for bleeding (prior gastrointestinal bleeding, peptic ulcer disease, or concurrent use of medication, such as nonsteroidal anti-inflammatory drugs or warfarin).[75] The accurate determination of CVD risk should be made with the use of clinical tools, such as the UKPDS Risk Engine, Atherosclerosis Risk in Communities (ARIC) CHD Risk Calculator, or ADA Risk Assessment Tool (Table 5).

TABLE 5

Indications for Aspirin Use for Primary Prevention in High-risk Diabetic Patients
▪ Obesity
▪ Hypertension
▪ Cigarette smoking
▪ Family history of coronary heart disease
▪ Micro- or macroalbuminuria
▪ Atherogenic dyslipidemia

Secondary Prevention

The efficacy of aspirin for secondary prevention of CV events is suggested by a meta-analysis of secondary prevention trials by the Antithrombotic Trialists' Collaboration (ATC). The ATC meta-analysis included 287 trials with the inclusion of 212,000 high-risk patients.[76] In more than 4,500 patients with diabetes, the incidence of vascular events was significantly reduced from 23.5% with control treatment to 19.3% with antiplatelet therapy ($p < 0.01$). While the overall incidence of vascular events in the diabetic subgroup was much higher, the benefit of antiplatelet therapy in the diabetic and nondiabetic patients was comparable. In the Hypertension Optimal Treatment (HOT) study, half of the 1,501 patients with diabetes included in each target group were randomized to receive aspirin. The CV event rate was reduced by 15% and MI by 36% compared to placebo. The relative effects of aspirin were similar in nondiabetic and diabetic subjects.[77]

CURRENT ISSUES AND CONTROVERSIES IN THE MANAGEMENT OF CORONARY ARTERY DISEASE IN DIABETES MELLITUS

Management of CAD in the presence of diabetes should follow current ACC/AHA guidelines, which are based on an evidence-based approach.[78] In addition, as discussed above, considerable emphasis should be placed on aggressive reduction of risk factors, as such strategies will yield greater benefit for a diabetic individual. Treatment of acute coronary syndrome should include measures to preserve myocardium, stabilize atherosclerotic plaques, and prevent prothrombotic activity with the goal to reduce both short-term and long-term morbidity and mortality.[79] Studies have indicated that hyperglycemia in the setting of ACS is a poor prognostic marker. The role of intensive glycemic control by means of insulin infusion in patients presenting with ACS remains controversial. Data from the Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI) trial, and the Hyperglycemia: Intensive Insulin Infusion in Infarction (HI-5) trial are contradictory, and all the studies have design flaws that make their findings unreliable.[80-82] In the absence of robust clinical data, the ACC/AHA 2009 update on ST-elevation MI gives a weak recommendation for the use of an insulin-based regimen to achieve and maintain blood glucose <180 mg/dL while avoiding hypoglycemia.[83]

CAD should preferentially be managed with medical therapy unless revascularization is necessary for acute coronary syndrome or to mitigate intractable symptoms based on findings from the

Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes (BARI 2D) trial.[84] BARI 2D was designed to determine whether early use of the most appropriate revascularization intervention, combined with aggressive medical management, reduced mortality rates compared with an initial strategy of equally aggressive medical management but delayed or no revascularization. Overall, patients with diabetes mellitus have a higher mortality and morbidity after any revascularization procedure as compared to patients without diabetes mellitus.

There is considerable ongoing debate regarding the most appropriate interventional approach in the setting of diabetes mellitus. Prior data comparing percutaneous coronary intervention (PCI) to coronary artery bypass grafting (CABG) come from studies in which stenting was not practiced and contemporary DAPT regimen was not established. Trials comparing CABG to PCI with bare-metal stents (BMS) demonstrated lower event-free survival with BMS, primarily due to higher incidence of repeat revascularization (Arterial Revascularization Therapies Study-I (ARTS-I) trial[85]). The ARTS-II study evaluating sirolimus eluting stents suggested no significant difference between drug eluting stents (DES) and CABG when outcomes were compared to the CABG arm in ARTS I trial.[86] The recently concluded Coronary Artery Revascularization in Diabetes (CARDia) trial also demonstrated no difference in all-cause mortality, MI, and stroke.[87] Another trials, the SYNergy between PCI with TAXus and cardiac surgery (SYNTAX) trial demonstrated higher event rate with DES primarily due to increased incidence of revascularization with stenting.[88] Additionally, mortality was higher with stenting in patients with complex lesions (as identified by the Syntax score). In summary, until further data are available, such as from the Future REvascularization Evaluation in patients with Diabetes mellitus: Optimal management of Multivessel disease (FREEDOM) trial, current evidence supports CABG with left internal mammary artery (LIMA) graft as a better option for revascularization in patients with diabetes mellitus particularly for complex left main disease, triple vessel disease, and for two-vessel disease with a complex left anterior descending disease.

Heart Failure in Diabetes

Heart failure can occur with diabetic cardiomyopathy without coexisting hypertension or CAD. Various postulated factors seem to contribute to the development of heart failure. These include autonomic neuropathy, impaired epicardial vessel tone, microvascular dysfunction, deposition of advanced glycation end-products, and insulin resistance, leading to shift toward

fatty acid metabolism in the myocardium. The management of heart failure in the setting of diabetes is along the same lines as in the absence of diabetes mellitus. An additional precaution to be taken in treating diabetes in the presence of diabetes mellitus is to be aware of potential side effects of medications, including TZDs and metformin. TZDs are not recommended in patients with symptomatic heart failure particularly with New York Heart Association class III and IV heart failure.

CONCLUSION

In conclusion, cardiodysmetabolic syndrome, impaired glucose tolerance, and diabetes mellitus likely reprsent a spectrum of metabolic disorders associated with varying degrees of insulin resistance that lead to endothelial dysfunction. The means to prevent and treat these disorders are similar and should include a multifactorial risk reduction approach to prevent associated cardiovascular disease.

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7 CHAPTER

Drugs for Acute Coronary Syndromes

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INTRODUCTION

The formation of an atherosclerotic plaque begins with endothelial dysfunction.[1] Dysfunctional endothelial cells increase expression of adhesion molecules (vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1)) that promote the adherence and extravasation of monocytes into the inner surface of the arterial wall.[2] Research has demonstrated that extravasated monocytes will subsequently differentiate into macrophages in response to the surrounding cytokine environment and accumulate lipid to form a subintimal layer of foam cells.[3,4] Smooth muscle cells then migrate from the media into the intima where they proliferate and construct a complex extracellular matrix that overlies the lipid core.[3] As the lesion progresses, ossification can occur with significant calcification of the thick fibrotic cap overlying the deposited lipid resulting in stabilization of the lesion.[5] Lipid-laden macrophages may then produce cytokines that perpetuate the inflammatory process and secrete enzymes that degrade this extracellular matrix.[6] Disruption of the extracellular matrix exposes the underlying lipid core to the vascular space, allowing it to serve as a nidus for thrombus formation.

Degradation of the extracellular matrix and exposure of the diseased vascular wall results in thrombus formation that instigates acute coronary syndromes (ACS) (Figure 1). As the plaque becomes unstable, subendothelial tissue factor produced by macrophages and smooth muscle cells will activate the coagulation cascade.[7-9] Activated coagulation factors result in the generation of thrombin, initiating the conversion of fibrinogen to fibrin.[10] Circulating platelets will subsequently adhere to the subendothelial space and become activated by the presence of von Willebrand factor, resulting in immediate aggregation and formation of the primary platelet plug.[11] Fibrin polymer cross-links will be attached to the adherent platelets resulting in thrombus formation. Although this thrombus is adherent to the

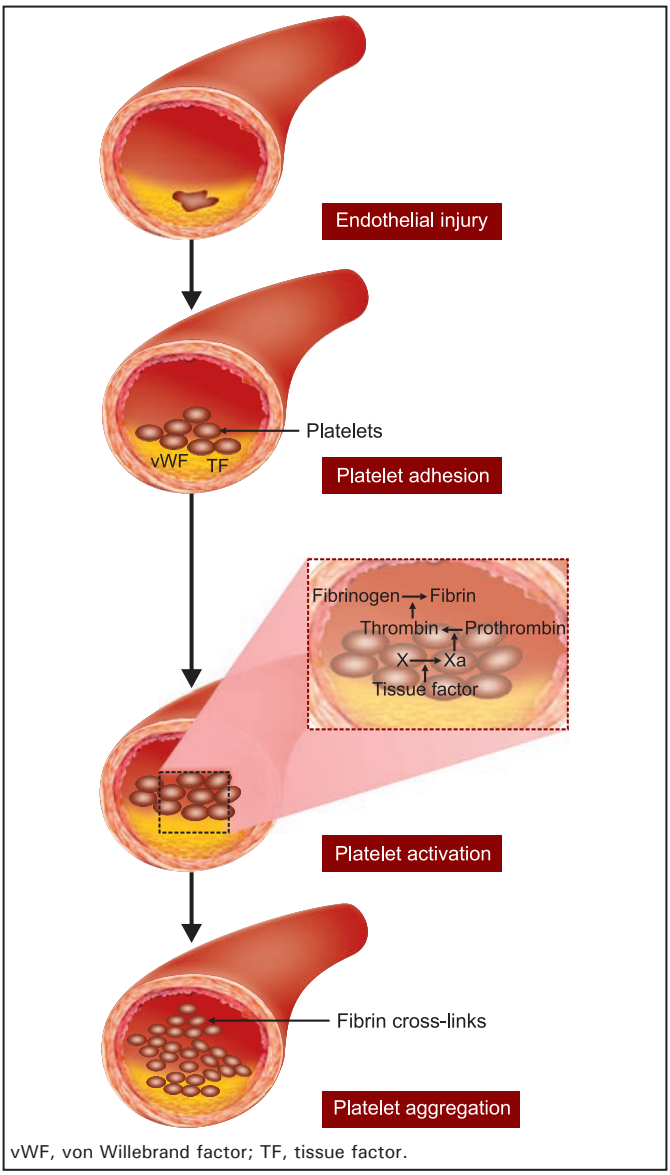
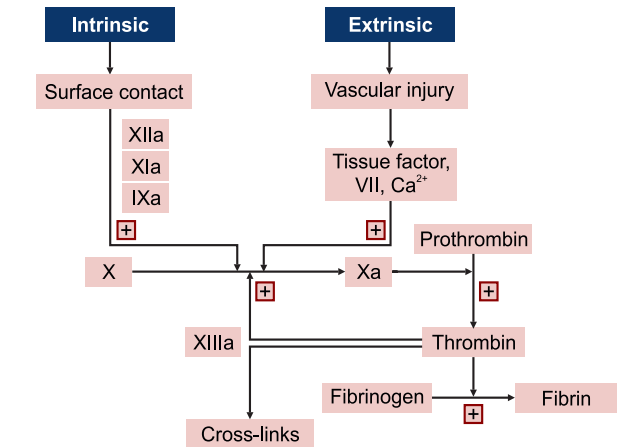


FIGURE 1. The pathogenesis of acute coronary syndrome. It begins with endothelial injury leading to exposure of the subendothelial space. vWF and TF lead to platelet adhesion and activation of the clotting cascade, respectively. Generation of thrombin leads to platelet degranulation and perpetuates platelet activation while also generating fibrin cross-links to facilitate platelet aggregation and complete occlusion of the arterial lumen.

vascular wall, there is a potential for embolization resulting in microvascular occlusion.

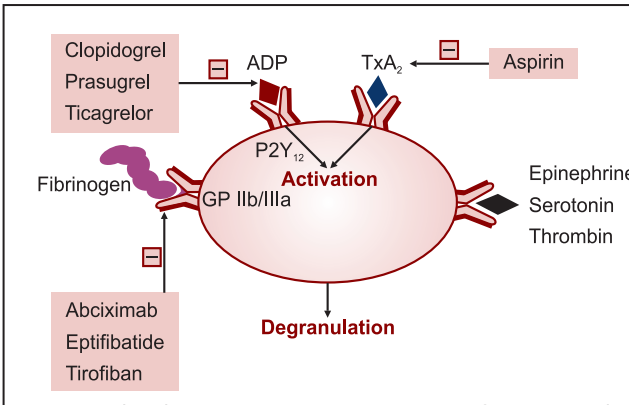
The clinical presentation of an epicardial thrombus encompasses unstable angina, non-ST elevation myocardial infarction (non-STEMI) and ST elevation myocardial infarction

(STEMI), collectively termed ACS. The pharmacologic therapy for ACS is fundamentally designed to reduce myocardial oxygen demand and increase myocardial oxygen supply to reduce the risk of myocardial infarction. Decreasing myocardial oxygen demand utilizes therapies that decrease cardiac rate and inotropy. Increasing myocardial oxygen supply utilizes therapies that inhibit both the coagulation system and platelet activation to restore normal coronary blood flow. A number of anticoagulants have been used clinically to affect different aspects of the clotting cascade (Figure 2). Similarly, a number of platelet receptors have been identified as therapeutic targets (Figure 3 and Table 1) to



TF, tissue factor; Ca^{2+}, calcium.

FIGURE 2. The intrinsic and extrinsic clotting cascade.



ADP, adenosine diphosphate; TxA_2, thromboxane A_2; GP, glycoprotein.

FIGURE 3. Clinical use of anticoagulants at various stages of the clotting cascade. Platelet activation and degranulation is mediated through ADP, TxA_2, and GP IIb/IIIa receptors. Each of these receptors is a potential target for therapeutic agents during the treatment of acute coronary syndrome.

TABLE 1

Platelet Receptors Identified as Therapeutic Targets			
Receptor	*Alternate name*	*Function*	*Inhibitor*
αIIbβ3	Glycoprotein IIb/IIIa	Cross-links fibrinogen and von Willebrand factor	Abciximab Eptifibatide Tirofiban
$P2Y_{12}$	ADP receptor	Platelet activation	Clopidogrel Prasugrel Ticlopidine Ticagrelor
PAR	Thrombin	Platelet activation	Aspirin

PAR, proliferator-activated receptor; ADP, adenosine diphosphate.

reduce the propagation of thrombus formation. In addition to these therapies, fibrinolytic agents can be used to disintegrate previously formed thrombus through destruction of fibrin cross-links. The pharmacology and clinical uses of each of these therapies will be reviewed in the following sections.

ANTI-ISCHEMIC THERAPIES

Introduction

The treatment of ACS begins with therapies to reduce the ischemic burden.[12] Current guidelines suggest that patients with ACS should be initially treated with bed rest (class I, level C) and supplemental oxygen (class II, level C) while pharmacotherapies are being pursued. Nitroglycerin, narcotics, β-blockers, and calcium-channel blockers serve as the primary anti-ischemic medications employed in the contemporary management of ACS.

Nitroglycerin

Pharmacology

Nitroglycerin degenerates *in vivo* to deliver nitric oxide throughout the vasculature. Within smooth muscle cells, nitric oxide activates guanylate cyclase resulting in an increase in guanosine 3′5′ monophosphate (cGMP).[13] The presence of cGMP within smooth muscle cells leads to dephosphorylation of myosin light chains and results in smooth muscle relaxation. A reduction in vascular tone produces a vasodilator effect on peripheral veins and, to a lesser extent, on peripheral arteries. The dilation of the capacitance vessels increases venous pooling and decreases myocardial preload, one of the measures of myocardial demand.[12] Nitroglycerin also induces the dilation of the arterial vasculature resulting in a slight decline in

afterload. It is important to note that this decline in afterload is often offset by a reflex increase in heart rate so that the optimal anti-ischemic effect of nitroglycerin is obtained when combined with the concomitant use of β-blockers.

Nitroglycerin also dilates normal and atherosclerotic epicardial coronary arteries. Research has suggested that endothelial dysfunction within the diseased coronary vasculature may impair the normal physiological response to changes in myocardial blood flow.[14] Because of this, patients suffering from ACS may not achieve maximum epicardial artery dilatation without the administration of exogenous nitroglycerin. As a result, nitroglycerin has the benefit of increasing myocardial oxygen supply through the dilation of the epicardial coronary arteries.[14]

Pharmacokinetics and Doses

Nitroglycerin is available in topical, oral, and intravenous formulations. To facilitate rapid absorption into the systemic circulation, oral formulations include sublingual tablets and translingual sprays (0.3–0.6 mg/dose). The oral formulations begin to take their effect on the vasculature within 1–3 minutes of administration with a peak effect occurring after approximately 5 minutes.[12] Because of extensive first-pass metabolism, these agents have a short half-life (1–4 minutes), and their effect dissipates completely after 25 minutes. The intravenous formulation of nitroglycerin (5–400 μg/min) has a rapid onset of action, but tolerance may develop after 8 hours of continuous therapy. The administration of nitroglycerin with phosphodiesterase inhibitors results in a profound decline in vasomotor tone resulting in recalcitrant hypotension. Because of this, nitroglycerin should not be used within at least 24 hours of inhibitors phosphodiesterase administration.

Clinical Use and Indications

There are no large randomized controlled trials, which support the use of nitroglycerin to reduce ischemia or mortality in ACS. A meta-analysis of several small studies conducted before the reperfusion era, however, demonstrated a 35% relative risk reduction in mortality among patients who received intravenous nitroglycerin for ACS.[15] Clinical trials in the reperfusion era have not been able to reproduce this magnitude of benefit.[16,17] However, studies have demonstrated that the abrupt discontinuation of intravenous nitroglycerin results in worsening electrocardiographic changes.[18] Despite the lack of controlled data, nitroglycerin continues to be a widely accepted anti-ischemic agent for the treatment of ACS.

Guidelines

Current guidelines recommend the use of sublingual nitroglycerin (0.4 mg) every 5 minutes for a total of 3 doses to reduce ongoing ischemic discomfort in the setting of ACS (class I, level C). Intravenous nitroglycerin is currently indicated in the first 48 hours after ACS for the treatment of persistent ischemia or hypertension (class I, level B).[12] The guidelines note that the administration of nitrates is contraindicated in the setting of hypotension [systolic blood pressure (SBP) <90 mmHg] or in patients who have recently used phosphodiesterase inhibitors because of the potential risk of cardiovascular collapse (class III, level C).

Narcotics

Pharmacology

Narcotics have potent analgesic and anxiolytic effects, which may reduce myocardial oxygen demand in ACS. Additionally, morphine sulfate causes a reduction in vasomotor tone and a decrease in heart rate resulting in a decline in SBP. These effects are mediated through an increase in vagal tone, and all result in decreased myocardial oxygen demand.[12]

Pharmacokinetics and Doses

Intravenous morphine sulfate (1–5 mg IV push) is the narcotic most frequently employed in ACS. The onset of action for the intravenous formulation is rapid (5–10 minutes) with a half-life of 2–4 hours. Morphine sulfate is metabolized via hepatic conjugation with glucuronic acid to morphine-6-glucoronide (active analgesic) and morphine-3-glucuronide (inactive analgesic) before being excreted predominantly in the urine.

Clinical Use and Indications

There are no large randomized controlled trials that support the use of narcotics to reduce ischemia or mortality during ACS. Despite this, narcotics have been included in the clinical treatment algorithm for ACS for the past 3 decades. A recent large observational cohort data (n = 57,039) suggests that the administration of morphine may be associated with an increased risk of mortality.[19] Patients who received morphine within this registry (29.8%) had a higher risk-adjusted likelihood of all-cause in-hospital death (OR 1.48) during treatment for ACS. As an observational cohort, there are likely selection biases contributing to this finding, and a randomized controlled trial should be conducted to answer this question definitively. In light of the data, however, recent guidelines have tempered the enthusiasm for the widespread use of narcotics in ACS.

Guidelines

In the absence of contraindications, current guidelines suggest that it is reasonable to administer intravenous narcotics (morphine sulfate) to patients with ACS and persistent ischemic discomfort despite the use of nitroglycerin (class IIa, level B).[12]

β-blockers

Pharmacology

The primary benefit of β-blockers in ACS is related to their antagonism of the β1-adrenergic receptors. β1-adrenergic receptors are primarily located on the surface of the myocardium.[20] Competitive inhibition of catecholamine action on these receptors reduces myocardial contractility as well as the intrinsic sinus rate resulting in a significant decline in myocardial oxygen demand.[12] The decrease in ventricular rate also increases the duration of diastole allowing increased time for the epicardial coronary arteries to perfuse the ventricular myocardium, thus, increasing myocardial oxygen supply. In contrast to β1-adrenergic receptors, β2-adrenergic receptors are primarily located on the vascular and bronchial smooth muscle. Inhibition of catecholamine action at these sites produces vasoconstriction and bronchoconstriction.[12] Because of this, severe bronchospasm is a relative contraindication to the use of β-blockers. Most β-blockers used in the contemporary management of ACS are selective β1-antagonists (Table 2).[12]

TABLE 2

β-Blockers Used in the Contemporary Management of Acute Coronary Syndrome

Drug	*Selectivity*	*Agonist activity*	*Dose*
Acebutolol	β1	Yes	200–600 mg BD
Atenolol	β2	No	50–200 mg every day
Betaxolol	β1	No	10–20 mg every day
Bisoprolol	β1	No	10 mg every day
Carvedilol	None	Yes	6.25–25 mg BD
Esmolol	β1	No	50–300 μg/kg/min
Labetalol	None	Yes	200–600 mg BD
Metoprolol	β1	No	50–200 mg BD
Nadolol	None	No	40–80 mg every day
Pindolol	None	Yes	2.5–7.5 mg TD
Propranolol	None	No	20–80 mg BD
Timolol	None	No	10 mg BD

BD, twice a day; TD, thrice a day.

Pharmacokinetics and Doses

Based on prior studies, metoprolol tartrate is the most commonly employed β-blocker in the immediate management of ACS.[12,21] The dosing regimens administered include intravenous metoprolol 5 mg IV push over 1 minute, repeated up to 3 times for a total dose of 15 mg.[12] The intravenous form of metoprolol reaches its peak action in 20 minutes with a duration of action of approximately 6 hours based on a half-life of 3–8 hours before being metabolized in the liver (CYP450 2D6) and excreted in the urine. In the patients who tolerate this regimen, oral therapy (25–50 mg) can be initiated 15 minutes after the last intravenous dose every 6 hours.

Clinical Use and Indications

The initial studies of β-blockade in the treatment of ACS were conducted prior to routine anticoagulation and revascularization. A collection of these early studies suggested that routine use of β-blockade in patients with unstable angina resulted in a 13% relative risk reduction in the eventual progression to an electrocardiographically significant myocardial infarction.[22] After the advent of routine percutaneous revascularization, another collection of small studies suggested that the use of β-blockers in ACS eventually treated with percutaneous coronary intervention reduced the absolute risk of death at 6 months by 2%.[23] Based on this data, β-blockers became widely employed in the immediate management of ACS.

The use of routine β-blockade has been challenged in the fibrinolytic era. In the Thrombolysis in Myocardial Infarction (TIMI)-II-B trial, patients with ACS treated with fibrinolysis were randomized to receive immediate treatment with β-blockers (metoprolol 5 mg IV) or deferred treatment.[24] After 6 weeks of follow-up, there was no difference in the primary outcome of mortality between the 2 groups. There was, however, a lower incidence of recurrent chest pain (18.8 vs. 24.1%) and recurrent infarction (2.7 vs. 5.1%) in the patients that received immediate treatment with β-blockade. These findings were reproduced with atenolol in a *post hoc* analysis of the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries-1 (GUSTO-1) database.[25] It is important to note that this trial demonstrated a slightly increased risk of heart failure.

The most recent randomized trial evaluating the use of intravenous metoprolol for ACS included 45,852 patients in Asia [Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT)].[21] The majority of this population presented with electrocardiographic evidence of STEMI (93%) and were randomized to receive immediate treatment with intravenous

β-blockers (metoprolol 5 mg IV) followed by oral metoprolol (200 mg daily) or placebo. The primary combined composite end-point of death, reinfarction, or cardiac arrest was equivalent between the 2 groups (9.4 vs. 9.9%). Treatment with β-blockers did result, however, in a reduction in the rate of reinfarction (2.0 vs. 2.5%) as well as an increase in the rate of cardiogenic shock (5.0 vs. 3.9%). Based on this data, greater caution is now suggested in the routine use of intravenous β-blockers for ACS. In particular, these agents should be avoided in patients with clinical evidence of heart failure or hemodynamic instability.[12]

Although the present discussion has focused on the immediate management of ACS, it is important to note that the treatment of stable coronary artery disease with left ventricular dysfunction may include the use of alternative β-blockers, particularly carvedilol.[26,27]

Guidelines

Current guidelines suggest that it is reasonable to administer intravenous β-blockers at the time of presentation in the absence of contraindications (class IIa, level B). Additionally, current guidelines suggest that oral β-blocker therapy should be initiated within the first 24 hours after ACS, unless there is a contraindication (class I, level B). Acceptable contraindications to therapy with oral β-blockers include clinical signs of heart failure or cardiogenic shock. Relative contraindications include the risk of evidence of a low-output state or conduction abnormalities.[12]

Calcium Channel Blockers

Pharmacology

Calcium channel blockers reduce transmembrane inward calcium flow, thus, inhibiting myocardial and vascular smooth muscle contraction. Like β-blockers, this reduces myocardial contractility resulting in a reduction in myocardial oxygen demand. Calcium channel blockers also dilate the epicardial coronary arteries resulting in an increase in myocardial oxygen supply.[12] Through these mechanisms, calcium channel blockers can serve as effective antianginal medications in certain patient populations presenting with ACS.

Pharmacokinetics and Doses

The nondihydropyridine calcium channel blockers include diltiazem and verapamil. Most clinical studies employing these agents in ACS have used oral formulations initiated several days after the acute event. Diltiazem is available in 30 mg oral tablets with a maximum daily dose of 360 mg. The oral dose of diltiazem reaches its peak plasma levels within 1 hour with a half-life of

5 hours before being excreted in the urine and feces. Verapamil is available in 80 mg oral tablets with a maximum daily dose of 480 mg. The oral dose of verapamil reaches its peak plasma levels within 1 hour with a half-life of 3–7 hours before being excreted in the urine and feces.

Clinical Use and Indications

Several randomized trials have been performed to evaluate the utility of calcium channel blockers in ACS. The Multicenter Diltiazem Postinfarction Trial (MDPIT) randomized 2,466 patients to diltiazem (240 mg daily) or placebo 3–15 days after presenting with a myocardial infarction.[28] After over 2 years of follow-up, the mortality between the 2 groups was identical (13.5%) with a nonsignificant trend toward fewer recurrent events in patients treated with diltiazem (16.4 vs. 18.3%). Similarly, the Danish Study Group on Verapamil in Myocardial Infarction II (DAVIT II) randomized almost 1,800 patients to verapamil (360 mg daily) or placebo in the second week after admission for ACS.[29] Treatment with verapamil had a nonsignificant reduction in mortality (11.1 vs. 13.8%). A meta-analysis including 19,000 patients derived from 28 independent trials assessing the utility of calcium channel blockers has confirmed these findings.[30,31]

It is important to note that retrospective analyses of the trials incorporating calcium channel blockers suggest that caution should be used in patients with reduced left ventricular ejection fraction. In the aforementioned MDPIT, patients with impaired left ventricular ejection fraction (<40%) with evidence of pulmonary congestion on chest radiograph, who were treated with diltiazem, had an increased number of cardiac events and worsened mortality.[28] Because of this, calcium channel blockers should be avoided in patients presenting with ACS with concomitant left ventricular systolic dysfunction.

Guidelines

Current guidelines suggest that it is reasonable to administer nondihydropyridine calcium channel blockers to patients presenting with ACS, if they have a contraindication to β-blockers and have absence of clinically significant left ventricular dysfunction (class I, level B).[12]

ANTICOAGULANT THERAPIES

Introduction

The treatment of ACS continues with agents designed to increase myocardial oxygen supply.[12] As previously described, ACS is

characterized by the presence of a platelet plug cross-linked with fibrin polymers that obstructs an epicardial coronary artery. A variety of agents have been used to reduce the efficacy of the coagulation system and, thus, prevent the propagation of thrombus. Unfractionated heparin, low-molecular weight heparin, and thrombin inhibitors, all have a role in the contemporary management of ACS.

Unfractionated Heparin

Pharmacology

Unfractionated heparin is a heterogeneous mucopolysaccharide with complex effects on the coagulation cascade. A unique pentasaccharide segment of the heparin molecule will bind to endogenous antithrombin. The antithrombin-heparin molecule will then bind to and inhibit the action of thrombin preventing the formation of fibrin.[32] In addition to inhibiting the action of thrombin, the antithrombin-heparin complex also prevents the serine protease activity of a number of members of the coagulation cascade, including factor Xa.

Pharmacokinetics and Doses

Since unfractionated heparin contains a heterogeneous group of molecules extracted by varying procedures, the dose-effect relationship is difficult to predict leading to strength variations among the different batches. The administration of unfractionated heparin, thus, requires frequent monitoring of the coagulation cascade via the activated partial thromboplastin time (aPTT). European guidelines recommend an intravenous bolus of 50–70 IU/kg (maximum 6,000 IU), followed by an infusion of 12–15 IU/kg/hour (maximum 1,000 IU/hour) of unfractionated heparin for the immediate management of ACS.[33] The intravenous infusion should then be titrated to obtain an aPTT that is within 1.5–2.5 times the control value, typically 50–75 seconds. The American Heart Association and American College of Cardiology (AHA/ACC) guidelines recommend a lower initial bolus of 60 units/kg (maximum 4,000 units) with an initial infusion rate of 12 units/kg/hour (maximum 1,000 units/hour) to obtain aPTT levels of 60–80 seconds.[12] More extreme disruption of the coagulation cascade results in an increased risk of intracranial hemorrhage without a benefit for ACS. Nomograms are widely available for titrating intravenous unfractionated heparin dosing.

Regardless of the doses used, unfractionated heparin has a short onset (20–60 minutes) with a short half-life (60–90 minutes) before being metabolized in the liver and excreted in the urine. Heparin is an appropriate anticoagulant in patients with renal dysfunction. The short half-life of this anticoagulant makes

it ideal for facilitating percutaneous coronary intervention. Unfractionated heparin can also be reversed with protamine sulfate (1 mg/100 U heparin), a basic compound derived from salmon that will bind to the acidic unfractionated heparin and form a stable inactive salt. Protamine sulfate also has a rapid onset (5 minutes) and a moderate duration of effect (2 hours). It is important to note that protamine should be used with caution in insulin-dependent diabetics, as anaphylactic reactions have been reported.[34]

Clinical Use and Indications

A number of small randomized trials in the prerevascularization era demonstrated the clinical benefit of unfractionated heparin for the treatment of ACS.[35-38] Taken together, these trials suggest that the rate of death or recurrent myocardial infarction could be reduced by approximately 54% during the first week of therapy with the anticoagulant. Several meta-analyses have confirmed these findings suggesting a relative risk reduction of 33–56%.[39,40] Most of these trials evaluated the use of unfractionated heparin for 2–5 days, yet the optimal duration of therapy continues to be undefined.[12] It is important to note that discontinuation of unfractionated heparin in ACS has led to a recurrent symptoms in some patients, particularly those not treated with aspirin.[41] Based on these findings, the administration of unfractionated heparin has become standard practice in the contemporary management of ACS and now serves as a bridge to revascularization.

Unfractionated heparin continues to be used to facilitate percutaneous coronary intervention despite the lack of randomized trials demonstrating its efficacy. The standard regimen for unfractionated heparin is the administration of weight-adjusted boluses (70–100 IU/kg) to maintain an activated clotting time of 250–300 seconds.[42] In Europe, higher bolus doses (140 IU/kg) are utilized without monitoring of the activated clotting time. Heparin should be immediately discontinued after the completion of the interventional procedure.

Complications

Heparin-induced thrombocytopenia (HIT) is an acquired prothrombotic disorder most commonly instigated by unfractionated heparin.[43,44] The pathophysiology underlying HIT has recently been elucidated. The administration of unfractionated heparin is thought to precipitate an antibody-mediated immune reaction after binding to platelet factor 4 (PF4), a heparin-neutralizing protein released from the α-granules of activated platelets. The heparin-PF4 complex will attract circulating antibodies (immunoglobulin G) that will adhere to the platelet surface

on FcγIIa receptors.[43] As these immune complexes assemble on the platelet surface, intracellular cross-linking of the FcγIIa receptors results in platelet activation and release of additional PF4 perpetuating the process and ultimately leading to platelet consumption. Ongoing platelet activation by immune complexes results in increased thrombin production and a systemic hypercoagulable state that makes patients susceptible to both venous and arterial thrombosis.[45] Assays for the presence of antibodies to the heparin-PF4 complex identify patients at risk for this condition.[46]

According to most case series, HIT is characterized by a 50% reduction in platelet count most commonly occurring 5–10 days after the initiation of heparin therapy.[47] It is important to note that HIT can also occur after the discontinuation of therapy and has been termed delayed-onset HIT. Registry data suggests that HIT occurs in 3–5% of patients treated with unfractionated heparin for 5 days.[44] It is important to note that the incidence of HIT is significantly lower (<1%) during treatment with low-molecular weight heparin. Since the risk of HIT is related to the duration of exposure, current guidelines stress that intravenous heparin should not be administered for more than 48 hours.[48] British guidelines suggest that patients treated with heparin should undergo platelet counts testing every 2–4 days of therapy to monitor for thrombocytopenia.[49] If HIT is suspected, heparin products must be discontinued immediately, and alternative anticoagulation should be initiated to mitigate the risk of thrombosis. Bivalirudin is an alternative anticoagulant utilized in the United States, used to facilitate percutaneous coronary intervention in the setting of ACS when HIT is a concern.[50]

Guidelines

The current guidelines suggest that anticoagulant therapy should be used in ACS as soon as possible after presentation (class I, level A). For patients in whom an early invasive strategy is selected, unfractionated heparin is recommended as an option for anticoagulation (class I, level A). Unfractionated heparin should be continued for 48 hours in patients who do not undergo diagnostic coronary angiogram with percutaneous coronary intervention (class I, level A).[12]

Low-molecular Weight Heparin

Pharmacology

Low-molecular weight heparins are heterogeneous in size and approximately one-third the molecular weight of unfractionated heparin. Like unfractionated heparin, low-molecular weight heparins bind to antithrombin and inhibit the action of factor Xa

with a more mild direct inhibition of thrombin. The ability of low-molecular weight heparin to inhibit thrombin depends upon the presence of 18 or more saccharide units allowing the molecule to bind both antithrombin and thrombin. The concentration of heparins with 18 or more saccharide units varies with each agent such that enoxaparin preferentially inhibits factor Xa (2:1) more than dalteparin (4:1). Like unfractionated heparin, the effects of low-molecular weight heparin can be reversed with the administration of protamine sulfate. Furthermore, low-molecular weight heparin can induce HIT, although at a much lower rate than unfractionated heparin and should be avoided when this condition is suspected.

Dalteparin

Pharmacokinetics and Dose

Dalteparin is available in a single-dose prefilled syringe or as a multidose vial. Each prefilled syringe contains between 2,500 and 10,000 IU of antifactor Xa in the form of 16–64 mg of dalteparin. Dalteparin is designed to be administered subcutaneously, rather than intramuscularly, to ensure adequate vascular absorption and reduce the risk of local hematoma. Subcutaneous dalteparin has a rapid onset of action (1–2 hours) with a half-life of 2–5 hours leading to approximately 12 hours of therapeutic effect. The standard dose administered for treatment of ACS is 120 IU/kg subcutaneously every 12 hours with concomitant aspirin therapy for 5–8 days.

Enoxaparin

Pharmacokinetics and Dose

Enoxaparin is available in prefilled single-dose syringes or as ampules in concentrations of 100 or 150 mg/mL. Enoxaparin is designed to be administered subcutaneously to ensure adequate vascular absorption and reduce the risk of a local hematoma. Subcutaneous enoxaparin has a moderate onset of action (3–5 hours) with a half-life of 4–7 hours leading to approximately 12 hours of therapeutic effect. The standard dose administered for treatment of ACS (non-STEMI) is 1 mg/kg subcutaneously every 12 hours. Treatment for STEMI is augmented with a supplemental 30 mg intravenous injection. Percutaneous coronary intervention can be performed with enoxaparin and no additional anti-coagulation is necessary if the last dose was within 8 hours. If a percutaneous intervention occurs 8–12 hours after the last dose of subcutaneous enoxaparin, a single intravenous dose of 0.3 mg/kg should be administered.[51,52]

Clinical Use and Indications

A number of randomized trials have been conducted evaluating the efficacy of low-molecular weight heparin in the immediate management of ACS. The largest trial [Fragmin during Instability in Coronary Artery Disease (FRISC)] randomized 1,506 patients with unstable angina or non-q wave myocardial infarction to receive dalteparin (120 IU/kg every 12 hours) or placebo for the first 6 days of therapy followed by a reduced dose (120 IU/kg daily) for another 35–40 days.[53] Dalteparin was associated with a 63% relative risk reduction in death or recurrent myocardial infarction during the first 6 days making it comparable in efficacy to unfractionated heparin.

Several heterogeneous randomized trials have compared the efficacy of low-molecular weight heparin to unfractionated heparin in ACS.[54-61] A meta-analysis of these studies including over 49,000 patients demonstrated an equivalent number of deaths or recurrent myocardial infarctions between these 2 therapies.[62] The bleeding risk in this population, however, was slightly higher with low-molecular weight heparin. This analysis held true for patients with STEMI who underwent fibrinolytic therapy as well.[63] Based on these findings, low-molecular weight heparin may be used as an alternative to unfractionated heparin for the immediate noninvasive management of ACS. The inability to monitor the degree of anticoagulation with low-molecular weight heparin and the lack of a complete antidote, however, make it less advantageous when urgent percutaneous coronary intervention is undertaken.[64]

Guidelines

The current guidelines suggest that anticoagulant therapy should be used in ACS as soon as possible after presentation (class I, level A). For patients in whom an early invasive strategy is selected, low-molecular weight heparin is recommended as an option (class I, level A). Low-molecular weight heparin is preferable to unfractionated heparin in patients who are managed with a noninvasive strategy (class I, level B). In these patients, low-molecular weight heparin should be continued for the duration of the hospitalization, up to a maximum of 8 days (class I, level A).[12]

THROMBIN INHIBITORS

Pharmacology

Direct thrombin inhibitors, such as hirudin and bivalirudin directly inhibit soluble and clot-bound thrombin without depending upon antithrombin for their anticoagulant activity.

Indirect thrombin inhibitors, such as fondaparinux inhibit thrombin through the inhibition of factor Xa greatly reducing the generation of activated thrombin. Both types of medications are highly specific and potent for thrombin inhibition. At therapeutic concentrations, these medications will inhibit 70% of circulating thrombin in contrast to only 20–40% inhibition with unfractionated heparin.

Bivalirudin

Pharmacokinetics and Dose

Bivalirudin inhibits both soluble and clot-bound thrombin resulting in prevention of thrombin-mediated platelet activation and aggregation.[65] Because of this, bivalirudin can be used for the conservative management of ACS. In this setting, a bolus is administered (0.1 mg/kg IV) followed by a continuous infusion (0.25 mg/kg/hour). This bolus dose should be increased (0.3 mg/kg) with an increased infusion rate (1.75 mg/kg/hour), if percutaneous coronary intervention will be performed. Patients with severe renal dysfunction (epidermal growth factor receptor <30 mL/min) will require a reduced infusion dose (1 mg/kg/hour). Bivalirudin has an immediate onset of action and a short half-life (25 minutes) such that coagulation parameters will return to normal within 1 hour of discontinuing the medication. There is no antidote available for bivalirudin.

Clinical Use and Indications

A number of randomized clinical trials have compared the efficacy of bivalirudin to heparin products in the immediate management of ACS. The largest trial enrolled 13,819 patients with ACS and randomized them to receive bivalirudin or unfractionated heparin combined with a glycoprotein IIb/IIIa inhibitor prior to coronary angiography. The use of bivalirudin in this setting was associated with a noninferior rate of the composite primary end-point, which included mortality, reinfarction, or revascularization.[66] There was, however, a statistically significant lower risk of major bleeding in patients treated with bivalirudin (5.3 vs. 5.7%). These findings were reinforced in a subsequent study that included 3,602 patients with STEMI randomized to receive bivalirudin or unfractionated heparin with a glycoprotein IIb/IIIa inhibitor. Once again, the use of bivalirudin resulted in a relative risk reduction of 40% for major bleeding. An analysis of the secondary outcomes also demonstrated a reduced 30-day total mortality (2.1 vs. 3.1%) with bivalirudin.[67] Similar results were reported in the setting of nonurgent percutaneous coronary intervention.[68] Economic

analyses have suggested that the use of bivalirudin may be more cost-effective than unfractionated heparin.[69] Based on the data, bivalirudin is currently recommended for the treatment of patients with unstable angina undergoing percutaneous coronary intervention.

Fondaparinux

Pharmacokinetics and Dose

Fondaparinux is a synthetic pentasaccharide molecule that is an antithrombin-dependent inhibitor of factor Xa without inhibition of the thrombin molecule itself. The agent is currently licensed for the prevention of deep venous thrombosis as well as for treatment of ACS. Most of the trials evaluating this medication utilized a fixed dose (2.5 mg) administered subcutaneously.[70] When delivered in this fashion, the agent is rapidly absorbed with a peak effect within 2 hours and a moderate half-life (17–21 hours) before being excreted in the urine. The urine excretion makes this agent contraindicated in patients with renal impairment (epidermal growth factor receptor <30 mL/hour). Although thrombocytopenia can occur, cases of HIT have not been reported with fondaparinux.

Clinical Use and Indications

Several randomized trials have evaluated the efficacy of fondaparinux in the immediate management of ACS. The Fifth Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS-5) trial enrolled 20,078 patients with a non-STEMI to treatment with fondaparinux (2.5 mg daily) or enoxaparin (1 mg/kg twice a day) for 6 days.[70] The primary composite of death, myocardial infarction, or refractory ischemia at 9 days was similar between the 2 groups (5.8 vs. 5.7%). The rate of major bleeding at 9 days, however, was markedly lower with fondaparinux than with enoxaparin (2.2 vs. 4.1%) and was associated with a reduction in all-cause mortality at 30 days. The OASIS-5 study was not sufficiently powered to assess the utility of fondaparinux in patients undergoing percutaneous coronary intervention. Because of this, European guidelines recommend the addition of unfractionated heparin to fondaparinux to reduce catheter thrombosis during percutaneous interventions.[33] This recommendation has been supported by a *post hoc* analysis of the original OASIS-5 trial.[71]

Further studies have evaluated fondaparinux in STEMI. The OASIS-6 trial included 12,092 patients with STEMI and randomized them to receive anticoagulation with fondaparinux with or without unfractionated heparin for up to 8 days. Patients treated with fondaparinux who were managed with anticoagulation or fibrinolysis alone had a 23% relative risk reduction in 30-day

mortality. Patients who were managed with primary percutaneous coronary intervention, however, had an increased risk of catheter thrombosis and coronary complications.[72] Based on these results, the role of fondaparinux in STEMI remains nebulous, particularly in patients undergoing percutaneous coronary intervention.

Guidelines

The current guidelines suggest that anticoagulant therapy should be used in ACS as soon as possible after presentation (class I, level A). For patients in whom an early invasive strategy is selected, direct thrombin or factor Xa inhibitors have received a recommendation for their use (class I, level B). Direct factor Xa inhibitors (fondaparinux) are preferable to unfractionated heparin in patients who are managed with a noninvasive strategy (class I, level B). In patients treated with a noninvasive strategy and an increased risk of bleeding, fondaparinux is preferable to alternative agents (class I, level B). Direct factor Xa inhibitors should be continued for the duration of the hospitalization up to a maximum of 8 days (class I, level A).[12]

ANTIPLATELET THERAPIES

Introduction

Antiplatelet therapies are designed to inhibit platelet activation and aggregation, thus, restoring patency to an occluded epicardial artery. A variety of agents with unique molecular targets are often used in concert to reduce the function of circulating platelets. Randomized trials have suggested that aspirin, adenosine 5'-diphosphate antagonists, and glycoprotein IIb/IIIa inhibitors, all have a role in the contemporary management of ACS.

Aspirin

Pharmacology

Records demonstrate that acetylsalicylic acid was isolated from willow bark and used as a pain reliever by Hippocrates over two millennia ago. A large pharmaceutical manufacturer synthetically produced acetylsalicylic acid for medicinal purposes in 1897 under the trade name "Aspirin." The CV benefits of aspirin were revealed 6 decades later when Nobel prize winning research demonstrated that the compound reduced the production of thromboxane, a potent mediator of platelet activation and aggregation.[73] Aspirin acetylates serine 529 on cyclooxygenase-1 irreversibly inhibits the enzyme. This results in decreased production of an important

mediator of platelet aggregation, thromboxane A_2 (TxA_2). Inhibition of cyclooxygenase-1 in vascular endothelium also leads to decreased prostaglandin I_2 (prostacyclin) production preventing vasodilation. Because platelets do not contain protein manufacturing machinery, the inhibition of platelet cyclooxygenase-1 persists for the life of the platelets (7–10 days). In contrast, the vascular endothelium is able to transcribe and translate new unhindered cyclooxygenase-1 within hours resulting in the renewed production of prostacyclins.[73] The net effect of aspirin is, thus, platelet inhibition with decreased risk of thrombosis.

Pharmacokinetics and Dose

Aspirin is available in an oral and rectal formulation. Aspirin is rapidly absorbed in its oral formulation with a peak effect 1–2 hours after ingestion. For more rapid inhibition of platelet function, sublingual formulations are available and recommended in the setting of ACS. The half-life of aspirin and its functioning metabolites is approximately 5 hours, but the irreversible inhibition of platelet cyclooxygenase-1 makes its therapeutic effect to persist for the lifetime of the platelet.

A number of medications may limit the efficacy of aspirin. Nonsteroidal anti-inflammatory agents that reversibly inhibit cyclooxygenase-1 (ibuprofen and naproxen) interfere with the cardioprotective effects of aspirin.[74] More recent work has suggested that all nonsteroidal anti-inflammatory medications increase the risk of cardiovascular events, even when administered for short durations.[75,76]

Clinical Use and Indications

A number of studies have demonstrated the benefits of aspirin therapy in ACS. The Veterans Administration Cooperative Study included 1,266 males with unstable angina and randomized them to receive aspirin (324 mg daily × 12 weeks) or placebo. Treatment with aspirin reduced the primary composite end-point of death or recurrent myocardial infarction by 50% (5 vs. 10%).[77] A subsequent study employing higher doses of aspirin (325 mg four times a day) in a Canadian population supported these findings.[78] A meta-analysis including over 212,000 high-risk patients demonstrated that aspirin reduced the risk of nonfatal myocardial infarction or death by 26% making aspirin a mainstay of therapy for unstable angina.[79]

Aspirin has also had demonstrated efficacy in the treatment of proven myocardial infarction. The Second International Study of Infarct Survival (ISIS-2) randomized 17,187 patients admitted to 417 hospitals to receive either a placebo or aspirin (160 mg daily)

with the possible addition of streptokinase. The administration of aspirin resulted in a significant reduction in vascular mortality (9.4 vs. 12%) when compared to placebo a 5-weeks follow-up.[80] Based on subsequent analyses, the administration of aspirin (162 mg daily) for 1 month prevented 25 deaths and 10 nonfatal myocardial infarctions. The survival benefit from aspirin therapy persisted over 10 years of subsequent follow-up.[81] Largely based upon the data, aspirin became a standard treatment of choice for the immediate management of ACS.

The appropriate dosing of aspirin has been a subject of intense debate. Previous research has demonstrated that *in vitro* platelet aggregation was similar after treatment with 81 or 325 mg of aspirin.[82,83] Recent studies have confirmed that the initial administration of low-dose aspirin (162 mg) was as effective as higher dose aspirin (325 mg) in ACS with less bleeding risk.[84] Lower aspirin doses *in vitro* (<162 mg) result in a prolongation (~2 days) to effective therapeutic inhibition of cyclooxgenase-1.[85] A recent meta-analysis confirmed that there is no cardiovascular benefit in secondary prevention for aspirin maintenance doses >81 mg/day.[86] Furthermore, a large clinical trial demonstrated that a lower aspirin dose (75–100 mg) was equivalent to a higher dose (300–325 mg) after percutaneous coronary intervention for ACS.[87] Based on these findings, most guidelines recommend an aspirin load of 162–325 mg with an indefinite maintenance dose of 75–81 mg in the treatment of ACS.[88]

Resistance

Aspirin resistance is a broad term that comprises biochemical resistance to the medication as well as aspirin underuse. Cellular studies suggest that some patients may have overexpression of cyclooxygenase-2 serving as a "sink" for aspirin within platelets.[89] Other work has elucidated genetic polymorphisms of other platelet proteins that may enhance their thrombogenicity despite the administration of aspirin.[90] Rather than biochemical resistance, however, a large proportion of aspirin resistance is related to aspirin underuse.[91] Epidemiological surveys suggest that as few as 60% of patients admitted to the hospital with a myocardial infarction receive aspirin.[92,93] This problem is not unique to the USA, as international registries report that as many as 14% of patients with coronary artery disease are not receiving any form of antiplatelet therapy.[94]

Complications

Aspirin also weakly inhibits cyclooxygenase-2, an enzyme that produces prostacyclins that protect the gastric lining from acidic irritation. Administration of aspirin may then produce gastric

irritation or an increased risk of gastrointestinal hemorrhage.[95] It is important to note that the risk of gastrointestinal bleeding induced by aspirin is proportional to the dose administered. Previous work has suggested that the rate of bleeding doubles when the maintenance dose is increased from 100 to 200 mg/day.[96] The risks of gastrointestinal bleeding can be mitigated with the addition of a proton-pump inhibitor.[97] In addition to gastrointestinal bleeding, aspirin has also been associated with a small increased risk of hemorrhagic stroke.[98] This has led some individuals to suggest that a history of gastrointestinal ulcers or bleeding is a relative contraindication to aspirin therapy. It is important to note that these risks are significantly lower than the reported cardiovascular benefits of aspirin described above.

Guidelines

The current guidelines suggest that aspirin should be used in ACS as soon as possible after presentation (class I, level A). Sublingual formations (162 or 325 mg) are preferable because of their rapid absorption. Aspirin should then be continued indefinitely in all patients who are not intolerant to the medication (class I, level A).[12]

ADENOSINE DIPHOSPHATE RECEPTOR ANTAGONISTS

Pharmacology

Platelet activation results in the release of adenosine diphosphate (ADP), a potent mediator of platelet aggregation. Circulating ADP mediates its effects primarily through the $P2Y_{12}$ receptor on the platelet surface. Activation of these receptors leads to morphologic changes in the platelet shape as well as increases in the expression in glycoprotein IIb/IIIa that mediates platelet cross-linking within a thrombus.[99,100] Inhibition of this receptor, thus, hinders platelet aggregation even in the presence of TxA_2 and thrombin.[101] Thienopyridines are irreversible antagonists of the $P2Y_{12}$ receptor and commonly employed in the immediate management of ACS.

Ticlopidine

Pharmacokinetics

The oral formulation of ticlopidine has a moderate onset of action with peak platelet serum level occurring 3–5 hours after ingestion. It is important to note that the kinetics of ticlopidine is nonlinear with a markedly decreased clearance upon repeated dosing. Because of this, ticlopidine does not achieve maximum

inhibition of platelet aggregation until it has been administered for 4–7 days.[102] After reaching steady state, ticlopidine undergoes extensive hepatic metabolism with a half-life of 13 hours with predominant renal excretion.

Clinical Use and Indications

One randomized, multicenter trial compared ticlopidine to "conventional therapy" among patients presenting with ACS. Among the 652 patient enrolled in this trial (40% with myocardial infarction), the administration of ticlopidine reduced the risk of vascular death and nonfatal myocardial infarction by over 50% (5.1 vs. 10.9%).[103] Further studies demonstrated that dual antiplatelet therapy with aspirin and ticlopidine produced superior outcomes during planned and unplanned percutaneous coronary intervention.[102,104] A meta-analysis of over 14,000 patients enrolled in trials or registries, however, suggests that clopidogrel results in a 50% relative risk reduction in major cardiovascular events when compared with ticlopidine.[105] Furthermore, this collection of registries identified numerous unfavorable side effects of ticlopidine. Because of this, ticlopidine has now been superseded by other thienopyridines for the immediate management of ACS.

Complications

Ticlopidine has been associated with an increased rate of neutropenia (2.4%) and thrombocytopenia purpura (0.03%).[106] The Clopidogrel Aspirin Stent International Cooperative Study (CLASSICS) demonstrated that clopidogrel was associated with a significantly lower risk of hematologic complications when compared with ticlopidine making it the standard thienopyridine used.[107]

Clopidogrel

Pharmacokinetics and Dose

Clopidogrel is an inactive prodrug that requires *in vivo* oxidation by hepatic cytochrome P450 3A4 and 2C19 isoenzymes before becoming an irreversible inhibitor of $P2Y_{12}$. A single loading dose of clopidogrel produces detectable inhibition of platelet aggregation within 2–24 hours of its administration.[108] Studies with patients undergoing percutaneous coronary intervention, however, have demonstrated that higher loading doses (600 mg PO) achieve maximal platelet inhibition within 2 hours.[109] Clinical studies have confirmed that the higher loading dose results in improved outcomes among patients undergoing percutaneous coronary intervention.[110] Pharmacokinetics of clopidogrel is nonlinear with a markedly decreased clearance upon repeated dosing. Half-life of clopidogrel in a steady state is approximately

5 hours, but the inhibition of the $P2Y_{12}$ receptor continues for the life of the platelet. Because of this, guidelines recommend cessation of clopidogrel 5 days prior to surgery to reduce the risk of perioperative bleeding.[33]

Clinical Use and Indications

The initial studies of clopidogrel were performed in the patients with history of vascular diseases. The Clopidogrel vs. Aspirin in Patients at Risk of Ischemic Events (CAPRIE) enrolled 19,185 high-risk patients and randomized them to receive clopidogrel (75 mg daily) or aspirin (325 mg daily). After a mean follow-up approaching 2 years, the administration of clopidogrel was associated with an 8.7% relative risk reduction in a composite end-point that included vascular death, myocardial infarction, or ischemic stroke.[111]

Clopidogrel also has demonstrated efficacy in the immediate noninvasive management of ACS. Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) randomized 12,562 patients with ACS to receive clopidogrel (300 mg followed by 75 mg once every day) or placebo. The average duration of clopidogrel exposure in this study was 9 months (range 3–12 months). Treatment with clopidogrel resulted in a 20% relative risk reduction and a 2.1% absolute risk reduction in the primary composite end-point of cardiovascular death, myocardial infarction, or stroke after 12 months of follow-up.[112] It is important to note that this benefit was accompanied by an increased risk of major (3.7 vs. 2.7%) and minor (5.1 vs. 2.4%) bleeding. The efficacy of clopidogrel in the invasive management of ACS was evaluated in a substudy of CURE, termed PCI-CURE. Patients who received pretreatment and maintenance therapy with clopidogrel had a 44% relative risk reduction and 2.6% absolute risk reduction in cardiovascular death, myocardial infarction, or urgent target vessel revascularization within 30 days of their index event.[113] Subsequent results from the Clopidogrel for the Reduction of Events During Observation (CREDO) trial supported these results, suggesting the importance of clopidogrel pretreatment for all patients undergoing percutaneous coronary intervention.[114]

Clopidogrel has also been investigated in the setting of STEMI. The COMMIT/Second Chinese Cardiac Study (CCS-2) randomized 45,852 patients with an acute myocardial infarction to clopidogrel (75 mg once a day) or placebo in addition to aspirin (162 mg once a day). The majority of these patients were managed conservatively without percutaneous coronary intervention and with only 50% receiving thrombolytics. The administration of clopidogrel for 4 weeks resulted in a 9%

relative risk reduction and a 1% absolute risk reduction in the primary composite end-point that included death, myocardial infarction, or stroke.[115] These findings were reinforced in the setting of thrombolysis during the CLopidogrel as Adjunctive Reperfusion TherapY THrombolysis In Myocardial Infarction 28 (CLARITY-TIMI 28) trial. This study randomized 3,491 patients with STEMI to receive clopidogrel or placebo in addition to aspirin and thrombolysis.The addition of clopidogrel within the first 24 hours of presentation reduced the rate of death, recurrent infarction, or infarct-related artery occlusion by 36% with an absolute risk reduction of 6.7%.[116] Once again, a substudy of CLARITY including 1,863 patients undergoing percutaneous coronary intervention reinforced the benefit of early clopidogrel administration.[116] Collectively, the data suggests that clopidogrel plays an integral role in the immediate management of ACS.

Surgery

Despite the demonstrated benefit of clopidogrel in ACS, some patients do not receive this medication because of the concern for increased bleeding, should surgical revascularization be necessary.[114] A substudy of the CURE trial revealed that there was a trend toward benefit when clopidogrel was administered prior to surgical revascularization. This was associated, however, with a nonsignificant increased risk of bleeding primarily among patients undergoing bypass surgery within 5 days of clopidogrel administration.[117] Registry studies confirmed these findings suggesting that patients with ACS who underwent bypass surgery within 5 days of clopidogrel administration had an increased need for large blood transfusions (>4 U packed red blood cells) when compared to patients who waited more than 5 days.[118] Despite the increased rate of bleeding, registries have also demonstrated that the administration of clopidogrel before urgent bypass surgery resulted in a 27% relative risk reduction and a 4.6% absolute risk reduction in the rate of ischemic events (death, myocardial infarction, or unplanned revascularization) within 30 days of the index admission.[119] Current guidelines continue to recommend 5 days of clopidogrel abstinence prior to proceeding with elective surgery.[12] These data reveal, however, that patients benefit from clopidogrel administration even if they eventually proceed to surgical revascularization. Despite this, recent registries have demonstrated that only a fraction of patients (27%) are discharged from the hospital with clopidogrel after bypass surgery.[120] This runs counter to the current guidelines that suggest all patients presenting with ACS, including those undergoing bypass surgery, benefit from 1 full year of clopidogrel therapy.[12]

Duration

The duration of clopidogrel therapy after percutaneous coronary intervention for ACS has been a controversial topic. Early registry data suggested that patients receiving drug-eluting-stents had increased rates of very late stent thrombosis.[121,122] Although the overall incidence of these events was low, the results were usually catastrophic.[123,124] Numerous registries have demonstrated that premature cessation of clopidogrel therapy is a strong predictor of late stent thrombosis within the first 12 months.[125-127] In contrast, retrospective data have suggested that continuation of dual antiplatelet therapy for >1 year does not reduce mortality.[128] Further research is needed to clarify the optimal duration of clopidogrel therapy. Current guidelines recommend at least 4 weeks of clopidogrel therapy for bare metal stents and 1 year of therapy for drug-eluting stents.[129]

Dosing

The initial trials investigating clopidogrel for the treatment of ACS employed a standard loading dose (300 mg) and maintenance dose (75 mg). Further research demonstrated that an elevated loading dose (600 mg) resulted in a more rapid inhibition of platelet function.[108] Furthermore, clinical studies have confirmed that the higher loading dose results in improved outcomes among patients undergoing percutaneous coronary intervention.[110,130] Additional studies have not demonstrated additional benefit from even higher loading doses of clopidogrel (900 mg) in the setting of ACS.[131,132] Current guidelines for percutaneous coronary intervention now reflect this data and recommend the higher loading dose (600 mg).[52] Clinical trials have also explored alternative maintenance doses for clopidogrel therapy. The CURRENT-OASIS 7 trial randomized 25,086 patients to receive double-dose clopidogrel (600 mg followed by 150 mg for 6 days) or standard dose clopidogrel (300 mg followed by 75 mg daily). The rate of cardiovascular death, myocardial infarction, or stroke was equivalent between the two treatment groups.[87] A subgroup of these 17,263 patients who received early invasive therapy with percutaneous coronary intervention, however, demonstrated a relative risk reduction of 14% and an absolute risk reduction of 0.6% in these outcomes.[113] This was associated with a 0.5% increased risk of major bleeding. The use of the increased clopidogrel maintenance dose has not yet been incorporated into national or international guidelines.

Resistance

Like aspirin resistance, patients who have had a recurrent event on clopidogrel have been denoted as suffering from clopidogrel

resistance. As mentioned previously, clopidogrel is a prodrug that requires activation from the cytochrome P450 system. Research has demonstrated that patients with reduced function alleles of cytochrome P450 isoform C19 who are treated with clopidogrel have significantly higher risk of in-stent thrombosis.[133] Functional assays have noted that reduced platelet inhibition by clopidogrel is also associated with worse outcomes.[134,135] Attempts to modulate clopidogrel dosing to functional assays as in the Gauging Responsiveness With A Verify Now Assay-Impact On Thrombosis And Safety (GRAVITAS) trial, however, has not yet proved fruitful.[136]

The administration of other medications may also interfere with the cytochrome P450 system and, thus, prevent the formation of active clopidogrel metabolites. Initial studies suggested that patients treated with omeprazole and clopidogrel had significantly reduced platelet inhibition.[137] A retrospective analysis of 8,205 veterans treated with clopidogrel and omeprazole had a 25% greater risk of death or recurrent ACS than those treated with clopidogrel alone.[138] The USFDA subsequently released a black-box warning regarding the interaction between clopidogrel and omeprazole. A recent randomized trial designed to assess the safety of a combined omeprazole-clopidogrel formulation, however, refuted these findings. The Clopidogrel and the Optimization of Gastrointestinal Events Trial (COGENT) enrolled and analyzed 3,761 patients randomized to receive clopidogrel with or without omeprazole in a single pill before being prematurely discontinued due to lack of funding. After 180 days of follow-up, the 2 groups had similar rates of cardiovascular events (4.9 vs. 5.7%), suggesting that omeprazole administration did not reduce the efficacy of clopidogrel in most patients.[139] Further prospective randomized studies are needed to definitively answer this question.

Prasugrel

Pharmacokinetics and Dose

Prasugrel is an inactive prodrug that requires *in vivo* oxidation by hepatic cytochrome P450 before becoming an irreversible inhibitor of $P2Y_{12}$. Unlike clopidogrel, however, prasugrel is converted to its active metabolite rapidly resulting in maximal serum concentrations within 30 minutes of administration.[140,141] Studies have also demonstrated that there is significantly less interpatient variability in platelet inhibition when compared to standard doses of clopidogrel.[142] The half-life of the active prasugrel metabolites is approximately 7 hours, but the clinical effect persists for lifetime of the treated platelets. The standard dose of prasugrel was established in the Joint Utilization of

Medications to Block Platelets Optimally-Thrombolysis In Myocardial Infarction (JUMBO-TIMI) 26 trial with a loading dose of 60 mg followed by a maintenance dose of 10 mg daily.[143] Clinical studies have confirmed that this dosing strategy results in earlier and more potent platelet inhibition than standard loading doses of clopidogrel.[144]

Clinical Use and Indications

A large multicenter randomized trial demonstrated the clinical efficacy of prasugrel in the treatment of ACS. The Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel (TRITON-TIMI 38) randomized 13,608 patients with ACS (26% STEMI) to receive prasugrel or clopidogrel for 6–15 months.[145] The primary end-point of cardiovascular death, recurrent myocardial infarction, or stroke was reduced from 12.1 to 9.9% in the patients that received prasugrel. The difference in primary end-point was primarily driven by recurrent myocardial infarction. A *post hoc* analysis demonstrated that prasugrel was also independently associated with a lower risk of in-stent thrombosis (2.4 vs. 1.1%).[146] It is important to note that the cardiovascular benefits of prasugrel were accompanied by an increased risk of major bleeding (2.4 vs. 1.8%).[145] Due to concern for increased intracranial bleeding, prasugrel is not recommended for patients with a history of cerebrovascular disease or pathological bleeding. Patients over the age of 75 or under 60 kilograms also have an increased bleeding risk and, thus, should not be given prasugrel.

A subgroup analysis of patients presenting with STEMI also demonstrated benefit. Of these 3,534 patients, the vast majority (>90%) were treated with percutaneous coronary intervention and followed for up to 15 months. Patients treated with prasugrel had a 2.4% absolute risk reduction in cardiovascular death, recurrent myocardial infarction, or stroke when compared to standard doses of clopidogrel.[147] It is important to note that this study did not demonstrate overall differences in major bleeding among the 2 groups. The subgroup of patients who underwent bypass surgery, however, did have a significant increase in major bleeding (18.8 vs. 2.7%). Collectively, the data suggest a decrease in cardiovascular events with an increased risk of major bleeding for prasugrel.

Ticagrelor

Pharmacokinetics and Dose

Ticagrelor is a potent oral reversible inhibitor of the $P2Y_{12}$ receptors. Unlike the thienopyridines, ticagrelor is a modification

of adenosine triphosphate to cyclopentyltriazolopyrimidine that does not require metabolic conversion prior to inhibiting its target. Ticagrelor is rapidly absorbed reaching its peak plasma levels within 2 hours of ingestion and providing approximately 12 hours of platelet inhibition. Dose finding studies demonstrated that ticagrelor is effective when administered as 90 or 180 mg twice a day.[148] These doses provide more rapid maximal platelet inhibition than standard doses of clopidogrel.[149] It is important to note that *post hoc* analyses have demonstrated a rebound in platelet aggregation in those patients who only take the medication once a day.[140]

Clinical Use and Indications

A large multicenter trial has demonstrated the promise of ticagrelor in the treatment of ACS. The PLATelet inhibition and patient Outcomes (PLATO) trial randomized 18,624 patients with ACS (38% STEMI) to receive ticagrelor (180 mg loading dose and 90 mg twice a day maintenance) or clopidogrel (300–600 mg loading dose and 75 mg once a day maintenance). After 12 months of follow-up, the primary composite end-point including vascular death, recurrent myocardial infarction, or stroke was reduced among the ticagrelor group (9.8 vs. 11.7%) with similar rates of major bleeding (11.6 vs. 11.2%).[150] Patients receiving ticagrelor did have, however, a slightly higher rate of fatal intracranial bleeding as well as a higher rate of dyspnea and bradycardia than those treated with clopidogrel. A regional analysis has suggested that the benefit of ticagrelor was not present in patients recruited from North America.[151] Some have suggested that the benefit was reduced in this population because of the concomitant use of higher aspirin doses (>100 mg/day). Based on this, regulatory agencies have recommended that high dose aspirin (>100 mg/day) should not be used in conjunction with ticagrelor. Future studies [Prevention of Cardiovascular Events (e.g., Death From Heart or Vascular Disease, Heart Attack, or Stroke) in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin (PEGASUS-TIMI 54)] will evaluate this anomaly further in patients with stable coronary artery disease.

Cangrelor

Pharmacokinetics and Dose

Cangrelor is a potent intravenous reversible inhibitor of the $P2Y_{12}$ receptors created from a chemical modification to ticagrelor. Like ticagrelor, cangrelor does not require conversion to an active metabolite and serves to immediately inhibit platelet aggregation

upon its administration. After it discontinuation, normal platelet function returns within 60 minutes and is not dependent upon renal or liver function.[152]

Clinical Use and Indication

Cangrelor has been studied in several large multicenter trials. The Cangrelor vs. standard Therapy to Achieve optimal Management of Platelet inhibition (CHAMPION) study randomized 5,301 patients with ACS to cangrelor with clopidogrel (600 mg) at the time of percutaneous coronary intervention or clopidogrel (600 mg) alone. The primary end-point of death, recurrent myocardial infarction, or revascularization at 48 hours was similar between the 2 groups (7 vs. 8%).[153] These results were confirmed in a similar study that included patients with STEMI.[154] Future studies may address the role of preoperative cangrelor in patients awaiting bypass surgery. Like ticagrelor, cangrelor has not yet been approved for treatment of ACS by the FDA.

Guidelines

The current guidelines suggest that clopidogrel should be used in ACS for all patients who are unable to take aspirin (class I, level A). Clopidogrel should also be initiated before diagnostic angiography in patients with ACS managed in an invasive fashion (class I, level A). For patients with ACS managed in a noninvasive fashion, clopidogrel should be added to aspirin as soon as possible and continued for at least 1 month, preferably up to 1 year (class I, level B). Clopidogrel is the thienopyridine of choice for ACS patients treated with fibrinolytic therapy (class I, level C).[155] Prasugrel can be administered to patients with ACS who will proceed to percutaneous coronary intervention when other thienopyridines are not used (class I, level B). In patients who have had a prior stroke or transient ischemic attack, prasugrel is not recommended as part of dual antiplatelet therapy (class III, level C). Patients over the age of 75 or under 60 kg should also avoid this medication. The duration of therapy with a thienopyridine should be at least 12 months for patients receiving percutaneous coronary intervention in the setting of ACS (class I, level B). Early discontinuation of dual antiplatelet therapy can be considered if the risks of bleeding outweigh the benefits (class I, level C).[12] Current guidelines recommend the discontinuation of clopidogrel and prasugrel 5 and 7 days respectively prior to planned surgical revascularization (class I, level C).[155]

GLYCOPROTEIN IIb/IIIa ANTAGONISTS

Pharmacology

Glycoprotein IIb/IIIa is a platelet adhesion receptor that facilitates the final steps of platelet activation and aggregation.

After platelet activation, glycoprotein IIb/IIIa receptors cross-link fibrinogen to form a platelet-rich thrombus.[156] Inhibition of this receptor thus hinders platelet aggregation in a unique fashion that is independent of the mechanisms of aspirin and ADP antagonists. Initial studies demonstrated that oral glycoprotein IIb/IIIa antagonists were unsuccessful.[157] Because of this, there are currently only 3 intravenous glycoprotein IIb/IIIa antagonists available for clinical use: abciximab, eptifibatide, and tirofiban. It is important to note that the majority of the glycoprotein IIb/IIIa antagonists were developed and tested prior to the widespread use of thienopyridines.[158,159] Because of this, previous trials may have overestimated the benefit of these agents in the contemporary management of ACS.[160]

Abciximab

Pharmacokinetics and Dose

Abciximab is a chimeric monoclonal antibody directed against the glycoprotein IIb/IIIa receptor. This agent is administered intravenously in a loading dose (0.25 mg/kg) followed by a maintenance infusion (0.125 μg/kg/hour) for up to 12 hours. Abciximab has a half-life of approximately 10–30 minutes but remains platelet bound in the circulation for up to 15 days after administration. The monoclonal antibody can generate immunological side effects, including severe thrombocytopenia in approximately 1% of patients. This thrombocytopenia may be effectively treated with platelet transfusions.[161,162]

Clinical Use and Indications

Abciximab was initially evaluated in the conservative management of ACS. The GUSTO IV randomized 7,800 patients with ACS to receive abciximab bolus and maintenance infusions (24 or 48 hours) or placebo. Patients who eventually underwent percutaneous or surgical revascularization were excluded. There was no significant difference in the primary composite endpoint of death or recurrent myocardial infarction within 30 days between the two groups. There was, however, higher rates of thrombocytopenia and bleeding in the patients treated with abciximab.[163] In contrast, abciximab has been demonstrated to have benefit in patients undergoing percutaneous coronary intervention. The C7e3 Fab Anti-Platelet Therapy in Unstable Refractory Angina (CAPTURE) trial enrolled 1,265 patients with ACS refractory to treatment with anticoagulation and nitrates. Patients were randomized to receive abciximab or placebo 2 hours prior to a planned percutaneous coronary intervention. The patients treated with abciximab had a significantly lower rate of death, myocardial infraction, or urgent intervention compared

to placebo (11.3 vs. 15.9%).[164] A subgroup analysis of this study demonstrated that patients who had positive cardiac biomarkers derived the greatest benefit from abciximab. Further studies have corroborated these findings.[165]

Abciximab has also been investigated in patients presenting with STEMI. The Abciximab before Direct angioplasty and stenting in Myocardial Infarction Regarding Acute and Long term follow-up (ADMIRAL) trial randomized 300 patients with ST-elevation myocardial infarction treated with aspirin, heparin, and a thienopyridine to receive either abciximab or placebo prior to percutaneous coronary intervention. The administration of abciximab reduced the composite primary end-point of death, recurrent myocardial infarction, or urgent target vessel revascularization by over 50% (7.4 vs. 15.9%).[166] Further investigations of patients with STEMI undergoing percutaneous coronary intervention in the Controlled Abciximab Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial support these findings.[167] The role of abciximab in ST-elevation myocardial infarction treated with fibrinolytics is not as clear. The GUSTO-V and Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT) trials compared abciximab with half-dose thrombolytics to thrombolytics alone in patients presenting with STEMIs. Both trials demonstrated a reduction in the secondary end-point of myocardial infarction without differences in mortality.[168,169] There was, however, an increased risk of bleeding particularly in patients over the age of 75 years. Based on this data, abciximab use is currently limited to patients with ACS who will undergo percutaneous coronary intervention.

Eptifibatide

Pharmacokinetics and Doses

Eptifibatide is a synthetic cyclic heptapeptide considered to be a small molecule inhibitor of the glycoprotein IIb/IIIa receptor. Like other small molecules in this class, eptifibatide has lower binding affinity for the receptor than abciximab but is significantly more specific. Because of this, eptifibatide does not produce the same degree of immunological side effects with a lower rate of thrombocytopenia.[170] Platelet transfusions are not helpful to reverse the effects of eptifibatide as the circulating small molecule is equally likely to bind to new platelets. Eptifibatide is administered as a bolus (180 μg/kg) and a maintenance infusion (2 μg/kg/min) that should be adjusted for renal function. The agent has a clearance half-life of 2.5 hours and effectively inhibits platelet aggregation for 4 hours after discontinuation.

Clinical Use and Indication

The initial studies of eptifibatide demonstrated a benefit to patients presenting with ACS. The Platelet glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) randomized 10,948 patients to eptifibatide (180 μg/kg followed by 1.3 or 2.0 μg/kg/min) or placebo. Approximately 60% of the patients enrolled eventually underwent percutaneous coronary intervention. The administration of eptifibatide resulted in a 2.2% absolute risk reduction in death or recurrent myocardial infarction after 30 days of follow-up.[171] A double-bolus of eptifibatide (180 μg/kg twice separated by 10 minutes) has been demonstrated to be equally effective in reducing mortality and recurrent myocardial infarction at 1 year (8 vs. 12.4%) for patients undergoing percutaneous coronary intervention.[172] Because of this, double-bolus eptifibatide has become the standard dosing regimen for many interventions.

Recent studies have evaluated the use of eptifibatide prior to percutaneous coronary intervention, termed "upstream." The EARLY glycoprotein IIb/IIIa inhibition in non-ST-segment elevation ACS (EARLY-ACS) trial randomized 9,492 patients with ACS and positive cardiac biomarkers (84%) or ischemic electrocardiographic changes to a double-bolus of eptifibatide upon presentation or a delayed administration after angiography if percutaneous coronary intervention was going to be pursued. The early administration of eptifibatide did not reduce death, recurrent myocardial infarction, or thrombotic complications during intervention. It did, however, significantly increase the risk of major bleeding.[160] Further trials to evaluate upstream administration of eptifibatide with thrombolysis or percutaneous coronary intervention for STEMI have not been powered to address clinical end-points.[173-176] It is important to note that the addition of eptifibatide to a regimen that includes bivalirudin leads to increased bleeding risk without a mortality benefit and, thus, is not currently recommended.[67] Eptifibatide is thus, now primarily employed in patients with ACS refractory to other medical management or prior to percutaneous coronary intervention.

Tirofiban

Pharmacokinetics and Dose

Tirofiban is a highly specific nonpeptide derivative of tyrosine that selectively inhibits the glycoprotein IIb/IIIa receptor. As a small molecule, tirofiban has a higher specificity for the receptor with a lower affinity than abciximab. Unlike other agents in

this class, tirofiban can be stored at room temperature without significant degradation. Tirofiban is administered in a loading dose (0.4 μg/kg/min over 30 minutes) and maintenance dose (0.1 μg/kg/min) with adjustments for impaired renal function. The half-life of the medication is approximately 2 hours, but platelet inhibition will continue for up to 4 hours after discontinuation.[161,162]

Clinical Use and Indication

The initial clinical studies of tirofiban demonstrated conflicting results. The Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) trial suggested that tirofiban was superior to heparin for the conservative management of patients with ACS.[177] Subsequent investigation, however, contradicted this claim. The PRISM-PLUS (Patients Limited by Unstable Signs and Symptoms) study randomized 1,915 patients with non-STEMI to tirofiban alone, heparin alone, or tirofiban with heparin. Coronary angiography was performed in the vast majority of these patients (90%) but percutaneous coronary intervention was performed in a minority (30.5%). The tirofiban alone arm was associated with an increased risk of death leading to its early termination. When combined with heparin, however, tirofiban significantly reduced the rate of death, recurrent myocardial infarction, or refractory ischemia over 7 days when compared to heparin alone (12.9 vs. 17.9%). This benefit was similar for patients treated noninvasively or invasively.[171] Tirofiban has been compared to abciximab and found to have similar efficacy.[178] Based on this data, tirofiban can be employed for the immediate management of ACS in the same settings as eptifibatide.

Guidelines

The current guidelines suggest that antiplatelet therapy in addition to aspirin should be initiated before diagnostic angiography for patients with ACS. Antiplatelet therapy can include clopidogrel or an intravenous glycoprotein IIb/IIIa inhibitor (class I, level A). A glycoprotein IIb/IIIa inhibitor can be omitted if a patient has been given 2 antiplatelet agents (aspirin and clopidogrel) and bivalirudin will be used as an anticoagulant during percutaneous coronary intervention (class IIa, level B). Abciximab is an appropriate choice for upstream glycoprotein IIb/IIIa inhibition, only if there is no appreciable delay to angiography and percutaneous coronary intervention is going to be performed. Abciximab should not be administered to patients that will not undergo percutaneous coronary intervention (class III, level A). In these cases, intravenous eptifibatide or tirofiban are the preferred agents (class I,

level B). In patients treated with this initial conservative strategy, recurrent signs of ischemia or serious arrhythmias may prompt the addition of these agents (class IIa, level C).[12]

FIBRINOLYTIC AGENTS

Introduction

The definitive management of ACS requires restoration of cardiac perfusion. Numerous studies have demonstrated that percutaneous coronary intervention improves morbidity and mortality in STEMI.[179] There are many regions of the world, however, which do not have access to percutaneous coronary intervention facilities. Fibrinolytic agents can be used in these cases to degrade epicardial coronary artery thrombus to preserve left ventricular function and decrease mortality.[180,181] It is important to note that these agents have a significant risk of hemorrhage and are not indicated in other forms of ACS, including unstable angina and non-STEMI.

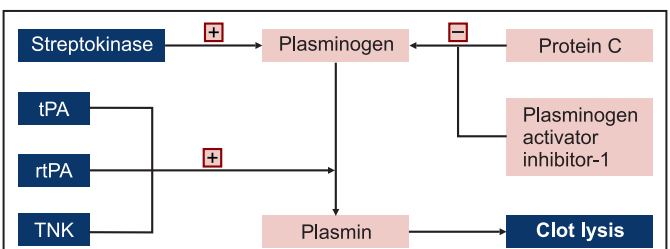
Pharmacology

All thrombolytic agents are designed to facilitate the conversion of plasminogen to plasmin (Figure 4). Active plasmin will then degrade fibrinogen resulting in the dissolution of the thrombus. Four agents are currently available to facilitate this process through different mechanisms.

Alteplase (Tissue Plasminogen Activator)

Pharmacokinetics and Dose

Alteplase is a naturally occurring enzyme that binds to fibrin and converts entrapped plasminogen to plasmin. The medication has a rapid onset of action and undergoes hepatic metabolism before leaving the bloodstream within 10 minutes of infusion discontinuation. Because of this short half-life, anticoagulation



tPA, tissue plasminogen activator; rtPA, recombinant tissue plasminogen activator; TNK, tenecteplase.

FIGURE 4. Thrombolytic agents. Most mechanisms of therapeutic thrombolysis accelerate the conversion of plasminogen to plasmin, thus, facilitating clot destruction.

should be administered with alteplase to prevent reocclusion. The standard intravenous regimen uses a bolus (15 mg) then a fast maintenance infusion (50 mg over 30 minutes) followed by a slower maintenance infusion (35 mg over 60 minutes). This dosing should be reduced for individuals weighing less than 68 kg. The major side effect of alteplase is the risk of major bleeding, including intracranial hemorrhage.

Reteplase

Pharmacokinetics and Dose

The removal of two nonactive domains from alteplase produces the mutant protein reteplase. Like its parent compound, reteplase initiates local fibrinolysis by binding to fibrin in a thrombus and converting entrapped plasminogen to plasmin. Changes to the protein structure result in a prolongation of its half-life to 13–16 minutes before being excreted in the feces and urine. The longer half-life allows reteplase to be administered in a double bolus regimen (10 units over 10 minutes twice 30 minutes apart). The major side effect of reteplase remains major bleeding, including intracranial hemorrhage.

Streptokinase

Pharmacokinetics and Dose

Streptokinase is a single-chain protein released by β-hemolytic streptococci that binds with human plasminogen. The streptokinase-plasminogen complex then becomes an active enzyme capable of converting plasminogen to plasmin to facilitate thrombolysis (Figure 4). Streptokinase was the original thrombolytic agent and continues to be used around the world because of its low cost. As a bacterial product, the administration of streptokinase can precipitate an immune response that includes anaphylaxis.[182] Repeated administration of streptokinase may result in the formation of antibodies to the agent, which would neutralize its efficacy. Streptokinase is administered as a slow infusion (1.5 million IU over 60 minutes) with an immediate effect. It is important to note that some generic formulations of streptokinase may have decreased efficacy ranging from 21 to 81% of the activity claimed.[183]

Tenecteplase

Pharmacokinetics and Dose

Tenecteplase is a genetically engineered mutant of tissue plasminogen activator. The resulting compound has 3 amino acid substitutions that result in decreased plasma clearance and a

longer half-life (20 minutes). These mutations may also increase the specificity of the compound to binding fibrin and increase its efficacy. A single bolus of tenecteplase (0.5 mg/kg) is administered for the treatment of STEMI.

Clinical Use and Indications

Fibrinolytic agents are most beneficial in the early stages of STEMI. The Myocardial Infarction Triage and Intervention (MITI) trial randomized 360 patients with STEMI to receive alteplase and aspirin before or after reaching the hospital. The early administration of thrombolytics (<70 minutes since symptom onset) resulted in a 7.5% absolute risk reduction in mortality (8.7–1.2%) while also decreasing infarct size when compared to those that received late thrombolytics (<180 minutes since symptom onset).[184] These findings were confirmed in the Fibrinolytic Therapy Trialists' (FTT) Collaborative Overview of 58,000 randomized patients in fibrinolytic trials.[185] Mortality was reduced by 25% in patients receiving fibrinolysis within 3 hours of symptom onset and 18% within 6 hours. Late administration of fibrinolytics is less efficacious as the thrombus matures and is less prone to pharmacological degradation. Because of this, fibrinolytic therapies administered 12 hours after symptom onset have a minimal reduction in mortality with a persistent risk of hemorrhage.[186] Current guidelines, thus, recommend that fibrinolytic agents be used within 30 minutes of presentation to the medical system.[43] Patients that present over 12 hours after symptom onset should only be considered for mechanical revascularization.

Several large randomized trials have compared different fibrinolytic regimens for the treatment of ACS. The GUSTO-I trial demonstrated that alteplase produced a 14% relative risk reduction and a 1% absolute risk reduction compared to streptokinase in patients with STEMI.[187] However, the administration of alteplase also resulted in an increased risk of hemorrhagic stroke. The ASSENT-2 trial demonstrated that tenecteplase was equivalent to alteplase with a decreased rate of major bleeding.[188] Each of the fibrinolytic agents were assessed with the concomitant use of anticoagulation.[189] Based on this data, all four agents are used for thrombolysis when primary percutaneous coronary intervention is not available. The absolute and relative contraindications of systemiclytic therapy are listed in the accompanying table (Table 3).[43]

Facilitation

A number of trials have evaluated the clinical utility in the administration of half-dose or full-dose thrombolytics prior to

TABLE 3

Contraindications to Thrombolysis

- Absolute contraindications
  - Intracranial process
    - Prior hemorrhage
    - Prior malignant neoplasm
    - Prior cerebral vascular lesion
    - Prior trauma (within 3 months)
    - Prior stroke (within 3 months)
  - Suspected aortic dissection
  - Active bleeding
- Relative contraindications
  - Cardiovascular comorbidities
    - Hypertension (SBP >180 mmHg and DBP >110 mmHg)
    - Prior ischemic stroke (>3 months)
  - Recent bleeding
    - Internal bleeding (within 2–4 weeks)
    - Non-compressible vascular punctures
    - Active peptic ulcer
    - Current use of anticoagulants
  - Other intracranial pathology
  - Pregnancy

proceeding to planned percutaneous coronary intervention, previously termed "facilitated PCI." The majority of these studies demonstrated no mortality benefit with an increased bleeding risk such that current guidelines recommend against this practice.[190,191] In contrast, the use of rescue percutaneous coronary intervention after failed fibrinolysis has demonstrated clinical benefit in patients with persistent ischemia or cardiogenic shock.[192] Percutaneous coronary intervention in these patients is more effective than repeat thrombolysis or no treatment for failed reperfusion.[193]

Guidelines

The current guidelines suggest that patients presenting with STEMI should be treated with primary percutaneous coronary intervention, within 90 minutes (class I, level A). If patients present to a facility without this capability, they should be transferred to a center with percutaneous coronary interventions, if they can then undergo the procedure within 90 minutes of their first medical contact (class I, level B). For patients suffering from STEMI who cannot be transferred, treatment with fibrinolytic therapy within 30 minutes of hospital presentation is recommended (class I, level B).[43] Patients receiving fibrinolytic therapy should be treated with concomitant anticoagulation for a minimum of 48 hours and preferably for the duration of the index hospitalization

(class I, level C). Because of the risk of heparin-induced thrombocytopenia, anticoagulation should be administered with agents other than unfractionated heparin if it will be administered for more than 48 hours (class I, level A).[43]

For patients with STEMI, a reperfusion strategy using fibrinolytic therapy followed by immediate percutaneous coronary intervention may be harmful and is not recommended (class III, level B). Coronary angiography with possible percutaneous coronary intervention (rescue PCI) can be pursued in patients who have received fibrinolytic therapy if they have persistent cardiogenic shock (class I, level B), severe congestive heart failure (class I, level B), or hemodynamically compromising ventricular arrhythmias (class I, level C).[48]

LONG-TERM DRUG THERAPY FOR PATIENTS WITH ACUTE CORONARY SYNDROMES

Introduction

The patients with ACS, whether STEMI, non-STEMI, or unstable angina, require long-term treatments to decrease the risks of adverse cardiovascular events. Both pharmacotherapy and nonpharmacologic treatments should be considered for these patients.

The pharmacologic agents that have been documented to decrease the risks of adverse cardiovascular events are:

- Antiplatelet agents
- Angiotensin inhibitors
- β-adrenergic antagonists
- Aldosterone antagonists
- Lipid-lowering agents.

ANTIPLATELET DRUGS

Introduction

The antiplatelet drugs are employed not only during the initial management of patients with ACS but also for their long-term management. Nonparenteral aspirin, clopidogrel, or prasugrel are used as antiplatelet drugs during long-term treatment of patients with ACS. The glycoprotein IIb/IIIa inhibitors are used only for patients requiring percutaneous coronary artery interventions.

Aspirin

Mechanism of Action and Dosage

Aspirin is the most commonly used antiplatelet drug in patients with cardiovascular disorders. Its mechanism of action, dosage,

and metabolism has been discussed earlier. It attenuates aggregations of platelets by inhibiting the enzyme cyclooxygenase and blocking the TxA_2 receptors. It has a relatively long half-life. The dose is between 75 and 325 mg daily. Because of its long half-life, it can be used, if necessary, 2–3 times weekly. However, it is preferable to use lower dose of aspirin daily, which is associated with lower risk of complications and appears to be equally effective to larger dose.[79]

Long-term use of aspirin has been reported to reduce the risk of nonfatal myocardial infarction by 32%, nonfatal stroke by 27%, total vascular event by 25%, and total cardiovascular death by 15%.[194]

It has been observed that aspirin in combination with angiotensin converting enzyme inhibitors (ACEIs) and satins significantly decrease mortality and morbidity of patients with ACS.[195]

Adverse Effects

The gastrointestinal complications are most frequent adverse effects of the long-term use of aspirin. Indigestion, symptoms of gastric erosions, and ulcerations are the usual manifestations. Frank hematemesis is a rare manifestation. Upper gastrointestinal endoscopy may be required to establish the diagnosis. The concomitant use of antacids and/or H_2-blockers is preferable to discontinuation of aspirin.

Slow gastrointestinal blood loss may cause anemia during long-term use of aspirin. If anemia develops, appropriate investigations, including upper endoscopy should be undertaken. After gastric complications are treated, aspirin treatment should be reinstated along with antacids and/or H_2-blockers. In patients intolerant to oral aspirin, it can be administered as a suppository. Intracranial hemorrhage is a rare complication of aspirin.

Contraindications

Aspirin may cause exacerbation of allergic sinusitis. Recurrent exacerbations with nasal bleedings are a relative contraindication for long-term use of aspirin. Recurrent gastric ulcerations, or erosions with or without blood loss, and unresponsive to antacids and H_2-blocker therapies is also a relative contraindication for the long-term use of aspirin. Severe bronchospastic disease, such as bronchial asthma is a contraindication for the use of aspirin. The Samter's triad, which consists of sensitivity to salicylates, asthma, and nasal polyps is regarded as an absolute contraindication to the long-term use of aspirin.[12] Aspirin is also contraindicated in patients with retinal hemorrhage, urogenital bleeding, hemophilia, and untreated severe hypertension.

Clopidogrel

Introduction

Clopidogrel is a thienopyridine derivative that exerts its antiplatelet effects by blocking the activity of the ADP receptors on the surface of the platelets.

Indications

The major indication for the long-term use of clopidogrel is to reduce the risk of restenosis after percutaneous coronary artery intervention. It is being increasingly used because primary coronary artery intervention with the use of stents is recommended therapy for patients with ACS. Clopidogrel is used along with aspirin (dual antiplatelet therapy). The duration of therapy depends on the type of the coronary artery stents used. When the bare metal stents are used, it is recommended that clopidogrel should be continued for at least 1 month. If drug eluting stents are used, it should be continued for at least 12 months.[129] The usual dose of clopidogrel is 75 mg daily.

Adverse Effects

Gastrointestinal upset and skin rash may occur with clopidogrel. Thrombocytopenia is a rare complication of clopidogrel.

Contraindication

Severe thrombocytopenia is a contraindication for the long-term use of clopidogrel.

Prasugrel

Introduction

Like clopidogrel, it exerts its antiplatelet activity by inhibiting platelet ADP receptors. The half-life of its active metabolites is approximately 7 hours. For the long-term use, the standard dose of prasugrel is 10 mg daily.[143]

Indications

The principal indication for the long-term use of prasugrel is to reduce the risk of restenosis after primary coronary artery intervention. In a large randomized trial of ST segment elevation myocardial infarction, it was reported that prasugrel caused a 2.4% absolute risk reduction in cardiovascular death, recurrent myocardial infarction, or stroke compared to standard doses of clopidogrel.[147]

Adverse Effects

The use of prasugrel is associated with increased risk of major bleeding compared to clopidogrel.[145]

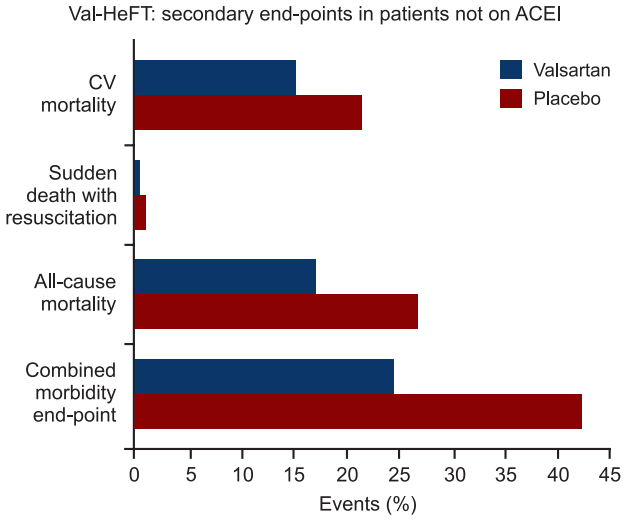
Contraindications

Prasugrel is contraindicated in patients with past history of cerebrovascular disease and pathological bleeding. It is also contraindicated in those over the age of 75 years or weight under 60 kg.

ANGIOTENSIN INHIBITORS

Introduction

ACEIs or angiotensin receptor blocking (ARB) agents have been demonstrated to decrease mortality and morbidity of patients with acute coronary artery syndromes.[16,17,195-202] The angiotensin converting enzyme inhibitors—captopril, lisinopril, ramipril, trandolapril, and zofenopril—have been used in various studies. With the use of these ACEIs, in general, there was a substantial reduction in all-cause mortality, incidence of fatal and nonfatal myocardial infarction, and development of overt heart failure. It is of interest that the beneficial effects of the ACEIs were observed in patients with depressed left ventricular systolic function. ARB agents exert similar beneficial effects in patients with reduced left ventricular ejection fraction (Figure 5).[201] In contrast, no beneficial effects were observed in patients who had preserved left ventricular ejection fraction after ACS.[202]



Val-HeFT, valsartan heart failure trial; ACEI, angiotensin converting enzyme inhibitor; CV, cardiovascular.

FIGURE 5. Effects of angiotensin receptor blocking agent valsartan in postmyocardial infarction patients showing decreased risk of all-cause mortality, sudden death with resuscitation, and combined morbidity. *Data from* Cohn JN, Tognoni G; Valsartan Heart Failure Trial Investigators. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med*. 2001;345(23):1667-75.

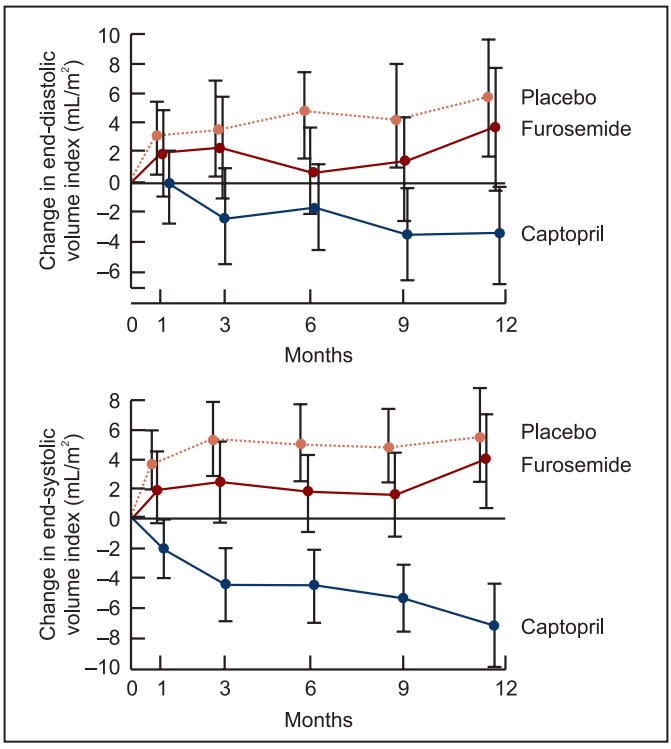


FIGURE 6. The effects of angiotensin converting enzyme inhibitors on left ventricular remodeling showing a decrease in end systolic and end diastolic volumes. Values shown are least squares means with upper and lower least significant difference intervals ($p < 0.05$). *From* Sharpe N, Murphy J , Smith H, Hannan S. Treatment of patients with symptomless left ventricular dysfunction after myocardial infarction. *Lancet*. 1988;1(8580):255-9, *with permission*.

ACEIs can produce left ventricular reverse remodeling (Figure 6).[203] There is a decrease in left ventricular end-diastolic and end-systolic volumes and an increase in ejection fraction. ARB agents also have the potential to produce beneficial left ventricular reverse remodeling.

Mechanism of Action and Doses

ACEIs reduce the formation of angiotensin by blocking the converting enzyme. The inhibitions of the converting enzymes are also associated with increased production of bradykinins which may exert vasodilatory, anti-inflammatory, and reverse remodeling effects. Commonly used ACEIs are enalapril, lisinopril, and captopril. The usual dose of enalapril is 10–20 mg twice a day. After oral dose of enalapril, the peak concentration of its active metabolite enalaprilat occurs at 3–4 hours and the half-life of enalaprilat is about 11 hours. Lisinopril has a half-life of about 12 hour. Doses of 10–80 mg once a day are effective in

majority of patients. The half-life of captopril is 2.2 hours, and the dose is 25–50 mg three times a day.

ARB agents directly blocks the angiotensin II receptors and attenuates the deleterious effects of angiotensin. Angiotensin promotes vasoconstriction, vascular smooth muscle cells hypertrophy, myocyte hypertrophy, and extracellular matrix degradation and myocardial fibrosis. Furthermore, angiotensin promotes atherothrombosis. The ARB agents counteract these deleterious effects of angiotensin. ARB agents do not exert any effect on bradykinin metabolism.

Valsartan is the most commonly used ARB agent in patients with acute coronary artery syndrome. It has a relatively long half-life. The usual dose of valsartan is 40–160 mg twice a day. Losartan has also been used in patients with ACS. The half-life of losartan is 1–2 hours but that of its active metabolite is 3–4 hours. The usual dose of losartan is 25–50 mg twice a day.

Adverse Effects

A marked fall in blood pressure may occur after the first dose of ACEIs, in patients with relative hypovolemia due to diuretic therapy. Acute renal failure is a serious adverse effect which occurs more frequently in patients with bilateral renal artery stenosis. During long-term treatment with ACEIs, worsening renal function due to hypotension may be observed in a few patients. Hyperkalemia tend to occur more frequently in patients with renal failure or diabetes.

The most frequent side effect of ACEIs is nonproductive paroxysms of cough. However, intractable cough is uncommon. Another uncommon complication is angioedema. Skin rash and altered taste are also uncommon complications. With high doses of ACEIs, neutropenia, or proteinuria may occur. The major side effects of the ARB agents are hypotension and worsening renal function. Hyperkalemia may also occur along with renal failure. The use of ARB agents is not usually associated with intractable cough or angioedema.

Contraindications

Intractable cough and angioedema are contraindications for the use of ACEIs. Hypotension, worsening renal function, and hyperkalemia are contraindications for the use of both ACEIs and ARB agents. Cardiogenic shock is a contraindication for the use of ACEIs or ARB agents. These agents are also contraindicated during second and third trimesters of pregnancy, as irreversible fetal renal failure can develop. There is also increased risk of teratogenicity.

β-ADRENERGIC ANTAGONISTS

β-blockers should be considered for long-term treatment of patients with ACS. In postmyocardial infarction patients with reduced left ventricular ejection fraction, long-term use of carvedilol is associated with decreased mortality and morbidity.[26] There is also decreased risk of development of overt heart failure. β-blockers have been shown to decrease the risk of mortality and nonfatal cardiovascular events in postmyocardial infarction patients already on angiotensin inhibition therapy.[201] In patients with chronic systolic heart failure due to ischemic cardiomyopathy, β-blocker therapy has been shown to reduce mortality and morbidity.[204] There is also reverse remodeling of the left ventricle. There is a reduction in left ventricular end-systolic and end-diastolic volumes and an increase in ejection fraction.

For the long-term use in chronic systolic heart failure, carvedilol, bisoprolol, or long-acting slow release metoprolol are used. Carvedilol is a nonselective β-blocking agent with also α-blocking property. It also has an antioxidant property. Compared to short-acting immediate release metoprolol, carvedilol has been reported to be more effective to decrease the risk of mortality and morbidity.[27] The half-life of carvedilol is about 7–10 hours. The optimal dose of carvedilol for systolic heart failure is 25 mg twice a day. The initiating dose is between 3.125 and 12.5 mg twice a day.

Bisoprolol is a selective β-receptor blocking agent with a direct vasodilating property. It has a relatively long-half life and can be administered once a day. The optimal dose of bisoprolol is 10 mg daily, but the initiating dose is 2.5–5 mg once a day.

Long-acting slow release metoprolol is a selective β1-receptor blocking agent. Short-acting metoprolol has a half-life of 3–4 hours, while the slow release metoprolol has a much longer half-life and can be administered once daily. The optimal dose of slow release metoprolol is 100–200 mg daily. The initiating dose is between 25 and 50 mg daily.

Adverse Effects

Hypotension, bradycardia, and exacerbation of heart failure are adverse effects that usually occur at the initiation of therapy. Worsening lower extremity claudication, depression, and bronchospasm are other adverse effects of β-blocker therapy.

Contraindications

Extreme bradycardia, heart block, and severe bronchospasm are contraindications for the use of β-blockers. Cardiogenic shock

and pulmonary edema are also contraindications for the use of β-adrenergic antagonists.

ALDOSTERONE ANTAGONISTS

Introduction

Aldosterone exerts adverse effects on ventricular function and promotes ventricular remodeling. It causes myocyte hypertrophy, and induces collagen synthesis and myocardial fibrosis. In addition, it can cause fluid retention and exacerbate heart failure. Aldosterone antagonists have the potential to reverse the adverse effects of aldosterone.

Indications

In postmyocardial infarction patients with reduced left ventricular ejection fraction, aldosterone antagonist, eplerenone, decreases mortality and morbidity.[205] It also reduces the risk of developing congestive heart failure. It has the potential of reducing myocardial fibrosis and to promote beneficial left ventricular reverse remodeling.

Mechanism of Action and Doses

Eplerenone is a competitive antagonist to aldosterone. It is a more selective aldosterone antagonist than spironolactone. It does not exert antiandrogenic effects and do not cause gynecomastia and breast enlargements. In kidney, its major site of action is on the distal tubule and collecting ducts. The optimal dose of eplerenone is between 25 and 50 mg twice a day. The initiating dose is between 12.5 and 25 mg once a day.

Adverse Effects

Hyperkalemia and worsening renal failure are the major adverse effects of aldosterone antagonists. When used with loop diuretics, it may exacerbate hyponatremia. Gynecomastia and breast enlargements are other side effects.

Contraindications

Renal failure with creatinine >2.5 mg/dL and/or serum potassium level ≥5 mEq/L are contraindications for the use of aldosterone antagonists.

STATINS

Introduction

In patients with ACS, intensive lipid-lowering therapy with 3-hydroxy-3-methylglutaryl coenzyme-A reductase inhibitors

(statins) decreases the risks of mortality and recurrent adverse cardiovascular events.[206,207] Based on the results of these studies, the National Cholesterol Education Program Adult Panel and ACC/AHA guidelines recommended early and intensive lipid lowering therapy with statins in patients with ACS.[208,209]

Mechanism of Action and Doses of Statins in Acute Coronary Syndrome

As the treatment with statins is associated with the beneficial effects which occur early and irrespective of the baseline levels of low-density lipoprotein, lipid-lowering effects do not appear to be the primary mechanism. Statins can improve endothelial function and decrease inflammation and myocardial ischemia. These beneficial effects which are independent of its lipid-lowering effects are referred as its "pleiotropic" effect. The dose of atorvastatin used in these trials was 80 mg/daily.

Clinical Trials

In the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial, 3,038 patients with ACS were randomized to receive either 80 mg of atorvastatin or placebo. The composite primary end-point in this trial was death, nonfatal myocardial infarction, cardiac arrest, or recurrent unstable myocardial ischemia. There was a relative risk reduction of the primary end-point by 50% in the treated group.[206]

In the Pravastatin or Atorvastatin Evaluation and Infection Therapy-TIMI 22 Trial (PROVE IT), 4,162 patients were randomized to receive either 40 mg of pravastatin or 80 mg of atorvastatin. The composite primary end-point was all-cause mortality, myocardial infarction, unstable angina requiring hospitalizations, need for revascularization, and stroke. During a mean follow-up period of 24 months, the incidence of primary end-point in the pravastatin group was 26.3% and that of in the atorvastatin group, 22.4%. There was a statistically significant 16% reduction in the relative risk of incidence of primary end-point with atorvastatin compared to pravastatin.[207] There was also a reduction in the rate of hospitalization for heart failure.[210] Intensive lipid-lowering treatment with large dose of atorvastatin (80 mg) appears to reduce the risk of major cardiovascular events by a greater magnitude compared to treatment with 40 mg of pravastatin in patients undergoing percutaneous coronary intervention for ACS.[211]

It has been also reported that early intervention with statin reduces the lipid components of the atherothrombotic plaques in

patients with ACS which may produce beneficial effect in plaque-stabilization.[212]

Pharmacokinetics

Atorvastatin is a metabolically active agent and its absorption after oral therapy varies between 40 and 75%. The half-life of atorvastatin is approximately 14 hours. In ACS, 80 mg of atorvastatin is employed.

Adverse Effects

The skeletal muscle "aches and pains" are common complaints during statin therapy. Until these symptoms are intolerable in patients with coronary artery disease, it should be continued indefinitely. The benefits of statin therapy are more than the risks, and the risk-benefits should be explained to the patients.

Slight elevation of muscle creatine kinase is common, but it is not a contraindication for discontinuing stain therapy. Similarly, slight or modest elevation of hepatic enzymes is frequent but not a contraindication for statin therapy.

Contraindications

Severe myopathy with a marked elevation of skeletal muscle creatine kinase enzyme, renal failure, obvious skeletal muscle wasting are contraindications for statin therapy. Progressive hepatic failure manifested by a marked elevation of hepatic enzymes is also a contraindication for statin therapy.

CONCLUSION

Several drugs are used both for immediate treatment and for long-term management of patients with acute coronary syndrome. Antiplatelet drugs, thrombin inhibitors anticoagulants, and thrombolytic drugs are used during the acute phase in patients undergoing either catheter based or pharmacologic reperfusion therapy. β-adrenergic blocking agents and angiotensin inhibitors are adjunctive therapy in patients with acute coronary synderome during the acute phase management.

In patients with non-STEMI/unstable angina, large doses of statins are used. In patients with reduced left ventricular ejection fraction, who have already received reperfusion therapy, aldosterone antagonists are indicated.

For long term management of patients with acute coronary syndromes, antiplatelet drugs, angiotensin inhibitors, β-blockers, and statins should be used indefinitely in absence

of contraindications. It should be appreciated that all drugs can produce complications. Some complications are minor and others are more severe. The major complications are usually contraindications for continued therapy.

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8 CHAPTER

Drugs for Dysrhythmia

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INTRODUCTION

Antiarrhythmic drugs (AADs) suppress cardiac arrhythmias through their effects on various cardiac ion channels and receptors. Although originally developed with the goal of improving survival in patients with structural heart disease and arrhythmias, large randomized clinical trials demonstrated that AADs have been a disappointment in this regard. The role of AAD therapy has undergone constant evolution over the years, as new therapies have emerged and the risk-benefit profile of these drugs on major clinical end-points are better understood. AAD therapy continues to have a critical role in the management of patients with both atrial and ventricular arrhythmias but, for the most part, is used as an adjunct to curative therapies, such as catheter ablation as well as those targeted at improving the underlying substrate. For primary and secondary prevention of sudden cardiac death, AADs have been surpassed by implantable cardioverter defibrillators (ICDs). Many older AADs have been taken off the market, and newer, perhaps, safer AADs have taken their place.

The biggest concern a clinician faces upon deciding to initiate and maintain AAD therapy is the risk of proarrhythmia as well as systemic toxicity with AADs. Very few classes of medications exist where the initiation of therapy is guided by a "safety first" approach. Proarrhythmia may have offset the efficacy of the AADs, resulting in failure to impact hard clinical end-points in large, randomized trials. Safety concerns also make AADs, as a class, the most complex to prescribe and monitor.

Compared to years past, a better understanding of the benefits and risks of specific AADs have led them to be used in a more selective and regulated fashion. Careful considerations of the proarrhythmic and toxic effects have led to elimination of several AADs from the market (oral procainamide, tocainide, and bretylium) and marked reduction in use of several others (quinidine, phenytoin, mexiletine, and disopyramide). At the

same time, research in this arena has been strong, leading to the development and marketing of several new AADs.

AADs continue to play an important role in treatment of a wide variety of atrial and ventricular ectopy as well as tachyarrhythmias. This, plus the fact that there has been constant evolution in the risk profile as well as indications for AADs, makes it extremely important that clinicians who use these drugs be familiar with their pharmacology, mechanisms of action, indications, dosing, adverse effects, including proarrhythmic effects, and drug interactions.

This chapter will describe the classification schema, clinical pharmacology, adverse effects, and interactions of individual drugs. A significant portion of the chapter will be devoted to discuss the clinical role of these agents in the modern era. We will also focus on the clinical applicability of the individual agents based on available clinical data. Available data on emerging and investigational AADs will also be discussed. β-blockers and calcium-channel blockers, given their pleiotropic properties, will be discussed in detail in separate chapters.

ARRHYTHMIA MECHANISMS AND ANTIARRHYTHMIC DRUGS

Three major mechanisms contribute to development of cardiac arrhythmias: automaticity, reentry, and triggered activity. AADs primarily affect ion channels (and/or receptors) in the heart and can affect various arrhythmia mechanisms by altering cardiac excitability, conduction, and refractoriness. Some AADs can affect more than one cardiac ion channel (and/or receptors) and so can affect more than one arrhythmia mechanism, whereas some newer AADs can have novel mechanisms of action altogether. Some AADs are specific for certain cardiac tissue, such as atrial, ventricular, or atrioventricular (AV) nodal, whereas others have more generalized effects.

INDICATIONS FOR ANTIARRHYTHMIC DRUG THERAPY

In the modern era, the most common indication for AAD therapy is atrial fibrillation (AF).[1] Secondary prevention of ventricular arrhythmias as well as treatment of other supraventricular arrhythmias constitutes other important indications. Occasionally, AADs are used to suppress ventricular and atrial ectopy, including nonsustained ventricular tachycardia (VT). The main goal of AAD therapy in AF is to reduce symptoms and improve quality-of-life,

although expectations have been raised by recent data on class III AAD dronedarone, which demonstrated mortality benefit in low-risk patients with paroxysmal AF.[2]

PROARRHYTHMIA

All AADs can be proarrhythmic, which further underlines the fact that these agents should be used judiciously. The same mechanisms that contribute to their antiarrhythmic effects can also induce arrhythmias that range from atrial or ventricular ectopy to QT prolongation and torsades de pointes. This makes it difficult to assess efficacy of the drug. Depending on drug properties, interactions with concomitant drugs, as well as patient factors, the following proarrhythmic effects are seen: (i) sinus bradycardia, (ii) atrioventricular (AV) block, (iii) increased ventricular or atrial ectopy, (iv) VT (monomorphic and polymorphic), including torsades de pointes related to QT interval prolongation, (v) ventricular fibrillation (VF), and (vi) slowing of atrial tachyarrhythmias allowing one to one AV conduction when this was not present before the drug.

CLASSIFICATION

Two major classification schemes exist. The Vaughan Williams classification classifies AADs based on their most prominent electrophysiological property and is the most clinically relevant (Table 1).[3] The "Sicilian Gambit" scheme classifies AADs based on their cellular mechanism of action, is complex, and is mostly utilized for research and drug development.[4] Neither classification is perfect. Most AADs and their active metabolites have multiple pharmacological effects, some of which are not well understood, and therefore, a "one scheme fits all" approach may be overly simplistic.

Pharmacokinetic properties and dosing of currently available oral AADs are shown in table 2. The common uses and adverse effects of AADs are shown in table 3 whereas the major drug interactions are listed in table 4.

Class I Antiarrhythmic Drugs

The class I AADs act primarily by blocking the cardiac sodium (Na^+) channel. These drugs, therefore, cause significant conduction slowing by interfering with the depolarization phase of the cardiac action potential ("phase 0") and also decrease excitability (reduction in V_{max}). The magnitude of Na^+ channel blockade is determined by specific drug properties, heart rate, membrane

TABLE 1

The Vaughan Williams Classification of Antiarrhythmic Drugs

	Drug	*Mechanism (Ion channel effect)*	*Electrophysiological effect*
Class I Sodium channel blockers			
IA	▪ Quinidine ▪ Procainamide ▪ Disopyramide	Combined sodium and potassium channel blockade, intermediate kinetics of binding and dissociation	Moderate conduction slowing (predominant effect) and increase refractoriness
IB	▪ Lidocaine ▪ Mexiletine	Sodium channel blockade, rapid kinetics of binding and dissociation	Shorten APD, especially in depolarized cells
IC	▪ Flecainide ▪ Propafenone	Sodium channel blockade, slow kinetics of binding and dissociation	Marked conduction slowing (minimal effect on refractoriness)
Class II β-blockers: β-adrenoceptor blockade			
β1-selective	▪ Acebutolol (membrane stabilizing) ▪ Atenolol ▪ Bisoprolol ▪ Esmolol (IV only) ▪ Metoprolol	—	—
Non-β1-selective	▪ Nadolol ▪ Propranolol	—	—

(continued)

Table 1 *(continued)*

	Drug	*Mechanism (Ion channel effect)*	*Electrophysiological effect*
Non-β-selective and α-receptor blockers	▪ Carvedilol ▪ Labetalol	–	–
Class III Potassium channel blockers			
	▪ Sotalol	Block Ikr and β-receptors	Prolong APD and refractoriness
	▪ Amiodarone	Blocks multiple potassium channels, Na^+ channels, Ca^{2+} channels, β-receptors	Prolong APD and refractoriness
	▪ Dronedarone	Blocks multiple potassium channels, Na^+ channels, Ca^{2+} channels, β-receptors	Prolong APD and refractoriness
	▪ Ibutilide	Blocks Ikr and late Na^+ current	Prolong refractoriness and APD
	▪ Dofetilide	Blocks Ikr	Prolong refractoriness and APD
	▪ Azimilide	Blocks Ikr and Iks	Prolong refractoriness and APD
Class IV Calcium channel blockers		Blocks L-type Ca^{2+} channels	Negative chronotropic and inotropic effects

APD, action potential duration; Na^+, sodium; Ca^{2+}, calcium; IV, intravenous; IKr, rapid delayed potassium rectifier current; IKs, slow delayed potassium rectifier current.

TABLE 2

Pharmacokinetic Properties of Common Antiarrhythmic Drugs

Drug	*Daily dose (mg/day)*	*Route of administration*	*Oral bio-availability (%)*	*Protein binding (%)*	*Major elimination route*	*Elimination half-life*	*Active metabolite*
Quinidine	600–1,600	Oral	80	80	Hepatic	6–12 hours	3-hydroxyquinidine
Procainamide	—	IV	—	15–20	Hepatic and renal	3–4 hours	N-acetyl procainamide
Disopyramide	400–600	Oral	80	50–65 (saturable)	Renal and hepatic	6–9 hours	Mono-N-dealkyldisopyramide
Lidocaine	—	IV, IM	—	60–80	Hepatic	2 hours	Monoethylglycinexylidide and glycinexylidide
Mexiletine	450–900	Oral	90–100	50–60	Hepatic	9–12 hours	None
Flecainide	200–400	Oral	95	40	Hepatic and renal	10–17 hours	None
Propafenone	450–675	Oral	5–50	85–97	Hepatic	2–10 hours	5-hydroxy propafenone
Metoprolol	25–200	Oral, IV	95	5–15	Hepatic	3–7.5 hours	None
Sotalol	160–320	Oral	100	0	Renal	12–16 hours	None
Dofetilide	0.5–1	Oral	90	60–70	Renal	8–10 hours	None

(continued)

Table 2 *(continued)*

Drug	*Daily dose (mg/day)*	*Route of administration*	*Oral bio-availability (%)*	*Protein binding (%)*	*Major elimination route*	*Elimination half-life*	*Active metabolite*
Ibutilide	1 mg over 10 minutes	IV	—	—	Hepatic and renal	6–9 hours	None
Amiodarone	200–400	Oral, IV	35–50	95	Hepatic	13–103 days	Desethylamiodarone
Dronedarone	800	Oral	15–20	98	Hepatic	24 hours	N-debutyl metabolite
Azimilide	75–125	Oral, IV	95	94	Hepatic and renal	4–5 days	None measurable
Verapamil	120–480	Oral, IV	20–35	90	Hepatic	3–7 hours	Norverapamil
Diltiazem	120–360	Oral, IV	40	70–80	Hepatic	4 hours	Desacetyl diltiazem; desmethyl diltiazem
Ranolazine	1,000–2,000	Oral	35–50	61–65	Hepatic and renal	1.4–1.9 hours	—
Vernakalant	3 mg/kg body weight	IV	—	—	Hepatic	1.7–5.4 hours	None

IV, intravenous; IM, intramuscular.

TABLE 3

Uses and Side Effects of Orally Available Antiarrhythmic Agents		
Drug	*Adverse effects*	*Uses*
Class IA		
Quinidine	▪ Gastrointestinal ▪ Tinnitus, hearing loss, visual disturbance, and confusion (cinchonism) ▪ Thrombocytopenia and hemolytic anemia ▪ Hypotension and anaphylaxis ▪ QRS prolongation, QT prolongation, and torsades de pointes	▪ Secondary prevention of VT and VF (in ICD patients) ▪ Short QT syndrome ▪ Brugada syndrome
Procainamide	▪ Rash, myalgia, and vasculitis ▪ Drug-induced lupus ▪ Fever and agranulocytosis ▪ Hypotension, bradycardia, QT prolongation, and torsades de pointes	▪ Sustained VT ▪ Unmasking Brugada syndrome ▪ Brugada syndrome ▪ AF in WPW syndrome
Disopyramide	▪ Urinary retention, constipation, glaucoma, and xerostomia ▪ QT prolongation and torsades de pointes ▪ Negative inotropic effects	▪ Symptomatic hypertrophic cardiomyopathy ▪ Vagally mediated AF
Class IB		
Mexiletine	▪ Tremor, anxiety, dysarthria, dizziness, and nystagmus ▪ Gastrointestinal ▪ Hypotension and bradycardia	▪ VT ▪ Reduction of ICD shocks ▪ LQT3

(continued)

Table 3 *(continued)*

Drug	*Adverse effects*	*Uses*
Class IC		
Flecainide	▪ Negative inotropy, AV block, and bradycardia ▪ Decreases pacing threshold ▪ Confusion and irritability	▪ Paroxysmal AF ▪ SVT ▪ PVCs and idiopathic VT
Propafenone	▪ Dizziness and blurred vision ▪ Bronchospasm (in slow metabolizers) ▪ AV block, bradycardia, and heart failure exacerbation ▪ Decreases pacing threshold	▪ Paroxysmal AF ▪ SVT ▪ PVCs and idiopathic VT
Class II		
β-blockers	▪ Hypotension, bradycardia, heart block, and heart failure exacerbation ▪ Bronchospasm ▪ Depression ▪ Impairment of sexual function	▪ Atrial arrhythmias ▪ Rate control in AF ▪ SVTs ▪ PVCs ▪ VT
Class III		
Amiodarone	▪ Pulmonary fibrosis ▪ Abnormal liver function tests ▪ Hyper or hypothyroidism ▪ Bradycardia and heart failure exacerbation ▪ Tremor and paresthesia	▪ VT ▪ VF ▪ Reduction of ICD shocks ▪ AF ▪ Atrial flutter

(continued)

Table 3 *(continued)*

Drug	*Adverse effects*	*Uses*
	▪ Photosensitivity ▪ Corneal deposits	▪ AF in WPW syndrome ▪ Other SVTs
Sotalol	▪ Bradycardia and torsades de pointes	▪ VT in ARVD ▪ Reduction of ICD shocks ▪ AF ▪ Atrial flutter
Dofetilide	▪ Torsades de pointes	▪ Rhythm control in AF
Dronedarone	▪ Gastrointestinal side effects ▪ Fulminant hepatic failure (rare) ▪ Heart failure exacerbation (in patients with severe left ventricular dysfunction)	▪ To reduce the risk of cardiovascular hospitalization in patients with paroxysmal and persistent AF and low cardiovascular risk ▪ Rhythm control in low risk AF patients
Class IV		
Calcium channel blocker (verapamil)	▪ Hypotension, bradycardia, and AV block	▪ Idiopathic VT ▪ PVCs ▪ Rate control in AF ▪ SVTs

VT, ventricular tachychardia; VF; ventricular fibrillation; ICD, implantable cardioverter defibrillator; AF, atrial fibrillation; WPW, Wolff-Parkinson-White; ARVD, arrhythmogenic right ventricular dysplasia; LQT3, long-QT syndrome type 3; SVT, supraventricular tachycardia; PVC, premature ventricular contraction.

TABLE 4

Major Drug Interactions of Antiarrhythmic Drugs		
Drug	*Interacting drug*	*Interaction*
Quinidine		
	Phenytoin	↓ Quinidine levels
	Phenobarbital	↓ Quinidine levels
	Rifampicin	↓ Quinidine levels
	Ketoconazole	↑ Quinidine levels
	Verapamil	↑ Quinidine levels
	Propafenone	↑ Propafenone level
	β-blockers	↑ β-blockade
	Digoxin	↑ Digoxin concentration
Mexiletine		
	Phenytoin	↓ Mexiletine levels
	Phenobarbital	↓ Mexiletine levels
	Rifampicin	↓ Mexiletine levels
	Ketoconazole	↑ Mexiletine levels
	Isoniazid	↑ Mexiletine levels
	Theophylline	↑ Theophylline levels
Flecainide		
	Digoxin	↑ Digoxin levels
	Amiodarone	↑ Flecainide levels
	Quinidine	↑ Flecainide levels
Propafenone		
	Digoxin	↑ Digoxin levels
	Warfarin	↓ Warfarin clearance
	Cyclosporine	↑ Cyclosporine levels
	Quinidine	↑ Propafenone levels
Amiodarone		
	Digoxin	↑ Digoxin effect
	Warfarin	↑ Warfarin effect
	QT prolonging drugs	↑ Risk of torsades de pointes
	β-blockers	Bradycardia and AV block
	Diltiazem and verapamil	Bradycardia and AV block
	Anesthetic drugs	Hypotension and bradycardia
	Cyclosporine	↑ Cyclosporine concentration
Sotalol		
	QT prolonging drugs	↑ Risk of torsades de pointes
Dofetilide		
	QT prolonging drugs	↑ Risk of torsades de pointes

(continued)

Table 4 *(continued)*

Drug	*Interacting drug*	*Interaction*
Dronedarone		
	Digoxin	↑ Digoxin effect
	Cyclosporine	↑ Cyclosporine concentration
	Simvastatin	↑ Risk of myopathy
β-blockers		
	Quinidine	↑ β-blockade
	Amiodarone, digoxin, diltiazem, verapamil	Bradycardia
CCBs (verapamil)		
	Digoxin	↑ Digoxin levels

AV, atrioventricular; CCBs, calcium channel blockers.

potential, and autonomic (parasympathetic and sympathetic) activation, among others.

Based on their affinity for the cardiac sodium channel, class I drugs are further classified into IA (quinidine, procainamide, and disopyramide), IB (mexiletine and lidocaine), and IC (flecainide and propafenone).[5] The specific pharmacodynamic properties of class I AADs are shown in table 5. The pioneering works of Hodgkin and Huxley demonstrated that sodium channels normally transit through 3 distinct conformational states during the action potential: open, inactivated, and closed.[6]

Only open channels conduct sodium current. Sodium channel blockers interact with open as well as inactivated channel states but not usually bind to closed channels. Thus, sodium channel blockade is phasic and depends on the conformational state of the channel. The extent of sodium channel blockers depends on the recovery rate of the sodium channel. Class IC AADs (flecainide and propafenone) cause significant conduction slowing secondary to very slow recovery from the sodium channel blockade. Alternatively, disease states, such as ischemia can slow sodium channel recovery and can increase sodium channel blockade.

Class I drugs exhibit use-dependence. Tachycardia increases the number of sodium channels in the open and inactivated states, and since sodium channel blockers have greater affinity for the open and inactivated channels, the extent of sodium channel blockade and consequent conduction slowing is greater during faster heart rates. This phenomenon is called use-dependence.

Class IA drugs exhibit moderate conduction slowing and have effects in both atrial and ventricular myocardium. As listed in table 5, they have potassium channel blocking properties and can

TABLE 5

Pharmacodynamic Properties of Class I Antiarrhythmic Drugs			
Drug class	*Recovery from sodium channel*	*Other ion channel blockade*	*Other properties*
Class IA			
Quinidine	Intermediate	Ito, IKr, IKs, IKATP, IKI	▪ Vasodilator ▪ Anticholinergic
Procainamide	Intermediate	IKr	▪ Active metabolite, N-acetyl procainamide is a pure class III agent ▪ β-blocking and anticholinergic properties ▪ Vasodilator (intravenous procainamide)
Disopyramide	Intermediate	Ito, IKr, IKACh	▪ Anticholinergic ▪ Negative inotropy
Class IB			
Lidocaine	Fast	—	—
Mexiletine	Fast	—	—
Class IC			
Flecainide	Slow	IKr, IKur	β-blocking properties
Propafenone	Slow	IKr, IKur	β-blocking properties

Ito, transient outward current; IKr, rapid delayed potassium recitifier current, IKs, slow delayed potassium recitifier current; IKATP, adenosine triphosphate-sensitive potassium current, IKI, inward potassium recitifier current, IKACh, acetylcholine-dependent cardiac and adenosine sensitive potassium current, IKur, ultrarapid potassium current.

prolong repolarization. Disopyramide, in particular, can have a marked anticholinergic effect.

A variety of serious side effects have limited the use of class IA AADs. Most importantly, they are all rapid delayed rectifier potassium current (IKr) blockers, which can result in dose-independent QT prolongation, and have the potential to cause torsades de pointes. Given modest efficacy for atrial and ventricular arrhythmias[7] and potential for serious toxicity, these agents are not used as first-line therapy anymore.

Class IA Antiarrhythmic Drugs

Quinidine

Quinidine is derived from the parent compound quinine, an antimalarial agent extracted from the bark of the cinchona tree. Quinidine blocks the rapid sodium current as well as multiple potassium currents including rapid (IKr) and slow (IKs) components of the delayed potassium rectifier current, the inward potassium rectifier current (IKI), the adenosine triphosphate (ATP)-sensitive potassium channel (IKATP) and transient outward current (Ito). Effects of quinidine on the sodium channel results in moderate conduction slowing. Quinidine can block IKr at very low concentrations with resultant action potential prolongation and potential for torsade de pointes that is nondose dependent. Thus, quinidine is best initiated in the hospital. The IKr blockade effect is blunted at higher doses, as the sodium channel blockade becomes prominent.[8]

Ito blockade by quinidine is believed to reduce the heterogeneity of repolarization in the right ventricular outflow tract and thereby attenuates anterior precordial ST-segment elevation in the Brugada syndrome. Quinidine has been shown to decrease ventricular arrhythmias and suppress electrical storm in small studies of Brugada syndrome patients.[9,10] Quinidine has, therefore, been used as an adjunct but not an alternative to ICD therapy in high-risk patients with Brugada syndrome.[11] Quinidine is also effective for short QT syndrome[12-15] and for idiopathic VF.[16] Quinidine has also been used to suppress ventricular arrhythmias in structural heart disease when other AADs have been tried and failed. Overall, the proarrhythmic and other adverse effects of quinidine have severely limited the role of quinidine in the management of atrial and ventricular arrhythmias.

Quinidine is an α-blocker and can result in hypotension when administered intravenously, but it is not a negative inotrope. Vagolytic effects of quinidine enhance AV conduction. Upon oral absorption, quinidine is 80% bound to plasma proteins as well as to α1 acid glycoprotein. Therefore, higher than normal

dosing may be needed to keep quinidine at therapeutic levels during depolarized states, such as acute myocardial infarction. Quinidine is metabolized predominantly by the cytochrome P450 3A4 (CYP3A4) system in the liver with an elimination half-life of 6–12 hours and ~20% is excreted unchanged by the kidneys. The major active metabolite of quinidine, 3-hydroxyquinidine, has marked sodium channel and IKr blocking properties and is partially responsible for the clinical effects of quinidine.[17] Quinidine is also a potent inhibitor of CYP2D6, decreasing clearance of drugs, such as propafenone.[18] It also inhibits p-glycoprotein, resulting in increased serum digoxin levels.[19] Effective therapeutic plasma concentrations of quinidine are between 2 and 5 μg/ml and no dosage adjustment is needed for renal failure or congestive heart failure.

Diarrhea is by far the most common adverse effect, happening in 30–50% of patients, and the mechanism is not well elucidated. In years past, Amphojel was used to offset this common problem, but now it is not used often due to concerns of toxicity. Thrombocytopenia can occur and is immunologic. Headache and tinnitus are dose-dependent side effects that are part of the symptom complex known as cinchonism. Quinidine can cause idiosyncratic QT prolongation and torsades de pointes, the incidence of which is estimated to be ~2–4%. High plasma levels of quinidine can result in monomorphic VT secondary to sodium channel blockade. Quinidine can increase and even double the digoxin levels. The dose of quinidine is generally 200–400 mg four times a day, but long-acting preparations are available to a limited extent. There has been recent serious talk about taking quinidine off the market despite the vital role it plays in the management of select channelopathies.[20-23]

Procainamide

Procainamide is currently only available in the intravenous form in USA. Procainamide blocks open sodium channels and has an intermediate recovery from channel block. It also blocks IKr, prolonging action potential duration. Like quinidine, procainamide slows atrial and ventricular myocardial conduction, suppresses automaticity, and increases refractoriness. The major metabolite of procainamide, N-acetyl procainamide (NAPA), a class III AAD, prolongs refractoriness but lacks sodium channel blocking properties. Procainamide has negligible negative inotropic properties but is a ganglionic blocker, resulting in hypotension on intravenous use.

Procainamide is metabolized by both hepatic and renal routes, with an elimination half-life of 3–4 hours, and its elimination is in part dependent upon the rapidity of acetylation.

NAPA is eliminated completely by renal excretion and, with its IKr blocking properties, can result in dose-dependent QT prolongation and torsade de pointes in patients with renal insufficiency.[24]

Like quinidine, the adverse effects as well as the proarrhythmic effects of procainamide outweigh the potential benefits in many cases, and, therefore, this drug is rarely used. Marked conduction slowing with infra-Hisian block (particularly in the presence of conduction system disease), QT prolongation, monomorphic VT, and hypotension can occur with intravenous administration. Nausea, lupus-like syndrome (positive ANA with anti-histone antibodies), and agranulocytosis are uncommon, since the oral form is not used anymore.

Intravenous procainamide is very useful in the acute management of supraventricular tachycardia, in particular, rapidly conducted AF and atrial flutter in patients with Wolff-Parkinson-White syndrome. Procainamide can help facilitate pace termination of atrial arrhythmias.[25] Intravenous procainamide is used commonly in the electrophysiology laboratory to unmask Brugada syndrome in patients with resuscitated cardiac arrest or unexplained syncope who have an abnormal baseline electrocardiogram. Procainamide may occasionally have a role in treating monomorphic VT, but this role has been generally supplanted by amiodarone.

Disopyramide

Disopyramide blocks the sodium channel resulting in moderate conduction slowing and has prominent anticholinergic and negative inotropic properties. Disopyramide is available in oral form but is hardly used.

Disopyramide is well absorbed orally (80–90% bioavailable) and undergoes hepatic metabolism, possibly utilizing the CYP3A4 system, to its major metabolite, mono-N-dealkyldisopyramide, and is excreted renally. The drug undergoes variable plasma protein binding (50–65%) which is saturable, and, therefore, measurement of disopyramide plasma concentrations is not useful clinically. The elimination half-life of disopyramide is 6–9 hours. Disopyramide can be removed by hemodialysis.

The primary use of disopyramide is in patients with hypertrophic cardiomyopathy and symptomatic left ventricular outflow tract obstruction as well as to treat vagally-mediated AF. A multicenter study of disopyramide in symptomatic hypertrophic obstructive cardiomyopathy demonstrated that 66% of patients remained asymptomatic at 3 years with a 50% reduction in outflow gradient. No mortality benefit was seen; nevertheless,

disopyramide, if tolerated, should be considered before invasive options, such as surgical myectomy.[26]

Long-term use of disopyramide, however, is limited due to its severe anticholinergic effects (constipation, dry mouth, and urinary retention). It cannot be used in elderly males due to the problem of urinary retention. It can prolong QT interval and cause torsades de pointes. Disopyramide is contraindicated in patients with heart failure due to marked negative inotropic properties. Disopyramide is usually used in a long-acting preparation with dosing between 400 and 600 mg/day.

Class IB Antiarrhythmic Drugs

The only currently available and utilized class IB drugs are lidocaine and mexiletine. As a group, class IB drugs block sodium channels in both open and inactivated states but have a "fast offset" in terms of channel recovery. They slow conduction primarily in ventricular myocardium and have little, if any, effect on atrial myocardium or on AV conduction. The result is shortening of action potential duration and refractoriness. They exhibit use-dependence and have marked effects in depolarized tissues, making them effective in suppression of VT in ischemic myocardium.

Lidocaine

Lidocaine, available intravenously, may be useful to treat patients who have had recurrent VT or VF (especially in the face of acute ischemia).[27] However, it has not been shown to be effective or beneficial (and may be harmful) as a prophylactic drug for patients who have had myocardial infarction.[28-30] It has negligible effects on atrial myocardium, likely attributable to very short atrial action potential duration leaving the atrial sodium channels in the open and inactivated states briefly. Lidocaine slows conduction preferentially in ischemic myocardium and can suppress reentrant arrhythmias. It can alter the excitability threshold and reduces the slope of phase-4 depolarization, thereby, reducing automaticity. Action potential duration is unaffected or shortened and no significant effects on PR interval and QRS duration are seen, whereas QT interval can shorten.

Its pharmacokinetics and dosing are complex. Since it undergoes extensive first pass metabolism in the liver, it can only be administered parenterally. Lidocaine has a rapid initial distribution (α half-life of 8 minutes) and so should be administered with multiple loading doses followed by a maintenance infusion to maintain levels in therapeutic range. The drug has 2 active metabolites, i.e., monoethylglycinexylidide and glycinexylidide that exert modest sodium channel blocking

properties. Up to 70% of the drug is protein bound, and this number increases in the acute phase of a myocardial infarction when the acute phase reactant α1 acid glycoprotein increases. As such, lidocaine levels tend to rise slowly after myocardial infarction. In congestive heart failure, where the central volume of distribution is reduced, lidocaine achieves higher than normal initial concentration and so reduction in loading dose is required to avoid toxicity. Similarly, active binding of lidocaine to α1 acid glycoprotein, whose levels are increased in heart failure, can result in reduced drug availability in heart failure.

Lidocaine has an elimination (β) half-life of about 2 hours and steady state plasma concentrations are reached in 8–10 hours (4–5 hours half-lives). Steady state concentration is determined by hepatic blood flow.[31] Thus, maintenance dose of lidocaine should be reduced in both hepatic failure and congestive heart failure, where hepatic blood flow is decreased. No dosage adjustment is needed in renal dysfunction.

Lidocaine is usually administered as a loading dose followed by a maintenance infusion. A commonly used regimen employs an initial bolus of 75 mg, followed by 50 mg 3 doses at 5 minutes interval for a total loading dose of 225 mg.[32] This method usually achieves and maintains plasma concentrations in the therapeutic range of 1.55 μg/ml. This is followed by a maintenance infusion at 1–4 mg/min. Wide interindividual variability in peak plasma concentration exists and, therefore, patients should be monitored closely for evidence of toxicity during loading.

Lidocaine is most commonly used for acute suppression of potentially life-threatening ventricular arrhythmias, especially in the setting of coronary ischemia. Lidocaine administration in this setting is based more on anecdotal experience than randomized controlled clinical trials. Lidocaine is frequently ineffective, has a narrow therapeutic range, and is frequently associated with neurological toxicity. A review of the randomized trials demonstrated no mortality benefit for lidocaine in this setting.[33] Lidocaine has little effect on atrial tissue, is not useful in treating supraventricular tachycardias, and has little role in treating Wolff-Parkinson-White syndrome.[34]

The most frequent adverse effects of lidocaine are related to the central nervous system and include paresthesias, confusion, drowsiness, perioral numbness, diplopia, dysarthria, nystagmus, and hallucinations. Toxic levels can result in seizures and coma. Lidocaine can worsen conduction in patients with known infranodal conduction abnormalities. Propranolol, metoprolol, and cimetidine can reduce hepatic blood flow, decrease lidocaine

clearance, and concomitant administration can potentially result in lidocaine toxicity.[35,36]

Mexiletine

Mexiletine is an oral congener of lidocaine, with little effects on atrial electrophysiology, hemodynamics, and ventricular function.[37] Mexiletine, almost completely absorbed orally, is primarily metabolized (90%) in the liver by the CYP2D6 system to inactive metabolites and excreted in urine. Renal excretion is pH dependent with increased renal clearance in the presence of acidic urine. Clearance is decreased in the presence of cirrhosis. Mexiletine has a plasma half-life of 9–12 hours and is only available in the oral form in USA.

Mexiletine is used primarily to suppress ventricular arrhythmias and ICD shocks in patients with structural heart disease, either as monotherapy or in combination with another AAD, such as amiodarone. Mexiletine has not been shown to improve survival in high risk patients,[38] and effectiveness of mexiletine in suppressing ventricular arrhythmias varies widely and ranges from 6 to 60%, with majority of studies suggesting a success rate around 20%.[39] Mexiletine may shorten the QT interval and has been used to suppress arrhythmias in patients with the congenital long QT syndrome type III and in those with history of drug-induced torsades de pointes.[40]

Mexiletine is usually initiated at a dose of 150 mg every 8 hours, with slow escalation to maximally effective or maximally tolerated doses. Maximum suggested dose for maintenance is 300 mg 3–4 times a day. Patients with renal failure should be initiated at a lower dose. Dosage adjustment is also advised in patients with hepatic failure. Mexiletine has been combined with quinidine. The combination was once touted as highly effective and less proarrhythmic.[41-46] Sometimes, mexiletine is combined with amiodarone as a synergistic drug in patients who have recurrent VT, but data supporting this approach are scant.[47]

The most common adverse events with mexiletine are gastrointestinal and neurologic, and the side effects can be severe. Tremor, nausea, and vomiting are common, and dizziness, confusion, blurred vision, and ataxia are also seen. Mexiletine-induced tremor may respond to β-blockers. Thrombocytopenia is an uncommon side effect.[48] Neurologic side effects are dose-dependent. Gastrointestinal side effects can be ameliorated by administering the drug with food. Severe bradycardia and abnormal sinus node recovery times have been reported.

The major drug interactions of mexiletine are listed in table 4. Inducers and inhibitors of the CYP2D6 system can influence

mexiletine metabolism and can affect effectiveness and/or toxicity. Plasma theophylline concentrations are increased with coadministration secondary to decrease in theophylline clearance.[49] Digoxin and warfarin levels are unaffected.

Class IC Antiarrhythmic Drugs

Flecainide and propafenone, the currently available class IC drugs, are potent sodium channel blockers with "slow offset" from the sodium channel, resulting in marked conduction slowing in cardiac tissues. Both drugs exhibit marked dose dependency, making them desirable agents in restoration and management of sinus rhythm in AF. At therapeutic doses, class IC drugs prolong PR and QRS intervals without having any significant effects on the QTc interval. In addition, they exhibit negative inotropic effects and can worsen heart failure in patients with left ventricular dysfunction. The use of these drugs is contraindicated in patients with left ventricular dysfunction, marked left ventricular hypertrophy, or any evidence for ischemic heart disease.[50]

Flecainide

Oral flecainide is well absorbed and is predominantly metabolized by CYP2D6 in the liver to inactive metabolites. Flecainide is also excreted renally to some extent and because of this, genetic variations in CYP2D6 does not significantly affect its pharmacological actions. Elimination half-life of flecainide ranges from 10 to 17 hours, permitting twice a day dosing. Flecainide absorption is delayed by milk products. Removal of milk or milk products from diet can result in higher serum levels and toxicity.[51]

Flecainide is highly effective in suppressing a variety of ventricular and supraventricular tachycardias[52] and is one of the most potent drugs to suppress ventricular ectopy.[50] At present, flecainide is most commonly used for restoration and maintenance of sinus rhythm in patients with paroxysmal AF and structurally normal hearts. It appears to be effective for vagally mediated AF. Flecainide is also effective as a "pill-in-the-pocket" drug for AF termination.[53,54] The drug is also used to suppress symptomatic right and left ventricular outflow tract arrhythmias[55] and to treat supraventricular arrhythmias in patients with Wolff-Parkinson-White syndrome.

Flecainide was recently shown to be effective in suppression of polymorphic ectopy and VT in catecholaminergic polymorphic VT (CPVT), an inherited, potentially lethal arrhythmic syndrome resulting from mutations in the ryanodine and calsequestrin receptors, causing abnormal calcium handling. Experimental

work demonstrated that flecainide has direct inhibitory effects on the defective ryanodine receptor-mediated calcium release.[56] Sodium channel blocking effects further reduced triggered activity.

In a multicenter prospective study of 29 symptomatic CPVT patients who received flecainide in addition to conventional therapy, 22 patients (76%) had partial (n = 8) or complete (n = 14) suppression of exercise-induced polymorphic ectopy and/or VT. The mean daily dose of flecainide was 150 mg in those who responded. One patient who had recurrent ICD shocks while on flecainide was found to have a low serum flecainide level. Although not randomized, these results support the utility of flecainide in CPVT.[57] Flecainide may also be beneficial for patients with long QT interval syndrome type III with a specific SCN5A (D1790G) mutation.[58] It is also used in the electrophysiology laboratory to unmask electrocardiographic conduction abnormalities in patients suspected of having Brugada syndrome.[59]

The Cardiac Arrhythmia Suppression Trial I (CAST I) demonstrated that flecainide, when used in postmyocardial infarction patients, increased mortality compared to placebo. Similar results were noted with another, now obsolete, class IC AAD—encainide.[50] In the CAST II trial, moricizine, another class I AAD, was shown to have an early proarrhythmic effect.[60] Based on these findings, class IC drugs are contraindicated in patients with ischemic and structural heart disease.

Several unique forms of proarrhythmias can occur with flecainide. In patients with monomorphic VT, especially if structural heart disease is present, flecainide can result in development of a persistent form of VT that can be impossible to cardiovert. For patients with AF, the AF can "organize" into atrial flutter, and as the flutter is rather slow, there can be one-to-one conduction in the form of a fairly rapid wide-complex tachycardia from bundle branch aberrancy. To prevent this concerning form of "IC" flutter, rate controlling drugs, such as β-blockers or calcium channel blockers are recommended in patients with AF who are started on flecainide.

Oral flecainide is usually initiated at a dose of 50–100 mg twice a day, and slowly titrated to a maximum recommended dose of 300 mg daily. Up to 25% increase in QRS duration is seen at effective doses and is usually evaluated by exercise treadmill testing at high heart rates.[61] A single dose of 300 or 600 mg flecainide is used as a "pill-in-the-pocket" dosing.[62] Serum flecainide levels can be measured, and there is little issue with regard to active metabolites. Lower initial dosing and slow up titration is advised in patients with hepatic and

renal dysfunction. Table 4 lists the major drug interactions of flecainide.

Flecainide is generally well tolerated. Common adverse effects are dose-dependent and include headache, ataxia, and blurred vision. Negative inotropic effects can precipitate heart failure in patients with left ventricular dysfunction.[63] The drug can significantly increase pacing and defibrillation thresholds and so should be used with caution.[64,65] Flecainide is contraindicated in patients with suspected sodium channelopathies like Brugada syndrome, as it can worsen this condition. Additionally, caution should be exercised in patients with advanced His-Purkinje conduction system disease, as infra-Hisian block can result. The current American College of Cardiology/American Heart Association/Heart Rhythm Society (ACC/AHA/HRS) AF guidelines recommend not using flecainide in patients with substantial left ventricular hypertrophy.[53] Flecainide may also increase pacing thresholds.

Propafenone

Propafenone is structurally similar to propranolol but has electrophysiological effects that are similar to flecainide. In addition to being a potent sodium channel blocker, propafenone has β-adrenergic blocking (about 1/30th of the potency of propranolol) and calcium channel blocking properties. Significant β-blocking property is seen in patients who are slow metabolizers of propafenone.[66]

Propafenone is metabolized through the hepatic CYP2D6 pathway into 5-hydroxy propafenone, which blocks sodium channels to a similar degree as the parent compound but lacks significant β-blocking properties. This process, however, is largely genetically determined. Approximately 7% of USA population is deficient in CYP2D6, resulting in very slow conversion of propafenone to 5-hydroxypropafenone, with consequent accumulation of high concentrations of propafenone and significant β-antagonism in poor metabolizers.[67,68] The genetic phenotype, while determining the degree of β-blockade, does not seem to alter the antiarrhythmic effects of propafenone for most patients.

Propafenone is most commonly used to maintain sinus rhythm in patients with paroxysmal or persistent AF who have no underlying structural heart disease. Oral dosing ranges from 150 to 300 mg 2–3 times a day (a long-acting form is available). Peak plasma concentrations are achieved in 1–3 hours following an oral dose and, like flecainide, propafenone increases the PR and the QRS intervals without prolonging the QT interval.

The most common side effects of propafenone are nausea, dizziness, and metallic taste. Neurological side effects like paresthesias and blurred vision are dose-dependent and are more common in poor metabolizers. Enhanced β-blockade resulting from poor metabolism can result in bronchospasm and asthma exacerbations. Sustained VT as a proarrhythmic effect of sodium channel blockade has been reported to occur in patients with structural heart disease and a history of VT. This is uncommon, as the drug is not used in this setting anymore. Propafenone can result in conversion of AF into slow atrial flutter with accelerated, at times 1:1 AV conduction. Therefore, when used for AF, administration of an AV nodal blocking drug along with propafenone is recommended. Propafenone is contraindicated in patients with prior myocardial infarction, known ischemic heart disease, severe ventricular hypertrophy, and history of sustained VT or severe structural heart disease.[53]

Propafenone, by inhibiting CYP2C9, increases the anti-coagulant effect of warfarin by decreasing clearance. Propafenone markedly increases digoxin levels by decreasing nonrenal clearance of digoxin, and concomitant administration is not recommended. Levels of metoprolol[69] and propranolol, which are also metabolized by CYP2D6, are increased in the presence of propafenone. Quinidine, cimetidine, and antidepressants like fluoxetine and paroxetine can all inhibit CYP2D6, thereby, increasing propafenone levels.

Class II Antiarrhythmic Drugs

β-adrenergic blocking drugs are one of the most commonly used drugs in clinical cardiology. β-blockers have antiaarhythmic properties and can reduce the risk of sudden cardiac death, can reduce ventricular arrhythmias in selected patients, inhibit sympathetically-mediated AF, prevent paroxysmal supraventricular tachyarrhythmias of various types, and have additive effects to other AADs. Specifically, β-blockers are efficacious in postoperative AF,[70] arrhythmias in the setting of thyrotoxicosis, suppression of catecholamine-mediated arrhythmias[71] that occur in CPVT, suppress delayed after depolarization mediated idiopathic outflow tract tachycardias, and polymorphic VT in patients with long QT interval syndrome type 1.[40] They are also used to slow AV nodal conduction in patients with rapid atrial tachyarrhythmias, including AF and atrial flutter.[72] In addition, β-blockers exhibit pleiotropic effects, which are translated into survival benefits in patients with heart failure, myocardial infarction, and ischemic heart disease.

By facilitating AV nodal block, β-blockers interfere with the

reentry circuit in patients with AV node reentry and with AV reentry tachycardia.[73] They can suppress automaticity and triggers for atrial tachycardias, AF, and VF. β-blockers can facilitate effectiveness of class I AADs. Furthermore, combination of the class III AAD amiodarone and β-blockers was most effective at preventing potentially life-threatening arrhythmias in an ICD population,[74] although the mechanism by which this occurs is not completely known.

Several β-blockers have central nervous system effects, and this effect depends on lipid solubility. Water-soluble and renally excreted β-blockers (atenolol, nadolol, sotalol, and pindolol) rarely cross the blood-brain barrier, whereas lipid soluble β-blockers (propranolol, metoprolol, acebutolol, and carvedilol) cross the blood-brain barrier easily. Additionally, agents, such as carvedilol, in addition to β-blocking properties and α1 antagonism, can inhibit IKr, IKs, Ito, and the L-type calcium current.[75] Pharmacology and properties of specific β-blockers will be discussed in detail in a separate chapter.

Class III Antiarrhythmic Drugs

Class III AADs prolong repolarization. As a class, they predominantly block cardiac potassium channels [mainly the rapid component of the delayed-rectifier potassium channel (IKr), and to a lesser extent, the slow component of the delayed-rectifier potassium channel (IKs)], resulting in an increase in action potential duration and refractoriness in various cardiac tissues. This makes these agents very useful in interruption of reentrant circuits, whose maintenance is dependent on a critical balance between conduction velocity and refractoriness.Class III agents, such as d, l sotalol (equimolar amounts of dextro and levo isomers) and NAPA, exhibit reverse use-dependence, where the AAD effect is most pronounced during slow heart rates. Quinidine, although classified as a class I AAD, can show reverse use-dependence for the potassium channel but use-dependence for the sodium channel.

Amiodarone, on the other hand, is a class III agent that does not demonstrate reverse use-dependence. In the current era, class III AADs are being used more and more to combat atrial and ventricular arrhythmias, whereas class I AAD use has faded.

Sotalol

Sotalol is a class III AAD with nonselective β-blocking properties. The currently available form is a racemic mixture of d- and l-stereoisomers. The dextro isomer of sotalol is a pure class III agent whereas the levo isomer is responsible for the β-blocking

properties. This combination thus results in sinus slowing, decrease in AV nodal conduction (prolongs PR and Atrial-His interval (AH)), and increased refractoriness in atria, AV node, ventricle (prolongs QT interval), and accessory pathways. Sotalol is a competitive β-blocker and the β-blocking properties are pronounced at lower doses. Sotalol exhibits a modest negative inotropic effect.

Oral bioavailability of sotalol is almost 100%. Peak concentrations are seen in 2.5–4 hours following a dose. The elimination half-life is 12–16 hours and the drug is excreted unchanged by the kidneys. Renal insufficiency results in drug accumulation, increasing the risk of torsades de pointes.

Sotalol is available in USA only in the oral form. Usual starting dose of sotalol is 80 mg twice a day with gradual increase up to 240–320 mg daily, provided the QTc is within accepted limits (<500 milliseconds (ms)). The effects on repolarization are dose-dependent and tend to occur at doses exceeding 80 mg twice a day in patients with normal renal function. Given the potential for torsades de pointes, sotalol should be started in the hospital, and the following proposed dosing algorithm is employed in patients with renal insufficiency (Table 6). Hepatic insufficiency does not require dosage adjustment. Substantial β-blocking effects makes the drug unsuitable in patients with heart failure and severe left ventricular dysfunction, with approximately 3.3% incidence of heart failure or pulmonary edema.[76]

The combined class III and β-blocking properties make sotalol effective for a wide range of supraventricular and ventricular arrhythmias.[77] Sotalol is most commonly used as a rhythm control agent to maintain sinus rhythm in AF and to suppress VT in patients with ICDs. Sotalol, unlike amiodarone, tends to decrease defibrillation thresholds modestly.

The Survival With Oral d-Sotalol (SWORD) trial tested the effect of d-sotalol, a pure class III drug and one that is no longer available vs. placebo, on mortality in patients with previous myocardial infarction and a left ventricular ejection fraction

TABLE 6

Dose of Sotalol with Respect to Creatinine Clearance	
Creatinine clearance (mL/min) (Measured by Cockroft-Gault method)	*Dosing frequency*
>60	Every 12 hours
30–60	Every 24 hours
10–30	Every 36–48 hours
<10	Individualize

≤40%. The trial was stopped prematurely due to increased mortality, primarily from arrhythmic death in the d-sotalol arm.[78] In another multicenter, double-blind study of 1,456 patients with recent myocardial infarction randomized to d, l-sotalol 320 mg once a day vs. placebo, the mortality rate at 1-year follow-up was not statistically different (8.9% in the sotalol group vs. 7.3% in the placebo group). The reinfarction rate, however, was 41% lower in the sotalol group ($p < 0.05$) and was attributed to the β-blocking properties of d, l-sotalol.[79]

In the Electrophysiologic Study Versus Electrocardiographic Monitoring (ESVEM) trial, a randomized, multicenter trial, primarily designed to determine the best method to guide AAD therapy for patients who had malignant ventricular arrhythmias, sotalol was effective in 31% of the patients, which was the best among the different AADs tested.[80] ESVEM, however, did not test amiodarone or ICDs. Sotalol has been shown to be effective in an ICD population where, when compared to placebo, significantly reduced the number of both appropriate and inappropriate ICD shocks and remains one of the commonly used agents for VT in the ICD population.[81]

The Sotalol Amiodarone AF Efficacy Trial (SAFE-T), a randomized, double-blind, placebo controlled trial that compared sotalol vs. amiodarone in restoration and maintenance of sinus rhythm in patients with persistent AF, randomized 665 patients to sotalol (n = 261), amiodarone (n = 261), and placebo (n = 137) who were followed for 1–4.5 years with weekly monitoring. Sotalol and amiodarone were equally efficacious in converting AF to sinus rhythm (24% in sotalol group vs. 27% in amiodarone group), and both were superior to placebo. The median time to AF recurrence, the primary end-point was 487 days in the amiodarone group when compared to 74 days in the sotalol group and 6 days in the placebo group. Amiodarone was clearly superior to sotalol and placebo for maintenance of sinus rhythm, except in the subgroup of patients with ischemic heart disease, where sotalol was equally effective as amiodarone. Major adverse events were comparable among the 3 groups.[82]

Sotalol can result in QTc prolongation of 10–40 ms at doses ranging from 160 to 240 mg/day. In the real world, sotalol toxicity is of particular concern in a situation where patients receive concomitant diuretics with frequent dose changes and inadequate potassium replacement. The overall incidence of torsades de pointes appears to be 2% and is more common in females, structural heart disease, and is exacerbated by hypokalemia, renal insufficiency, doses >320 mg/day, recent cardioversion, bradycardia, and concomitant use of other AADs or QT-prolonging

agents. β-blocker induced adverse effects, such as bronchospasm, masking of hypoglycemia, and rebound tachycardia and hypertension on drug withdrawal may also be seen with sotalol.

Dofetilide

Dofetilide is a potent and selective oral IKr blocker that prolongs action potential duration and refractoriness, more so in the atrium than in the ventricle.[83] IKr blockade by dofetilide exhibits reverse use-dependence. Dofetilide does not exhibit any negative inotropic properties and has no effect on conduction velocity or hemodynamics.

Oral bioavailability of dofetilide exceeds 90%. Peak plasma concentrations are attained in 2–3 hours following a dose and slightly longer if the drug is taken with food. Dofetilide is excreted predominantly (80%) in the urine with an elimination half-life of 8–10 hours and partially metabolized by hepatic CYP3A4 to inactive metabolites. Drug accumulation results in renal failure, necessitating dosage adjustment and/or discontinuation. Similarly, drug that inhibits CYP3A4 can increase dofetilide concentrations and can potentially lead to adverse effects.[84]

Dofetilide is used primarily for the restoration and maintenance of sinus rhythm in AF, especially in patients with structural heart disease. Dofetilide, like amiodarone has a neutral effect on mortality when used in patients with structural heart disease and left ventricular dysfunction. The Danish Investigations of Arrhythmia and Mortality on Dofetilide (DIAMOND) trial, which evaluated dofetilide vs. placebo on all-cause mortality in 1,518 patients with symptomatic congestive heart failure and severe left ventricular dysfunction, demonstrated no difference in all-cause mortality between the two arms. A significant decrease in the risk of heart failure hospitalization was observed in the dofetilide group. In patients with AF, dofetilide was significantly more effective in maintaining sinus rhythm than placebo (hazard ratio (HR) 0.35; 95% confidence interval (CI) 0.22–0.57; $p < 0.001$). There was a high incidence of torsades de pointes in the dofetilide group (3.3%; n = 25) when compared to the placebo group.[85]

Given the risk of torsades de pointes, dofetilide prescribing is highly regulated[86]and physicians are required to receive special training prior to prescribing dofetilide. The recommended dosage of dofetilide is 500 μg twice a day, but this is determined by baseline renal function. The drug has to be initiated in the hospital with continuous electrocardiographic monitoring for either 3 days or 12 hours after conversion to sinus rhythm, whichever is greater. Creatinine clearance needs to be measured (using the Cockroft-Gault formula) prior to initiation. A 500 μg twice a day dosing is

TABLE 7

Dose of Dofetilide with Respect to Creatinine Clearance	
Creatinine clearance (mL/min) (measured by Cockroft-Gault method)	*Dosing frequency*
>60	500 μg twice a day
40–60	250 μg twice a day
20–39	125 μg twice a day
<20	Contraindicated
Hemodialysis	Contraindicated

initiated only in patients with creatinine clearance >60 mL/min. The renal dosing algorithm for dofetilide is shown in table 7. Once initiated, if the QTc at 2–3 hours following the first dose is >15% from baseline or >500 ms (>550 ms for bundle branch block or intraventricular conduction delay), then the dose needs to be cut in half. If the QTc is >500 ms (>550 ms for bundle branch block or intraventricular conduction delay) at any time during doses 2–6, dofetilide needs to be discontinued and an alternative agent sought.

The major adverse effect of dofetilide is torsades de pointes, the incidence of which is dose-dependent and is also influenced by structural heart disease, renal insufficiency, and concomitant use of QT-prolonging medications.[85,87] The overall incidence during maintenance therapy at 500 μg twice a day is around 1.7%.[88] Verapamil, trimethoprim, thiazides, azole antifungals, and cimetidine should be discontinued prior to dofetilide initiation, as concomitant administration results in markedly elevated plasma concentrations of dofetilide and increases risk of torsades de pointes.[84] Inducers of CYP3A4, such as phenobarbital and rifampicin, can enhance dofetilide metabolism and decrease its efficacy. Dofetilide does not interact with digoxin or warfarin.

Ibutilide

Ibutilide is a methane sulfonamide analog of sotalol that is a potent IKr blocker, resulting in prolongation of action potential duration and refractoriness. Experimental studies have also shown ibutilide to be an inducer of the slow inward sodium current.[89] No significant effects on heart rate, PR interval, or QRS duration is noted. Ibutilide is currently approved for rapid conversion of recent-onset AF and atrial flutter and is only available for intravenous use.

The Ibutilide Repeat Dose Study, a multicenter trial that randomized 266 patients with AF or atrial flutter of recent onset (3–45 days) to ibutilide or matching placebo, demonstrated a conversion rate of 47% with ibutilide vs. 2% with placebo

($p < 0.0001$), with the drug being more efficacious in atrial flutter than in AF (63 vs. 31%; $p < 0.0001$). Following infusion, the mean time to cardioversion was 27 minutes. Of concern was the high incidence (8.3%) of torsades de pointes in the ibutilide arm.[90] Ibutilide is useful in improving the success of subsequent cardioversion when the initial attempt is followed by immediate return of AF.[91] Ibutilide is also effective in patients with AF and rapid conduction down an accessory pathway, by virtue of conversion of AF to sinus rhythm as well as by increasing accessory pathway refractoriness.[92]

Recommended intravenous dose is 1 mg to be given over 10 minutes. A second 1 mg dose, separated from the first dose by 10 minutes, can be given if the atrial arrhythmia persists. The elimination half-life is ~6 hours (range 2–12 hours) and the drug is primarily metabolized by the liver. No dosage adjustments are recommended for hepatic or renal dysfunction.

The major side effect of ibutilide is QTc prolongation and torsades de pointes, which developed in 8.3% of patients in the Ibutilide Repeat Dose Study.[90] Because of this, patients receiving ibutilide must have continuous electrocardiographic monitoring for at least 4–6 hours following treatment, with skilled personnel and resuscitation equipment on standby. Given higher risk of torsade de pointes, ibutilide should be avoided in patients with prolonged baseline QTc (>440 ms), advanced structural heart disease, and marked hypokalemia or hypomagnesemia.

Use of ibutilide for pharmacological cardioversion of AF or atrial flutter was never popular, given the modest efficacy, risk of torsades de pointes, and the need for close monitoring following drug administration. Concurrent administration of intravenous magnesium appears to improve efficacy and safety of ibutilide.[93-97] A better method to improve the safety and efficacy of ibutilide was addressed in a recent randomized trial that assigned patients with recent onset AF to receive ibutilide alone or a combination of ibutilide and esmolol. The study demonstrated that intravenous β-blockade significantly improved the conversion rate (67% for the combination vs. 46% for ibutilide alone) with marked improvement in the safety profile (no cases of polymorphic VT in the combination group vs. 6.5% in the ibutilide group).[98] This combination of ibutilide and esmolol, along with newer agents like vernakalant, may result in an expanded role for pharmacological agents in acute conversion of rapid AF.[99]

Amiodarone

Amiodarone is structurally similar to thyroxine. It is an iodinated benzofuran derivative that was initially identified during work on

the *Ammi visnaga* plant and became popular as an antianginal agent in Europe in the 1960s.[100]

Although classified as a class III AAD, amiodarone is a complex drug that is essentially in a "class of its own" due to electrophysiologic properties spanning all 4 Vaughan Williams classes. In addition to its multichannel blocking properties, amiodarone interacts with and can block cell surface receptors and various other molecules. To date, the exact mechanism responsible for the antiarrhythmic actions of amiodarone remains unclear. Animal experiments have shown amiodarone to prolong action potential duration and refractoriness in the atria, ventricles, AV node, and His-Purkinje system.[101] Amiodarone tends to have a potent effect on prolongation of the action potential and repolarization uniformly and perhaps for this reason, the risk of torsades de pointes is low. It also blocks inactivated sodium channels, slows phase 4 depolarization in sinus node, and delays AV nodal conduction.[102] Amiodarone blocks α- and β-receptors in a noncompetitive fashion, blocks L-type calcium channels, and blocks conversion of thyroxine to triiodothyronine. Intravenous administration can result in coronary and peripheral vasodilatation.

Amiodarone is available in oral and intravenous forms with each formulation exhibiting differing electrophysiological properties. During intravenous use, amiodarone exhibits sodium and calcium channel blocking properties, exhibits use-dependence, and has a greater effect in depolarized tissues, making it very useful in treatment of ischemic ventricular arrhythmias. Oral maintenance therapy with amiodarone predominantly prolongs action potential duration and refractoriness but does not exhibit reverse use-dependence.

Amiodarone is highly lipophilic with a large volume of distribution that averages 60 L/kg (range: 20–200 L/kg).[103] Oral bioavailability is highly variable and is approximately between 35 and 65% and peak plasma concentrations are achieved 3–7 hours after an oral dose. A dose of >10 g, which is usually needed to saturate the fat stores, requiring weeks before a steady state is reached. Elimination is by hepatic excretion into bile. Amiodarone is metabolized by the liver to its major metabolite, desethylamiodarone. The plasma half-life after intravenous administration ranges from 4.8 to 68.2 hours.[104] Therapeutic plasma levels range, from 1 to 2.5 μg/mL, can be measured but does not correlate well with clinical efficacy. Elimination is slow and extremely variable with a half-life ranging from 13 to 103 days. There is negligible renal excretion and so no dosage adjustment is needed in renal disease. Amiodarone

and desethylamiodarone cannot be removed by peritoneal or hemodialysis. It is a potent inhibitor of CYP3A4, CYP2C9, and p-glycoprotein, resulting in significant drug-drug interactions.

Amiodarone is widely used for the management of both atrial and ventricular arrhythmias despite the fact that the drug is currently FDA approved only for refractory, life-threatening ventricular arrhythmias. Clinical data supporting the use of amiodarone for both atrial and ventricular arrhythmias as well as for primary and secondary prevention of sudden cardiac death are discussed below.

The impact of amiodarone in outcomes postmyocardial infarction was evaluated in the European Myocardial Infarction Amiodarone Trial (EMIAT)[105] and Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT).[106] EMIAT randomized 1,486 postmyocardial infarction patients with a left ventricular ejection fraction <40% to receive either amiodarone (n = 743) or matching placebo (n = 743). Presence of ventricular arrhythmia was not needed for inclusion. After a mean follow-up of 21 months, a 35% risk reduction ($p < 0.05$) in arrhythmic death was seen in the amiodarone group but no difference in all-cause or cardiovascular death was seen.[105]

In CAMIAT, 1,202 patients who were 6–45 days after a myocardial infarction and had a mean of at least 10 premature ventricular contractions (PVCs)/hour were randomly assigned to amiodarone (n = 606) or placebo (n = 596) and followed for a mean of 1.8 years. When compared to placebo, patients in the amiodarone group had a 48.5% reduction ($p = 0.016$) in the combined end-point of resuscitation from VF or arrhythmic death (3.3% in the amiodarone group vs. 6.6% in the placebo group). Like EMIAT, there was no significant difference in all-cause mortality ($p = 0.13$) between the two groups.[106]

EMIAT and CAMIAT demonstrated that amiodarone given postmyocardial infarction can reduce arrhythmic death and had a neutral effect on total mortality. A pooled *post hoc* analysis of EMIAT and CAMIAT demonstrated that the combination of amiodarone with a β-blocker significantly improved arrhythmic death or resuscitated cardiac arrest when compared to β-blockers alone, amiodarone alone, or placebo. Nonsignificant reductions in total mortality were noted with the combination when compared to those not receiving β-blockers.[107]

Estudio Piloto Argentino de Muerte Súbita y Amiodarone (EPAMSA), Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina (GESICA), and Congestive Heart Failure Survival Trial of Antiarrhythmic Therapy (CHF-STAT) were

randomized trials that evaluated the role of amiodarone in patients with congestive heart failure.[108-110] EPAMSA randomized patients with a left ventricular ejection fraction ≤35% and asymptomatic ventricular arrhythmias to receive either amiodarone (n = 66) or placebo (n = 61) and demonstrated a significant reduction in total mortality (10.6 vs. 28.8%, p = 0.02) and sudden death (7 vs. 20.4%, p = 0.04) in patients receiving amiodarone compared to placebo.[108]

GESICA was a multicenter, randomized trial of 516 patients in Argentina with congestive heart failure and left ventricular systolic function ≤35% but no history of symptomatic ventricular arrhythmias. Only 39% of the patient population had ischemic cardiomyopathy. Compared to placebo, amiodarone resulted in a 28% reduced risk of death and a 31% reduced risk of heart failure hospitalizations.[109]

In CHF-STAT, 647 patients with congestive heart failure, a left ventricular ejection fraction ≤40%, and at least 10 PVCs/hour, were randomized to amiodarone (n = 336) or placebo (n = 338). Over a median follow-up of 45 months, amiodarone was associated with PVC suppression and improved left ventricular function, but no significant difference in total mortality or sudden death was found between the two groups.[110] Discontinuation rate for amiodarone in these studies ranged from 20 to 40%. The higher percentage of ischemic cardiomyopathy in CHF-STAT is a potential reason for differences in outcomes in CHF-STAT vs. EPAMSA and GESICA.

A meta-analysis of 15 randomized controlled trials (n = 8,522) of amiodarone vs. placebo for prevention of sudden cardiac death demonstrated that amiodarone was associated with a 29% reduced risk of sudden cardiac death (7.1 vs. 9.7%; OR 0.72, p< 0.001) and an 18% reduced risk of cardiovascular death (14.0 vs. 16.3%; OR 0.82, p = 0.004). No significant difference in all-cause mortality was demonstrated. The modest improvement in cardiac and arrhythmic death came at a cost as patients who received amiodarone had a significantly higher incidence of thyroid problems (OR 5.68; p < 0.0001), hepatotoxicity (OR 2.1; p = 0.015), lung toxicity (OR 1.97; p = 0.002), and bradyarrhythmias (OR 1.78; p = 0.008) when compared to the control group.[111]

In summary, amiodarone is beneficial to treat ventricular arrhythmias in patients with structural heart disease and is a reasonable option for secondary prevention of sudden cardiac death in patients who either refuse or are not otherwise candidates for an ICD. Currently, however, the most common use for amiodarone in patients with structural heart disease is to suppress recurrent episodes of VT and VF leading to ICD shocks. Amiodarone can increase the defibrillation threshold in ICD patients, but the effects may be modest.[64,74] Amiodarone can

also slow VT rates to below the programmed detection limits for the ICD.[64]

Amiodarone remains the most potent AAD to maintain sinus rhythm in patients with AF. This was shown clearly in the Canadian Trial of AF (CTAF), a prospective, multicenter trial that randomized 403 patients with at least 1 episode of AF in the past 6 months to receive amiodarone or either, sotalol or propafenone. Patients were followed for a mean of 16 months with the primary end-point being first recurrence of AF. The primary end-point was reached in 35% of patients in the amiodarone group vs. 63% in the sotalol or propafenone groups ($p < 0.001$). Adverse reactions were higher in the amiodarone group (18 vs. 11% in the sotalol/propafenone group) but were not statistically significant.[112]

Amiodarone was equally efficacious as sotalol in restoring sinus rhythm but was vastly superior to sotalol in maintaining sinus rhythm, with major adverse events comparable to placebo.[82] A Cochrane database review of 45 randomized controlled studies (n = 12,559) that evaluated the different AADs used for rhythm control of AF demonstrated that class IA, class IC, and class III drugs all demonstrated a significant reduction in AF recurrence (odds ratio 0.19–0.60, number needed to treat: 2–9) compared to placebo, but none improved mortality. Class IA drugs actually increased mortality and all drugs, except propafenone and amiodarone, increased proarrhythmic risk.[7]

Given huge volume of distribution, a loading dose regimen is essential to ensure onset of therapeutic action within a reasonable timeframe. Loading can be via the intravenous or oral route. The manufacturer recommended intravenous infusion regimen follows 3 phases over 24 hours: 150 mg over 10 min (with an additional bolus dose of 150 mg for patients with recurrent VT), followed by 1 mg/min over the next 6 hours, followed by 0.5 mg/min over next 18 hours.

Even with intravenous loading, the actual class III electrophysiological effects do not necessarily take place for several days. Alternatively, if possible, oral loading with high dosages can be useful for patients with recurrent VT and those patients for whom AF is highly problematic. In the hospital, oral loading can be initiated with doses as high as 600 mg thrice a day for up to 7–10 days. At this high dose, various neurological and gastrointestinal side effects may be observed.

For outpatient initiation, we routinely employ a loading regimen (400 mg three to four times a day) that ensures a 10–15 g loads within 7–10 days after initiation. Following completion of the loading period, the patient is switched to a maintenance dose

of 200 mg/day for AF and 400 mg a day for secondary prevention of VT.

Intravenous amiodarone infusion should preferably be through a central line to avoid risk of phlebitis and cellulitis in the event of extravasation. Hypotension is common with intravenous use and should be monitored closely. Chronic oral therapy with amiodarone is reasonably well-tolerated, provided close attention is paid to screen for and recognize adverse events.[113]

Side effects are common and can range from 15% in the first year to 50% with long-term use. Amiodarone prolongs PR, QRS, and QT intervals, but the incidence of torsades de pointes is extremely rare, perhaps, resulting from multichannel and β-blocking properties.[114] No significant negative inotropic effects are seen at maintenance doses. Sinus bradycardia and AV block can occur.[113]

Amiodarone has significant extracardiac side effects, with the most serious one being interstitial pneumonitis leading to pulmonary fibrosis.[115] The incidence of pulmonary fibrosis ranges from 1 to 7% and is very difficult to predict and challenging to detect with reduction in diffusion capacity for carbon monoxide (DLCO) being the best screening test.[115,116] Thyroid problems are common, and both hyper-and hypothyroidism can occur. Hepatotoxicity can occur but rarely progresses to cirrhosis. Other significant extracardiac side effects include hypersensitivity to the sun, bluish skin discoloration, central and peripheral neurological effects (weakness, difficulty walking especially in the elderly), and rarely, optic neuritis resulting in vision loss. Almost all patients on chronic amiodarone therapy develop corneal micro-deposits, but these are of little clinical importance.[113]

Majority of the adverse reactions secondary to amiodarone can be easily managed and do not necessitate drug discontinuation. Since most side effects of amiodarone depend, inpart, on the dose and the duration of therapy, the lowest possible effective dose should be used for chronic maintenance therapy. Despite this, regular screening for adverse events is essential. At initiation of therapy, all patients should have a 12-lead electrocardiogram, chest x-ray, pulmonary function test with DLCO, and laboratory evaluation for electrolytes and renal function, liver function, and thyroid function. An ophthalmological evaluation is recommended at baseline if there is visual impairment and a follow-up evaluation should be done for new eye-related symptoms. Liver function and thyroid function tests are assessed every 6 months. An electrocardiogram and a chest x-ray should be repeated yearly. Follow-up pulmonary function tests should be done for new or

unexplained dyspnea or if there are abnormalities in the chest x-ray compared to baseline.[113]

Amiodarone increases serum levels of digoxin, quinidine, procainamide, flecainide, cyclosporine, and warfarin. It also decreases statin metabolism through CYP3A4, resulting in increased statin levels and increasing risk of myopathy. Warfarin as well as statin dose should be reduced in half and digoxin should be discontinued if a patient is started on amiodarone. The major drug interactions of amiodarone are listed in table 4.

Dronedarone

Dronedarone is structurally similar to amiodarone except that it lacks the iodine moiety and was developed with idea of maintaining potency while eliminating amiodarone-induced systemic toxicity attributable to the iodine moiety. Although it has multichannel blocking properties similar to amiodarone,it is far less potent in maintenance of sinus rhythm in AF. For clinical purposes, dronedarone is classified as a Vaughan Williams class III AAD but exhibits myriad electrophysiological properties including inhibitory effects on the rapid delayed rectifier, slow delayed rectifier, acetylcholine-activated, inward rectifier potassium channels, inward sodium current, T- and L-type calcium channels, and α- and β-adrenoceptors.[117,118] Suppressed sinus node automaticity and alteration of the slope of phase 4 depolarization in the sinus node results in sinus slowing.[119] Dronedarone also slows AV conduction, increases AV nodal and ventricular effective refractory period and has been shown to reduce VT and PVCs in ischemic animal models.[117,120]

Dronedarone has negligible proarrhythmic effect but has been shown to increase mortality and heart failure hospitalization in patients with acute heart failure, severe left ventricular dysfunction, and high-risk patients with permanent AF.[121,122] When compared to amiodarone, dronedarone appears devoid of pulmonary, hepatic, thyroid, and neurological toxicity. Like amiodarone, dronedarone causes mild increase in serum creatinine without affecting the glomerular filtration rate. This is secondary to inhibition of the renal tubular cation transport.[123]

Dronedarone is metabolized by the hepatic CYP3A4 system. Dronedarone, in turn, is an inhibitor of the CYP3A4, CYP2D6, and P-glycoprotein systems. These inhibitory properties can result in increased levels of drugs like cyclosporine, digoxin, and some statins when coadministered with dronedarone.[123] No drug interactions with warfarin have been reported.

Several randomized trials have evaluated the role of dronedarone in AF and heart failure.[2,121,122,124-127] These are listed in table 8 and the recent major trials are summarized below.

TABLE 8

Summary of Randomized Clinical Trials that Assessed the Efficacy and Safety of Dronedarone in Patients with Atrial Fibrillation and Heart Failure

Clinical trial	*Patient profile*	*Numbers of patient*	*Intervention (mg)*	*Primary end-point*	*Follow up (month)*	*Results*
DAFNE[124]	Persistent AF post-cardioversion	199	Dronedarone (400–800 BD) vs. placebo	Time to first recurrence of AF	6	Use of dronedarone associated with longer median time to AF recurrence (60 vs. 5.3 days for dronedarone and placebo, respectively, p = 0.026; 55% relative risk reduction, p = 0.001); likewise, patients receiving dronedarone, 400 mg orally twice a day, more likely to maintain sinus rhythm compared with patients receiving placebo
EURIDIS[127]/ ADONIS[127]	Paroxysmal AF	1,237	Dronedarone (400 BD) vs. placebo	Time to first recurrence of AF	12	Dronedarone significantly lengthened the time to AF recurrence (41 vs. 96 days [EURIDIS] and 59 vs. 158 days [ADONIS] for dronedarone and placebo, respectively), as well as symptoms associated with atrial fibrillation, compared with placebo. Ventricular rates during AF recurrence were significantly lower with dronedarone
DIONYSOS[125]	Persistent AF for >3 days	504	Dronedarone (400 BD) vs. amiodarone (600 and then 200/day)	AF recurrence or drug intolerance resulting in discontinuation	7	More patients on dronedarone had AF recurrence or stopped the drug due to intolerance or lack of efficacy compared with patients receiving amiodarone (75.1 vs. 58.8% for dronedarone and amiodarone, respectively, HR 1.59).

(continued)

Table 8 *(continued)*

Clinical trial	*Patient profile*	*Numbers of patient*	*Intervention (mg)*	*Primary end-point*	*Follow up (month)*	*Results*
ERATO[126]	Permanent AF with ventricular rates > 80 bpm on rate-controlling agents	630	Dronedarone (400 BD) vs. placebo	Mean ventricular rate at 2 weeks	1	Dronedarone use associated with decrease in ventricular rate, at rest (12.3 bpm with dronedarone vs. 0.2 bpm with placebo) and with exercise (25.6 bpm with dronedarone vs. 2.2 bpm with placebo)
ATHENA[2]	Paroxysmal or persistent AF or atrial flutter with one or more associated risk factors	4,628	Dronedarone (400 BD) vs. placebo	Composite of all-cause mortality and cardiovascular hospitalization	21 ± 5	The use of dronedarone was associated with decreased cardiovascular deaths and arrhythmic deaths compared with placebo (31.9% in dronedarone arm vs. 39.8% in placebo arm, HR 0.76). There was also a decrease in hospitalizations for AF and acute coronary syndrome in patients receiving dronedarone compared with placebo
ANDROMEDA[122]	Congestive heart failure (NYHA Class III-IV); left ventricular ejection fraction < 35%	627	Dronedarone (400 BD) vs. placebo	All-cause mortality or heart failure hospitalization	2	Trial stopped early. Dronedarone associated with increase in all-cause mortality (8.1% in the dronedarone arm vs. 3.8% in placebo arm, HR 2.13)

(continued)

Table 8 *(continued)*

Clinical trial	*Patient profile*	*Numbers of patient*	*Intervention (mg)*	*Primary end-point*	*Follow up (month)*	*Results*
PALLAS[121]	Permanent AF with high risk for vascular events	3,236	Dronedarone (400 BD) vs. placebo	Composite of stroke, mayocardial infarction, systemic embolism, or death from cardiovascular causes	~1 year	Trial stopped early due to safety concerns. Primary outcome occurred in 43 patients in the dronedarone arm when compared to 19 in the placebo arm (HR 2.29; 95% CI 1.34–3.94; p = 0.002). Cardiovascular deaths, arrhythmic deaths, stroke, and heart failure hospitalizations were higher in the dronedarone arm when compared to placebo

DAFNE, the phase II Dronedarone Atrial FibrillatioN study after Electrical cardioversion; EURIDIS/ADONIS, European Trial In Atrial Fibrillation Or Flutter Patients Receiving Dronedarone For The Maintenance of Sinus Rhythm/American-Australian-African Trial With Dronedarone In Atrial Fibrillation/flutter Patients For The Maintenance of Sinus Rhythm studies; DIONYSOS, the Efficacy & Safety of Dronedarone vs. Amiodarone for the Maintenance of Sinus Rhythm in Patients With Atrial Fibrillation study; ERATO, the Efficacy and safety of dRonedArone for the cOntrol of ventricular rate during atrial fibrillation study; ATHENA, A Placebo-Controlled, Double-Blind, Parallel Arm Trial to Assess the Efficacy of Dronedarone 400 mg BD for the Prevention of Cardiovascular Hospitalization or Death from Any Cause in Patients with Atrial Fibrillation/Atrial Flutter trial; ANDROMEDA, Antiarrhythmic Trial with Dronedarone in Moderate to Severe Congestive Heart Failure Evaluating Morbidity Decrease; PALLAS, the Permanent Atrial Fibrillation Outcome Study Using Dronedarone on Top of Standard Therapy trial; NYHA, New York Heart Association; BD, twice a day; AF, atrial fibrillation; HR, hazard ratio; CI, confidence interval.

The ATHENA (A Placebo-Controlled, Double-Blind, Parallel Arm Trial to Assess the Efficacy of Dronedarone 400 mg BD for the Prevention of Cardiovascular Hospitalization or Death from Any Cause in Patients with Atrial Fibrillation/Atrial Flutter) trial assessed the effect of dronedarone in reducing a composite end-point of death or cardiovascular hospitalizations in 4,628 paroxysmal or persistent AF patients who had risk factors for stroke and/death.[2] Patients were randomized to dronedarone or placebo and were followed for a median of 21 ± 5 months. Fewer cardiovascular deaths (HR = 0.71; 95% CI 0.51–0.98; p = 0.03), arrhythmic deaths (HR = 0.55; 95% CI 0.34–0.88; p = 0.01), as well as cardiovascular hospitalizations were seen in the dronedarone arm when compared to placebo. A *post hoc* analysis of ATHENA demonstrated that patients randomized to dronedarone had significantly less incidence of strokes or transient ischemic attacks.[128] ATHENA was the first trial to demonstrate mortality benefit for an AAD in AF. Based on the study results, dronedarone was approved for use in USA.

Another trial told a completely different story. The ANDROMEDA (Antiarrhythmic Trial with Dronedarone in Moderate to Severe Congestive Heart Failure Evaluating Morbidity Decrease) trial compared dronedarone with placebo in AF patients hospitalized with new or worsening congestive heart failure and a left ventricular ejection fraction <35%.[122] The study was terminated after a median follow-up of 2 months, as there was a significant increase in mortality in the dronedarone arm (8.1 vs. 3.8% in the placebo arm), that was secondary to worsening heart failure and treatment with dronedarone was the most powerful predictor of death. ANDROMEDA resulted in a black box warning for dronedarone that warns against its use in patients with New York Heart Association (NYHA) class IV heart failure or NYHA class II and III heart failure with recent decompensation requiring hospitalization or referral to a heart failure clinic.[123]

The drug manufacturer recently released postmarketing follow data that reported several cases of hepatocellular injury and at least 2 cases of acute hepatic failure requiring liver transplantation. These cases occurred 4.5–6 months following drug initiation, prompting a manufacturer recommendation to consider serial liver enzyme monitoring at least for the first 6 months while being on dronedarone.[129]

The effectiveness of dronedarone in improving hard clinical end-points in the low risk AF population in the ATHENA prompted the Permanent Atrial Fibrillation Outcome Study Using Dronedarone on Top of Standard Therapy (PALLAS) trial, which hypothesized that dronedarone will reduce major

vascular events in patients with permanent AF who were at high risk for vascular events. The study randomized patients ≥65 years with at least 6 months of permanent AF and risk factors for major vascular events to dronedarone or placebo. The primary end-point was a composite of stroke, myocardial infarction, systemic embolism, or death from cardiovascular causes. After enrollment of 3,236 patients, the trial was stopped due to safety concerns, as the primary outcome occurred in 43 patients in the dronedarone arm when compared to 19 in the placebo arm (HR 2.29; 95% CI 1.34–3.94; p = 0.002). Cardiovascular deaths, arrhythmic deaths, stroke, and heart failure hospitalizations were significantly higher in the dronedarone arm when compared to placebo. The study concluded that dronedarone should note used in high-risk patients with permanent AF.[121] The results of this study prompted a recent label revision on dronedarone (December 2011) from the USFDA. The following changes have been recommended:

- Health care professionals should not prescribe dronedarone to patients with AF who cannot or will not be converted into normal sinus rhythm (permanent AF), because dronedarone doubles the rate of cardiovascular death, stroke, and heart failure in such patients
- Health care professionals should monitor cardiac rhythm by electrocardiogram at least once every 3 months. If the patient is in AF, dronedarone should be stopped or, if clinically indicated, the patient should be cardioverted. Dronedarone is indicated to reduce hospitalization for AF in patients in sinus rhythm with a history of nonpermanent AF
- Patients prescribed dronedarone should receive appropriate antithrombotic therapy.[130]

It would be fair to say that dronedarone, at the present moment, is at the crossroads in terms of its role in AF. Although not a very effective rhythm control agent by itself, it was the first AAD to show a reduction in cardiovascular mortality in low risk, predominantly paroxysmal AF patients. This resulted in the 2011 ACC/AHA/HRS focused update of the 2006 AF guidelines, including dronedarone as the first line agent in the rhythm control arm for paroxysmal AF in patients without structural heart disease.[53]

The favorable safety profile as well as the fact that a loading dose is not needed made dronedarone an ideal drug to start as an outpatient. The fact that it improves mortality and reduces cardiovascular hospitalizations in patients with AF makes it attractive from a health care expenditure standpoint. However, reports of fulminant hepatic failure cast doubts on the purported

safety profile. Debate also centered around whether mortality reduction, as compared to symptom reduction as well as improving quality of life, is a clinically meaningful end-point in the treatment of AF management.

Furthermore, the ANDROMEDA trial clearly demonstrated that dronedarone did not belong in AF management in patients with congestive heart failure and severe left ventricular dysfunction.[122] With the recent results of the PALLAS trial[121] showing increased mortality in high-risk patients with permanent AF, the clinician is confused as to "where the buck stops" with respect to treating an AF patient with dronedarone. No clear understanding exists at the present moment as to the mechanisms behind the markedly different effects of dronedarone depending upon the patient's vascular risk.[131] In summary, although it is fair to say that dronedarone has definitely expanded the horizon in terms of management options for AF, more studies are needed to understand the mechanisms underlying the diametrically opposite effects of this drug in low risk vs. high-risk AF patients.

Azimilide

Azimilide dihydrochloride is a class III AAD that blocks both the rapid (IKr) and the slow (IKs) delayed rectifier potassium channels.[132] Unlike other class III drugs, azimilide does not exhibit reverse use-dependence and this is presumed to be secondary to IKs blockade.

Azimilide prolongs the action potential duration and refractoriness in atrial and ventricular myocardium and has been shown to cause dose-dependent QTc prolongation.[132] In a randomized study of 3,713 patients, 1–3 weeks after a myocardial infarction and with a left ventricular ejection fraction of 15–35%, azimilide did not show any survival advantage when compared to placebo. The incidence of torsades de pointes and severe neutropenia were 0.3 and 0.9%, respectively, and were slightly higher than in that placebo group.[133]

The effectiveness of azimilide in reducing ICD therapies was evaluated in the international SHock Inhibition Evaluation with azimiLiDe (SHIELD) trial. SHIELD randomized 633 patients to azimilide, either 75 mg (n = 220) or 125 mg (n = 199) daily, or matching placebo (n = 214). All enrolled patients had an ICD implanted and had either a documented episode of cardiac arrest or spontaneous sustained VT with left ventricular ejection fraction ≤0.40 during 42 days prior to the first ICD implantation or an ICD shock for spontaneous VT or VF within the previous 180 days. Patients were followed for a median of 1 year and the primary end-point was all-cause shocks plus

symptomatic tachycardias terminated by antitachycardia pacing and appropriate ICD therapies.[134] Azimilide at 75 mg/day demonstrated a 57% reduction in the primary end-point compared to placebo (HR = 0.43; CI 0.26–0.69; p = 0.0006), whereas a 47% reduction was seen in the azimilide 125 mg/day group (HR = 0.53; CI 0.34–0.83; p = 0.0053). When compared to placebo, azimilide 75 and 125 mg/day reduced appropriate ICD shocks and ATP by 48% (p = 0.017) and 62% (p = 0.0004), respectively. Drug discontinuation rates were high (35–40%) but comparable in both the drug and placebo groups. Four patients in the azimilide group and one in the placebo group had torsades de pointes. Thus, it appears that azimilide has beneficial effects in prevention of ventricular arrhythmias in ICD patients and is currently approved for this clinical use in Europe but not in USA. A multicenter placebo-controlled randomized trial (SHIELD 2) to assess the efficacy of azimilide in reducing cardiovascular hospitalizations/emergency visits has already started enrolling patients.

Two trials evaluated the effectiveness of azimilide in maintenance of sinus rhythm in AF. The North American Azimilide Cardioversion Maintenance Trial (A-COMET II) study compared azimilide (125 mg once a day) with sotalol (160 mg twice a day) or placebo for maintaining sinus rhythm in 658 patients with persistent AF who were undergoing electrical cardioversion.[135] Azimilide was found to be superior to placebo in preventing recurrence of AF but was significantly inferior to sotalol in this regard.

The Azimilide Supraventricular Tachyarrhythmia Reduction (A-STAR) trial[136] randomized 220 patients to azimilide (125 mg once a day) vs. matching placebo. There was no significant difference between the azimilide and placebo groups in terms of time to first recurrence of AF. A dose-dependent increase in torsades de pointes was noted with the incidence rates ranging from 0.3% for the 75 mg dose to 1.2% for the 100 mg dose.[137] Thus, in terms of AF rhythm control, the risk-benefit ratio has not been in favor of azimilide and the drug, therefore, has faded from the AF scene.

Class IV Antiarrhythmic Drugs

Verapamil and diltiazem are the most commonly employed calcium channel blockers to combat arrhythmias. Both verapamil and diltiazem block the slow calcium channel and decreases the L-type calcium current in all cardiac myocytes. Electrophysiological effects include reduction in the plateau height of the action potential without significant changes in action potential amplitude or rate of rise of phase 0. Verapamil and diltiazem

suppress sinus and AV nodal conduction and, therefore, are used to control the ventricular response rate in atrial flutter and AF as well as to suppress AV-node dependent supraventricular arrhythmias. Furthermore, these drugs can prevent delayed after depolarization-mediated triggered activity and can inhibit idiopathic ventricular outflow tract tachycardias as well as certain focal atrial tachycardias by this mechanism. A specific reentrant form of VT, the idiopathic left septal VT, is exquisitely sensitive to verapamil. The dose of verapamil is 120–480 mg/day in single or divided doses and diltiazem 120–360 mg/day in divided doses. Both verapamil and diltiazem are available in oral and intravenous formulations.

Other Drugs

Adenosine

Adenosine is an ultrashort acting endogenous purine nucleoside agonist that is approved for the acute termination of symptomatic supraventricular arrhythmias and certain idiopathic VT. It is also vagotonic. Adenosine exerts its cardiac actions by binding to the adenosine A1 receptor on the extracellular surface of the cardiac myocytes, in turn, activating the acetylcholine-dependent cardiac and adenosine-sensitive potasium channels (IKACh/Ado). This results in increased outward potassium current which leads to shortening of atrial action potential duration and membrane hyperpolarization and transient AV nodal block and sinus node depression.[138] IKAdo channels are absent in the ventricular myocytes and so adenosine has not much of an effect in the ventricular myocardium.

Indirectly, adenosine has an antiadrenergic action due to inhibition of adenylate cyclase, resulting in a decrease in cyclic AMP and subsequent decrease in L-type calcium current. This property accounts for its suppressive effect on outflow tract VT as well subgroup of focal atrial tachycardias, which are delayed after depolarization-mediated triggered rhythms resulting from intracellular calcium overload. Adenosine also decreases the funny channel (I_f) current in the sinus node cells, resulting in a reduction in V_{max}. Similar actions are seen in the AV node, resulting in increase in AH interval, and high degree, transient, AV block. His-Purkinje conduction is not usually affected.

Adenosine is administered commonly as an intravenous bolus of 6 or 12 mg followed by a flush. If given by a central venous route, a smaller dose (3 mg) is recommended. Pediatric dose is 0.1–0.3 mg/kg administered intravenously. Adenosine is eliminated rapidly from the extracellular space by various mechanisms, including enzymatic degradation, phosphorylation, or cellular

reuptake with an elimination half-life of a few seconds. Adenosine has a rapid onset of action following intravenous administration and results in almost immediate sinus node slowing and transient AV block, making this as an excellent choice to terminate AV node-dependent supraventricular tachycardias, such as AV node reentry and orthodromic AV reentry tachycardias. Adenosine can terminate idiopathic VT originating from the ventricular outflow tract location[139] as well as some focal atrial tachycardias mediated by triggered activity.[140] Adenosine normally does not affect accessory pathway conduction, and this property is made use of in the electrophysiology laboratory to diagnose the presence of a concealed accessory pathway. The vasodilatory properties of adenosine make it a suitable agent for pharmacological stress testing in the diagnosis of myocardial ischemia.

Adverse effects of adenosine typically include dyspnea, flushing, and bronchospasm. These are short-lasting and resolves quickly. Adenosine should be used cautiously in patients with reactive airway disease. Shortening of atrial refractory periods can result in AF in 10–15% of patients and the drug is sometimes used to test the efficacy of pulmonary vein isolation procedure for AF. Transplanted hearts are exquisitely sensitive to adenosine and dose reduction up to 1 mg is recommended.[141] Methylxanthines (caffeine and theophylline) block adenosine receptors and counteract the effects of adenosine. Dipyridamole reduces the reuptake of adenosine, thereby prolonging the effect of adenosine and so people on oral dipyridamole who are undergoing pharmacologic stress testing should not receive adenosine but should instead receive intravenous dipyridamole as the stressing agent.

FUTURE OF ANTIARRHYTHMIC THERAPY

Throughout this discussion, there is an underlying theme that AADs are by no means perfect in terms of arrhythmia treatment and that substantial side effects and proarrhythmia have changed their use. Results from the controlled clinical trials [International Mexiletine and Placebo Antiarrhythmic Coronary Trial (IMPACT),[142] CAST,[60] SWORD,[78] Acute Lung Injury Ventilator Evaluation (ALIVE), DIAMOND, CHF-STAT, Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), CAMIAT, EMIAT, SHIELD, Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM), and PALLAS) do not suggest a brilliant future but, instead, a jaded past. In fact, many of the drugs, such as procainamide, phenytoin, bretylium, encainide, moricizine, tocainide, quinidine, etc. are disappearing. Optimism

over dronedarone has also faded. So where does that leave us? The future of AADs in many ways remains bright and includes atrial selective ion channel blockers, I_f blockers, ranolazine, sarcoendoplasmic reticulum ATPase (SERCA) modifiers, ion channel modification by gene therapy, stem cells, and therapy for genetic disorders.

NEWER ANTIARRHYTHMIC AGENTS

Vernakalant

Vernakalant is the first in the new generation of AADs that demonstrate electrophysiological effects preferentially in the atrium and not in the ventricle. Atrial-selective agents are currently being developed to restore and maintain sinus rhythm in AF while avoiding adverse ventricular events, such as QTc prolongation and torsades de pointes.[143]

Vernakalant acts selectively in the atrium, targeting multiple ion channels including the ultrarapid potassium current IKur, acetylcholine-mediated potassium current IKACh, IKATP, Ito, and late sodium current (INa).[144] These actions result in prolongation of atrial refractoriness as well as atrial conduction slowing. The recommended dose is a single intravenous infusion of 3 mg/kg administered over 10 minutes. No dose adjustment is necessarily based on patient characteristics and concomitant drugs.[145]

Three randomized, placebo-controlled, double blind ACT (Atrial Arrhythmia Conversion Trials) trials[146-148] tested the efficacy and safety of intravenous vernakalant (administered as a 10-minute intravenous infusion at a dose of 3 mg/kg followed by a second 10-minute infusion at a dose of 2 mg/kg 15 minutes later if AF had not been terminated) for treatment of AF. The ACT I and ACT III trials investigated vernakalant in the treatment of patients with sustained AF (duration >3 hours, but not more than 45 days). These two trials enrolled a total of 612 patients and found that vernakalant was significantly more efficacious than placebo for conversion of AF to sinus rhythm. In ACT I, sinus rhythm was achieved in 62% of patients receiving vernakalant compared with 4.9% of patients receiving placebo for AF of 3–48 hours duration.[146] In ACT III, 51.2% of patients receiving vernakalant converted to sinus rhythm compared with 3.6% of patients receiving placebo for AF of 3 hours to 7 days.[148] The median time conversion was 10 minutes from the start of infusion and sinus rhythm was maintained >24 hours in 97% of patients. The ACT II trial evaluated the efficacy of intravenous vernakalant in 150 patients with sustained AF (3–72 hours duration) that occurred between 24 hours and 7 days after coronary

artery bypass graft and/or valvular surgery and showed that vernakalant resulted in a 47% conversion rate of AF to sinus rhythm compared to 14% for placebo.[147]

The AVRO (A Phase III Superiority Study of Vernakalant vs. Amiodarone in Subjects With Recent Onset Atrial Fibrillation) trial randomized 254 patients with recent onset AF (3–48 hours duration) to intravenous vernakalant or intravenous amiodarone and demonstrated that vernakalant achieved a superior conversion rate (51.7% of patients to sinus rhythm at 90 minutes) compared to amiodarone (5.2%).[149]

Available data show that vernakalant does not appear to be effective in atrial flutter or AF of longer duration (>7 days).[148] Studies are ongoing to determine efficacy and safety of an oral formulation (5 mg/kg). Vernakalant is well tolerated with common side effects being nausea, dysgeusia, paresthesias, and hypotension.[148] No episodes of drug-induced torsades de pointes were reported in the ACT trials.

Intravenous vernakalant is currently approved in Europe for rapid conversion of recent-onset AF (≤7 days duration for nonsurgery patients and ≤3 days duration for postcardiac surgery patients) to sinus rhythm in adults.[150] In USA, although the FDA recommended approval of vernakalant in 2007, the drug is not currently available for clinical use as more safety and efficacy data are being collected.[151] The study, called the ACT 5, is currently suspended as one patient developed cardiogenic shock. The study has not been restarted after almost 2 years. Thus, vernakalant, by virtue of its atrial selectivity, good conversion rate, and excellent safety profile, appears to be an important agent for pharmacological conversion of AF, although it is not clear whether it is time yet to "get into the ACT" even if oral vernakalant becomes available.[152]

Tedisamil

Tedisamil blocks multiple potassium channels, including IKr, IKs, IKur, Ito, and IKATP, and is classified as a Vaughan Williams class III AAD.[153] These ion channel effects prolong atrial and ventricular action potential duration and refractoriness. The effects of tedisamil, however, appear to be more pronounced in the atrial tissue. Tedisamil also causes sinus node slowing and appears to have antianginal properties.[137] The elimination half-life of tedisamil is 8–13 hours. The drug is not metabolized and is renally excreted.

A small, randomized, placebo-controlled dose-response study of 175 patients demonstrated that tedisamil at doses of 0.4 and 0.6 mg/kg was superior to placebo in converting new-

onset AF to sinus rhythm, with a 41% conversion rate for 0.4 mg/kg and 51% conversion rate for the 0.6 mg/kg group. Two patients in the tedisamil group had ventricular arrhythmias (1 case of torsades de pointes and 1 case of monomorphic VT).[153] Tedisamil appears promising, but more studies are needed to further evaluate its safety and efficacy.

Ivabradine

High resting sinus heart rates have been independently associated with mortality and major adverse cardiovascular outcomes.[154-157] Ivabradine is a selective I_f current blocker in the sinus node, resulting in sinus slowing, independent of autonomic tone.[158]

Results from the prospective, randomized, double-blind, placebo-controlled parallel group Systolic Heart Failure Treatment with I_f Inhibitor Ivabradine Trial (SHIFT)[159] of patients with congestive heart failure (left ventricular ejection fraction ≤0.35 and heart rate ≥70 despite standard medical therapy) indicated that ivabradine (titrated to a maximum of 7.5 mg twice a day) can consistently lower the heart rate over long-term when compared to matching placebo and can significantly improve the primary end-point of cardiovascular death or hospitalization for worsening heart failure.

In this rather large study (n = 6,558), hospitalizations for worsening heart failure (672 placebo vs. 514 ivabradine; HR 0.74; 0.66–0.83; $p < 0.0001$) and mortality due to heart failure (151 vs. 113; HR 0.74; 0.58–0.94; $p = 0.014$) was clearly better in the ivabradine group and with few serious side effects, but more patients in the ivabradine group (5%) had symptomatic bradycardia vs. the placebo group (1%), $p < 0.0001$.

Ivabradine, to lower heart rate, may not be beneficial for all patients at risk. In the randomized, prospective, double-blind, placebo-controlled BEAUTIFUL (morBidity mortality EvAlUaTion of the I_f inhibitor ivabradine in patients with coronary disease and left ventricULar dysfunction) trial[160] of 10,917 eligible patients who had coronary artery disease and a left-ventricular ejection fraction of <40%, outcomes were not clearly improved by ivabradine. Considering the primary composite end-point of cardiovascular death, admission to hospital for acute myocardial infarction, and admission to hospital for new onset or worsening heart failure, ivabradine did not affect the primary composite end-point but in patients with a heart rate ≥70 beats per minute (bpm), ivabradine treatment did reduce secondary end-points: admission to hospital for fatal and nonfatal myocardial infarction (0.64; 95%

CI 0.49–0.84; p = 0.001) and coronary revascularization (0.70; 95% CI 0.52–0.93; p = 0.016).

Ivabradine, in combination with a β-blocker, can be effective to prevent angina.[161] Several small controlled clinical trials also demonstrated benefit of ivabradine to slow heart rate and improve symptoms and outcomes in patients with inappropriate sinus tachycardia, and possibly even those with postural orthostatic tachycardia syndrome.[162-173]

While the exact role for heart rate reduction with ivabradine remains somewhat uncertain, for select individuals, it may be time to redefine tachycardia.[157] Usual dose for ivabradine is 5–7.5 mg twice a day. This drug is currently not available for use in USA.

Ranolazine

Ranolazine is an antianginal drug approved for the treatment of chronic angina in patients who have not responded to standard antianginal medications.[174] The antianginal mechanism of ranolazine was believed to result from the drug's ability to block the late sodium current, thereby, suppressing calcium and sodium overload in response to ischemia. This selective affinity for the late sodium current has resulted in ranolazine being investigated as a novel AAD.[175]

In ventricular myocardium, ranolazine inhibits the late sodium channel (late INa) and the rapidly activating component of the IKr.[175,176] In atrial myocardium, in addition to late INa and IKr, ranolazine also inhibits the peak INa.[177,178] Ranolazine does not seem to have any effect on IK1 and Ito.[176] Ranolazine has no effect on resting membrane potential in the atria as well in the ventricle. In therapeutic concentrations, action potential amplitude and duration in the ventricle is not affected, but the rate of rise of action potential upstroke (V_{max}) in the atria is significantly depressed and action potential duration prolonged. The drug prolongs effective refractory period, increases the diastolic excitation threshold, and reduces conduction velocity in the atrial myocardium.[176]

In the Metabolic Efficiency With Ranolazine for Less Ischemia in Non ST-Elevation Acute Coronary Syndrome Thrombolysis in Myocardial Infarction 36 (MERLIN-TIMI 36) trial, ranolazine significantly lowered nonsustained VT and supraventricular tachyarrhythmias in patients with non-ST elevation myocardial infarction when compared to placebo.[179] Recent data from a canine model suggests that ranolazine in combination with dronedarone may be a potent combination to reduce AF.[180] Early clinical studies

have shown that a single dose of 2 g of ranolazine was highly effective as a "pill-in-the-pocket" approach to AF, converting 77% of patients, without any significant side effects.[181] These included patients with structural heart disease, a contraindication for current class IC agents, and could potentially expand the use of ranolazine.

Available data show that ranolazine is associated with a good safety profile, even in patients with structural heart disease.[179] Although it can block IKr and prolong QT interval, torsade de pointes has not been reported, possibly secondary to late INa inhibition.[176,182] What is sorely lacking, despite encouraging animal and early clinical data, is a randomized placebo-controlled trial evaluating antiarrhythmic efficacy of ranolazine in both atrial and ventricular arrhythmias. One such study, examining the role of ranolazine in reducing ICD shocks in patients with structural heart disease and VT/VF, is scheduled to start in 2011/2012 (ClinicalTrials.gov identifier NCT01215253).[176]

ON THE HORIZON

Cellular Calcium Handling

SERCA appears to be potentially critical in the regulation of intracellular calcium along with stabilization by the ryanodine (RyR2) receptor.[183,184] There is a dynamic interplay between the sarcolemmal transport of calcium, the intracellular transport of calcium and sodium, the autonomic nervous system, and morphological and ultrastructural remodeling. The ryanodine receptor has been implicated as causal for the development for CPVT. Additionally, the ryanodine receptor, affecting intracellular calcium handling has been implicated as a cause for ventricular arrhythmias in heart failure. Furthermore, calcium modulated-dependent protein kinase (CaMKII) has been considered an effector of the ryanodine receptor. This may also influence the presence of ventricular arrhythmias. SERCA may also be a cause for ventricular arrhythmias that lead to sudden cardiac death. Therefore, therapies that affect these potential targets may be valuable to reduce the risk of potentially life-threatening ventricular arrhythmias. To date, the data are rather sketchy that therapy can be developed in this regard.

JVT-519 is ryanodine receptor (RyR2) stabilizer, which enhances the binding of the protein calstabin-2 to the ryanodine receptor, thereby, correcting abnormal calcium handling.[185,186] The common form of the disease CPVT is due to a gain of function ryanodine receptor mutation, resulting in increased intracellular calcium leading to delayed after depolarization-

mediated triggered VT. JTV-519 can attenuate increased diastolic sarcoplasmic reticulum calcium leak of the mutant ryanodine receptor. One problem, however, is that JTV-519 may bind to other ryanodine receptor regions under other specific conditions. Other drugs are being developed to affect this potential target.

Another approach is to consider gene transfer. In experimental models, it is possible to affect SERCA2 and prevent triggered activity leading to VF.[187] The risk of developing alternans in the action potential and the incidence of VF is markedly reduced. This would suggest that perhaps gene transfer is a new approach to be considered.

Gene Therapies—Potential ("Near Practical") Applications

There are a variety of exciting possibilities with regard to the use of gene therapies as antiarrhythmic therapy.[188] Consideration has been given to use gene therapy to enhance automaticity in patients with bradycardia (a biological pacemaker), gene therapy to affect AV conduction and slow conduction in AF, and gene therapy to affect the presence of VT by affecting repolarization and accelerating conduction.

With regard to attempts to create a biopacemaker, genes only can be transferred into cells. In this way, there would be episomal overexpression of ion channels (Adv-Kir2.1AAA, NCN, and SPC). Another approach is to have a hybrid of genes and cells that can lead to either cell fusion [hyperpolarization-activated cyclic nucleotide-gated (HCN) in a fibroblast] or spontaneous junctional coupling (HCN in mesenchymal stem cells). Another approach that has been considered is to use stem cells to "entrain" and pace cells.[188]

Gene therapy has also been considered to reduce the ventricular rate in AF.[189] In one report, gene therapy was performed using wild type GEM gene transfer in swine hearts. After 7 days, the AH and PR intervals increased, and the ventricular rate in AF decreased with or without atropine or isoproterenol compared with baseline controls. The ventricular refractory period can also be extended using gene therapy. In rats, Kv1.3 fibroblast transplants can be shown to almost double the ventricular effective refractory period.[190] Additionally, in an animal model of inducible VT, use of a viral vector to transfect the KCNH2-G628S channel completely eliminated VT and markedly prolonged action potential duration when compared to controls.[191]

To date, there is a long list of potential gene therapies to affect electrical dysfunction, including therapies and targets

for atrial arrhythmias and ventricular arrhythmias as well as for biopacemaker development.[192] There are various gene targets and various vectors to deliver the gene. The methodology is rather complex and the target tissue quite variable. All of the studies have been performed in animals. Nevertheless, the data are intriguing and suggestive that there may be potent ways to affect arrhythmias using gene transfer.

One major concern, however, is that stem cells could be proarrhythmic and, therefore, a double-edged sword.[193] Nevertheless, stem cell technology is progressing rapidly and further developments and refinement may indeed bring about the dawn of "personalized medicine."

OLD DRUGS WILL BE NEW AGAIN

There still may be a role for old drugs which can affect clinical syndromes and channelopathies that are only now being understood. For example, while rather uncommon, the short QT interval syndrome (SQTS) cannot be well treated by standard AAD therapy. Nevertheless, for SQTS1, quinidine (or disopyramide) may be the only drug(s) that could be effective.[12,15] For SQTS2, 3, class III AADs may be effective and for SQTS4, 5, quinidine due to its Ito blocking effects may be helpful.[12-15] Due to its effect on the Ito channel, quinidine may be effective for the Brugada syndrome.[9] Furthermore, propafenone appears to have unique benefits to treat AF in patients with SQTS.[15] For patients with long QT interval syndrome (LQTS 3), mexiletine, flecainide, or ranolazine may be effective therapy.[15]

DRUGS WITH NOVEL ANTIARRHYTHMIC MECHANISMS

Several novel agents with antiarrhythmic properties are under various stages of preclinical research. These include nifekalant, an IKr blocker, for use in ventricular arrhythmias, several IKur (and multichannel) blockers (AVE0118, AZD7009, and NIP-141/142), sodium current blockers (pilsicainide), amiodarone analogues (celivarone, ATI-2042, and PM 101), selective IKs blockers (HMR1556), and Kv1.5 blockers (XEN-D0101).[194]

Other drugs, which work by novel mechanisms, are also being developed and include tertiapin-Q, a specific inhibitor of the atrial acetylcholine regulated potassium current (IKACh), KB-R7943, that acts as a sodium/calcium exchange inhibitor, GsMTx-4 as a SAC (stretch channel) blocker, those that are gap junction modifiers (rotigaptide, GAP-134), those that antagonize

the serotonin 5-hydroxytryptamine receptors (RS-100-302), and those that are long-acting adenosine A1 receptors (tecadenoson and selodenoson).[194]

ANTIARRHYTHMIC DRUG SELECTION IN ATRIAL FIBRILLATION

The primary principle that guides AAD selection in AF is "safety over efficacy." This principle is reflected in the 2011 ACC/AHA/European Society of Cardiology (ESC) guidelines for management of AF that provide recommendations regarding AAD selection if rhythm control is planned for AF.[53] For patients with no evidence of structural heart disease or who have hypertension without substantial left ventricular hypertrophy, flecainide, propafenone, sotalol, or dronedarone is first-line therapy, followed by amiodarone, dofetilide, or catheter ablation. For patients with hypertension and substantial left ventricular hypertrophy, amiodarone is the first choice AAD, with catheter ablation as the second-line choice. In patients with coronary artery disease, dofetilide or sotalol is first-line therapy followed by amiodarone or catheter ablation. For heart failure patients, amiodarone or dofetilide is first-line therapy, followed by catheter ablation. The guidelines state the role of dronedarone, given the mortality benefit noted in the ATHENA trial, as "an AAD indicated to reduce the risk of cardiovascular hospitalization in patients with paroxysmal or persistent AF or atrial flutter, with a recent episode of AF or atrial flutter and associated cardiovascular risk factors (i.e., age >70, hypertension, diabetes, prior cerebrovascular accident, and left atrial diameter ≥50 mm or left ventricular ejection fraction <40%), who are in sinus rhythm or who will be cardioverted."[123] Based on recent data from the PALLAS trial, the recommendations may change.

OUTPATIENT VS. IN-HOSPITAL INITIATION FOR ANTIARRHYTHMIC DRUG THERAPY

The severity of the arrhythmia and the proarrhythmic risk of the AAD determine whether the drug should be initiated in the hospital. All class IA AADs should be started in the hospital given the potential risk of idiosyncratic, nondose dependent torsades de pointes. Mexiletine, the only orally available class IB AAD, can be started and titrated as an outpatient treatment, as the risk of proarrhythmia is low. Class IC AADs have a very low risk of proarrhythmia and can be started as an outpatient treatment, provided structural heart disease and severe left ventricular hypertrophy are ruled out. If initiated for AF, it is recommended

to add an AV blocking drug along with the class IC agent to reduce the risk of atrial flutter with rapid ventricular rates. Sotalol and dofetilide should be initiated in the hospital due to the risk of developing dose-dependent QT prolongation and torsades de pointes. Dofetilide must be started in the hospital and strict regulations govern its initiation and titration. Amiodarone can be started as an outpatient for patients who have AF and atrial flutter, as the proarrhythmic risk is low. On the other hand, if used for secondary prevention of VT, it is preferable to initiate amiodarone in the hospital. Although amiodarone prolongs QT interval, incidence of torsades de pointes with amiodarone is extremely low. Dronedarone is generally not proarrhythmic and can be started outside the hospital.

ANTIARRHYTHMIC DRUGS IN PREGNANCY AND LACTATION

An overview of the effect of various AADs in pregnancy and lactation is presented in table 9. Sotalol is the only pregnancy category B [either animal-reproduction studies have not demonstrated a fetal risk, but there are no controlled studies in pregnant women, or animal-reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of a risk in later trimesters)] agent, while amiodarone is classified as pregnancy category D (there is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective). Dronedarone is a pregnancy category X drug (studies in animals

TABLE 9

Antiarrhythmic Drugs in Pregnancy and Lactation

Agent	*Pregnancy*	*Lactation*
Quinidine	C	Excreted
Procainamide	C	Excreted
Disopyramide	C	Excreted
Mexiletine	C	Excreted
Flecainide	C	Excreted
Propafenone	C	?
Sotalol	B	Excreted
Dofetilide	C	?
Dronedarone	X	?
Amiodarone	D	Excreted

or human beings have demonstrated fetal abnormalities, or there is evidence of fetal risk based on human experience or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit) and so is contraindicated in women who are or may become pregnant. The rest of the AADs are considered pregnancy category C [either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other), and there are no controlled studies in women, or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus]. β-blockers can be safely used in pregnancy except atenolol which is a pregnancy category D drug.

ANTIARRHTYHMIC DRUG-DEVICE INTERACTIONS

AADs, especially amiodarone and sotalol, are commonly used in an ICD population to suppress VT and prevent ICD shocks. When used in this setting, AADs can affect pacemaker and defibrillation thresholds. In addition, AADs can slow VT rate to below the programmable limits, can cause sinus node dysfunction and AV block, and, occasionally, can be proarrhythmic. The effect of various AADs on pacing and defibrillation thresholds are listed in table 10.

The Optimal Pharmacologic Therapy in cardioverter Defibrillator Patients (OPTIC) trial was a prospective, randomized study that compared the effects of β-blockers, β-blocker plus amiodarone, and sotalol on defibrillation energy requirements in 94 ICD patients. The study found that changes in defibrillation threshold with amiodarone and sotalol are at best modest

TABLE 10

Effect of Antiarrhythmic Drugs on Defibrillation and Pacing Thresholds

Drug	*Pacing threshold*	*Defibrillation threshold*
Quinidine	Increase	Increase
Procainamide	Increase	No change/increase
Lidocaine	No change	Increase
Flecainide	Increase	Increase
β-blockers	Increase	Decreases
Digoxin	Decrease	Decrease or no change
Ibutilide	Not known	Decrease
Sotalol	No effect	Decrease
Amiodarone	No effect	Increase
Dofetilide	No change	Decrease
Verapamil	Increase	Not known

and argues against repeat defibrillation threshold testing after initiating therapy with either drug.[195] The combination of amiodarone and a β-blocker was the most effective in preventing ICD shocks at 1 year and was more effective than sotalol (10.3 vs. 24.3% for sotalol; HR 0.43; p = 0.02).[74]

CONCLUSION

AADs therapy continue to play an important role in the management of a wide variety of atrial and ventricular arrhythmias. Their role has changed over time, as newer and better therapies aimed at curing arrhythmias and modifying underlying disease process have taken center stage. While the future of AAD therapy may not necessarily be as bright as it once was, many enticing possibilities exist, and the field is by no means without future. Translating therapeutic possibility into clinical reality remains the challenge. Several currently available drugs have found new indications for use. Novel therapeutic targets for patients with arrhythmias are far from over, but, as we have learned, innovation will require extensive clinical testing in lieu of important hard end-points.

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9 CHAPTER

Drugs for Heart Failure

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INTRODUCTION

Heart failure is a common clinical syndrome and can be caused by valvular, myocardial, and pericardial diseases. It can be acute and of recent onset or chronic and may be present for months or years. It can result primarily from left ventricular systolic dysfunction or from diastolic dysfunction. When it is due to systolic dysfunction, it is called systolic heart failure (SHF). When it is primarily due to diastolic dysfunction, it is termed diastolic heart failure (DHF). SHF is also called heart failure with reduced ejection fraction and DHF, heart failure with preserved ejection fraction.

The incidence of heart failure resulting primarily from myocardial disease is high. It has been estimated that the lifetime risk of developing heart failure is about 20% at all ages older than 40 years.[1] The prevalence of heart failure is approximately 2.4% in the adult population of USA. In 2011, approximately 5.7 million people had established diagnosis of heart failure.[2] It has been estimated that by the year 2040, 10 million people will have heart failure in the USA. Presently, the worldwide prevalence of heart failure is approximately 23 million.

The prevalence of heart failure increases with age irrespective of gender. Management of heart failure is expensive. In many developed countries, the cost of management of heart failure is about 1–2% of the total healthcare budget. In 2007, it exceeded 35 billion dollars in the USA. This enormous cost is primarily due to recurrent admissions to hospital for treatment of heart failure. Thus, one of the major goals of management of patients with heart failure is to reduce the rate of hospital admissions.

The prevalence of DHF and SHF are similar. Approximately 50% of patients with heart failure have DHF.[3] DHF is more frequent in women than in men. In the cardiovascular health study, the prevalence of DHF was 67% in women and only 42% in men.[4]

The risk factors for developing DHF are similar to those of SHF.[5] In both SHF and DHF, advancing age, hypertension,

diabetes, and obesity are the major risk factors. The incidence of coronary artery disease (CAD) is higher in SHF than in DHF. However, the incidence of CAD in DHF is about 54% as compared to 63% in SHF. The patients with SHF are younger than patients with DHF. The average age of patients with SHF and DHF is 69.9 and 74.2 years, respectively.[5]

Diagnosis of heart failure is based on the analysis of signs and symptoms. Paroxysmal nocturnal dyspnea, orthopnea, elevated jugular venous pressure, a positive hepatojugular reflux, and presence of a S3 gallop or gallop rhythm are its diagnostic features.[6] An elevated B-type natriuretic peptide (BNP) or nitro-BNP (N-terminal pro-BNP) confirms the diagnosis of heart failure. It should be appreciated that BNP and nitro-BNP levels are elevated in both SHF and DHF.[6]

Noninvasive tests, such as echocardiography, electrocardiography, and chest radiography are routinely performed. Echocardiography is essential to distinguish between SHF and DHF. In SHF, left ventricular ejection fraction (LVEF) is reduced and is preserved in DHF. Invasive tests, such as coronary angiography are also performed to establish presence or absence of CAD.

PATHOPHYSIOLOGY

There has been a considerable advance in the understanding of pathophysiology of both SHF and DHF. In SHF, the primary hemodynamic abnormality is reduced ejection fraction. Reduced ejection fraction is associated with reduced stroke volume and an increased in left ventricular end-diastolic and end-systolic volumes. Increased left ventricular volume is associated with increased left ventricular diastolic pressures, a passive increase in left atrial and pulmonary venous pressure. There is also an obligatory increase in pulmonary artery pressure which is right ventricular afterload which may cause right ventricular failure.

In DHF, the primary functional abnormality is increased left ventricular stiffness. Increased left ventricular stiffness is associated with an increase in left ventricular diastolic pressure, a passive increase in left atrial and pulmonary venous pressure. There is an obligatory increase in pulmonary artery pressure, which may precipitate right ventricular failure. It is apparent that the hemodynamic abnormalities of both SHF and DHF are similar.

It should be appreciated that left ventricular contractile function is reduced in SHF and is preserved in DHF (Figure 1).

In both SHF and DHF, there is myocyte hypertrophy. In SHF, myocyte is thinner but longer, whereas in DHF, the myocyte is

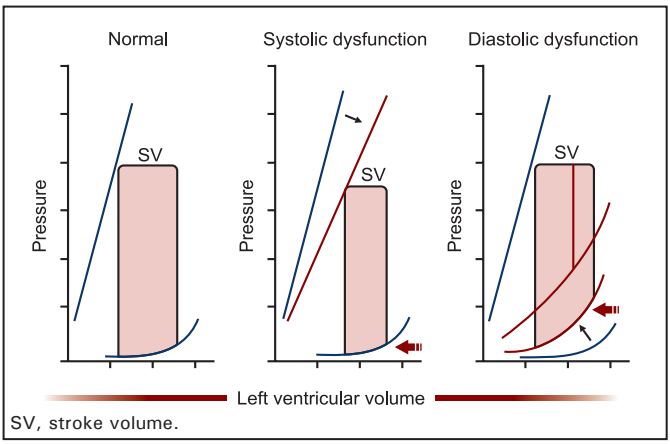


FIGURE 1. The pressure volume loops in systolic and diastolic heart failure are illustrated. In systolic heart failure, contractile function is impaired as evident from the downward shift of the end systolic pressure volume line. In diastolic heart failure, diastolic compliance is decreased as evident from upward and leftward shift of the diastolic pressure-volume curve.

TABLE 1

Morphologic Differences in Systolic and Diastolic Heart Failure		
	SHF	*DHF*
Myocyte hypertrophy	+	+
Myocyte necrosis	+	+
Myocyte apoptosis	+	+
Fibrosis	+	+
Collagen-cross links	–	+
Calcium regulation	–	–

SHF, systolic heart failure; DHF, diastolic heart failure; +, increased; –, decreased.

thicker. Calcium regulation is abnormal in both SHF and DHF. The collagen cross-links are decreased in SHF but increased in DHF (Table 1).

In SHF, left ventricle is dilated. There is an increase in end-diastolic and end-systolic volumes. The magnitude of increase in end-systolic volume is greater than that of the increase in end-diastolic volume; as a result, LVEF is decreased. Left ventricular wall is thinner or remains unchanged in SHF. Left ventricular wall stress, therefore, is increased in SHF. The mechanism of decreased ejection fraction is not only due to impaired contractile function but also due to increased wall stress.

There is a considerable change in the geometry and shape of the left ventricle. Left ventricle is spherical and globular. Synchronous contraction of left ventricular walls is frequently absent in SHF. The lateral wall contracts earlier than the

TABLE 2

Morphologic and Functional Changes in Systolic Heart Failure
▪ Usually eccentric hypertrophy
▪ Disproportionate increase in ventricular cavity size
▪ Increased ventricular mass
▪ Wall thickness—decreased or unchanged
▪ Increased wall stress
▪ Reduced ejection fraction
▪ Altered ventricular shape and geometry
▪ Frequent mechanical dyssynchrony with or without electrical dyssynchrony

TABLE 3

Morphologic and Functional Changes in Diastolic Heart Failure
▪ Ventricular hypertrophy is usually concentric
▪ Increased left ventricular mass
▪ Increased left ventricular wall thickness
▪ Little or no change in left ventricular volumes
▪ Decreased left ventricular wall stress
▪ Maintained ejection fraction
▪ Little or no change in ventricular shape
▪ Mechanical dyssynchrony with or without electrical dyssynchrony is present in approximately 30% of patients

interventricular septum. This mechanical dyssynchrony occurs most frequently in presence of left bundle branch block. However, it may occur in absence of conduction abnormality. The altered shape and geometry and dyssynchrony are the principal mechanisms for secondary mitral regurgitation in SHF. The morphologic and functional changes in SHF are summarized in table 2.

In DHF, there is little or no increase in left ventricular end-diastolic or end-systolic volumes. LVEF remains unchanged. Left ventricular wall thickness in general is increased and left ventricular wall stress is decreased. Decreased wall stress is associated with increased ejection fraction. The morphologic and functional changes in DHF are summarized in table 3.

Based on pathophysiology, the clinical subset, whether compensated or decompensated and acute or chronic, several pharmacologic therapeutic strategies have evolved. In this chapter, the drugs that are used for management of heart failure will be discussed.

MANAGEMENT OF SYSTOLIC HEART FAILURE

The severity of heart failure is classified by New York Heart Association (NYHA). The class I patients are asymptomatic, class II

are symptomatic during more than usual physical activity, class III are symptomatic during less than usual physical activity, and the class IV patients are symptomatic at rest.

The classification is based on the presence of risk factors for developing heart failure, presence or absence of symptomatic or asymptomatic systolic dysfunction, and response to therapy. There are 4 stages of heart failure. Stage A patients are those who have only the risk factors for developing heart failure but do not have structural heart disease. The risk factors are hypertension, diabetes, obesity, hyperlipidemia, and smoking. Patients in stage B have reduced LVEF but are asymptomatic. Patients in stage C have symptoms of heart failure and are being treated with recommended treatments. Patients in stage D are refractory to standard therapy and waiting for cardiac transplant or requiring ventricular assist devices.

In all patients, irrespective of whether they are symptomatic or asymptomatic (stages A–D), modification of risk factors for developing heart failure are essential. Adequate treatment of hypertension, diabetes, and obesity should be undertaken. In patients with suspected CAD, antilipid therapy is indicated.

In stage B patients, in addition to treatments to modify the risk factors for developing heart failure, the pharmacologic treatments with proven benefit to decrease mortality and morbidity are recommended. The pharmacologic treatments that have been documented to improve prognosis of patients with SHF are: (i) angiotensin inhibition, (ii) β-adrenergic receptor blockade, (iii) aldosterone antagonists, and (iv) hydralazine-isosorbide dinitrate (nitric oxide donors). The treatment strategies based on the stages of heart failure and the effects of various drug classes that are used are summarized in tables 4 and 5, respectively.

Neurohormonal Modulation

Introduction of neurohormonal modulators has been a major advance in the management of SHF. The rationale for the use of neurohormonal modulators is to attenuate the adverse effects of neurohormones. Neurohormones, such as angiotensin, norepinephrine, and aldosterone produce a number of adverse effects on morphologic, structural, and myocardial function. The adverse hemodynamic effects include increased systemic and pulmonary vascular resistance resulting from systemic and pulmonary vascular constriction. This may result in low cardiac output, pulmonary hypertension, and right ventricular failure.

Neurohormonal activation also causes vascular remodeling. There is hyperplasia of vascular smooth muscle cells and intimal thickening. There is also vascular endothelial dysfunction.

TABLE 4

Treatment Strategies Based on Stage of Systolic Heart Failure	
Stage A	▪ Treat hypertension ▪ Encourage smoking cessation ▪ Treat lipid disorders ▪ Encourage regular exercise ▪ Discourage alcohol abuse ▪ Discourage illicit drug use ▪ Angiotensin inhibition in appropriate patients
Stage B	▪ Treatment for stage A ▪ Angiotensin inhibition in appropriate patients ▪ β-blockers in appropriate patients
Stage C	▪ Angiotensin inhibition therapy ▪ Adrenergic blocking agents ▪ Aldosterone antagonists in severe heart failure ▪ Hydralazine-isosorbide dinitrate, in self reported Blacks ▪ Diuretics to relieve congestive symptom ▪ Chronic resynchronization treatment ▪ Implantable cardioverter defibrillator ▪ Chronic resynchronization treatment-implantable cardioverter defibrillator ▪ Digitalis in selected patients ▪ Treatments for stage A
Stage D	▪ Those who have failed or have become refractory to recommended therapy ▪ Those who are waiting for cardiac transplantation or for assist devices treatment ▪ Treatment strategies for stages A–C with modifications

TABLE 5

Effects of Various Drug Classes in Chronic Heart Failure	
Reduce mortality	▪ ACEIs of ARBs ▪ β-blockers ▪ Aldosterone antagonists ▪ Isosorbide-hydralazine (in selected pateints)
Provide symptomatic improvement	▪ Diuretics ▪ Low-dose digoxin ▪ Nitrates ▪ Iron for anemia
May have deleterious effects and should be cautiously used	▪ Inotropes and inotropic dilators ▪ Antiarrhythmics (do not use β-blockers and amiodarone) ▪ CCBs ▪ High-dose digoxin

ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; CCBs, calcium channel blockers.

The neurohormonal activation also causes ventricular myocardial adverse remodeling. There is myocyte hypertrophy with dysregulation of myosin metabolism. There are also changes in extracellular matrix. There is increased synthesis of collagen with increased collagen volume and fibrosis along with disruption of collagen architecture. Neurohormones promote atherothrombosis partly due to endothelial dysfunction. There is also abnormal lipid metabolism. The risk of vascular thrombosis resulting from enhanced coagulopathy is increased by elevated neurohormones. The adverse effects of neurohormones are summarized in table 6.

In patients with heart failure, plasma levels of several neurohormones are elevated (Figure 2).[7] Plasma renin activity is increased. There is also an increase in aldosterone plasma level. Plasma catecholamines, including norepinephrine, dopamine,

TABLE 6

Adverse Effects of Neurohormonal Activation
▪ Adverse hemodynamic effects
▪ Vascular remodeling
▪ Ventricular remodeling
– Myocyte hypertrophy
– Extracellular matrix changes
▪ Promotes atherothrombosis
▪ Increased oxidative stress
▪ Endothelial dysfunction
▪ Myocardial necrosis
▪ Apoptosis

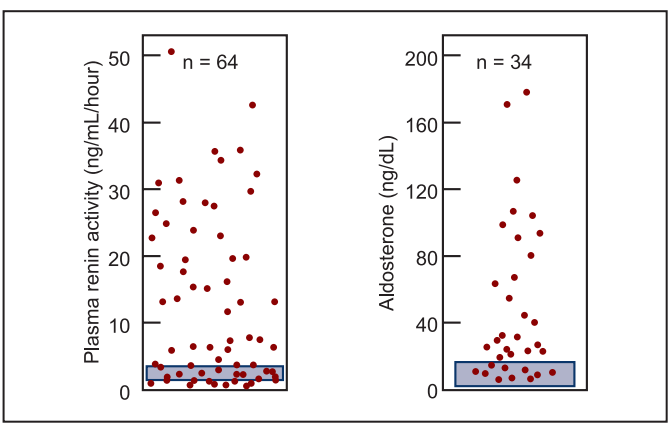
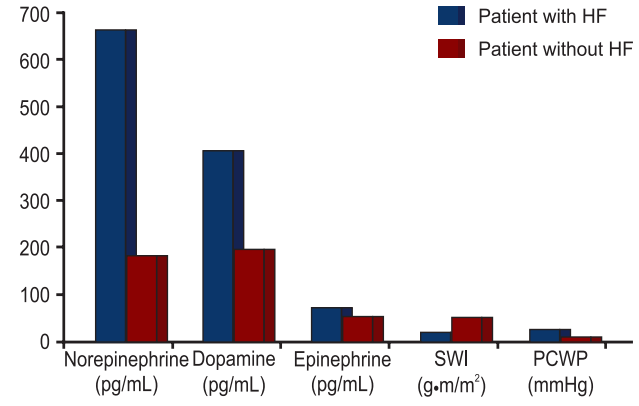


FIGURE 2. In patients with systolic heart failure, plasma renin activity and aldosterone blood levels are increased. *From* Viquerat CE, Daly P, Swedberg K, Evers C, Curran D, Parmley WW, et al. Endogenous catecholamine levels in chronic heart failure. Relation to the severity of hemodynamic abnormalities. *Am J Med.* 1985;78(3):455-60, *with permission*.



HF, heart failure; SWI, stroke work index; PCWP, pulmonary capillary wedge pressure.

FIGURE 3. Mean values of circulating catecholamines and hemodynamic parameters in patients with or without heart failure.

and epinephrine are increased (Figure 3). In a substudy of Study of Left Ventricular dysfunction, plasma norepinephrine levels, plasma renin activity, antidiuretic hormone levels, and vasopressin levels were determined in control subjects, in asymptomatic patients and symptomatic patients with systolic dysfunction. These hormone levels were elevated by a greater magnitude in symptomatic than in asymptomatic patients. The levels of these hormones, however, were greater in patients compared to controls[7] (Figure 4). Endothelins are also significantly elevated in patients with SHF. Endothelins are potent vasoconstrictors and produce adverse vascular and ventricular remodeling.

Angiotensin Inhibitors

A large number of clinical trials have documented the beneficial effects of angiotensin inhibitors in patients with SHF. Angiotensin I is formed from angiotensinogen in the liver by renin. Renin is primarily synthesized in the juxtaglomerular cells of kidney. The stimuli for the release of renin are reduced renal blood flow, hypotension, salt depletion, diuresis, and β-adrenergic stimulation. Angiotensin II is formed from angiotensin I by angiotensin converting enzyme. Angiotensin II stimulates the angiotensin receptor subtype-I, the principal mechanism of the adverse cardiovascular effects of angiotensin. The synthesis of angiotensin II can be attenuated by inhibiting renin and angiotensin converting enzymes. The adverse effects of angiotensin II can also be attenuated by blocking angiotensin I receptors. For treatment of heart failure, angiotensin converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) have been investigated most extensively.

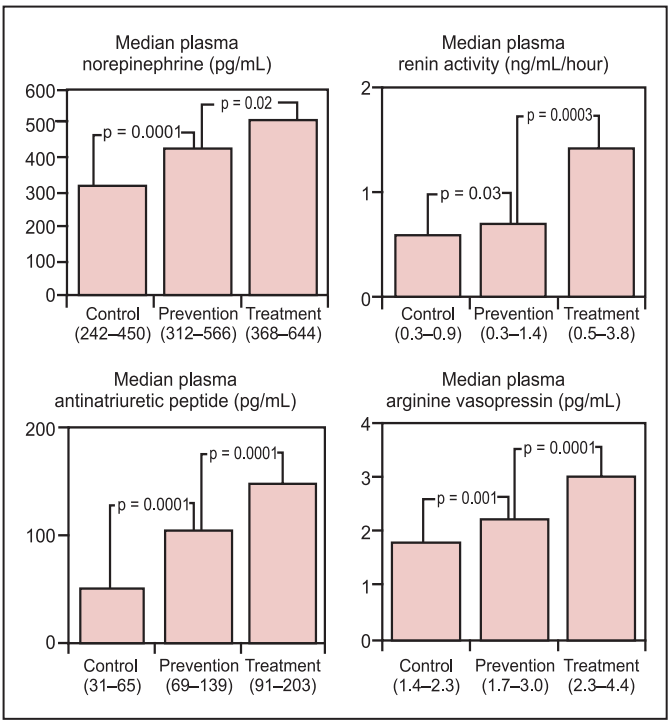
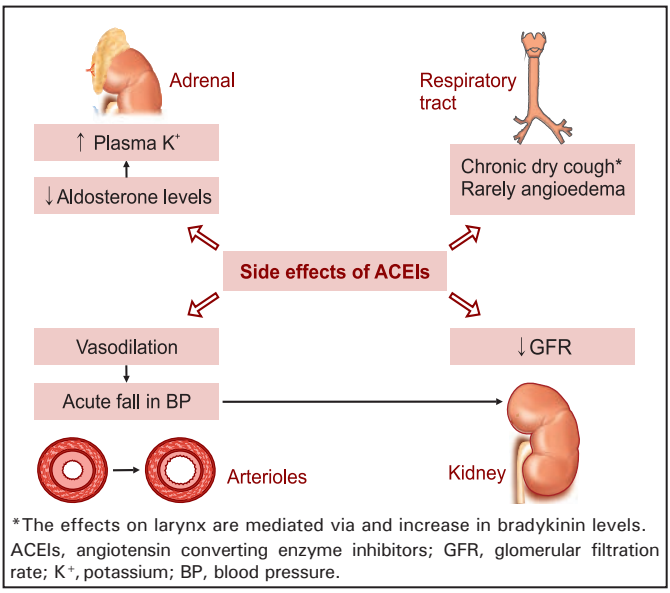


FIGURE 4. Neurohormonal activation in patients with systolic heart failure is illustrated. Plasma norepinephrine, angiotensin, and vasopressins are higher in patients with heart failure compared to controls. Neurohormonal activation is more pronounced in symptomatic than asymptomatic patients with systolic dysfunction. *From* Francis GS, Benedict C, Johnstone DE, Kirlin PC, Nicklas J, Liang CS, et al. Comparison of neuroendocrine activation in patients with left ventricular dysfunction with and without congestive heart failure. A substudy of the Studies of Left Ventricular Dysfunction (SOLVD). *Circulation*. 1990;82(5):1724-9, *with permission*.

In the first placebo controlled randomized clinical trial, the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS), enalapril was used. Patients with severe heart failure were randomized to receive enalapril or placebo. The use of enalapril was associated with a substantial reduction in mortality and morbidity.[8] In a study results of 32 randomized prospective clinical trials, the effects of various types of ACEIs in systolic heart failure were summarized.[9] The risk of total mortality decreased by 23% with the use of ACEIs. The risk of death or hospitalization for heart failure decreased by 35% and that of fatal myocardial infarction (MI) by 20%.[9] The exercise tolerance and symptoms also improved with the use of ACEIs.

ARBs have also been used for treatment of patients with SHF. The agents that have been used are candesartan, losartan, and valsartan. In the Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity (CHARM) trial, the use



*The effects on larynx are mediated via and increase in bradykinin levels. ACEIs, angiotensin converting enzyme inhibitors; GFR, glomerular filtration rate; K^+, potassium; BP, blood pressure.

FIGURE 5. Side effects of angiotensin coverting enzyme inhibitors.

of candesartan was associated with similar benefit in reduction in mortality and morbidity to those of ACEIs.[10] In the losartan heart failure study (ELITE II), the effects of ARBs (losartan) were compared to those of the ACEIs (enalapril).[11] The beneficial effects of losartan and enalapril in decreasing mortality and morbidity in patients with SHF were similar.

The major side effect of ACEIs is cough, and it is related to increased bradykinin production. Angioedema rarely occurs. The incidence of angioedema is approximately 1%. It is a contraindication for the use of ACEIs. Significant hyperkalemia is also uncommon but is a contraindication for their use. Another contraindication for their use is pregnancy. Occasionally, skin rash and extreme bradycardia can develop, but these complications are extremely rare (Figure 5). The dose of various ACEIs and ARBs used in heart failure are summarized in table 7.

American College of Cardiology/American Heart Association Guidelines for the Use of Angiotensin Converting Enzymes Inhibitors or Angiotensin II Receptor Blockers

Class I

- ACEIs should be used in patients with reduced LVEF and no symptoms of heart failure even if they have not experienced MI (level of evidence A)
- An ARB should be used in post-MI patients who are intolerant of ACEIs and have low LVEF (level of evidence B).

TABLE 7

Dose of Various Angiotensin Converting Enzymes Inhibitors and Angiotensin II Receptor Blockers Used in Heart Failure

Agents	*Dose (mg)*	*Frequency*
ACEIs		
Captopril	75–150	BD
Enalapril	10–40	BD
Fosinopril	10–40	OD
Lisinopril	10–40	OD
Quinapril	10–40	OD or BD
Ramipril	2.5–20	OD or BD
Trandolapril	1–4	OD
ARBs		
Losartan	25–50	BD
Valsartan	150–300	BD
Candesartan	4–16	OD

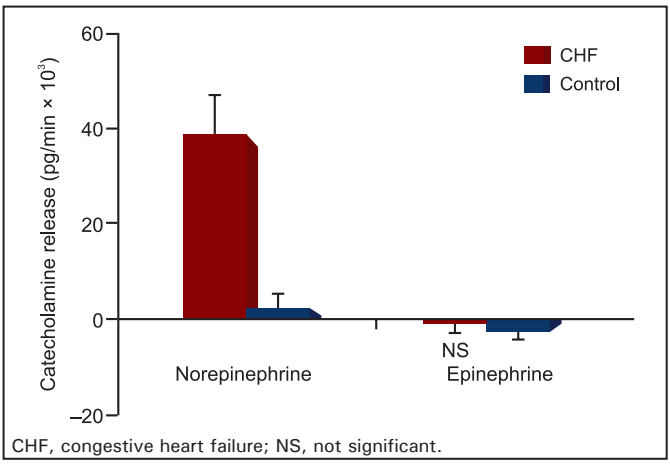
ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin II receptor blockers.

Class IIa

- ACEIs or ARBs can be beneficial in patients with hypertension and left ventricular hypertrophy and no symptoms of heart failure (level of evidence B)
- ARBs can be beneficial in patients with low ejection fraction and no symptoms of heart failure on who are intolerant of ACEIs (level of evidence C).

In patients with heart failure, sympathoadrenergic systems are activated. The centrally mediated muscle sympathetic nerve activity is increased. The circulating catecholamines are increased. There is also increased cardiac adrenergic activity. There is increased cardiac norepinephrine release, as evident from the higher norepinephrine concentration in the coronary sinus blood compared to that in arterial blood (Figure 6). Increased cardiac adrenergic activity is associated with increased myocardial oxygen demand, calcium overload, and myocardial ischemia. There is myocyte hypertrophy and myocyte necrosis and apoptosis.

Increased systemic sympathetic activity is associated with peripheral venous and arterial vasoconstriction. There is increased systemic vascular resistance, which is associated with impaired left ventricular systolic function. There is also adverse ventricular and vascular remodeling. Ventricular dilatation with increase in end-diastolic and end-systolic volume along with reduction in ejection fraction occurs. There is also disruption of extracellular matrix with increased myocardial fibrosis.



CHF, congestive heart failure; NS, not significant.

FIGURE 6. Cardiac adrenergic activity in patients with systolic heart failure is illustrated. Cardiac catecholamine release is substantially increased in patients with systolic heart failure. Catecholamine release was calculated from the product of coronary sinus blood flow and the difference of the coronary sinus venous and arterial catecholamine concentrations. *From* Swedberg K, Viquerat C, Rouleau JL, Roizen M, Atherton B, Parmley WW, et al. Comparison of myocardial catecholamine balance in chronic congestive heart failure and in angina pectoris without failure. *Am J Cardiol*. 1984;54(7):783-6, *with permission*.

The rationale of β-blocker therapy in SHF is to produce beneficial reverse ventricular remodeling to relieve symptoms and to decrease mortality and morbidity.

A number of β-adrenergic antagonists have been reported to produce beneficial effects in SHF. The three β-blockers that have been demonstrated to decrease mortality and morbidity of patients with SHF in large randomized clinical trials are carvedilol, slow release metoprolol, and bisoprolol.

Carvedilol is a nonselective β-blocker and blocks both β1 and β2 receptors. It also possess α-adrenergic antagonist property and has antioxidant effect.

A number of clinical trials have been performed with the use of carvedilol in the management of SHF. In the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial, 2,289 patients were randomized to receive either carvedilol or placebo.[10] The target dose of carvedilol was 25 mg twice a day. During a follow-up of 24 months, there was a 35% reduction in the risk of mortality. In the USA carvedilol trial, 1,094 patients were randomized either to receive carvedilol or placebo. There was a 65% reduction in all-cause mortality with treatment with carvedilol.[11]

In the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF), 3,991 patients were

randomized to receive either metoprolol XL or placebo.[12] During a follow-up period of average 12 months, there was a reduction of mortality by 34%. The target dose of metoprolol XL in this trial was 200 mg daily.

In the Cardiac Insufficiency Bisoprolol Study II (CIBIS–II), 2,647 patients were randomized to receive either bisoprolol or placebo. There was a 34% reduction in the risk of total mortality, 44% reduction in the risk of sudden cardiac death, and a 20% risk reduction in hospitalization for treatment of heart failure.[13]

In the Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure (SENIORS) study, effect of nebivolol was evaluated in patients with SHF. Nebivolol, a selective β1-adrenergic antagonist with nitric oxide mediated vasodilating property decreased the risk of composite end-point of death or cardiovascular hospitalization.[14]

The effects of carvedilol have been compared to those of short-acting immediate release metoprolol in the Carvedilol Or Metoprolol European trial (COMET).[15] In this trial, 3,000 patient with moderately severe heart failure were randomized either to receive placebo or carvedilol. The target dose of carvedilol was 25 mg twice a day and that of metoprolol tartrate, 50 mg twice a day. With carvedilol, there was 17% greater reduction of mortality.

Bucindolol, a β-blocker similar to carvedilol was investigated and used in the β-blocker Evaluation Survival Trial (BEST). In all, 2,708 NYHA class III or IV heart failure patients were randomized either to receive bucindilol or placebo.[16] There was no survival benefit of bucindolol. Lack of bucindolol benefit may be related to its inverse agonist and intrinsic sympathomimetic activity.[17,18]

Centrally acting sympatholytic agents, such as moxonodine can produce adverse effects on cardiovascular mortality in patients with heart failure. In the Moxonidine in Congestive heart failure (MOXCON) trial, there was a higher mortality and morbidity in patients treated with moxonidine.[19] Thus, the adrenergic antagonists that are recommended for treatment of SHF presently are carvedilol, bisoprolol, and long-acting slow-release metoprolol.

The β-blockers should be instituted slowly. The initiating dose should be lower in patients with more severe heart failure. Particularly in relatively hypotensive patients, the lowest possible dose should be used initially. The initiating dose of carvedilol is usually 3.125 mg, metoprolol XL 12.5 mg, and bisoprolol 2.5 mg in these patients. In patients without hypotension, larger doses of β-blockers can be used as the initiating dose. The doses should be increased gradually till optimal dose or the maximal tolerated doses are attained. When larger doses are used initially, hypotension is likely to develop.

The usual complications of β-blockers are fatigue, impaired exercise tolerance, and sometimes worsening symptoms of heart failure. It should be appreciated that these side effects occur initially and resolve within 6–8 weeks of treatment. Thus, the patients and the physicians should be encouraged to continue treatment.

American College of Cardiology/American Heart Association Guidelines Recommendation for the Use of β-blockers in Systolic Heart Failure

Class I

- β-blockers should be used in all patients with a recent or remote history of MI regardless of left ventricular ejection fraction or presence of heart failure (level of evidence A)
- β-blockers should be used in all patients without a history of MI who have reduced LVEF with no symptoms of heart failure (level of evidence C).

Aldosterone Antagonists

In patients with SHF, aldosterone levels are elevated. Aldosterone promotes myocyte hypertrophy, increased collagen synthesis, and myocardial fibrosis and adverse ventricular remodeling. In a substudy of the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), serum levels of collagen biomarkers were measured and, after treatment with eplerenone, levels of aminoterminal peptide of types I and III procollagen were significantly lower at 6 months.[20,21] It also promotes coronary atherosclerosis. There is decreased norepinephrine uptake.

Renal adverse effects consist of glomerulosclerosis, tubulointerstitial fibrosis, sodium and water retention, and potassium and magnesium wasting. In the vasculature, it promotes atherosclerosis, endothelial and vascular smooth muscle cell, hypertrophy, and vasomotor dysfunction.

Aldosterone receptor antagonists, spironolactone and eplerenone, have the potential to produce beneficial left ventricular reverse remodeling. There is a decrease in end-systolic and end-diastolic volumes with an increase in ejection fraction. There is also reduction in myocardial fibrosis.[21-23]

In randomized clinical trials, aldosterone antagonists have been demonstrated to decrease mortality and morbidity in patients with SHF. In the Randomized Aldactone Evaluation Study (RALES), 1,663 patients with SHF in NYHA class III or IV were randomized to receive either spironolactone (target dose

25 mg/day) or placebo. After an average follow-up of 24 months, there was a 30% reduction in all-cause mortality. The risk of sudden cardiac death decreased by 29%, death due to progressive heart failure decreased by 36%. The rate of cardiovascular hospitalization and that of hospitalization due to progressive heart failure by 30 and 35.5 respectively.[24]

The effects of eplerenone, a selective aldosterone antagonist, have also been evaluated both in post-acute MI patients and in patients with chronic SHF trial.

In the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS),[21] 6,642 post-infarction patients with LVEF of 40% or less were randomized within 3–14 days after infarction to receive either placebo or eplerenone (target dose 50 mg daily). With the treatment of eplerenone, there was a 31% relative risk reduction (RRR) in all cause mortality (risk ratio 0.69); a 13% RRR in death from cardiovascular causes or hospitalization for cardiovascular causes (risk ratio 0.87); a 32% RRR in death from cardiovascular causes (risk ratio 0.68); and a 37% RRR in sudden cardiac death (risk ratio 0.63).[25] Treatment with eplerenone in post-acute MI patients also decreases the mean length of hospital stay.[26]

The effects of eplerenone on mortality and morbidity in patients with NYHA class II chronic SHF was assessed in the placebo controlled randomized Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) trial.[27] In this trial, 2,737 patients >55 years with LVEF ≤ 35% were randomized either to receive eplerenone or placebo.[27] Patients with an estimated glomerular filtration rate (GFR) of <30 mL/min/1.73 m^2 or serum potassium ≥5.0 mmol/L were excluded. The inclusion criteria were: cardiac hospitalization within 6 months; BNP level >250 pg/mL, N-terminal pro-BNP >500 pg/mL (men), or >750 pg/mL (women); and QRS duration 130 ms or greater in patients with ejection fraction between 31 and 35%. The background treatment consisted of β-blockers and angiotensin inhibitors in the majority of patients in both groups. After a median of 21 months of follow-up, there was a significant reduction of primary composite end point of cardiovascular death or hospitalization for heart failure (HR 0.63, 95% CI 0.54–0.74, p < 0.001) and of all-cause mortality (HR 0.76, 95% CI 0.62–0.93). There was also a significant reduction in the composite end-point of all-cause, cardiac, and heart failure hospitalizations.

The number of patients needed to be treated was 51 to postpone one death/year during follow-up. The annualized mortality rate in the placebo group was 7.1%.

The active metabolite of spironolactone is canrenone. The effect of canrenone on left ventricular remodeling was evaluated in a randomized placebo-controlled double-blind trial in patients with mild SHF [anti-remodeling effect of canrenone in patients with mild chronic heart failure (AREA IN-CHF) study].[28] In all, 467 patients in NYHA class II heart failure with LVEF ≤ 45% were randomized to receive canrenone or placebo. Almost all patients also received angiotensin inhibitors and β-blockers before randomization. During follow-up of 12 months, there was no significant change in left ventricular end-diastolic volume with canerone; however, the magnitude of LVEF was higher with canrenone than with placebo. There was a trend but statistically insignificant reduction in all-cause mortality with canrenone (2.8 vs. 5.4%, p = 0.17). However, there was a significant reduction of the composite of cardiac death or hospitalization with canrenone compared to placebo (79 vs. 15.1%, p = 0.02).

In a meta-analysis of 19 randomized clinical trials, 10,807 patients were included for analysis. In 14 studies of spironolactone, 3 eplerenone, and 3 canrenone, the aldosterone antagonists were studied. There was 20% reduction in all-cause mortality and 3.1% increase in LVEF with aldosterone antagonists in patients with SHF.[29]

The major side effects of aldosterone antagonists are hyperkalemia. In a meta-analysis of 19 randomized trials, incidence of serious hyperkalemia was 5.9% with the use of aldosterone antagonists.[29] In the EMPHASIS-HF[27] trial, serum potassium concentration of >5.5 mmol/L occurred in 11.8% patients with eplerenone. Serum potassium >6 mmol/L occurred in 2.5% of eplerenone treated patients. In a nonrandomized cohort study, the incidence of serum potassium >6 mmol/L was 2.9%.[30] It should be appreciated that in randomized trials, the patients at a risk of hyperkalemia are excluded. Thus, the reported incidences in these trials are likely to be lower than what occurs in clinical practice.

There are several risk factors for hyperkalemia. Advanced age, diabetes, preexisting renal dysfunction, hypovolemia, and concomitant use of angiotensin inhibitors increase the risk of hyperkalemia. The use of nonsteroidal drugs, potassium supplements, K^+ containing salt substitutes, and concurrent use of other potassium sparing drugs may precipitate hyperkalemia.

Whenever aldosterone antagonist therapy is initiated, careful monitoring of electrolytes, including serum potassium and renal function should be performed. Lack of adequate monitoring may be associated with severe unexpected hyperkalemia and increased mortality.[31]

Aldosterone antagonists should be initiated at low doses (spironolactone 6.25–12.5 mg and eplerenone 12.5 mg). Serum potassium and renal function should be monitor at 72 hours, at 1 and 2 weeks and then at 3 months or as required, based on the changes in clinical status.

Renal function impairment may occur but is uncommon. Severe hyponatremia is also an uncommon complication of these agents. Gynecomastia and breast enlargements are complications of spironolactone and do not occur with eplerenone.Spironolactone possesses antiandrogenic effects. It inhibits the effects of dihydrotestosterone at receptor sites. It also increases peripheral conversion of testosterone to estradiol.[32] The overall incidence of gynecomastia in the randomized trials is 2.8%.[29]

Drug Interactions

Spironolactone inhibits P-glycoprotein and as digoxin is a substrate for P-glycoprotein, spironolactone can decrease renal clearance of digoxin and increase serum level of digoxin.[33]

The serum concentration of eplerenone is affected by the concomitant use of cytochrome P450 3A4 inhibitors as eplerenone is a substrate of cytochrome P450 3A4.[34,35] Drugs like ketoconazole can increase the serum level of eplerenone by 5-fold and should not be used concurrently. Erythromycin increases the serum level of eplerenone by 2–3-fold and the dose of eplerenone should be reduced when use of both drugs is necessary.

Contraindications

Aldosterone antagonists are contraindicated in patients with serum potassium >5.0 mEq/L or with serum creatinine >2.5 mg/dL.

Recommendations for the Use of Aldosterone Antagonists in Systolic Heart Failure

- Class I: Administration of aldosterone antagonist is recommended for patients with NYHA classes II–IV from reduced LVEF of <35% while receiving standard therapy, including ACEI (or ARB) and β-blocker (level of evidence A)
- Class IIa: Administration of an aldosterone antagonist should be considered in patients following an acute MI with clinical heart failure or history of diabetes mellitus and LVEF of <40%. Patients should be on standard therapy, including ACEI (or ARB) and a β-blocker (level of evidence A)
- Class III: Aldosterone antagonists are not recommended when creatinine is >2.5 mg/dL or creatinine clearance is < 30 mL/min or serum potassium is >5 mmol/L or in conjunction with other potassium-sparing diuretics (level of evidence A).

Hydralazine and Nitrates

Hydralazine is an arteriolar dilator, and it dilates primarily the resistance vessels. The hemodynamic effects of hydralazine are characterized by a decrease in systemic vascular resistance associated with an increase in cardiac output. Frequently mean arterial pressure and heart rate remain unchanged.[36] In patients with associated severe mitral regurgitation, hydralazine causes a greater increase in forward stroke volume because of reduction of systemic vascular resistance.[37] Hydralazine can produce sustained beneficial hemodynamic effects in patients with chronic heart failure during its long-term administration.[38]

Nitrates are predominantly venodilators. They also cause a modest increase in aortic compliance, which decreases left ventricular afterload.

Because of venodilatation with nitrates, there is a decrease in venous return and a reduction in ventricular preload. There is a reduction in systemic (right atrial) and pulmonary venous (pulmonary capillary wedge) pressures with a little or no change in stroke volume and cardiac output. In patients with heart failure, there is also no reflex increase in heart rate.

The hemodynamic profile of patients with severe SHF are low cardiac output and increased right atrial and pulmonary capillary wedge pressures. Hydralazine increases cardiac output and nitrates decrease right atrial and pulmonary capillary wedge pressures. The hemodynamic advantage of combining hydralazine and nitrates in treating SHF is apparent.[39]

The effects of combination of hydralazine and nitrates have been assessed in a number of randomized clinical trials. In the Veteran Administration Heart Failure trial (V-HeFT), 1,642 veterans were randomized to receive either hydralazine and isosorbide dinitrate combination or prazosin (α-adrenergic blocking agent) or placebo. The patients were in NYHA class II or III. There was no difference in mortality between prazosin and placebo. However, with hydralazine and isosorbide dinitrate combination therapy there was a significant improvement in survival compared to placebo.[40]

A large randomized trial (African-American heart failure trial—A-HeFT) was performed to assess the effects of combination of hydralazine and isosorbide dinitrate in the self-reported black patients with severe SHF.[41] In this trial, 1,050 patients in NYHA class III or IV heart failure were randomized to receive hydralazine and isosorbide dinitrate combination or placebo. The majority of patients received as background treatments, angiotensin inhibitors (87%) and β-blockers (74%). Only 39% were on spironolactone. The dose of hydralazine was 37.5–75 mg

thrice a day and that of isosorbide dinitrate, 20–40 mg thrice a day. The trial was terminated prematurely, as there was a substantial survival benefit with hydralazine and isosorbide dinitrate combination therapy. The risk of all-cause mortality decreased by 43% and of first hospitalization by 39%.

It has been postulated that the beneficial effects of hydralazine and isosorbide dinitrate combination therapy is related to nitric oxide availability. Nitrates are nitric oxide donors, and it has been suggested that hydralazine decreases nitric oxide break down and enhances nitric oxide availability. However, some studies have suggested that hydralazine does not decrease nitric oxide resistance in chronic heart failure.[42]

Complications

The dose of hydralazine that is used for treatment of SHF rarely produces any complication. Occasionally, hypotension can occur. Lupus-like syndrome only occurs with larger doses. Skin rashes are rarely observed.

The complications of nitrates are headache at the initiation of treatment. Nitrate tolerance is decreased when used with hydralazine. Rarely hypotension occurs with nitrates in heart failure.

American College of Cardiology/American Heart Association Guidelines for the Use of Hydralazine and Nitrate Combination

- Class I: A combination of hydralazine and nitrate is recommended to improve outcomes for patients self-described as African-Americans with moderate to severe symptoms on optimal therapy with ACEIs, β-blockers, and diuretics (level of evidence B)
- Class IIa: The addition of a combination of hydralazine and nitrate is reasonable for patients with reduced LVEF who are already taking ACEI and β-blocker for symptomatic heart failure and have persistent symptoms (level of evidence B)
- Class IIb: A combination of hydralazine and nitrate might be reasonable in patients with current or prior symptoms of heart failure and reduced LVEF who cannot be given an ACEI or ARB because of drug intolerance, hypotension, or renal insufficiency (level of evidence C).

Calcium Channel Blockers

Both dihydropyridine and nondihydropyridine calcium channel blockers (CCBs) exert negative inotropic effects and they are contraindicated in patients with SHF. Although, they also exert peripheral and coronary vasodilatation, the beneficial effects due to vasodilatation have not been documented.

Amlodipine is a dihydropyridine CCB. The effect of amlodipine has been assessed in prospective randomized trials. In the Prospective Randomized Amlodipine Survival Evaluation (PRAISE) studies, there was a trend for benefit in patients with nonischemic dilated cardiomyopathy, but the overall results were neutral.[43] Thus, its use is not recommended except in patients with persistent hypertension despite adequate angiotensin inhibition and β-blocker therapy.

American College of Cardiology/American Heart Association Guidelines Recommendation

- Class III: CCBs are not indicated as routine treatment for heart failure in patients with current or prior symptoms of heart failure and reduced LVEF (level of evidence A).

Diuretics

Diuretics are necessary to relieve congestive symptoms in patients with SHF (stages C and D). For long-term management, usually oral loop diuretics are used. The most frequently used loop diuretic is furosemide. However, ethacrynic acid, bumetanide, and torsemide are also used but much less frequently than furosemide.

In an open label randomized trial, the efficacy of furosemide and torsemide was compared.[44] In this trial, 234 patients were randomized to receive either furosemide or torsemide. The primary end-point in this trial was the rate of hospital admissions. During the follow-up period of approximately 12 months, the hospital admission rate with torsemide was 17% and that with furosemide 32%.

Doses

The daily dose of furosemide is 20–240 mg, bumetanide 0.5–10 mg, ethacrynic acid 50–200 mg, and torsemide 10–200 mg. However, the usual daily dose of furosemide is 40–80 mg, bumetanide 2–3 mg, and torsemide 20–50 mg.

Complications

Aggressive diuretic therapy can produce several complications. The electrolyte imbalance, such as hypokalemia and hypomagnesemia are risk factors for life-threatening ventricular arrhythmias. Diuretic therapy can also produce hyponatremia, hyperuricemia, and hyperglycemia. When large dose of furosemide is used, transient deafness may occur.

Intravenous administration of furosemide can produce transient depression of left ventricular function with decreased cardiac output and increased pulmonary capillary wedge

pressure. This hemodynamic deterioration results from transient increase in norepinephrine and vasopressin.[45]

Deterioration of renal function is common. Increased uric acid excretion and precipitation of gout may occur during diuretic therapy. Skin rash is also observed with loop diuretics.

Positive Inotropic Agents

The positive inotropic drugs, such as digoxin, catecholamines, and cardiospecific phosphodiesterase inhibitors are, in general, contraindicated in patients with stable chronic SHF.

Digoxin

Digoxin and other cardiac glycosides exert their positive inotropic effect by increasing intracellular calcium. It inhibits Na^+/K^+ adenosine triphosphatase (ATPase) and increases intracellular sodium. Sodium-calcium exchanger system is activated resulting in an increase in intracellular calcium.

Digitalis also exerts electrophysiologic effects both directly and by modulating autonomic nervous system. It decrease sinus rate and atrioventricular nodal conduction. Electrocardiogram shows sinus bradycardia and prolonged PR interval. Repolarization effects of digoxin are manifested by decreased T-wave amplitude and scooping of the ST segments.

Long-term oral digoxin therapy has been reported to improve hemodynamics and left ventricular function in patients with SHF.[46] There is an increase in left ventricular stroke work index along with a decrease in pulmonary capillary wedge pressure, indicating improvement in left ventricular function. Two randomized digoxin withdrawal studies have been performed. In the Prospective Randomized study Of Ventricular failure and the efficacy of Digoxin (PROVED) study and in the Randomized Assessment of Digoxin in Inhibitors of Angiotensin-Converting Enzyme (RADIANCE) study, the withdrawal of digoxin therapy was associated with a decrease in LVEF and deterioration in clinical status, functional capacity, and exercise performance. It should be appreciated that these studies were performed before the introduction of β-blocker therapy in SHF.[47,48] In the randomized (Digitalis Investigation Group—DIG) trial, long-term oral digoxin therapy was not associated with any improvement in survival in patients with chronic SHF.[49] In this trial, 6,800 patients with symptoms and signs of heart failure with LVEF of $\leq 45\%$ were randomized either to receive digoxin or placebo. The median dose of digoxin used in this trial was 0.25 mg/day. Although, digoxin did not decrease total mortality, heart failure mortality tended to be lower. There was a statistically significant

reduction in the composite end-points of heart failure mortality or hospitalization for heart failure. However, toxicity was higher in digoxin treated patients compared to placebo (2 vs. 0.9%, $p < 0.001$). Furthermore, in patients with digoxin blood level of 1.2 ng/ml or higher, there was increased mortality due to arrhythmia. Thus, if digoxin is used, the digoxin blood level should be kept below 1.2 ng/mL. It should be appreciated that the DIG trial was performed before β-blocker therapy was introduced. Presently, digoxin is used primarily in patients with atrial fibrillation to decrease ventricular response.

The oral dose of digoxin is 0.0625–0.25 mg daily. In presence of renal failure, the dose should be decreased and administered less frequently. The usual maintenance dose of digoxin is 0.125 mg daily. The intravenous dose of digoxin is 0.25–1.0 mg which should be given by slow infusion. Rapid bolus injection of digoxin is associated with coronary and mesenteric vasoconstriction.

American College of Cardiology/American Heart Association Guidelines Recommendations for the Use of Digoxin in Systolic Heart Failure

- Class IIa: Digitalis can be beneficial in patients with current or prior symptoms of heart failure and reduced LVEF to decrease hospitalization in heart failure (level of evidence B)
- Class III: Digoxin should not be used in patients with low ejection fraction, sinus rhythm, and no history of heart failure symptoms, because, in this population, the risk of harm is not balanced by any known benefit (level of evidence C).

American College of Cardiology/American Heart Association Guidelines Recommendation for Parenteral Positive Inotropic Drugs

- Class III: Long-term use of an infusion of a positive inotropic drug may be harmful and is not recommended for patients with current or prior symptoms of heart failure and reduced LVEF, except as palliation for patients with end-stage disease who cannot be stabilized with standard medical treatment (level of evidence C).

DRUG TREATMENT FOR ACUTE HEART FAILURE SYNDROMES

Definition of Acute Heart Failure Syndrome

All patients with exacerbation of chronic heart failure with congestive symptoms require aggressive diuretic therapy. Most frequently, intravenous furosemide either by bolus or by infusion

is used. The rationale for the use of intravenous diuretics is that, following oral administration, the absorption is slow and the critical serum level is obtained slowly.

In hypotensive patients, the use of vasopressors and inotropic agents are necessary. The vasopressors that are commonly used are dopamine, phenylephrine, norepinephrine, and vasopressins.

Dopamine can exert vasodilation, inotropic, and vasoconstrictive effects which is determined by the dose used. The low levels of dopamine (1–2 μg/kg/min) activate dopaminergic receptors 1 and 2 (DA1 and DA2). Activation of DA1 receptors produce renal and mesenteric vasodilatation. Activation of DA2 receptors decrease presynaptic reuptake of norepinephrine, which also promote vasodilatation.

With larger doses of dopamine (3–10 μg/kg/min) positive inotropic effects are observed. This is due to activation of β1- and β2-adrenergic receptors. There is an increase in cardiac output along with a modest increase in heart rate. With a further increase in the dose of dopamine, the vasopressor effects occur. The dose of dopamine that exerts vasopressor effects is usually higher than 10 μg/kg/min. Sometimes, very large doses exceeding 20 μg/kg/min, are used to increase blood pressure. The larger doses of dopamine stimulates vascular α-receptors and cause an increase in systemic vascular resistance and arterial pressure.

It should be appreciated that with an increase in systemic vascular resistance (left ventricular afterload), there might be a decrease in cardiac output. The larger doses of dopamine may also cause excessive tachycardia. Pulmonary capillary wedge and pulmonary artery pressure may also increase.[50]

Norepinephrine and phenylephrine are also used in hypotensive patients to increase blood pressure. Norepinephrine is predominantly an α-adrenergic agonist with a modest β-receptor agonist property. Phenylephrine is primarily an α-agonist. Both norepinephrine and phenylephrine increase systemic vascular resistance and blood pressure. However, cardiac output may decrease due to increased left ventricular afterload.

A synthetic catecholamine, dobutamine is predominantly a β1-adrenergic receptor agonist. It also stimulates β2-adrenergic receptors. The hemodynamic effects of dobutamine are characterized by a substantial increase in cardiac output, a reduction in systemic vascular resistance, and a slight decrease in mean arterial pressure. There is only a slight increase in heart rate. The pulmonary capillary wedge and pulmonary artery pressure usually do not change significantly.

The relatively cardiospecific phosphodiesterase inhibitor, milrinone, is frequently used in patients with refractory SHF (stage IIIb or D). It exerts a positive inotropic and vasodilatory effect. The vasodilatory effect is much more pronounced than its positive inotropic effect.[51] It increases cardiac output and decreases pulmonary capillary wedge and pulmonary artery pressures. There is a slight or no increase in heart rate; however, ventricular arrhythmias may be precipitated. Inotropic drug therapy may be associated with myocyte necrosis, myocardial injury, and worsening heart failure. It can be associated with a higher incidence of ventricular arrhythmias and increased mortality.

In hypertensive patients with acute heart failure syndromes or patients after being stabilized, intravenous vasodilators, particularly sodium nitroprusside should be considered. Then standard therapy with proven benefit should be instituted.

DRUG TREATMENT OF HYPONATREMIA

Hyponatremia is defined as serum sodium level of >135 mEq/L and is observed in approximately 20–30% of patients with decompensated SHF. It is associated with increased mortality and morbidity. It can occur in hypovolemic, euvolemic, or hypervolemic patients. In congestive heart failure (CHF), it occurs most frequently in patients with volume overload.

Most patients with CHF who develop hyponatremia do not experience symptoms related to hyponatremia till the serum sodium level falls to 120 mEq/L or less. Signs and symptoms include nausea, vomiting, headache, confusion, lethargy, and muscle spasms. With more severe hyponatremia, decreased consciousness, coma, and seizures may occur. The neurologic complications of severe hyponatremia results from cerebral edema.

The mechanisms of hyponatremia are multifactorial. In CHF, hyponatremia results when water retention exceeds sodium retention. Decreased renal perfusion, activation of renin-angiotensin-aldosterone system, and impaired natriuretic response cause sodium retention. Water retention results from excessive water reabsorption in proximal tubules and increased arginine vasopressins activation. Patients with CHF also develops excessive thirst due to stimulation of thirst center by angiotensin, which is elevated in heart failure. Excessive thirst is associated with increased intake of sodium free water. In hyponatremic patients, total body water is greater than total body sodium.

Correction of Hyponatremia in Heart Failure

Fluid restriction to 1–2 L or less/day should be encouraged. However, most patients cannot adhere to fluid restriction because it is uncomfortable, and it induces thirst, which is associated with increased water intake.

Intravenous administration of isotonic or hypertonic saline with or without concomitant use of loop diuretics have been used to correct hyponatremia. However, in patients with heart failure, there is increased risk of volume overload and pulmonary congestion with intravenous saline infusion. Furthermore, rapid correction of hyponatremia can cause central pontine myelinolysis that is often fatal. It should also be appreciated that the use of loop diuretics can exacerbate hyponatremia due to activation of renin-angiotensin-aldosterone system. Thiazide diuretics and aldosterone antagonists also exacerbate hyponatremia. Diuretics can cause electrolyte disturbances such as hypokalemia and hypomagnesemia, which can precipitate life threatening arrhythmias.

Demiclocycline that is a tetracycline antibiotic has been used for treatment of hyponatremia. It inhibits effects of arginine vasopressin and induces diabetes insipidus and enhances free water clearance. However, it can produce nephrotoxicity.

Hyponatremia can also be corrected by arginine vasopressin antagonists in patients with heart failure. There are 3 subtypes of arginine vasopressin receptors—V1a, V1b, and V2. Activation of V1a receptors causes vasoconstriction and cardiac myocyte hypertrophy. Stimulation of V1b receptors is associated with increased adrenocorticotropic hormone and β-endorphin release. The V2 receptors are primarily present in the principal cells of renal collecting duct and their stimulation causes renal free water reabsorption. The V2 receptors activates water channel aquaporin-2 which is associated with decreased water permeability, increased water retention, volume overload, and hyponatremia.

For correction of hyponatremia, V1a and V2 receptors antagonists are used. Tolvaptan, lixivaptan, and conivaptan are the vasopressin antagonists that have been used for treatment of hyponatremia in heart failure.

Tolvaptan is a selective nonpeptide V2 receptor antagonist. It is administered orally and it has a half-life of 6–8 hours. In the Acute and Chronic Therapeutic Impact of Vasopressin Antagonist in Congestive Heart Failure (ACTIV in CHF) trial, 319 patients with SHF with LVEF of <40% were randomized to receive either 30, 60, or 90 mg/day of tolvaptan or placebo.[52] The patients receiving tolvaptan had a significant reduction in body weight. There was an improvement in dyspnea score

and also the length of hospital stay decreased with tolvaptan treatment compared to placebo.

In the Efficacy of Vasopressin Antagonism in hEart failuRE Outcome Study with Tolvaptan (EVEREST) trial, 4,133 patients were randomized to receive 30 mg/day of tolvaptan or placebo. All patients were hospitalized patients and were in NYHA class III or IV and had LVEF of <40%.[53] The treatment was continued for 60 days. The mean follow-up period was 9.9 months. There was no significant difference in total mortality, cardiovascular mortality, or hospitalizations with tolvaptan treatment compared to placebo. However, there was an improvement in dyspnea scores, a decrease in body weight, and peripheral edema. Serum sodium increased to a greater extent compared to placebo.

Lixivaptan is a nonpeptide highly specific V2 receptor vasopressin antagonist. It is administered orally. In a randomized clinical trial, one dose of lixivaptan was found to increase urine volume and free water clearance. There was also significant increase in serum sodium concentration.[54]

Conivaptan is a nonpeptide and both V1a and V2 vasopressin receptors antagonist. It is administered intravenously. In a randomized trial, the effects of conivaptan were assessed in hyponatremic hospitalized patients.[55] In this trial, 84 patients were randomized either to receive intravenous conivaptan (20 mg loading dose followed by 40 or 80 mg infusion for 96 hours) or placebo. There was a significant increase in serum sodium. In another randomized trial, the hemodynamic effects of conivaptan were determined in patients with advanced SHF who first underwent pulmonary artery catherization.[56] In this trial, 142 patients with NYHA class III or IV with SHF were randomized to receive either a single dose of conivaptan or placebo. With conivaptan, there was a significant decrease in pulmonary capillary wedge and right atrial pressures. There was also significant increase in urine volume and free water clearance and decrease in urine osmolality.

MANAGEMENT OF DIASTOLIC HEART FAILURE

The drug treatment of DHF is limited. The congestive symptoms are treated with diuretics and or nitrates. However, there is no improvement in survival. In the Honk Kong Diastolic Heart failure Study, the patients were randomized to receive diuretic alone, or diuretics and an ACEI, or diuretics and the ARB, irbesartan. The hospital admission rates decreased and exercise performance improved in all 3 groups. There was, however, no survival benefit.[57]

In a large randomized clinical trial, the efficacy of perindopril, an ACEI, was evaluated in elderly patients (≥70 years) with DHF. In this trial, 850 patients were randomized to receive either perindopril or placebo. The primary end-point was combined all-cause mortality and unexpected hospitalization for the treatment of heart failure. There was no significant reduction in the primary end-points with perindopril vs. placebo.[58]

In a number of randomized clinical trials, the efficacies of ARBs were assessed in the management of DHF. In the Candesartan Preserved trial, 3,023 patients were randomized to receive either candesartan or placebo. The primary end-point in this trial was cardiovascular death or hospitalization for heart failure.[59] There was no significant benefit with candesartan treatment. In another randomized prospective clinical trial, 4,128 patients were randomized to receive irbesartan or placebo.[60] There was no difference in mortality or morbidity between irbesartan and placebo during the follow-up of over 4 years.

To assess the efficacy of aldosterone antagonists in the management of DHF, prospective randomized trials have been undertaken.[61] The results are not yet available.

The β-blockers are useful to decrease heart rate and improve ventricular filling. However, β-blockers do not improve prognosis.

The phosphodiesterase-5 inhibitor, sildenafil, has been reported to improve clinical outcomes in patients with DHF with pulmonary hypertension.[62] In this study, 50 mg of sildenafil, thrice a day was used. Treatment with sildenafil was associated with a decrease in pulmonary artery pressure and pulmonary vascular resistance. There was also improvement in exercise tolerance. The sample size in this study was too small to assess any effect on survival.

NEWER PHARMACOLOGIC AGENTS FOR TREATMENT OF HEART FAILURE

The newer drugs that are being developed for treatment of heart failure are not yet available for clinical use and are not approved by USFDA.

Systolic Heart Failure

Inotropic Drugs

Calcium sensitizing agents, such as levosimendan and pimobendan enhance the affinity of cardiac myosin filaments to calcium. They also inhibit cardiac specific PDE III. The effect of levosimendan on human coronary hemodynamics has been evaluated. Levosimendan does not appear to increase myocardial

oxygen consumption.[63] The use of levosimendan in patients with acute decompensated heart failure has been associated with increased incidence of atrial fibrillation and flutter, ventricular arrhythmias, and hypotension and increases mortality.[64]

Cardiac myosin activator, omecamtiv mecarbil, increases contractility, directly affecting the sarcomere function. It does not change intracellular calcium metabolism. The inotropic effect is related to prolongation of ejection time. A clinical prospective, randomized, double blind, clinical trial has reported that the positive inotropic effect of omecamtiv mecarbil is directly proportional to the magnitude of prolongation of left ventricular systolic ejection time.[65] Excessive prolongation of systolic ejection time may compromise diastolic filling time and induce myocardial ischemia.[66]

Istaroxime is an inotropic agent that inhibits Na^+/K^+ ATPase activity and stimulates the sarcoplasmic reticulum calcium ATPase activity. It increases contractility and also enhances relaxation. In a phase II trial (Hemodynamic effects of Istaroxime in patients with worsening heart failure and Reduced LV Systolic Function—HORIZON-HF), 120 patients with SHF were randomized either to receive istaroxime or placebo. There was a reduction in pulmonary capillary wedge pressure and with the highest dose, there was also an increase in cardiac output.[67]

Vasodilators—Relaxin

Relaxin is a circulating peptide and it is a potent vasodilator. It is normally found in pregnant women. The vasodilatation is mediated by activation of nitric oxide synthase. The hemodynamic effects consist of decreased systemic vascular resistance and increased cardiac output. There is also a decrease in pulmonary capillary wedge pressure. In human, infusion of relaxin increases renal plasma flow without any change in GFR. In a prospective phase IIb, Pre-Relax-AHF study, 214 patients with acute heart failure with systolic blood pressure >125 mmHg were enrolled. These patients also had mild-to-moderate renal impairment with estimated creatinine clearance of 30–75 ml/min/1.73 m^2. With the infusion of relaxin, there was an improvement in dyspnea score compared to placebo and there was a trend for reduction for in-hospital worsening heart failure, length of hospital stay, and mortality at 60 days.[68] Based on the results of this trial, a phase III trial has been undertaken.

Sarcoplasmic Reticulum Calcium Adenosine Triphosphatase Activators

In SHF, myocardial calcium handling is abnormal. There is decreased uptake of calcium by sarcoplasmic reticulum. In

animal models of heart failure, enhanced calcium uptake by the sarcoplasmic reticulum is associated with improved systolic and diastolic function, improved metabolic reserve and decreased mortality, and increased resistance for developing heart failure during prolonged pressure overload.[69]

A randomized clinical trial of gene therapy to increase sarcoplasmic reticular calcium has been performed. Thirty four patients with NYHA class III or IV were randomized in Calcium Upregulation by Percutaneous Administration of Gene Therapy in Cardiac Disease (CUPID) study to receive gene therapy or placebo. Gene therapy to enhance sarcoplasmic reticular calcium was associated with symptomatic improvement, beneficial reverse remodeling, and decreased natriuretic peptide levels.[70]

Although these results are encouraging, large clinical trials will be required to establish the efficacy of such gene therapy for treatment of heart failure in clinical practice.

Ryanodine Receptor Stabilizers

In the myocyte calcium, dependent calcium release is mediated by activation of ryanodine receptor 2. Dysfunctional ryanodine receptor 2 may cause diastolic Ca^{2+} leak and abnormal calcium handling in heart failure which may cause cardiac dysfunction. There is increasing interest to develop drugs to prevent diastolic Ca^{2+} leak and stabilize ryanodine receptors. A new class of drugs known as Ca^{2+} release channel stabilizers (rycals) are being developed to prevent sarcoplasmic Ca^{2+} leak[71] which might be beneficial in treatment of heart failure.

It has been demonstrated that Ca^{2+}/calmodulin-dependent kinase II (CaMKII) can mediate Ca^{2+} leakage through ryanodine 2 receptors. It has been also reported that CaMKII is upregulated in heart failure and correlates with reduced ejection fraction. In end-stage failing myocardium, both in animals and humans, CaMKII inhibition reduces sarcoplasmic reticular calcium leak and enhances myocardial contractile function. Thus, CaMKII inhibitors may be useful in treatment of SHF.[72]

Neuregulins

The neuregulins are growth promoting proteins. Neuregulin-1 appears to exert a protective effect in heart failure.[73] The potential beneficial effects of neuregulin-1 were evaluated in rats with coronary ligation models. Recombinant neruregulin-1β was used, and there was an improvement in ventricular function and reverse ventricular remodeling.[74] Early phase II studies have been performed with recombinant neuroregulin-1β in patients

with heart failure, and a beneficial effect on cardiac function and structure was reported. It increased cardiac output and produced vasodilation.[75] It should be appreciated that there are potential adverse effects, including acceleration of tumor growth.

New Renin-Angiotensin-Aldosterone Blocking Agents

The effects of direct renin inhibitors, such as aliskerin in the management of heart failure have been investigated. In the Aliskerin Observation of heart Failure Treatment (ALOFT) trial, 302 patients with heart failure were randomized to receive aliskerin (150 mg/day) or placebo.[75] The patients were in NYHA classes II–IV, but majority of patients were in NYHA class II. With aliskerin treatment, there was a significant reduction in BNP as well as in adverse ventricular remodeling. However, there are potential adverse effects of adding aliskerin to ACEIs. Significant hyperkalemia may develop.

Neutral endopetidase inhibitors block ACEIs and prevent degradation of natriuretic peptides. Large randomized clinical trials have been performed to assess the efficacy of neutral endopeptidase inhibitors in the management of SHF. Omapatrilat was used in the Inhibition of Metallo Protease by BMS-186716 in a Randomized Exercise and Symptoms (IMPRESS) study.[76] In this study, 573 patients were randomized to receive either 40 mg of omapatrilat or 20 mg of lisinopril every day. The patients were in NYHA classes II–IV and had ejection fraction of <40%. During 24 weeks of treatment, there was no difference in the primary end-point of exercise tolerance between the two groups. However, with omapatrilat, there was a significant reduction in the predefined composite end-point of death, admission for heart failure, or discontinuation of heart failure treatment because of worsening symptoms. In a large phase III Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE) study, 5,770 patients were randomized either to receive 40 mg of omapatrilat once a day or 10 mg of enalapril twice a day. During follow-up of 14.5 months with omapatrilat, there was a nonsignificant small reduction in the composite end-point of death or hospitalization for heart failure requiring intravenous treatment.[77] Furthermore, increased incidence of angioedema occurred with omapatrilat. Thus, the omapatrilat studies have been discontinued.

Neprilysin inhibitor slows break down of natriuretic peptides. It has been combined with ARBs. A large clinical trial (PARADIGM-HF) has been undertaken to assess the potential efficacy of such combination therapy in treatment of heart failure.

Aldosterone Blockade

Nonsteroidal mineralocorticoid blocking agents have been developed to assess their efficacy in treatment of hypertension and heart failure. These agents are undergoing clinical trials.

Aldosterone Synthase Inhibitors

The aldosterone synthase inhibitors have the potential to attenuate the deleterious effects of aldosterone on ventricular remodeling. In a rat model of failing ventricle, aldosterone synthase inhibitor has been reported to improve hemodynamics, left ventricular function, and to produce beneficial effects on ventricular remodeling.[78]

Diastolic Heart Failure

Presently, there is no effective treatment available for the management of patients with DHF. Thus, there is increasing interest to develop newer treatment modalities for DHF. Advanced glycation end-products and collagen cross-linking modulators are being investigated.

To decrease myocardial stiffness, titin modulators are being developed. However, large clinical trials are lacking to assess the efficacy of such therapeutic approaches for management of DHF.

The efficacy of sildenafil in patients with DHF and mixed pulmonary arterial hypertension has been already discussed.

CONCLUSION

There has been a considerable advance in the understanding of pathophysiology and ventricular remodeling in both SHF and DHF. There have been advances in the management of SHF. Recognition and management of acute decompensated heart failure has improved. However, the treatment of DHF has been disappointing. Furthermore, the drug treatment of SHF has reached a plateau. Thus, research should continue to develop new drugs for treatment of heart failure.

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10 CHAPTER

Drugs for Stable Angina

Kanu Chatterjee, Wassef Karrowni

INTRODUCTION

In the Oxford Dictionary, "Angina pectoris" is defined as, "strangulation in the chest". Angina is the most common manifestation of coronary artery disease. It is the presenting symptom in approximately 50% of patients with chronic ischemic heart disease.[1] It remains as a very common symptom in patients with acute coronary syndromes, even after revascularization.[2]

INCIDENCE AND PROGNOSIS OF CHRONIC STABLE ANGINA

It has been estimated that for every patient admitted to the hospital with acute myocardial infarction, there are 30 patients with chronic stable angina.[1] Thus, stable angina is a very common clinical condition. In the United States of America, approximately 400,000 new patients/year are diagnosed to have stable angina, and it has been estimated that the incidence is likely to increase by 50% in the next 3 decades.[3] Presently, in the United States, 6.5–16.5 million patients have stable angina. Its global incidence remains unknown.

Stable angina is also associated with considerable mortality and morbidity. Chronic ischemic heart disease with silent or manifested myocardial ischemia has been reported to cause 1 out of 5 deaths/year, indicating that the prognosis of patients with chronic stable angina is not entirely benign. It has been estimated that the rate of death and nonfatal myocardial infarction in the first year after the diagnosis of stable angina is approximately 3.9 per 100-patient years in patients with angiographically confirmed coronary artery disease.[4] The adverse prognostic factors are age >75 years, diabetes, and left bundle branch block and reduced left ventricular ejection fraction. The costs of management of stable angina are also considerable. Noninvasive and invasive tests that are performed to establish the diagnosis, to formulate therapies, and to determine prognosis are

expensive procedures. Furthermore, treatment of comorbidities, such as diabetes and hypertension are also expensive.

PATHOPHYSIOLOGY

Angina is a manifestation of myocardial ischemia. Myocardial ischemia results from an imbalance between myocardial oxygen demand and oxygen supply. The determinants of myocardial oxygen demand and supply are summarized in tables 1 and 2. The major determinants of myocardial oxygen demand are heart rate, left ventricular wall stress, and contractility. Higher the heart rate, greater is the myocardial oxygen demand. Enhanced contractility is also associated with increased myocardial oxygen demand. Left ventricular wall stress is directly proportional to its pressure and volume. An increase in left ventricular volume or pressure, left ventricular wall stress increases with a concomitant increase in myocardial oxygen demand. Increase in both systolic and diastolic wall stress is associated with increased myocardial oxygen requirement. Systolic wall stress is primarily determined by systemic arterial pressure (blood pressure). Higher the systolic blood pressure, greater is the myocardial oxygen demand. The rationale for the use of antihypertensive drugs for treatment of angina is apparent. Left ventricular diastolic pressure and volume are the major determinants of diastolic wall stress. Higher the left

TABLE 1

Major Determinants of Myocardial Oxygen Demand
▪ Heart rate
▪ Contractility
▪ Wall stress
– Systolic blood pressure
– Ventricular volume
– Wall thickness

TABLE 2

Major Determinants of Oxygen Supply in Chronic Stable Angina
▪ Arterial oxygen content
▪ Coronary blood flow
– Perfusion pressure
– Perfusion time
– Degree of coronary artery stenosis
– Coronary vascular resistance
– Coronary sinus venous pressure
– Ventricular diastolic pressure
▪ Collateral blood flow

ventricular diastolic pressure, greater is the myocardial oxygen demand. Similarly, larger the left ventricular diastolic volume, greater is the myocardial oxygen demand. Pharmacologic agents that decrease left ventricular diastolic volume and/or pressure have the potential to decrease myocardial ischemia and relieve angina. The determinants of myocardial oxygen supply are summarized in table 2.

Myocardial oxygen consumption is the product of coronary blood flow and myocardial oxygen extraction. The myocardial oxygen extraction remains maximum even at rest and does not vary significantly with changes in myocardial oxygen demand. Thus, myocardial oxygen supply is primarily determined by coronary blood flow.

Coronary blood flow occurs predominantly during diastole. Aortic diastolic pressure is the perfusion pressure and remains as the major determinant of coronary blood flow and left ventricular myocardial perfusion. Normally, coronary blood flow remains relatively constant during changes in perfusion pressure due to autoregulation. Changes in coronary vascular resistance are the major regulatory mechanism of autoregulation. When aortic diastolic pressure decreases, coronary vascular resistance also decreases to maintain the coronary blood flow. When aortic diastolic pressure increases, coronary vascular resistance increases and coronary blood flow remains unchanged. In the absence of autoregulation however, coronary blood flow is proportional to perfusion pressure. During myocardial ischemia, coronary blood vessels are maximally dilated and autoregulation is absent. Therefore, coronary blood flow decreases with decreasing aortic diastolic pressure.

When there is stenosis of the epicardial coronary arteries, the perfusion pressure is the pressure distal to the stenosis. The post-stenotic pressure is related to pressure gradient across the stenotic segment. More severe the stenosis, greater is the pressure drop distal to the stenosis, and lower is the perfusion pressure. It should also be appreciated that the autoregulatory reserve is reduced in presence of severe coronary artery stenosis. Autoregulatory reserve is the capacity to maintain coronary blood flow by decreasing coronary vascular resistance. Although at-rest coronary blood flow may be maintained by autoregulation, autoregulatory reserve can be exhausted during exercise. When coronary vascular resistance becomes minimal, there is no further increase in coronary blood flow and myocardial ischemia is precipitated. In patients with classic (Heberden's) angina, the mechanism of angina during exercise is not only due to increased myocardial oxygen demand but also due to reduced autoregulatory reserve (Figure 1).

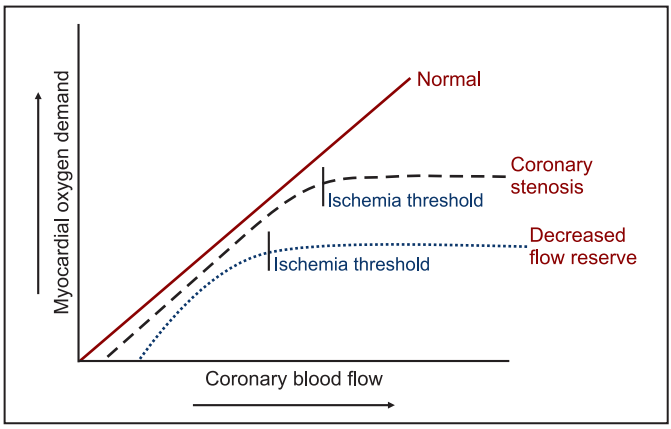


FIGURE 1. Ischemia threshold in stable angina.

Myocardial oxygen supply is also related to hemoglobin content and oxygen saturation of arterial blood. In presence of normal oxygen saturation, lower hemoglobin content is associated with decreased oxygen supply. However, there is a compensatory and obligatory increase in coronary blood flow resulting from decreased coronary vascular resistance.

Increased coronary sinus pressure increases coronary venous pressure and impairs myocardial perfusion. Left ventricular diastolic pressure is an important determinant of subendocardial blood flow. Higher the left ventricular diastolic pressure, lesser is the subendocardial blood flow, which may be associated with subendocardial ischemia. The pharmacologic agents that decrease left ventricular diastolic pressure can decrease subendocardial ischemia and relieve angina.

The magnitude of collateral blood flow to myocardial segments is an important determinant of maintaining perfusion to the myocardial segments supplied by the stenotic coronary arteries. At rest, collateral blood flow is frequently adequate to prevent myocardial ischemia. During increased myocardial oxygen demand like during exercise, collateral blood flow can be inadequate and is associated with myocardial ischemia and a greater risk of myocardial necrosis. An increase in collateral blood flow by angiogenesis has the potential to decrease myocardial ischemia and can relieve angina.

SUBSETS OF STABLE ANGINA

A number of subsets of angina can be recognized clinically (Table 3). A careful history is usually sufficient to establish the diagnosis of these clinical subsets. However, it is often necessary to perform other investigations to determine the etiology and

TABLE 3

Clinical Subsets of Stable Angina and their Pathophysiologic Mechanisms	
Clinical subset	*Mechanism*
Classic angina (Heberden's angina, effort angina)	Demand and supply ischemia
Vasospastic angina (Prinzmetal angina)	Supply ischemia
Mixed Angina	Demand and supply ischemia
Walk through angina	Supply ischemia
Linked angina	—
Syndrome "X"	Supply ischemia

pathophysiologic mechanism of the clinical subsets. Noninvasive tests, such as stress tests and invasive tests, including coronary angiography may be required to confirm the presence of myocardial ischemia and to establish its mechanism. The pathophysiologic mechanism of angina in these clinical subsets is also summarized in table 3.

CLASSIC ANGINA (HEBERDEN'S ANGINA, EFFORT ANGINA)

Clinical Manifestations

The classic description of angina was first given by Dr. William Heberden in 1768, while he delivered his lecture in the Royal College of Physicians of London.[5] There has not been a better description of effort angina since then. In his presentation, he said, "Those who are inflicted with it, are seized while they are walking, and more particularly after they walk soon after eating, with a painful and most disagreeable sensation in the breast, which seems as if it would take their life away, if it were to increase or to continue: the moment they stand still all this uneasiness vanishes".

The most common site of the chest discomfort is retrosternal; however, it can be located over epigastrium, left pectoral, and inter-scapular regions. The predictive value of localization of the site of discomfort by the patient, in the diagnosis of presence of coronary artery disease, has been evaluated in a prospective observational study.[6] When the patient localizes the site of pain with a fist over the sternum, it is called "Levine sign". The "Levine sign"has been regarded as diagnostic of angina for many years. Sometimes, the patient cannot localize the site of chest discomfort precisely and indicates the site of pain over left precordium by the hand. This is termed as "hand sign". If

the patient can localize the site of the pain with finger tips it is termed as "point sign". The "point sign" has a negative predictive value for angina and significant coronary artery disease over 97%. The positive predictive value of "Levine sign" and "hand sign" is approximately, 50%.Thus, these classical clinical signs cannot be used for the diagnosis of obstructive coronary artery disease.

The radiation of pain may occur to left or right arm, or to both arms. Radiation to lower jaw is very suggestive of angina. Radiation to lower extremities, on the other hand, is extremely unlikely to be due to angina.

The character of pain is more often like that of pressure or heaviness rather than actual pain. It can be squeezing or like indigestion. It is usually "deep and dull" and not "sharp and superficial". The chest discomfort usually lasts for few minutes. If the duration is very brief like a "fraction of a second" or very prolonged like hours, it is unlikely to be angina. The chest discomfort is usually relieved with sublingual nitroglycerin in 1–3 minutes. If the relief is instantaneous with sublingual nitroglycerin, it is unlikely to be angina.

For establishing the diagnosis of myocardial ischemia, stress electrocardiography, or stress myocardial perfusion imaging are frequently performed. For the diagnosis of presence or absence of obstructive coronary artery disease, invasive coronary arteriography or noninvasive contrast-enhanced coronary computed tomographic angiography (CCTA) is necessary.

Management

There are two major therapeutic goals for management of stable angina: (i) to reduce the risk of myocardial infarction and death and (ii) to relieve angina/angina equivalent and to decrease myocardial ischemia.

Pharmacologic Management to Reduce the Risks of Future Adverse Cardiovascular Events

There are a number of drugs that have been demonstrated to reduce the risk of adverse cardiovascular complications in patients with stable angina.

Antiplatelet Drugs

Aspirin

Aspirin is the most frequently used antiplatelet drug in patients with atherosclerotic coronary artery disease. Aspirin inhibits synthesis of platelet thromboxane A2 by irreversible acetylation

of the enzyme cyclooxygenase. It is an effective antithrombotic agent and decreases the risk of myocardial infarction. In studies involving more than 3,000 patients with stable angina, there was an average 33% reduction of adverse cardiovascular events with aspirin.[3,7,8] In asymptomatic patients, 325 mg of aspirin given on alternate days has been reported to decrease the incidence of myocardial infarction.[9] The use of low dose (75 mg) of aspirin decreases the risk of myocardial infarction and sudden cardiac death by approximately 32% in patients with stable angina.[10]

Aspirin should be used in all patients with stable angina, if there is an absence of contraindication. It should be used for primary prevention of cardiovascular complications in patients with risk factors for coronary artery disease, such as diabetes, hypertension, obesity, hyperlipidemia, and smoking. Aspirin is indicated for secondary prevention of adverse cardiovascular events in all patients with documented coronary artery disease with or without previous myocardial infarction, and with or without manifested myocardial ischemia.

Dose: The usual dose of aspirin is 75–325 mg both for primary and secondary prevention of cardiovascular events. In Europe, 75 mg strength is available. In the USA, 81 mg (baby aspirin) strength is available. Both lower and higher doses of aspirin produce similar cardiovascular beneficial effects. However, the risks of complications are higher with larger doses.

Side Effects: The most common side effect of aspirin are gastric intolerance and symptoms of indigestion. Frank gastric and duodenal ulcers are less common. However, gastric erosion can occur. Hepatotoxicity, exacerbation of asthma, skin rashes, and renal toxicity are also uncommon complications of long-term use of aspirin. The gastrointestinal blood loss is the most serious complication after long-term use of aspirin. The fecal blood loss is dose related. In patients who develop anemia, appropriate investigations for gastrointestinal blood loss, including endoscopy should be undertaken. After treatment of gastritis or gastric erosions, lower dose of aspirin can be reinstituted and can be given every other day or even twice in a week. Long-term use of aspirin is contraindicated in patients with severe asthma.

American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend the use of aspirin in all patients with stable angina in absence of absolute contraindications (Class I; level of evidence A).

Clopidogrel

Clopidogrel exerts its antithrombotic effect by reducing platelet aggregation by inhibiting adenosine diphosphate pathway

(ADP). It is a thienopyridine derivative, and it irreversibly blocks platelet surface ADP receptors affecting ADP-dependent activation of glycoprotein IIb-IIIa complex. It does not affect prostaglandin metabolism.

In a randomized clinical trial, clopidogrel was compared with aspirin in patients at risk of adverse cardiovascular events. It was reported that clopidogrel was slightly better than aspirin in reducing the adverse cardiovascular events.[11]

Clopidogrel is not used routinely in patients with stable angina, except when coronary artery stents are used. It is used for 4–6 weeks when bare metal stents are used and for at least 1 year when drug eluting stents are used.

Dose: The dose of clopidogrel for its long-term use is 75 mg daily orally. The duration of antiplatelet effect is 7–10 days. Clopidogrel is well tolerated and the side effects are uncommon. Skin rash has been observed infrequently. Neutropenia and thrombocytopenic purpura are very rare complications of clopidogrel.

Aspirin and clopidogrel resistance has been observed and its reported incidence varies between 5 and 75%. This wide variation in their incidence is partly due to the various definitions used for resistance. Various methods have also been developed and approved by the USFDA to detect and treat aspirin and clopidogrel resistance.

ACC/AHA guidelines recommend use of clopidogrel in patients with stable angina, when aspirin is absolutely contra-indicated (Class IIa; level of evidence B).

Dipyridamole

Dipyridamole is an antiplatelet agent, and it exerts its antiplatelet function by inhibiting adenosine uptake and cyclic guanosine monophosphate diesterase activity. It also possesses vasodilatory property. It is seldom used as an antiplatelet agent for the management of patients with atherosclerotic cardiovascular diseases. In cardiology, dipyridamole is primarily used as a pharmacologic stress agent for nuclear perfusion myocardial imaging test. Occasionally, it is used in combination with warfarin for prevention of thromboembolic complications in patients with prosthetic mechanical valves.

ACC/AHA guidelines recommend against dipyridamole use in patients with stable angina (Class III; level of evidence B).

Cilostazol

Cilostazol is a phosphodiesterase inhibitor. It inhibits platelet aggregation and also has vasodilatory effect. It is primarily used for treatment of intermittent claudication.

Warfarin

The potential beneficial effect of low-intensity anticoagulation with warfarin has been investigated in asymptomatic patients with risk factors of atherosclerosis. It has been suggested that warfarin can be beneficial in selected patients with stable angina. However, presently it is not clear, whether anticoagulation therapy with warfarin alone, is any better than aspirin alone.[3]

ACC/AHA guidelines recommend use of long-term low intensity anticoagulation with warfarin along with aspirin in selected patients with stable angina (Class IIb; level of evidence B).

Lipid-lowering Agents

All patients with established coronary artery disease or with high risk for coronary artery disease should be treated with 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors (statins) in the absence of contraindications.

The Scandinavian Simvastatin Survival Study (4S) randomized 4,444 patients with dyslipidemia and coronary artery disease to either placebo or simvastatin. During a follow-up period of 5.4 years, treatment with simvastatin was associated with 26% reduction in new onset or worsening of angina and a 37% reduction in the need for revascularization.[12] There was also a significant reduction in the risk of fatal and nonfatal myocardial infarction.[12] In the Cholesterol and Recurrent Events (CARE) study, statin therapy with pravastatin was associated with a 37% reduction in the relative risks of fatal myocardial infarction in patients with documented myocardial infarction.[13] In the atorvastatin vs. revascularization treatment (AVERT) trial, patients with stable angina associated with coronary artery disease were randomized to receive 80 mg of atorvastatin or percutaneous coronary intervention with or without stent implantation. Atorvastatin treatment was associated with a statistically significant lower risk of the primary composite end-point defined as one of the outcomes: death from cardiac causes, nonfatal myocardial infarction, cerebrovascular accident, coronary artery bypass graft surgery (CABGS), angioplasty, resuscitation after cardiac arrest, and worsening angina requiring hospitalization. Studies comparing the effects of intensive vs. moderate lipid-lowering strategies on the extent of myocardial ischemia in patients with stable coronary artery disease have been performed.[14,15] There was a significant reduction in myocardial ischemia with both intensive and moderate lipid-lowering therapies.[14,15]

In the double-blind atorvastatin, amlodipine (DUAAL) trial, the anti-ischemic effects of atorvastatin were compared to

that of amlodipine. After 24 weeks of treatment, both treatment modalities caused similar reduction of myocardial ischemia detected by stress testing or by ambulatory electrocardiography.[16]

In the vascular basis for the treatment of myocardial ischemia study, intensive or moderate strategies were compared in patients with dyslipidemia and stable coronary heart disease.[15] During 12 months of treatment, both treatment strategies reduced the incidence and duration of myocardial ischemia detected by stress testing or ambulatory electrocardiography.

In the study assessing goals in the elderly (SAGE) trial, the effects of intensive statin therapy (atorvastatin 80 mg daily) was compared to moderate statin therapy (pravastatin 40 mg daily) in 900 elderly patients with coronary heart disease.[17] After 1 year of treatment, both strategies were associated with a 37% reduction of total duration of myocardial ischemia during ambulatory electrocardiography. Intensive lipid-lowering therapy with atorvastatin was associated with a 77% risk reduction in total mortality.

In the clinical outcome utilizing revascularization and aggressive drug evaluation (COURAGE) trial, patients with chronic stable angina were randomized to receive medical therapy or revascularization.[18] Medical therapy included statin therapy. In this trial, medical therapy was as effective as percutaneous coronary artery intervention in reducing the future adverse coronary events and myocardial ischemia.

The results of these clinical trials suggest that statins should be used in patients with chronic stable angina.

ACC/AHA guidelines recommend the use of lipid lowering therapy in patients with documented or suspected coronary artery disease and low density lipoproteins (LDL) >130 mg/dL with a target LDL <100 mg/dL (Class I; level of evidence A).

The currently available statins for clinical use are: simvastatin, lovastatin, atorvastatin, rosuvastatin, pravastatin, and fluvastatin. Statins should be taken in the evening after dinner, as cholesterol synthesis occurs predominantly at night.

Lovastatin and simvastatin are prodrugs. Atorvastatin, rosuvastatin, and fluvastatin are active when they are administered. Gastrointestinal absorption of statins is 40–70% except that of fluvastatin which is fully absorbed. The half-lives of most of the statins are between 1 and 3 hours except atorvastatin (14 hours) and rosuvastatin (19 hours).

The mechanism of action of statins is primarily due to inhibition of HMG-CoA reductase inhibition. They increase

the hepatic high-affinity LDL receptors which lead to increased scavenging of the circulating LDL. This is the primary mechanism for the reduction of LDL levels with statins.

Side Effects

The major adverse effect of statin therapy is elevation of serum aminotransferase activity. If the liver function abnormalities continue, statins should be discontinued. Skeletal muscle-ache is rather common; however, marked myositis and rhabdomyolysis are rare. The metabolism of lovastatin, simvastatin, and atorvastatin involves primarily cytochrome P450 3A4 (CYP3A4) and that of fluvastatin and rosuvastatin cytochrome P450 2C9 (CYP2C9). Pravastatin is metabolized by different mechanisms, including sulfation.

The drug interactions of statins with macrolide antibiotics, cyclosporine, ketoconazole, human immunodeficiency virus (HIV) protease inhibitors, and fibrates have been observed. Concomitant use of verapamil or amiodarone and statin increase the risk of myopathy.

For monitoring the adverse effects of statin therapy, periodic assessment of liver functions and measurement of creatinine kinase (CK) is recommended.

Dose

The dose of simvastatin is 5–80 mg daily. Recently, USFDA has recommended not to use 80 mg dose of simvastatin because of the increased risk of rhabdomyolysis.

The dose of lovastatin is 10–40 mg, atorvastatin 10–80 mg, rosuvastatin 10–40 mg, and pravastatin 10–80 mg daily.

Angiotensin Inhibiting Drugs

Angiotensin inhibition therapy has the potential to reduce the adverse cardiovascular events in patients with stable angina. The use of an angiotensin converting enzyme (ACE) inhibitor ramipril, in a high risk population like those with a history of coronary artery disease, stroke, peripheral vascular disease, diabetes, hypertension, hyperlipidemia, and without overt manifestation of myocardial ischemia, is associated with a substantial reduction of adverse cardiovascular events.[19] Perindopril, another ACE inhibitor, was associated with decreased risk of adverse cardiovascular complications in patients with ischemic heart disease.[20] In post-myocardial infarction patients with decreased left ventricular ejection fraction, captopril has shown to decrease the risk of mortality and morbidity.[21] Some studies have, however, reported lack of benefit of routine ACE

inhibitor treatment in low risk patients with stable coronary artery disease.[22] In the prevention of events with ACE inhibition (PEACE trial), trandolapril, another ACE inhibitor was used in patients with chronic ischemic heart disease. During this trial, the risk factors were also treated in the patients. Majority of patients were treated with statins and also had revascularization therapy.[23] The rate of adverse cardiovascular events was lower in the placebo treated group than in the trandolapril treated group. Based on the result of PEACE trial, ACC/AHA guideline committee recommends against the use of ACE inhibitors in low risk patients.[24] However, even in the low risk patients with elevated biomarkers of cardiovascular stress, such as of midregional pro-atrial natriuretic peptide, midregional proadrenomedullin, C-terminal proendothelin-I, and copeptin, use of trandolapril was associated with decreased risk of cardiovascular death and heart failure.[25] It should also be appreciated that in the majority of the randomized studies, it was observed that angiotensin inhibition therapy is beneficial and thus should be used in patients with documented coronary artery disease in absence of absolute contraindications.[22]

ACC/AHA guidelines recommend that ACE inhibitors should be used in all patients with coronary artery disease and diabetes and/or left ventricular systolic dysfunction (Class I; level of evidence A). It should be also used in patients with coronary artery disease or other vascular disease (Class IIa; level of evidence B).

β-adrenergic Receptors Antagonists (β-blockers)

It has been amply demonstrated that β-blockers improve left ventricular systolic function and decrease mortality and morbidity in patients with reduced left ventricular ejection fraction.[26] However, there are limited data available to assess the effect of β-blocker therapy on mortality and morbidity of patients with stable angina without previous myocardial infarction and with preserved left ventricular systolic function. In the atenolol silent ischemia study (ASIST), asymptomatic or minimally symptomatic patients were randomized to receive either atenolol or placebo.[27] Treatment with atenolol was associated with a significant lower risk of the primary combined end-point (death, resuscitation from ventricular tachycardia/fibrillation, nonfatal myocardial infarction, hospitalization for unstable angina, aggravation of angina requiring known antianginal therapy, or need for myocardial revascularization during the follow-up period of one year). There was, however, no difference between atenolol or placebo treatments in the individual hard end-points such as death and nonfatal myocardial infarction.

ACC/AHA guidelines recommend the use of β-blockers in patients with stable angina if not contraindicated to reduce the risk of future adverse cardiovascular events (Class I; level of evidence B).[3]

Other Therapies to Decrease the Risks of Adverse Cardiovascular Events

Folate therapy should be considered when homocysteine levels are elevated. The treatment of depression is also recommended.

Adequate control of hypertension and diabetes is essential. Cessation of smoking is highly recommended. Weight loss should be encouraged in overweight patients. Sedentary lifestyle should be discouraged and regular aerobic exercise should be encouraged. The therapies to decrease the risks of adverse cardiovascular events are summarized in table 4.

Drugs to relieve angina and myocardial ischemia in stable angina are summarized in table 5.[28-30]

TABLE 4

The Therapies to Decrease the Risks of Adverse Cardiovascular Events in Patients with Stable Angina
▪ Antiplatelet drugs
▪ Lipid lowering agents
▪ Angiotensin inhibiting drugs
▪ β-blockers
▪ Adequate control of hypertension
▪ Adequate control of diabetes
▪ Folate therapy if homocysteine level is elevated
▪ Treatment of depression
▪ Cessation of smoking
▪ Weight loss in overweight patients
▪ Regular exercise

TABLE 5

Drugs to Relieve Angina and Myocardial Ischemia
▪ β-adrenergic receptor antagonists (β-blockers)
▪ Nitroglycerin and nitrates
▪ Calcium channel blocking agents
▪ Late sodium current blocking agent—Ranolazine
▪ Nicorandil
▪ Trimetazidine
▪ I_f (funny) current inhibition—Ivabradine
▪ Vasopeptidase inhibition—Omapatrilat
▪ Rho-kinase inhibition—Fasudil

Pharmacologic Management to Relieve Angina and to Decrease Myocardial Ischemia

β-adrenergic Receptors Antagonists (β-blockers)

Three types of β-adrenergic receptors, β1, β2, and β3 have been recognized. β1 receptors are present in cardiac myocytes and sinoatrial and atrioventricular nodal cells. Activation of β1 receptors is associated with increased contractility and heart rate, and enhanced atrioventricular nodal conduction.

β2 receptors are present in cardiac myocytes but are more abundant in bronchial and peripheral vascular smooth muscle cells. Activation of β2 receptors causes bronchodilatation and peripheral vasodilatation. There is a small increase in myocardial contractility.

β3 receptors are present in the heart and in adipose tissue. Activation of β3 receptors reduces contractility.[28]

β-blockers in general inhibit β1 and β2 adrenergic receptors. Inhibition of β1 receptors is associated with a decrease in heart rate and contractility, which decreases myocardial oxygen demand. Activation of β2 receptors causes vasodilatation and decreases systemic vascular resistance. β2 receptors stimulation is also associated with coronary vasodilatation and increased coronary blood flow. Thus, with the use of β-blockers, a potential exists for the decrease in coronary blood flow with inhibition of β2 receptors due to increase in coronary vascular resistance. The clinical relevance of this effect of β-blockers on coronary hemodynamics remains uncertain.

β-blockers can be selective or nonselective. Some β-blockers also possess intrinsic sympathomimetic activity (ISA). β-blockers with ISA have partial agonist property and exert stimulation of adrenoreceptors at rest. Thus, resting heart rate and contractility are not diminished. However, exercise-induced increase in heart rate and contractility is inhibited.

Selective β-blockers inhibit β1 receptors that are present predominantly in the cardiac myocytes. Selective β-blockers decrease heart rate and contractility. They cause less broncho-constriction and less peripheral vasodilatation than the nonselective β-blockers which inhibit both β1 and β2 receptors. There are β-blockers, which also inhibit α-adrenergic receptors and have direct vasodilatory properties.

The major mechanism by which β-blockers relieve angina and myocardial ischemia is by reduction of myocardial oxygen demand. However, with a reduction in heart rate, myocardial perfusion time increases with improved myocardial perfusion.

It should be appreciated that with a marked reduction in heart rate, left ventricular end-diastolic volume increases, which also increases myocardial oxygen demand. Thus, the beneficial effect of β-blockers may be partially offset. Concomitant use of nitrates which decrease left ventricular end-diastolic volume may be more effective for relief of myocardial ischemia.

It has also been reported in several studies that selective and nonselective β-blockers decrease the frequency and severity of episodes of angina and increase exercise tolerance in patients with stable angina.[1,3,18-20] The nonselective β-blocker with α-blocking property, carvedilol has been reported to be effective in the treatment of stable angina.[31-33] Carvedilol (25–50 mg twice a day) appears to be as effective as nifedipine (20 mg twice a day), verapamil (120 mg twice a day), or immediate release metoprolol (100 mg twice a day) in reducing the frequency of angina and in improving exercise duration.[31-33] β-blockers with ISA are not generally recommended for treatment of angina. The pharmacokinetics of β-blockers is summarized in table 6.

ACC/AHA guidelines recommendations for the use of β-blockers in stable angina:

- β-blockers should be used as initial therapy in absence of contraindications in patients with prior myocardial infarction (Class I; level of evidence A)
- β-blockers should be used as initial therapy in the absence of contraindications in patients without prior myocardial infarction (Class I; level of evidence B).

Nitroglycerin and Nitrates

Nitroglycerin was introduced for treatment of angina by William Murrell in 1879.[34] It has been used since then for the treatment

TABLE 6

β-adrenergic Blocking Agents in Stable Angina

Agent	*Selectivity*	*Partial agonist activity (ISA)*	*Half-life (hours)*	*Dose (mg/day)*
Atenolol	β1	No	6–9	25–100
Acebutolol	β1	Yes	3–4	1,200
Bisoprolol	β1	No	9–12	10
Carvedilol	None	No	7–10	50
Metoprolol	β1	No	3–4	200
Nadolol	None	No	14–24	160
Propranolol	None	No	3.5–6	180
Timolol	None	No	4–5	20

ISA, intrinsic sympathomimetic activity.

of all subsets of angina. Presently, it is used not only for stable angina, but also for acute coronary syndrome.

Mechanism of Action

Nitroglycerin and nitrates cause dilatation of veins and arteries by relaxation of vascular smooth muscle cells. Relaxation of vascular smooth muscle cells is mediated by generation of nitric oxide and sulfhydryl-nitrosothiols. Nitroglycerin and nitrates are first metabolized to 1, 2-glyceryl dinitrate and nitrite and then to nitric oxide and sulfhydryl-nitrosothiols.

Effects on Systemic and Coronary Hemodynamics

Nitroglycerin and nitrates are predominantly venodilators and cause dilatation primarily of veins with larger capacitance and the venules are least affected. Venodilatation is associated with decreased systemic venous return which decreases ventricular volumes.

Dilatation of arterial system with nitroglycerin is much less pronounced. It causes minimal or no dilatation of the smaller arteries such as of the intramyocardial coronary arteries. Nitrates also have minimal effects on arterioles. However, nitroglycerin and nitrates decrease stiffness of the larger arteries such as of aorta and cause dilatation of the larger arteries, including aorta. Decreased aortic stiffness (increased compliance) is associated with a modest decrease in systolic blood pressure. Nitrates also cause dilatation of the epicardial coronary arteries. In the atherosclerotic coronary artery disease, nitroglycerin dilates not only the nonstenotic segments but also the atherosclerotic stenotic epicardial coronary artery segments. The epicardial coronary artery vasodilatory effects are associated with an increase in coronary blood flow. Dilatation of the smooth muscles of the epicardial coronary arteries relieves coronary artery spasm-the principal mechanism for relief of vasospastic angina. An improvement in endothelial function has been proposed to be a mechanism of epicardial coronary artery dilatation.

The systemic hemodynamic effects of nitroglycerin are characterized by a decrease in right atrial and pulmonary capillary wedge pressures. There is usually no change in cardiac output. There is a reduction in right and left ventricular diastolic volumes and pressures. As there is also a decrease in arterial pressure, both systolic and diastolic wall stress is decreased, which is associated with decreased myocardial oxygen demand. If there is a marked reduction in ventricular volumes, stroke volume and arterial pressure may decrease and syncope may occur (reflex syncope).

A fall in arterial pressure is associated with a reflex increase in heart rate and contractility. It should be appreciated that nitroglycerin does not possess any direct positive inotropic effect.

Usually, with a fall in blood pressure with nitroglycerin, there is a reflex increase in heart rate. In some patients, if there is a marked decrease in left ventricular volume associated with a reflex increase in contractility, ventricular vagal afferent "C" fibers can be stimulated and may cause cardioinhibitory and vasodepressor responses resulting in bradycardia and hypotension (paradoxical response of nitroglycerin).

Mechanism of Relief of Angina and Myocardial Ischemia

The principal mechanism of relief of myocardial ischemia by nitroglycerin and nitrates is by reduction of myocardial oxygen demand. The decrease in ventricular volumes and arterial pressure is associated with a reduction in wall stress which decreases myocardial oxygen demand. Decreased left ventricular diastolic volume and pressure can also increase subendocardial blood flow and decrease subendocardial ischemia. A reduction in subendocardial ischemia may contribute in providing relief of angina.

It should be appreciated that the reflex increase in heart rate and contractility in response to fall in blood pressure may decrease the beneficial effects of nitroglycerin. The concurrent use of β-blockers can minimize these potential adverse effects of nitroglycerin. For maintenance treatment of stable angina combination of nitrates and β-blockers are frequently employed.

Nitroglycerin and Nitrate Preparations

The nitroglycerin and nitrate preparations that are used for treatment of angina are summarized in table 7.

Sublingual, buccal, or spray preparations of nitroglycerin are used for the immediate relief of angina. For maintenance

TABLE 7

The Dose and Duration of Action of Nitroglycerin and Nitrates

Nitroglycerin and nitrates	*Dose*	*Duration of action*
Nitroglycerin (SL, Buccal)	0.15–1.2 mg/PRN	10–30 minutes
Nitroglycerin patch	10–25 mg/day	8–10 hours
Isosorbide dinitrate	10–60 mg 4–6 times a day	4–6 hours
Isosorbide mononitrate	30–120 mg/day	6–10 hours

SL, sublingual; PRN, *pro-re nata* (as the circumstance arises).

therapy, isosorbide dinitrate or mononitrate are used. Short-acting nitrates can be used before undertaking physical exercise. The dose and duration of action of nitroglycerin and nitrates are summarized in table 7.

The most common side effect of nitroglycerin and nitrates is headache. Dizziness and presyncope may also occur. Frank syncope is a rare complication. Nitrate tolerance may develop during its prolonged use. A nitrate-free interval of 10–12 hours is recommended to decrease the incidence of nitrate tolerance.[35]

ACC/AHA guidelines recommendation for the use of nitroglycerin and nitrates in stable angina:

- Sublingual nitroglycerin or nitroglycerin spray for the immediate relief of angina (Class I; level of evidence C).
- Long-acting nitrates with or without calcium channel blockers as initial therapy when β-blockers are contraindicated (Class I; level of evidence B)
- Long-acting nitrates with or without calcium channel blockers in combination with β-blockers when initial treatment with β-blockers is not successful. (Class I; level of evidence B)
- Long-acting nitrates with or without calcium channel blockers as a substitute for β-blockers if initial treatment with β-blockers leads to unacceptable side effects (Class I; level of evidence C).

Calcium Channel Blockers[3]

Mechanism of Action

Calcium channel blocking agents decrease transmembranous influx of calcium via the calcium channels. Three types of voltage dependent calcium channels are recognized—L-type, T-type, and N-type. The L-type channels have large conductance. The T-type exerts transient duration of opening of calcium channel. The N-type has primarily neuronal distribution.

For treatment of angina, most frequently L-type calcium channel blockers are used. The major mechanism of action of L-type calcium channel blockers is by inhibition of calcium influx into myocytes as well as into vascular smooth muscle cells. Reduced calcium influx into myocytes causes decrease in contractility which decreases myocardial oxygen demand. Non-dihydropyridine heart rate regulating calcium channel blockers, such as verapamil and diltiazem, exert inhibitory effect on sinus node cells which is associated with decreased sinus rate. In addition, verapamil and diltiazem slow atrioventricular nodal conduction which is associated with decreased ventricular rate. Decreased sinus rate and ventricular rate are also associated with decreased myocardial oxygen demand.

Reduced calcium influx into vascular smooth muscle cells cause vasodilatation of the systemic and coronary arteries. Systemic vasodilatation is associated with decreased systemic vascular resistance and arterial pressure, factors that decrease myocardial oxygen demand. Coronary vasodilatation decreases coronary vascular resistance and increases coronary blood flow. Calcium channel blockers dilate both epicardial conductance vessels and myocardial resistance vessels.

The major mechanism of relief of angina and myocardial ischemia with calcium channel blockers is by reduction of myocardial oxygen demand. However, increased coronary blood flow may be contributory. Dilatation of the epicardial coronary arteries is the primary mechanism of the beneficial effect of calcium channel blockers in patients with vasospastic angina.

Dilatation of the myocardial resistance vessels, though is associated with increased coronary blood flow, creates a potential for diversion of coronary blood flow from the ischemic myocardium to non ischemic myocardium. This may enhance ischemia in the ischemic myocardial segments (Steal phenomenon).

With dihydropyridine calcium channel blockers, there is a reflex increase in heart rate which increases myocardial oxygen demand, partially offsetting their beneficial effects. Concomitant use of β-blockers however, prevents tachycardia.

Slow-release and long-acting dihydropyridines are effective for treatment of stable angina. Similarly, heart rate regulating non-dihydropyridine calcium channel blockers are effective as maintenance therapy of stable angina. Although both dihydropyridine and non-dihydropyridine calcium channel blockers relieve angina and improve exercise tolerance, they do not improve angina threshold.[33]

The T-type calcium channel blocker mibefradil also exerts negative inotropic effect and decrease myocardial oxygen demand. It has been withdrawn from clinical use because of adverse drug interaction.

Calcium channel blockers that are used for treatment of angina are summarized in table 8.

Side Effects

The adverse effects of calcium channel blockers are primarily related to their pharmacologic properties.

Hypotension can occur with the use of any of the calcium channel blockers. However, it is more pronounced with dihydropyridines such as nifedipine. All calcium channel blockers

TABLE 8

Calcium Channel Blocking Agents for the Treatment of Stable Angina		
Agent	*Half-life*	*Dose*
Amlodipine	30–50 hours	5–10 mg/day
Nifedipine	4–5 hours	20–40 mg TD
Diltiazem	3–4 hours	30–80 mg QD
Diltiazem slow release	Long	120–320 mg/day
Verapamil	6 hours	80–160 mg TD
Verapamil slow release	Long	120–480 mg/day
Felodipine	11–16 hours	5–10 mg/day
Isradipine	8 hours	2.5–10 mg BD
Nicardipine	2–4 hours	20–40 mg TD
Nimoldipine	1–2 hours	40 mg six times a day
Nisoldipine	6–12 hours	20–40 mg/day
Nitrendipine	5–12 hours	20 mg OD or BD

OD, once a day; BD, twice a day; TD, thrice a day; QD, four times a day.

exert negative inotropic effect and can exacerbate or cause worsening of systolic heart failure.

Lower extremity edema is a major complication of all types of calcium channel blockers during their long-term use. The severity of edema is dose dependent—larger the dose of calcium channel blockers used, worse is the lower extremity edema. The calcium channel blockers-induced edema is usually diuretics resistant. It should be noted that the mechanism of edema caused by the calcium channel blockers remains unexplained.

Constipation, often severe, can occur with the use of any type of calcium channel blockers. This is related to decreased calcium influx to the vascular smooth cells of the intestine which is associated with decrease in intestinal motility.

Calcium channel blockers can cause arrhythmia. Dihydropyridines cause reflex tachycardia due to activation of adrenergic system. Dihydropyridines do not alter sinus node discharge rate or atrioventricular conduction. Thus, they do not cause sinus node dysfunction or atrioventricular block.

Non-dihydropyridine calcium channel blockers such as diltiazem or verapamil can cause sinus bradycardia and AV block. They decrease sinus node discharge rate and slow AV conduction. Sinus bradycardia and AV block with diltiazem or verapamil is accentuated with concomitant use of digoxin or amiodarone which also exert similar pharmacologic effects

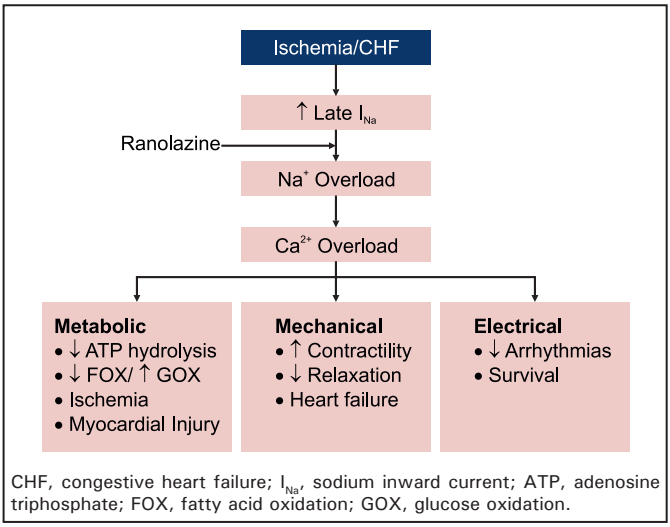
on sinus node function and AV conduction. Calcium channel blockers also alter digoxin clearance and digitalis toxicity may occur with the concomitant use of the calcium channel blockers and digoxin.

ACC/AHA guidelines recommendations for the use of calcium channel blockers for management of stable angina:

- Heart rate regulating calcium channel blockers as initial therapy when β-blockers are contraindicated (Class I; level of evidence B)
- Heart rate regulating calcium channel antagonist in combination with β-blockers when initial treatment with β-blockers is not successful (Class I; level of evidence B)
- Heart rate regulating calcium channel antagonists as a substitute for β-blockers if initial treatment with β-blockers leads to unacceptable side effects (Class I; level of evidence C).

Ranolazine

Ranolazine is an antianginal drug which neither decreases myocardial oxygen demand nor increases coronary blood flow. It has been proposed that it decreases myocardial ischemia by inhibiting late sodium inward current (Figure 2). The late sodium current channels are up-regulated during ischemia and heart failure. Activation of these channels causes increased sodium influx into myocytes. Increased intracellular sodium increases intracellular calcium by activating sodium-calcium exchange mechanism. Myocardial calcium overload causes metabolic, functional, and electrical dysfunction.[36,37]



CHF, congestive heart failure; I_{Na}, sodium inward current; ATP, adenosine triphosphate; FOX, fatty acid oxidation; GOX, glucose oxidation.

FIGURE 2. Potential role of ranolazine in modifying pathophysiology of angina.

Myocardial metabolic dysfunction is characterized by increased adenosine triphosphate (ATP) hydrolysis, increased free fatty acid oxidation, and decreased glucose oxidation. This metabolic dysfunction is associated with myocardial injury, myocyte necrosis, and apoptosis.

Myocardial mechanical dysfunction is manifested by decreased contractility and impaired relaxation. Impaired relaxation is associated with increased left ventricular end diastolic pressure. Myocardial calcium overload may also cause subendocardial ischemia and myocardial necrosis.

Calcium overload-induced electrical dysfunction causes ventricular and atrial arrhythmias. There is increased frequency of ventricular premature beats and non-sustained ventricular tachycardia. There is increased risk of arrhythmogenic mortality.

Ranolazine has been demonstrated to attenuate these adverse effects of calcium overload. It improves myocardial metabolic, mechanical, and electrical function. In the metabolic efficiency with ranolazine for less ischemia in non-ST-elevation, acute coronary syndrome–thrombolysis in myocardial infarction 36 (MERLIN-TIMI 36) trial 6,560 patients were randomized to receive either placebo or ranolazine. Treatment with ranolazine was associated with a significant reduction in the incidence of ventricular premature beats and non-sustained ventricular tachycardia. There was also a significant reduction of recurrent episodes of myocardial ischemia.

Ranolazine inhibits inward sodium influx and decreases calcium overload. Ranolazine has the potential to ameliorate the deleterious effects of calcium overload. Decreased metabolic dysfunction is associated with reduced myocardial injury. Experimental studies suggest that ranolazine can decrease myocardial injury.

Ranolazine has been shown to improve left ventricular compliance and decreases left ventricular end-diastolic pressure. It can also reduce subendocardial ischemia. The antiarrhythmic effects of ranolazine are characterized by the reduction of frequency of premature ventricular complexes and ventricular tachycardia.

The potential beneficial antianginal effects of ranolazine have been studied in a number of placebo-controlled studies. In the monotherapy assessment of ranolazine in stable angina (MARISA) trial, ranolazine compared to placebo improved exercise tolerance, increased time to ST-segment depression during treadmill exercise test.[38] It also improves exercise tolerance with a background treatment with β-blockers and calcium channel blockers.[39]

Ranolazine is extensively metabolized, approximately 70% through the CYP3A4 pathway. Ranolazine is the major bioactive compound. The maximum dose of ranolazine should be reduced when it is used with the drugs that also inhibit CYP3A4 pathway, such as verapamil and diltiazem.

Contraindications

Ranolazine is contraindicated in patients receiving ketoconazole which is a strong inhibitor of CYP3A4 pathway. It is also contraindicated in patients with severe hepatic insufficiency or cirrhosis.

Concomitant doses of statins that inhibit P450 cytochrome pathway should be reduced. Thus the doses of lovastatin and simvastatin should be reduced. The dose of simvastatin should not exceed 20 mg daily and the dose of ranolazine should also be reduced.

Side Effects

The side effects of ranolazine are relatively minor. The dizziness and nausea can occur at the initiation of the treatment with ranolazine. Dose-related asthenia and constipation occur in 3–10%. Although electrocardiogram (ECG) can reveal prolongation of QT interval, ventricular arrhythmias resulting from prolongation from QT do not occur. Indeed, ranolazine exerts protective effect against ventricular arrhythmia.

ACC/AHA guidelines recommendations for use of ranolazine in chronic stable angina:

- Refractory angina (Class IIa; level of evidence A).

Trimetazidine

Under normal conditions free-fatty acid oxidation is the chief metabolic source for myocardial energy utilization. In presence of hypoxia, glucose oxidation is preferable to free-fatty acid oxidation as there is more generation of ATP for maintaining myocyte and myocardial metabolic functions. The agents that inhibit oxidation of free fatty acids have the potential to enhance oxygen supply and relieve ischemia and angina.

Trimetazidine is a partial inhibitor of oxidation of free fatty acids and has been demonstrated to be effective for treatment of stable angina. In a number of randomized clinical trials, it has been shown to relieve frequency of angina and improve exercise tolerance.[40-42] In a randomized clinical trial, effects of trimetazidine were assessed on the frequency of myocardial ischemia, in patients with non-insulin dependent diabetes. The frequency of ischemia was assessed by ambulatory electrocardiography. The use of trimetazidine was associated with a significant reduction

in the frequency of ischemia.[43] Trimetazidine is usually used in combination with other antianginal drugs.

Side Effects

Myalgia, nausea, vomiting, and fatigue are the reported side effects.

Contraindications

Trimetazidine is well tolerated and there are no absolute contraindications.

European Society of Cardiology (ESC) guidelines recommendations for the use of trimetazidine:

- Metabolic agents should be used were available as add-on therapy, or as substitute therapy when conventional drugs are not tolerated (Class IIb; level of evidence B).

Nicorandil

Nicorandil is similar to nitroglycerin in its pharmacodynamic effects. It also produces similar hemodynamic effects.

Nicorandil enhances production of nitric oxide but also activates ATP sensitive inward rectifier potassium channels. The hemodynamic effects are characterized by a significant reduction of right atrial and pulmonary capillary wedge pressures with a modest increase in cardiac output. There is little or no change in heart rate or contractility. There is reduction of left ventricular preload and afterload.[44-46] The net effects on coronary hemodynamics are reduction of myocardial oxygen demand.

Reduction of myocardial oxygen demand is the principal mechanism for reduction of myocardial ischemia and relieving angina.

In the impact of nicorandil in angina trial (IONA),[44] over 5,000 patients with stable angina were randomized to receive either nicorandil or placebo. The results of this study reported a significant reduction in the composite end point of death from coronary heart disease, nonfatal myocardial infarction, and hospital readmission for cardiac chest pain during a follow-up of about 18 months. The predominant beneficial effect was related to the reduction in hospital admission rates for chest pain but not in the reduction of death or nonfatal myocardial infarction. It is also of interest that the beneficial effects of nicorandil were not observed in women which might be related to a smaller number of women enrolled in the study.

The report of a meta-analysis of 20 studies indicated no advantage of nicorandil in reducing the frequency of angina attacks or in the time to ST-segment changes during exercise tests.[46]

Dose and Side Effects

The usual dose of nicorandil is 10–20 mg twice a day. The major side effect is development of tolerance like nitrate tolerance.

The ESC Guidelines recommendations for the use of nicorandil:

- For patients with intolerance or contraindications to β-adrenergic receptor or calcium channel blockers (Class I; level of evidence C)
- For patients who have been unsuccessfully treated with two antianginal drugs, (Class IIa; level of evidence C).

Ivabradine

Ivabradine is a selective inhibitor of the funny (I_f) current.[47,48] The I_f current is an inward potassium current and it is activated by hyperpolarization of the myocytes. The myocytes of the sinoatrial nodal cells possess the I_f current channels and they are absent in the AV nodal cells. Inhibition of I_f currents is associated with a reduction in sinus rate and a prolonged sinus node recovery time. The complete blockade of I_f currents by ivabradine is associated with a 30–40% reduction of sinus rate. It has no effect on AV conduction and thus it does not decrease ventricular response in patients with atrial fibrillation. The magnitude of reduction in heart rate by ivabradine depends on the resting heart rate. The faster the resting heart rate, greater is the magnitude of reduction heart rate by ivabradine. The QT-interval is prolonged by ivabradine; however, corrected QT-interval for heart rate is only slightly prolonged.

It should be appreciated that the I_f current inhibitor ivabradine does not exert negative inotropic effects like β-adrenergic antagonists.

In randomized clinical trials ivabradine has been reported to decrease the frequency of angina, nitroglycerin consumption, and to increase exercise duration and the time to ST-segment depression during treadmill exercise test.[49-53] In the morbidity-mortality evaluation of the I_f inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction (BEAUTIFUL) trial,[54] almost 11,000 patients with LV ejection fraction <40% were randomized to receive either ivabradine or placebo. The majority of patients received β-blockers as background therapy. During the follow up of approximately two years, there was no change in cardiovascular mortality with ivabradine. However, there was a significant reduction in the rate of hospital admission for myocardial infarction or heart failure. In the BEAUTIFUL trial about 14% of patients had stable angina at baseline. In patients with resting heart rate of 70 beats/min or higher, there was almost 60% reduction in the need for revascularization.

Dose and Side Effects

The usual dose is 5.0–7.5 mg twice a day. In elderly patients, a lower dose is recommended. Blurred vision or sharp flashes are the most common side effects (The retina and brain cells have I_f channel isoforms). Other side effects are headache, dizziness, and symptomatic bradycardia.

Contraindications

Ivabradine is metabolized through the CYP3A4 hepatic pathway. It is contraindicated in patients receiving inhibitors of this metabolic pathway. It is also contraindicated in patients with moderate-to-severe hepatic insufficiency.

Rho-kinase Inhibitors

Rho-kinase is a guanosine triphosphate binding protein (GTP) which is involved in signaling pathway for intracellular calcium handling. It promotes intracellular calcium entry and increases vascular tone. In coronary circulation, it enhances coronary vasoconstriction. Rho-kinase inhibitors decrease coronary vascular resistance and increase coronary blood flow. This is the principal mechanism for relief of myocardial ischemia and angina by Rho-kinase inhibitors.

In a randomized, double blind placebo-controlled trial, the efficacy of a Rho-kinase inhibitor, fasudil was compared to that of placebo.[55] Fasudil was reported to increase the time to ST-segment depression during treadmill exercise test.

Allopurinol

Allopurinol is a xanthine oxidase inhibitor and has been reported to be of benefit in patients with stable angina. In a randomized placebo-controlled study, allopurinol in a dose of 300 mg daily was reported to improve exercise tolerance and to increase the time to ST-segment depression during treadmill exercise test.[56] The precise mechanism of the beneficial effect of allopurinol remains unknown.

Vasopeptidase Inhibitors

These agents inhibit both bradykinin and angiotensin formation by inhibiting ACE. They have the potential to decrease coronary vascular resistance, increase coronary blood flow and decrease myocardial oxygen demand concurrently. These agents, therefore, have the potential to be of benefit in management of chronic stable angina. The risks of angioedema prohibit their use.

Angiogenesis

Promotion of development of adequate and new blood vessels to the ischemic myocardial segments potentially can be of benefit in relieving ischemia and angina. Vascular endothelial growth

factors and fibroblast growth factors as angiogenic factors have been studied and the results remain inconclusive.

Intracoronary infusion of stem cells and angiogenic agents to the ischemic myocardium to improve angiogenesis has also been attempted but with no conclusive results.

VASOSPASTIC ANGINA

Vasospastic angina (Prinzmetal angina) results from focal spasm of the epicardial coronary arteries. Coronary vasodilators, such as nitrates and calcium channel blocking agents, are the appropriate pharmacologic agents.

MIXED ANGINA

Mixed angina is characterized by variable angina threshold. The patients can exercise on occasions more without developing angina; on other occasions angina develops at a much lower level of exercise. The mechanism appears to be due to increase in myocardial oxygen demand and concurrent increase in coronary vascular resistance. Pharmacologic agents that decrease myocardial oxygen demand and cause coronary vasodilatation are appropriate.

WALK-THROUGH ANGINA

In these patients, angina develops at the beginning of exercise. The angina is relieved even when patients continue to the same level of exercise. The mechanism appears to be due to increase in coronary vascular resistance and decrease in coronary blood flow at the beginning of exercise. During continued exercise, metabolically related coronary vascular resistance declines with a concomitant increase in coronary blood flow. The pharmacologic agents with coronary vasodilatory properties are appropriate.

LINKED ANGINA

In these patients, there is a reflex increase in coronary vascular resistance and centrally mediated decrease in coronary blood flow. The activation of the afferent receptors, which are located in the gastroesophageal junction, occurs during acid reflux. The histamine receptors (H_2) blockers appear to be appropriate treatment.

SYNDROME "X"

In this syndrome, exercise-induced angina with evidence of myocardial ischemia develops in absence of significant atherosclerotic obstructive coronary artery disease. Inadequate

coronary vasodilatory reserve appears to be the principal mechanism. Pharmacologic agents with coronary vasodilatory property are appropriate.

CONCLUSION

Chronic stable angina is a common clinical manifestation of ischemic heart disease. It usually results from disproportionate increase in myocardial oxygen demand. However, a concomitant reduction in autoregulatory reserve decreases angina threshold.

The effective pharmacologic treatment consists of agents that decrease myocardial oxygen demand. In certain clinical subsets, however, the pharmacologic agents that increase coronary blood flow concurrently may be useful.

The newer pharmacologic agents have some beneficial effects but only in selected patients. Reperfusion therapy should be reserved only for patients with refractory angina.

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11 CHAPTER

Drugs for Pulmonary Hypertension

Ravinder Kumar, Sif Hansdottir

INTRODUCTION

The pulmonary vasculature under normal conditions is a low pressure and low resistance system. Pulmonary hypertension (PH) is a hemodynamic state characterized by elevated pressure in the pulmonary vascular bed. The pressure in the pulmonary artery is considered elevated when the resting mean pulmonary arterial pressure (mPAP) is >25 mmHg, as measured by right heart catheterization (RHC). Many clinical conditions can lead to pulmonary hypertension (PH) and an extensive evaluation focused on elucidating underlying etiologies is the key to successful management as the treatment varies greatly depending on underlying etiologies.

NOMENCLATURE AND CLASSIFICATION

Clinically, the WHO classifies PH into 5 major categories on the basis of pathological, physiological, and therapeutic characteristics (Table 1).[1] The nomenclature can be quite confusing and is worth reviewing. The term PH encompasses all WHO categories. WHO group 1 pulmonary arterial hypertension (PAH) includes idiopathic PAH (iPAH), hereditary PAH (hPAH), and PH associated with several clinical conditions. The clinical conditions are detailed in table 1 and have similar pathophysiology and treatment response as iPAH. iPAH was previously referred to as "primary PH," but this term has been abandoned. WHO group 2 PH is PH owing to elevated left heart pressures that result from either left sided valvular disease or heart failure. This group is also referred to as pulmonary venous hypertension (PVH) or postcapillary PH. The other 2 major categories of PH are WHO group 3 PH due to lung disease or sleep disordered breathing and WHO group 4 PH from chronic thrombotic and/or embolic disease. Lastly, WHO group 5 PH consists of various miscellaneous conditions that have been found to be risk factors for PH, but the pathophysiology is unclear.

TABLE 1

Updated WHO Clinical Classification of Pulmonary Hypertension (Dana Point, 2008)

1. Pulmonary arterial hypertension
   - Idiopathic (previously primary pulmonary hypertension)
   - Heritable (bone morphogenetic protein receptor type 2 (BMPR2), activin receptor-like kinase type 1 (ALK1), endoglin)
   - Drugs and toxins
   - Associated with: connective tissue disease, human immunodeficiency virus (HIV), portal hypertension, congenital heart disease, schistosomiasis, and chronic hemolytic anemia

1′. Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis

2. Pulmonary hypertension owing to left heart disease
   - Systolic or diastolic dysfunction
   - Valvular disease

3. Pulmonary hypertension owing to lung disease
   - Chronic obstructive pulmonary disease, interstitial lung disease, sleep disordered breathing, and chronic exposure to high altitude

4. Chronic thromboembolic pulmonary hypertension

5. Pulmonary hypertension with unclear multifactorial mechanism
   - Hematological, systemic, or metabolic disorders

The hemodynamic classification of PH has 2 major components—mean pulmonary arterial pressure (mPAP) and left heart pressures. The 4th World Symposium at Dana Point in 2008 recommends that mPAP ≥25 mmHg at rest by RCH should be considered elevated.[2] Based on left heart pressures, i.e., left atrial pressure as estimated by pulmonary capillary wedge pressure (PCWP) or the more directly measured left ventricular end-diastolic pressure (LVEDP), PH can be further categorized as precapillary (PCWP or LVEDP ≤15 mmHg) and postcapillary (PCWP or LVEDP >15 mmHg).[3] WHO group 1 PAH, WHO group 3 PH due to lung disease and/or hypoxia, WHO group 4 chronic thromboembolic PH (CTEPH), and WHO group 5 PH with unclear or multifactorial mechanism all result in precapillary PH and cannot be distinguished based on hemodynamics alone.

WHO Group 1 Pulmonary Arterial Hypertension

WHO group 1 PAH has been the focus of intense research over the last 15 years and major advances have been made in the understanding of pathophysiology and treatment of this condition. The clinical conditions that fall into this category (Table 1) have been found to have similar clinical presentation,

hemodynamics, pathology, and response to treatment. The exact prevalence of PAH is unclear but ranges between 15 and 50 cases per million in Western countries.[4,5] PAH is a progressive and often fatal disease and the pathophysiology is characterized by vasoconstriction, excessive cellular proliferation, inflammation, and *in situ* thrombosis. Patients with PAH have an imbalance between endothelial production of vasodilatory and anti-proliferative agents like nitric oxide[6] and prostacyclin,[7] and vasoconstrictive and proliferative substances like endothelin-1.[8] The outcome is obstructive remodeling of the pulmonary vessels and an increase in PAP and pulmonary vascular resistance (PVR). The progressive increase in PVR ultimately leads to right ventricular (RV) hypertrophy and dilatation and, eventually, RV failure.

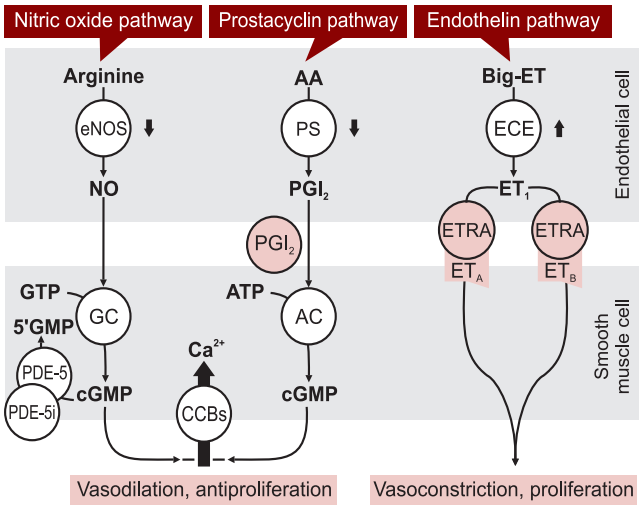
Increased understanding of the pathophysiology of PAH has resulted in the availability of multiple medical treatment options that all target one of 3 pathways, i.e., the prostacyclin, nitric oxide, or endothelin pathways[9] (Figure 1). Prior to 1995, there was no specific treatment for PAH, and patients were treated empirically with calcium channel blockers (CCBs), digoxin, diuretics, and anticoagulation. The first PAH specific treatment, epoprostenol, was approved by the USFDA in 1995. Since then, the number of USFDA approved therapeutic options has increased steadily with 9 PAH specific therapies available at the end of the year of 2011 (Figure 2).

TREATMENT

This chapter focuses on the treatment of WHO group 1 PAH, starting with general treatment measures, followed by supportive therapies and the role of CCBs, and lastly disease specific therapies. These therapeutic options are generally not applicable to non-WHO group 1 PH.

Goals of Treatment in Pulmonary Arterial Hypertension

- To improve symptoms and signs—mainly dyspnea, fatigue, lightheadedness, and edema
- To enhance functional capacity—measured objectively by an assessment of exercise tolerance, such as the 6-minute walk distance (6-MWD) or a cardiopulmonary exercise test
- To improve hemodynamics—elevated right atrial pressure (RAP), high PVR, and low cardiac output are all poor prognostic factors
- To reverse or at least prevent the progression of the disease



AA, arachidonic acid; ET, endothelin; NO, nitric oxide; eNOS, endothelial NO synthase; PS, prostacyclin synthase; ECE, endothelin-converting enzyme; PGI_2, production of prostaglandin I_2; ETRA, endothelin receptor antagonist; GTP, guanylate triphosphate; ATP, adenosine triphosphate; GC, guanylate cyclase; AC, adenylate cyclase; PDE-5i, phosphodiesterase 5 inhibitor; CCB, calcium channel blocker; cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanylate monophosphate.

FIGURE 1. Three mechanistic pathways disturbed in patients with PAH. The short, thick, black arrows depict aberrations observed in these pathways in patients with PAH. The points at which drug treatment affects these mechanistic processes are shown in gray circles.

Left, the NO pathway. NO is created in endothelial cells by type III (i.e., endothelial) eNOS, which in pulmonary arterial smooth muscle cells (PASMCs) induces GC to convert GTP to cGMP. cGMP is a second messenger that constitutively maintains PASMC relaxation and inhibition of PASMC proliferation by ultimately reducing inward flux of calcium ions (Ca^{2+}). Cyclic GMP is removed by the PDE-5 enzyme to yield the inactive product 5′GMP. Patients with PAH have reduced expression and activity of eNOS.

Middle, the prostacyclin pathway. The production of PGI_2 is catalyzed by PS in endothelial cells. In PASMCs, PGI_2 stimulates AC, thus increasing production of cAMP from ATP. cAMP is a second messenger that constitutively maintains PASMC relaxation and inhibition of PASMC proliferation. Patients with PAH have reduced expression and activity of PS.

Right, the ET pathway. Big- (i.e., pro-) ET is converted in endothelial cells to ET_1 (a 21-amino acid peptide) by endothelin-converting enzyme (ECE). ET_1 binds to PASMC ET_A and ET_B receptors, ultimately leading to PASMC contraction, proliferation, and hypertrophy. Endothelin-1 also binds to endothelial cell ET_B receptors (not illustrated). Patients with PAH have increased expression and activity of ECE.

Adapted from McGoon MD, Kane GC. Pulmonary hypertension: diagnosis and management. *Mayo Clin Proc*. 2009;84(2):191-207, *with permission*.

- To improve survival—which, while important, is rarely an end-point in clinical trials of PAH treatment due to the small number of patients and limited duration of trials.

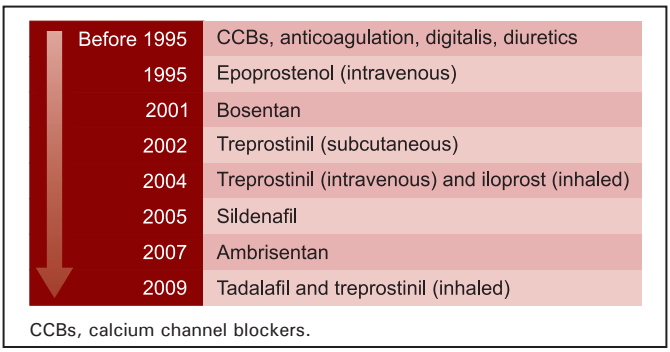


FIGURE 2. Timeline of USFDA approval of pulmonary arterial hypertension specific therapies.

General Treatment Measures

Diet

Limiting fluid and sodium intake (<2.4 g/day) is advised and is particularly important in patients with symptomatic right heart failure for managing the volume status.

Exercise

While there is limited data on which recommendations regarding exercise can be given, low intensity, graded aerobic exercise, like walking, as tolerated by the patient is usually encouraged. Intensive exercise training was studied in a randomized trial in 30 patients who were stable on disease-specific medical treatment. After 15 weeks of exercise training, the patients demonstrated improvements in 6-MWD, functional class, quality of life, and peak oxygen consumption.[10] Patients should be advised to avoid heavy physical exertion (expert opinion, strong recommendation) or isometric exercise (straining against a fixed resistance) as this can evoke exertional syncope.

Immunizations

Routine immunizations against influenza and pneumococcal pneumonia are advised.

Pregnancy

According to current guidelines, pregnancy should be avoided or terminated as early as possible in women with PAH.[11] The hemodynamic fluctuations during pregnancy, labor, delivery, and the postpartum period are potentially devastating. In fact, maternal mortality rates as high as 30–50% have been observed in some series.[12] It is important to discuss effective methods of birth control with women with PAH of childbearing age. Use of contraceptive preparation, which have estrogen may increase

the risk of venous thromboembolism, but preparations with a lower-dose can be used with concurrent warfarin anticoagulation. Use of barrier methods or surgical sterilization can also be used as alternatives.

Supportive Therapies for Pulmonary Arterial Hypertension

Supportive therapies are treatments that are directed at the consequences of PAH. Supportive therapies have only been studied in retrospective and/or nonrandomized trials. Recommendations regarding their use are thus based on expert opinion.[13]

Oxygen (Expert Opinion, Strong Recommendation)

Oxygen supplementation is recommended to maintain oxygen saturation above 90% to avoid hypoxia mediated pulmonary vasoconstriction. Patients with hypoxemia should be evaluated for pulmonary embolism and right-to-left shunt. Exposure to high altitudes may worsen hypoxia and result in hypoxic pulmonary vasoconstriction. Similarly, some patients may require oxygen during air travel. Although there is no data from controlled trials, it is recommended that if the patient's preflight oxygen saturation as determined by pulse oximetry is less than 92%, he or she should receive supplemental oxygen.[14]

Anticoagulation (Expert Opinion, Moderate Recommendation)

The pathologic evidence of *in situ* thrombosis and abnormal platelet function provides a rationale for anticoagulation in patients with PAH.[15] Anticoagulants have been studied in 3 non-controlled observational series in patients with mainly iPAH.[16-18] An improvement in survival with warfarin anticoagulation has been observed. Anticoagulation is recommended in patients with iPAH and those with advanced disease requiring intravenous therapy (International Randomized Ratio goal of 1.5–2.5).[19] The role of newer anticoagulants, such as dabigatran, has not been studied in PAH.

Diuretics (Expert Opinion, Strong Recommendation)

Diuretics are used to manage RV volume overload, which manifests as elevated jugular venous pressure, lower extremity edema, and abdominal distension. Loop diuretics including furosemide, bumetanide, and torsemide are frequently used

in clinical practice. Goals of therapy are to reduce the central venous pressure and eliminate renal and hepatic congestion without causing hypotension. Aldosterone antagonists, such as spironolactone can be used in patients to help conserve K^+ and may also have beneficial effects on RV remodeling. Renal function and electrolytes should be closely monitored in patients receiving diuretics.

Digoxin (Expert Opinion, Weak Recommendation)

Digoxin is sometimes used in patients with RV failure and low cardiac output or in patients with atrial arrhythmias. One study demonstrated that giving intravenous digoxin to iPAH patients produced a modest increase in cardiac output and a reduction in circulating norepinephrine levels after 2 hours. Longer-term data are not available.[20] There is a narrow therapeutic window and the goal serum digoxin level, as with any other heart failure patient being treated with digoxin, is 0.5–0.8 ng/mL. Levels should be closely monitored in elderly and patients with renal dysfunction.

Calcium Channel Blockers

Acute vasodilator testing and the use of CCBs in PAH have mainly been studied in patients with iPAH. The rationale for vasodilator testing in diagnostic evaluation of PAH is based on 2 factors: (i) acute vasodilator responsiveness identifies patients with a better prognosis and (ii) responders are more likely to have a sustained response to oral CCBs than nonresponders and can be treated with these less expensive drugs.[21] Acute vasodilator testing should be done only in referral centers and preferably using inhaled nitric oxide (iNO), although intravenous epoprostenol or intravenous adenosine may be used as an alternative. A positive response is defined as a decrease in mPAP by at least 10 mmHg to an absolute level of mPAP <40 mmHg without a decrease in cardiac output.

CCBs have been used in iPAH since 1992 when a study demonstrated 95% 5-year survival in patients who exhibited an acute vasodilator response.[16] The typical agents used in PAH are dihydropyridines, including amlodipine or nifedipine, or the nondihydropyridine diltiazem. The choice of CCB is based upon the patient's heart rate with relative bradycardia favoring the dihydropyridines and tachycardia favoring diltiazem. Verapamil is not used because of its potential negative inotropic effects. If a patient who meets the definition of an acute responder does not improve to WHO functional class I or II on CCB, the patient

should no longer be considered a responder, and alternative or additional PAH-specific therapy should be instituted. Only approximately 8% of iPAH will continue to respond to CCB therapy over the following year.[21] In order to achieve the maximum benefit, patients generally need high doses of CCBs that are higher than those conventionally used to treat systemic hypertension, 20–30 mg/day of amlodipine, 180–240 mg/day of nifedipine, and 720–960 mg/day of diltiazem.

The usefulness of acute vasoreactivity testing and long-term treatment with CCBs in PAH types other than iPAH is not clear. Based on expert opinion, the European guidelines recommend doing vasoreactivity testing in patients with iPAH, hPAH, and in PAH associated with anorexigen use.[3] Vasoreactivity testing is not recommended in non-WHO group 1 PH. Lastly, testing should be done with caution in patients with concomitant left ventricular disease as pulmonary edema has been reported in patients with stable left-sided heart failure.

Disease Specific Therapies for Pulmonary Arterial Hypertension

Prior to 1995, there was no specific treatment for PAH. Extensive research over the last 2 decades has resulted in the development of several new treatment options. Currently, 3 classes of drugs form the mainstay of treatment: prostacyclin analogues, endothelin receptor antagonists (ERAs), and phosphodiesterase-5 inhibitors. Approval of these therapies in PAH is largely supported by data from relatively small, randomized, placebo-controlled studies of 12–16 weeks duration demonstrating modest improvements in functional class, exercise capacity, and hemodynamics. Few studies have been designed to prospectively assess long-term morbidity and mortality, but several studies are currently under way. Evidence supporting survival benefits of current PAH therapies is mostly surmised from observational *post hoc* analyses, referencing historical control data, and meta-analysis. It should be noted that PAH-specific therapies have mainly been evaluated in patients with iPAH, hPAH, PAH associated with connective tissue disease (CTD), and in patients with PAH from anorexigen use. Extrapolation of findings to other PAH subgroups should be done with caution. Lastly, it is worth emphasizing that PAH-specific therapies are USFDA approved only for WHO group 1 PH but not for WHO groups 2–5 PH (Table 2).

Prostacyclins

Prostacyclins are generated through the breakdown of arachidonic acid using prostacyclin synthase, an enzyme that is reduced in

TABLE 2

Disease Specific Therapies for Pulmonary Arterial Hypertension			
Drug	*Dose*	*Side effects*	*Comments*
Prostacyclin analogues			
Epoprostenol (IV)	Started at low dose of 1–2 ng/kg/min and increased by 1–2 ng/kg/min weekly or biweekly, as tolerated to an optimal dose of 20–45 ng/kg/min	Headache, flushing, jaw pain, nausea, diarrhea, hypotension, dizziness, thrombocytopenia, leg pain, cough (inhaled), and site pain (subcutaneous)	Interruption of IV therapy can cause life-threatening worsening of pulmonary hypertension
Treprostinil (SC, IV, and inhaled)	Treprostinil (SC and IV) started at low dose of 1–2 ng/kg/min and increased to 20–80 ng/kg/min. Treprostinil (inhaled), 3–9 breaths 4 times daily while awake		Bolus of IV therapy can cause severe side effects, in particular hypotension
Iloprost (inhaled)	Iloprost (inhaled), every 2 hours 6–9 times a day		Line infections and thrombosis in patients with indwelling catheters
Endothelin receptor antagonists			
Bosentan	Started at 62.5 mg BD and titrated to 125 mg BD after 4 weeks	Peripheral edema, liver toxicity, anemia, teratogenicity, reduced hormonal contraceptive efficacy, reduced sperm count, and drug-drug interactions with strong inducers or inhibitors of CYP450 enzymes	Monthly LFTs with bosentan (FDA recently removed the monthly monitoring requirement for ambrisentan)
Ambrisentan	Ambrisentan is started at a dose of 5 mg daily and is up titrated to 10 mg daily		Monthly pregnancy test for women of childbearing potential
Phosphodiesterase-5 inhibitors			
Sildenafil	USFDA approved dose—20 mg TID	Headache, dizziness, nausea, priapism, epistaxis, hearing loss, AION and optic atrophy	Nitrates contraindicated due to potential life threatening hypotension
Tadalafil	USFDA approved dose—40 mg daily		

BD, twice a day; TID, thrice a day; LFT, liver function test; AION, anterior ischemic optic neuropathy.

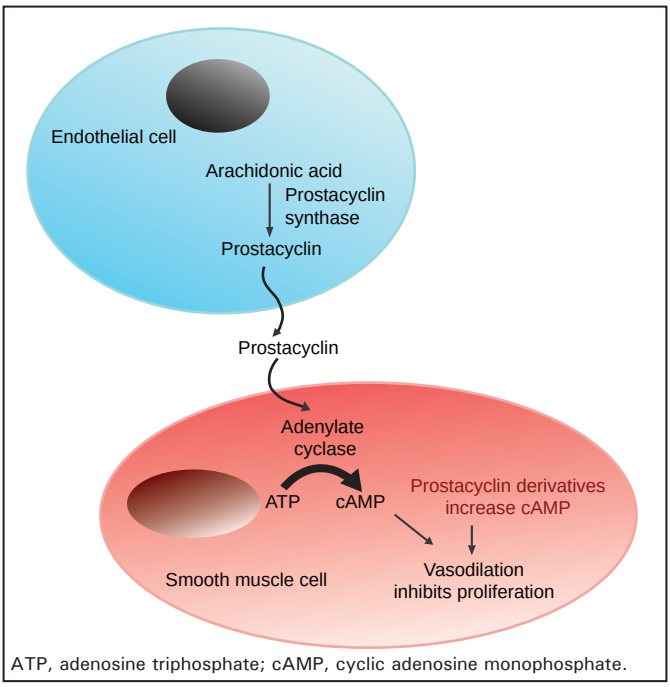


FIGURE 3. Prostacyclins: Mechanism of action in pulmonary arterial hypertension.

PAH patients (Figure 1). The arachidonic acid metabolism is shifted towards production of thromboxane (a vasoconstrictor and promoter of platelet aggregation), which contributes to the pathogenesis of PAH. The vasodilator and antiproliferative effects of prostacyclin I_2 are mediated through the production of cyclic adenosine monophosphate (cAMP) (Figure 3).[22] Prostacyclin and its analogues also inhibit platelet aggregation.

Prostacyclins are USFDA approved for use in patients with PAH. Their use has been associated with reduced survival in patients with systolic heart failure (WHO group 2 PH)[23-25] and increased pulmonary shunt flow and hypoxemia in patients with lung disease (WHO group 3 PH).[24,25]

There are 3 approved prostacyclins and 3 different modes of delivery:

- Intravenous epoprostenol
- Intravenous treprostinil
- Subcutaneous treprostinil
- Inhaled treprostinil
- Inhaled iloprost.

The choice of prostacyclin and the route of administration are determined by a combination of severity of illness and patient factors. Severity of illness is based mainly on WHO

TABLE 3

Determinants of Prognosis in Pulmonary Arterial Hypertension		
Determinants of risk	*Lower*	*Higher*
Clinical evidence of RV failure	No	Yes
Progression	Gradual	Rapid
WHO class	II and III	IV
6-MWD	Longer (>400 m)	Shorter (<300 m)
CPET	Peak VO_2 >10.4 mL/kg/min	Peak VO_2 <10.4 mL/kg/min
BNP	Minimally elevated	Significantly elevated
Echocardiographic findings	Minimal RV dysfunction	Pericardial effusion and significant RV dysfunction
Hemodynamics	RAP <10 mmHg CI >2.5 L/min/m^2	RAP >20 mmHg CI <2.0 L/min/m^2

6-MWD, 6-minute walk distance; CPET, cardiopulmonary exercise testing; RV, right ventricular; BNP, B-type natriuretic peptide; RAP, right atrial pressure.

functional class, but other risk factors should also be taken into consideration (Table 3). Patient factors include patient's preference of route, social support, manual dexterity, and distance of the patient from a hospital with staff trained in their management.

Epoprostenol

Epoprostenol has a very short half-life of 3–6 minutes and is administered as a continuous intravenous infusion through a central venous catheter.

Epoprostenol was found to be beneficial in a landmark trial with significant improvement in the primary end-point of 6-MWD (32 m increase with epoprostenol vs. 15 m decrease with conventional therapy alone), and in secondary end-points, including hemodynamics and quality of life.[26] This 12-week prospective, randomized, multicenter, open label trial included 81 functional class III and IV iPAH patients. Eight patients in the conventional therapy arm died over the course of the study, suggesting a survival benefit of epoprostenol ($p = 0.003$). Longer-term observational studies have confirmed the chronic benefits of intravenous epoprostenol in iPAH patients. In a series of 178 functional class III and IV iPAH patients, Sitbon et al. reported improved survival with intravenous epoprostenol in comparison to historical controls with 1-, 2-, 3-, and 5-year survival rates of 85, 70, 63, and 55%, respectively.[27] Similarly, in a series of 162 WHO functional class III and IV patients, intravenous epoprostenol resulted in improved survival as compared to the

predicted survival based on the National Institutes of Health equation with 1-, 2-, 3-, and 5-year survival rates of 88, 76, 63, and 56%, respectively.[28] Both these observational studies demonstrated improvement in functional class, exercise tolerance, and hemodynamics.

Epoprostenol is USFDA approved therapy for PAH. It is unstable at room temperature and needs to be maintained on ice after reconstitution. In 2010, a room temperature stable form of epoprostenol was approved for usage in PAH. Epoprostenol is started at a low dose of 1–2 ng/kg/min and increased slowly by 1–2 ng/kg/min weekly or biweekly, depending on tolerability and side effects to an optimal dose of 20–45 ng/kg/min. A more rapid up-titration can be done under close monitoring in an intensive care unit. Because epoprostenol has a very short half-life, interruption of the infusion can result in rebound worsening of PH, which can be life threatening. Likewise, inadvertent bolus administration can lead to life threatening systemic vasodilation and hypotension.

Treprostinil

Treprostinil is a more stable prostanoid with an elimination half-life of about 4.5 hours. Treprostinil was initially studied as a subcutaneous infusion but is now also available as an intravenous infusion and as an inhaled formulation.

In a 12-week, double blind, placebo-controlled, multicenter trial of 470 patients with functional classes II, III, or IV PAH [iPAH, CTD, or congenital heart disease (CHD) related], subcutaneous treprostinil resulted in a modest but statistically significant median increase of 16 m of the 6-MWD, which was dose related.[29,30]

The TRUST trial (Treprostinil for Untreated Symptomatic PAH Trial) was a 12-week placebo-controlled study of intravenous treprostinil. There were 44 patients with New York Heart Association (NYHA) class III symptoms due to iPAH and hPAH in this study. 6-MWD improved by a placebo corrected median of 83 m in patients treated with treprostinil ($p = 0.0008$).[31] Treprostinil patients also had a reduction in Borg scale of dyspnea by a median of 2 units ($p = 0.02$) and improved NYHA functional class by a median of 1 class ($p = 0.051$).

The TRIUMPH-1 trial (Treprostinil Sodium Inhalation Used in the Management of Pulmonary Hypertension-1), a 12-week double blind, placebo-controlled trial studied inhaled treprostinil in 235 PAH patients with NYHA functional classes III–IV who remained symptomatic on bosentan or sildenafil.[32] At baseline, 70% of patients were on bosentan and 30% were

on sildenafil. At 12 weeks, change in 6-MWD, measured 10–60 minutes after treprostinil inhalation was 21.6 m in the treprostinil group and 3.0 m in the placebo group. The between group median difference was 20 m ($p = 0.0004$). Although quality of life measures and N-terminal pro-B-type natriuretic peptide (NT-proBNP) improved with therapy, there was no change in the secondary end-point of time to clinical worsening.

The USFDA approved subcutaneous treprostinil in 2002 for use in functional classes II, III, and IV PAH and intravenous treprostinil in 2004 for patients who do not tolerate the subcutaneous infusion.

Treprostinil (subcutaneous and intravenous) is started at a low dose of 1–2 ng/kg/min and is increased gradually to a dose of 20–80 ng/kg/min. If a rapid up-titration is needed, it should be done with close monitoring of the hemodynamic status. The USFDA approved inhaled treprostinil in 2009. Inhalational treprostinil is administered via an ultrasonic nebulizer and the total dose is administered in less than a minute with 3–9 breaths four times a day.

Iloprost

Iloprost is a synthetic analogue of prostacyclin PGI_2. In the AIR trial (Aerosolized Randomized Iloprost Study), 207 functional class III and IV patients with iPAH, PAH associated with scleroderma spectrum of disease or anorexigens, or PAH associated with inoperable CTEPH (WHO group 4) were randomized to inhaled iloprost vs. placebo for 12 weeks.[33] Sixteen percent of patients in the iloprost group as compared to 4.9% of the placebo group met the combined primary end-point of improvement by at least 1 NYHA functional class and 6-MWD increase by 10% in the absence of clinical deterioration ($p = 0.007$). The treatment effect on the 6-MWD was a mean increase of 36 m in favor of iloprost ($p = 0.004$).

The USFDA approved inhaled iloprost in 2004 for functional class III and IV PAH. Iloprost is administered via the hand-held portable I-neb Adaptive Aerosol Delivery System every 2 hours while the patient is awake for a total of 6–9 treatments daily. The device also contains a computer microchip, which can be analyzed with software that provides useful information, such as patient compliance and treatment times.

Prostacyclin Side Effects

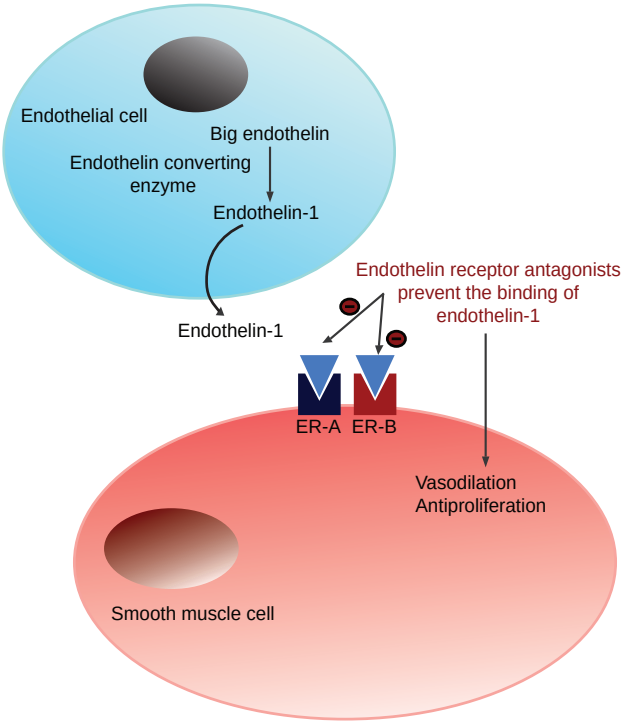
Common side effects of prostacyclins and prostacyclin analogues include headache, flushing, jaw pain, nausea, diarrhea, hypotension, dizziness, and leg pain. Patients with intravenous

catheters are at risk of infection and thrombosis as well as interruption of therapy. When given as a subcutaneous infusion (treprostinil), approximately 85% of patients experience infusion pain and/or infusion site reactions, which can be mitigated by rotating the infusion site. However, 5–23% of patients discontinue the subcutaneous infusion due to this complication. The inhaled agents are commonly associated with cough.

Endothelin Receptor Antagonists

Endothelin-1 is a vasoconstrictor and smooth muscle mitogen that may contribute to the development of PAH. The actions of endothelin-1 are mediated via 2 endothelin receptors, ET-A and ET-B (Figure 1). Although activation of ET-A leads to vasoconstriction and ET-B tends to lead to vasodilatation and release of antiproliferative factors, selective vs. nonselective blockade of receptors does not appear to affect clinical outcome (Figure 4).

Like prostacyclins, ERAs are only approved for use in WHO group 1 PAH. Benefits of therapy have not been shown in other



ER-A, endothelin receptor A; ER-B, endothelin receptor B.

FIGURE 4. Endothelin receptor antagonists: Mechanism of action in pulmonary arterial hypertension.

types of PH and inappropriate use may result in harm. Kaluski et al. conducted a double-blind study of 87 patients with chronic left heart failure and PVH (WHO group 2) treated with bosentan for 20 weeks and found no hemodynamic improvement.[34] More patients treated with bosentan stopped therapy due to adverse effects, including worsened heart failure symptoms and death. Similarly, studies on patients with WHO group 3 PH due to lung disease have not found ERAs to be beneficial and some have shown a decrease in exercise capacity and worsening of hypoxemia.[35,36]

Bosentan

Bosentan is a dual endothelin receptor antagonist and was the first oral medication approved for PAH. In a small, randomized, double-blind, placebo-controlled, multicenter study, 32 functional class III or IV iPAH or scleroderma-associated PAH patients were randomized to receive bosentan vs. placebo.[37] After 12 weeks, the mean difference between treatment arms in the 6-MWD was 76 ± 31 m [mean ± SEM (standard error of mean)] in favor of bosentan ($p = 0.021$). Bosentan improved functional class, cardiac index, and reduced mPAP and PVR. The BREATH-1 trial (Bosentan Randomized trial of Endothelin Antagonist Therapy for pulmonary Hypertension) corroborated these findings in a pivotal 16-week double blind, placebo-controlled trial of 213 patients with WHO functional classes III–IV PAH (idiopathic or associated with CTD).[38] Patients were randomized to placebo or bosentan 125 or 250 mg twice a day. The primary end-point was change in exercise capacity and secondary end-points included changes in Borg dyspnea index, WHO functional class, and time from randomization to clinical worsening. Bosentan resulted in an increase in 6-MWD by 36 m, whereas patients receiving placebo experienced a decrease in 8 m ($p < 0.0002$). Patients in BREATH-1 who received bosentan experienced a significantly greater time to clinical worsening as compared to placebo treated patients ($p = 0.0015$) and 89% of the patients on bosentan were event-free after 28 weeks as compared to 63% of the patients treated with placebo ($p = 0.0038$).

Most studies on PAH specific therapies have been performed on patients with advanced functional class (III or IV). In the EARLY (Endothelin Antagonist trial in Mildly Symptomatic Pulmonary Arterial Hypertension Patients) study, bosentan therapy was evaluated in 168 mildly symptomatic or WHO functional II PAH [iPAH, hPAH, PAH associated with CTD, anorexigen use, human immunodeficiency syndrome (HIV), or CHD] patients. Patients were randomized to receive bosentan

or placebo for 26 weeks. There was a significant improvement in PVR, but not in 6-MWD. There was a significant improvement in time to clinical worsening.[39] Lastly, the use of bosentan has been studied in patients with Eisenmenger syndrome. Galiè et al. conducted a multicenter, double-blind, placebo-controlled, study in functional class III Eisenmenger patients (the BREATHE-5 study).[40] Fifty-four patients were randomized to bosentan vs. placebo for 16 weeks. Bosentan did not worsen oxygen saturation, and compared to placebo, bosentan reduced PVR index, decreased mPAP, and increased exercise capacity.

Bosentan was the first oral agent approved by the USFDA, and it was approved in 2001. It is administered orally, and the recommended starting dose is 62.5 mg twice a day with up-titration to 125 mg twice a day after 4 weeks.

Ambrisentan

Ambrisentan is a relatively selective endothelin-A receptor antagonist. The efficacy and safety of 4 doses of ambrisentan in patients with PAH was evaluated in a phase 2 double-blind, dose-ranging study. Sixty-four patients with iPAH or PAH associated with CTD, anorexigen use, or HIV infection were randomized to receive various doses of ambrisentan (1, 2.5, 5, or 10 mg) once a day for a total duration of 12 weeks.[41] The 6-MWD improved from baseline with ambrisentan (36.1 m, $p < 0.0001$) with similar increases for each dose group (range 33.9–38.1 m). AIRES-1 and 2 trials (Ambrisentan in Pulmonary Arterial Hypertension, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy Study 1 and 2) were concurrent, randomized, double-blind, placebo-controlled studies that compared different doses of ambrisentan vs. placebo.[42] The AIRES-1 trial compared 5 and 10 mg of ambrisentan, whereas AIRES-2 trial compared 2.5 and 5 mg of ambrisentan vs. placebo. After 12 weeks, there was improvement in 6-MWD in both studies. The change in mean 6-MWD in AIRES-1 was 22.8 and 43.6 m for the 5 and 10 mg doses, respectively, and –10.1 m in the placebo group. In AIRES-2, it was 22.2 and 49.4 m for the 2.5 and 5 mg doses, respectively, and –10.1 m in the placebo group. Time to clinical worsening was improved with active therapy in AIRES-2.

Use of ambrisentan has been studied in a small cohort of patients with portopulmonary hypertension (POPH). In this small study, 13 patients with POPH were given ambrisentan. The investigators found that ambrisentan decreased mPAP and PVR but no change in liver function tests (LFTs).[43]

The USFDA approved ambrisentan for use in PAH in 2007. It is given orally and the recommended starting dose is 5 mg daily, and it can be up-titrated to 10 mg daily.

Side Effects of Endothelin Receptor Antagonists

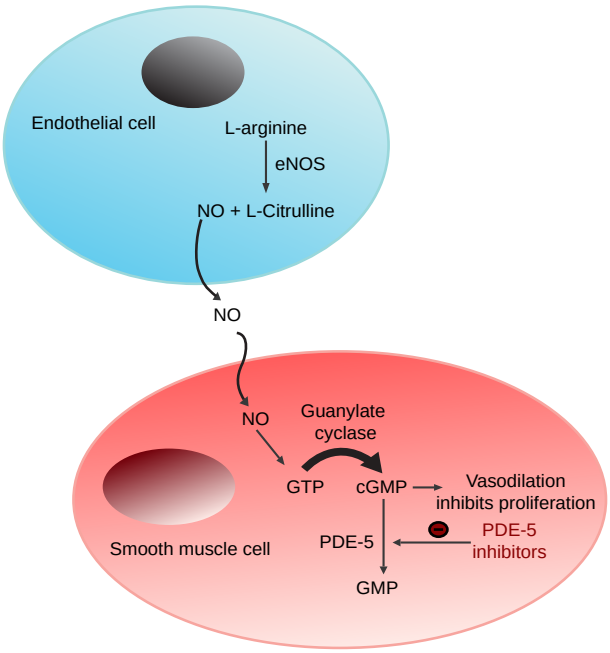
Side effects of the ERAs include peripheral edema, potential for liver toxicity, anemia, teratogenicity, and drug-drug interactions with strong inducers or inhibitors of cytochrome P450 enzymes.

Bosentan leads to dose-related increases in liver transaminases in 10–15% patients.[38,44] For this reason, the USFDA had mandated that LFTs be monitored monthly with all ERAs. The rate of elevation in serum transaminases levels >3 times upper limit of normal in patients taking ambrisentan was zero compared to 2.3% in patients taking placebo (not statistically different) in the AIRES trials. The USFDA recently removed the monthly LFTs monitoring requirement for patients taking ambrisentan based on postmarketing data indicating that it is not associated with increased risk of liver toxicity. However, periodic liver function testing is still recommended as part of the routine management of all patients with PAH, who may develop right heart failure and associated liver dysfunction.

Lower extremity edema can develop in up to 28% of patients treated with ambrisentan but appears to occur less frequently with bosentan.[38,42] Although the etiology of edema has not been established, it is likely related to fluid retention rather than peripheral vasodilation. The side effect can usually be anticipated and controlled with diuretic adjustment without the need for drug discontinuation in most patients. It may be better to avoid initiating these therapies in patients with acutely decompensated right heat failure until the congestion has been adequately treated.

Phosphodiesterase Inhibitors

The vasodilatory effects of nitric oxide depend upon its ability to augment and sustain cyclic guanylate monophosphate (cGMP) content in vascular smooth muscle. Nitric oxide activates guanylate cyclase, which increases cGMP production. This cGMP in turn causes vasorelaxation, but the effects are short-lived, as cGMP undergoes rapid degradation to GMP, and this is mediated by PDEs. PDE-5 hydrolyzes cAMP and cGMP, limiting their intracellular signaling (Figure 1). phosphodiesterase-5 inhibitors, sildenafil and tadalafil, enhance the effects of these vasodilating (and perhaps antiproliferative) cyclic nucleotides (Figure 5).



eNOS, endothelial nitric oxide synthase; NO, nitric oxide; GTP, guanosine triphosphate; cGMP, cyclic guanosine monophosphate; PDE-5, phosphodiesterase-5; GMP, guanosine monophosphate.

FIGURE 5. Phosphodiesterase-5 inhibitors: Mechanism of action in pulmonary arterial hypertension.

Like prostacyclins and ERAs, phosphodiesterase-5 inhibitors are currently only approved for use in PAH. Several small studies have looked at the role of phosphodiesterase-5 inhibitors in the treatment of WHO group 2 PH secondary to congestive heart failure.[45-47] These studies indicate that phosphodiesterase-5 inhibitors may improve exercise capacity in patients with PH due to heart failure, but further studies are needed. Phosphodiesterase-5 inhibitors have also been studied in patients with WHO group 3 PH due to lung disease. A small study of patients with chronic obstructive lung disease found that sildenafil acutely improved hemodynamics but inhibited hypoxic vasoconstriction resulting in impairment of arterial oxygenation.[48] A study of 180 patients with idiopathic pulmonary fibrosis found no improvement in 6-MWD after 12 weeks of sildenafil therapy.[49] At this time, there is no clear role for phosphodiesterase-5 inhibitors in the setting of PH due to lung disease.

Sildenafil

Sildenafil was the first phosphodiesterase-5 inhibitor that was approved for use in patients with PAH. It has a short half-life of 3–4 hours and needs to be administered thrice a day. Sildenafil is mostly used orally but is also available intravenously.

The SUPER-1 (Sildenafil Use in Pulmonary Arterial Hypertension) study was a randomized, double-blind, placebo-con-trolled trial of 278 patients with iPAH, CTD-PAH, and CHD-PAH assigned to placebo or sildenafil (20, 40, or 80 mg) orally 3 times a day for 12 weeks.[50] The 6-MWD increased from baseline in all sildenafil groups, with mean placebo-corrected treatment effect of 45, 46, and 50 m for 20, 40, and 80 mg doses of sildenafil, respectively ($p < 0.001$ for all comparisons). All sildenafil doses reduced the mPAP and improved functional class. The incidence of clinical worsening did not differ significantly between the patients treated with sildenafil vs. placebo. Long-term data (available only at a dose of 80 mg thrice a day) in 222 patients completing 1 year of sildenafil monotherapy demonstrated sustained improvement from baseline at 1 year in the 6-MWD (51 m).

The USFDA approved sildenafil in patients with PAH in 2005 and the recommended dose is 20 mg orally thrice a day.

Tadalafil

Tadalafil is a longer acting phosphodiesterase-5 inhibitor with a half- life of 17.5 hours and can be dosed once a day. The PHIRST trial (Pulmonary Arterial Hypertension and Response to Tadalafil) was a 16-week randomized, double-blind, dose-ranging, double-dummy, placebo-controlled study of 405 patients with iPAH.[51] Patients were randomized to 2.5, 10, 20, or 40 mg daily of tadalafil vs. placebo. A statistically significant improvement in 6-MWD was only seen in the 40 mg dose group with mean placebo-corrected treatment effect of 33 m ($p < 0.01$). Patients that received tadalafil at 40 mg daily had increased time to clinical worsening as compared to placebo ($p = 0.041$). There were no significant differences in change in functional class or Borg dyspnea score between any of the treatment groups, although improvement in quality of life was seen with 40 mg daily dose compared to placebo.

The USFDA approved tadalafil for use in patients with PAH in 2009, and the recommended dose is 40 mg daily.

Side Effects of Phosphodiesterase-5 Inhibitors

Side effects of phosphodiesterase-5 inhibitors include headache, dizziness, nausea, epistaxis, and priapism. There have been rare reports of patients treated with phosphodiesterase-5 inhibitors developing anterior ischemic optic neuropathy and optic atrophy, but causal association has not been clearly defined. Patients who develop visual changes while taking these medications should

seek medical attention and discontinue use in the event of sudden vision loss. Hearing loss has been reported, but causality and mechanism remain unclear.

Use of nitrates is contraindicated in patients on phosphodiesterase-5 inhibitors because of the potential for life threatening hypotension. Patients on phosphodiesterase-5 inhibitors should be advised to avoid all nitrates, including nitroglycerin and isosorbide mononitrate and isosorbide dinitrate. In patients who develop acute coronary syndrome, nitrates can be administered with close hemodynamic monitoring, 24 hours after the last dose of sildenafil and 48 hours after the last dose of tadalafil. Caution should be exercised when using α-blockers with phosphodiesterase-5 inhibitors because of the potential for orthostatic hypotension.

Combination of Currently Approved Disease Specific Therapies for Pulmonary Arterial Hypertension

The management of PAH has been extensively studied over the last 2 decades, resulting in the development of many new treatment options. However, many questions remain; for example, is one drug therapy better than another, should more than one therapy be started simultaneously upon diagnosis, should a second drug be added later in the course of the disease, and if so, when. Given the availability of medications that target different pathologic processes, combination therapy is an attractive theoretical option. The fact that PAH is an orphan disease makes it difficult to conduct studies that have enough power to answer questions like this. However, several small studies have been performed on combination therapies, and more studies are underway. Even though the effectiveness of combination therapy is still under investigation, most PAH specialists will institute combination therapy in higher risk patients, patients who do not improve to functional class I or II, or those patients whose disease progress while on monotherapy.

Completed Studies

Prostacyclins and Endothelin Receptor Antagonists

The BREATH-2 trial evaluated functional class III or IV patients with either iPAH or CTD-PAH starting on intravenous epoprostenol and randomized to receive bosentan or placebo.[52] This small, underpowered study failed to demonstrate the benefits of combination therapy. The STEP (Safety and pilot

efficacy Trial in combination with bosentan for Evaluation in Pulmonary arterial hypertension) trial studied inhaled iloprost in patients who remained symptomatic (NYHA functional class III or IV) while on stable bosentan therapy for at least 3 months.[53] In this multicenter, placebo-controlled, randomized trial, 67 patients with PAH (mostly functional class III) were randomized to receive inhaled iloprost (5 μg, 6–9 times per day) or placebo. After 12 weeks, primary efficacy measure, postinhalation 6-MWD improved by 30 m in the iloprost group and 4 m in the placebo group, for a placebo-adjusted difference of plus 26 m ($p = 0.051$). Improvements were seen in NYHA functional class ($p = 0.002$), time to clinical worsening ($p = 0.022$), postinhalation mPAP ($p < 0.001$), and PVR ($p < 0.001$). However, a study with similar design (COMBI: Combination Therapy of Bosentan and aerosolized Iloprost in Idiopathic Pulmonary Arterial Hypertension) was terminated early due to futility analysis.[54]

Prostacyclins and Phosphodiesterase-5 Inhibitors

The PACES trial (Pulmonary Arterial Hypertension Combination Study of Epoprostenol and Sildenafil) studied the effects of the addition of sildenafil (target dose 80 mg thrice a day) or placebo in 267 PAH patients who remained symptomatic with 6-MWD of 100–450 m while on stable dose of intravenous epoprostenol for at least 3 months.[55] Patients treated with sildenafil experienced a placebo-adjusted improvement in 6-MWD of 28.8 m ($p = 0.0002$) at 16 weeks, as well as improvement in mPAP, cardiac output, and time to clinical worsening.

Prostacyclins and Endothelin Receptor Antagonists and/or Phosphodiesterase-5 Inhibitors

In the TRIUMPH-1 study, 235 PAH patients on either bosentan or sildenafil were randomized to inhaled treprostinil.[32] The primary end-point was 6-MWD and the between-treatment median difference in change from baseline in peak 6-MWD was 20 m at week 12 ($p = 0.0004$).

Endothelin Receptor Antagonists and Phosphodiesterase-5 Inhibitors

The combination of an ERA and phosphodiesterase-5 inhibitor is probably the most frequently used combination therapy in PAH. Currently, no large studies have been published studying the effects of the combination of ERAs and phosphodiesterase-5 inhibitors but several are underway. The COMPASS-1 study

(The Effects of Combination of Bosentan and Sildenafil vs. Sildenafil Mono-therapy on Morbidity and Mortality in Symptomatic Patients with Pulmonary Arterial Hypertension) investigated the acute pharmacodynamic effects of sildenafil in patients with PAH and concomitant bosentan treatment, in view of a mutual pharmacokinetic interaction between the 2 drugs.[56] A total of 45 patients were enrolled in this prospective, open-label, noncomparative, multicenter, phase II study. These patients had stable PAH (iPAH, hPAH, or related to corrected congenital systemic-to-pulmonary shunts, drugs, or toxins) and were on bosentan treatment for at least 3 months. Patients underwent RHC to evaluate the acute hemodynamic effects of (a) iNO and (b) single oral dose of sildenafil (25 mg). Mean PVR decreased from baseline following iNO ($p = 0.0001$). Mean PVR was significantly reduced from baseline 60 minutes following sildenafil administration ($p < 0.0001$). The reduction in PVR following sildenafil was comparable to that resulting from iNO. This study suggests that addition of sildenafil to bosentan treatment can elicit additional hemodynamic benefits.

Studies Underway and/or Awaiting Results

Endothelin Receptor Antagonists and Phosphodiesterase-5 Inhibitors

The AMBITION trial (A Study of First-Line Ambrisentan and Tadalafil Combination Therapy in Subjects With PAH) is a multicenter, double-blind, phase III/IV clinical trial with the purpose of comparing two treatment strategies; first-line combination therapy (ambrisentan and tadalafil) vs. first-line monotherapy (ambrisentan or tadalafil) in subjects with PAH. The primary end-point is time to the first clinical failure event. The estimated study completion date is August 2013.

The ATHENA trial (Study of Ambrisentan and Phosphodiesterase Type-5 Inhibitor to Treat PAH) is an open-label multicenter study, evaluating the change from baseline in PVR and other hemodynamic parameters, following the addition of ambrisentan to background phosphodiesterase-5 inhibitor therapy in subjects with PAH who have demonstrated a suboptimal response to phosphodiesterase-5 inhibitor monotherapy. This study has been completed but the results are pending.

The COMPASS-2 trial (Effects of the Combination of Bosentan and Sildenafil vs. Sildenafil Monotherapy on PAH) is a multicenter, double-blind, placebo-controlled, phase IV study that is currently underway. This study is a morbidity/mortality trial, investigating the effects of the combination of bosentan and

sildenafil. Patients with symptomatic PAH treated with a stable dose of sildenafil equal to or greater than 20 mg thrice a day for at least 12 weeks are randomized to placebo or bosentan 125 mg twice a day. All randomized patients are treated with study drug until the predefined target number of morbidity/mortality events is reached.

Invasive Therapies

Lung and Combined Heart and Lung Transplantation

None of the current medical therapies for PAH are curative. Patients who have continued progression of the disease on medical therapies and patients with advanced disease (WHO functional classes III–IV) should be referred to a center that specializes in lung transplantation. Patients who undergo lung transplantation for PAH have higher perioperative mortality, reflecting the hemodynamic severity of the disease; however, the long-term post-transplant outcomes among those who survive the first year are similar to lung transplant recipients with other indications.

Atrial Septostomy

As the right heart function worsens in response to ongoing severe PAH, patients experience progressive dyspnea, ascites, lower extremity edema, and may have presyncope or syncope. Atrial septostomy creates a right to left interatrial shunt, decreasing RV filling, pressures, and improving RV function and LV filling. While the created shunt decreases systemic arterial oxygen saturation, it is anticipated that improved cardiac output will result in overall augmentation of systemic oxygen delivery.

The procedure can be performed either surgically or in the cardiac catheterization laboratory with balloon septostomy. A percutaneous approach is preferred in most patients because of the very high risk of surgery. The procedure can be considered for patients with recurrent syncope despite optimization of medical therapies as a bridge to lung transplantation or palliation in patients who are not transplant candidates. The procedure-related mortality is high (around 16%). Several recommendations have been made to minimize the risk. Atrial septostomy should be performed in centers with experience in its use and management of potential complications. A mean-RAP >20 mmHg, PVR index >55 Wood units/m^2, and a predicted 1-year survival <40% are significant predictors of a procedure-related death. Before cardiac catheterization, patients should have systemic oxygen saturation >90% in room air and optimized cardiac function.

Pulmonary Thromboendarterectomy

Patients with suspected PAH should undergo evaluation for CTEPH. The screening tool of choice for CTEPH is a ventilation perfusion scan. If indicative of CTEPH (WHO group 4 PH), a pulmonary angiogram should be performed. Patients are considered to be candidates for pulmonary thromboendarterectomy (PTE) if they have surgically accessible disease and present acceptable surgical risk. The goal of PTE is to remove sufficient material from the pulmonary arteries to substantially lower PVR and improve cardiac output. This complex and life-saving procedure is best performed at high volume centers.

PROGNOSIS

PAH is a progressive disease, and the overall prognosis is poor. Estimated median survival of patients with iPAH before available therapy was 2.8 years after diagnosis.[57] With the advent of new therapies over the last 2 decades, however, contemporary survival and quality of life of patients with PAH have improved substantially compared with prior survival estimates.[57-59] A meta-analysis of all the randomized, controlled trials performed from 1990 to 2008 demonstrated a reduction in mortality of 43% ($p = 0.023$). Number of patients to be treated to prevent one death was 61.6 and 16.2 deaths were prevented in each 1,000 patients treated.[60] Predictors of a poor outcome include clinical evidence of RV failure, rapid progression of disease and advanced functional class, poor exercise capacity as measured by 6-MWD or cardiopulmonary exercise test, elevated brain natriuretic peptide, RV dysfunction or pericardial effusion by echocardiogram and high RA pressure, high PVR, and low cardiac index by right heart catheterization (Table 3). Information from 2 large present-day registries of patients with PAH gives us the opportunity to better understand the prognosis of PAH, its determinants, and outcomes in the current treatment era. These registries are the French National Registry and the REVEAL Registry (the Registry to Evaluate Early and Long-Term PAH Disease Management). French National Registry enrolled 354 consecutive idiopathic, heritable, and anorexigen-associated patients from October 2002 to October 2003. The 1-, 2-, and 3-year survival rates per this registry are 82.9, 67.1, and 58.2%, respectively. Univariate analysis suggested that the factors associated with better prognosis were female, functional class I or II symptoms, greater 6-MWD, lower RAP, and higher cardiac output. The multivariate analysis reduced this list to 3 independent factors, namely, sex, 6-MWD, and cardiac output

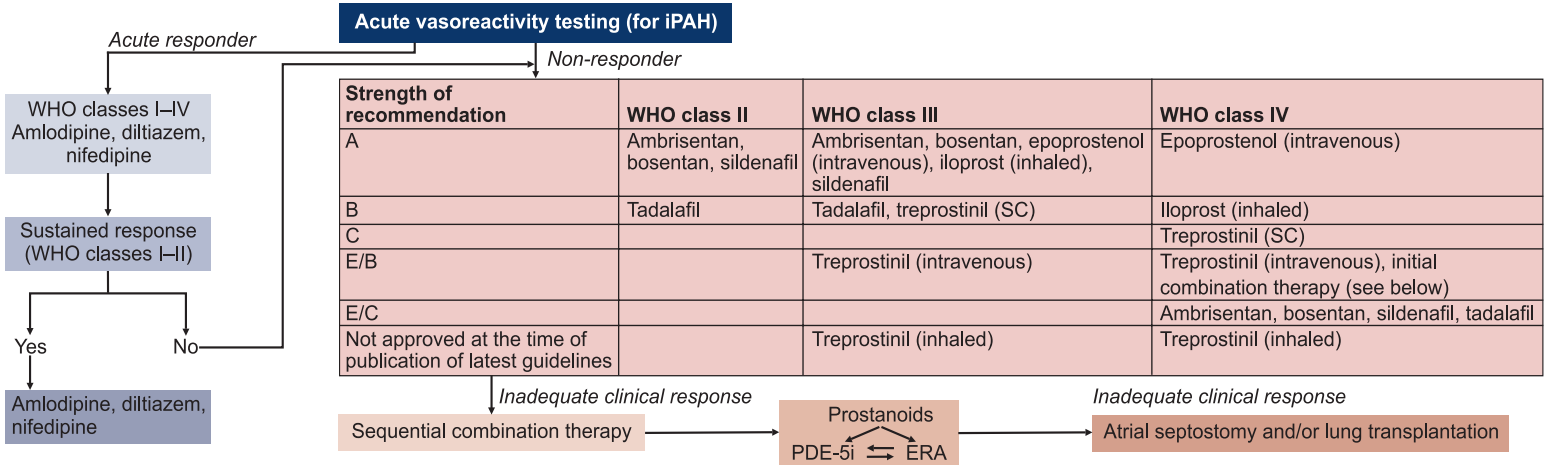
at diagnosis.[58,61] The REVEAL Registry analyzed 2,716 patients with PAH and found 1-year survival to be 91% from the date of enrollment and the 1- and 3-year survival rates from the time of PAH diagnosis of 87.7 and 72.1%, respectively. Sex, functional class, 6-MWD, origin of PAH, age, PVR, RAP, renal insufficiency, resting systolic blood pressure and heart rate, BNP, presence of a pericardial effusion, and diffusing capacity of the lung for carbon monoxide were predictive of outcome.[62]

TREATMENT ALGORITHM AND EVALUATING RESPONSE TO THERAPY

There is emerging evidence that earlier initiation of therapy when patients are mildly symptomatic improves functional and clinical status.[39] The decision to initiate vasodilator therapy and the specific agents used depend on the patient's WHO functional class, risk profile, and preference. PAH patients with symptoms that result in slight limitation of physical activity (WHO functional class II) should be started on oral agents, either ERAs or phosphodiesterase-5 inhibitors. Patients that are unable to carry out any physical activity without symptoms (WHO functional class IV) need more aggressive therapy and prostacyclin therapy should be considered. The guidelines propose a wide range of treatment options for patients who are asymptomatic at rest but have marked limitation of physical activity (WHO functional class III). Patients with WHO functional class III symptoms and poor prognostic factors should be considered for prostacyclin therapy, while patients with good prognostic profile can be started on oral therapy.

Close follow-up is crucial in all patients started on PAH-specific therapy. Stable patients on oral therapy can be followed every 4–6 months. Patients with more advanced and/or progressive symptoms, right heart failure, and patients on intravenous therapy need to be seen at least every 3 months. With each clinic visit, WHO functional class, BNP/NTproBNP, and exercise capacity (6-MWD or graded treadmill) is checked to help determine response to therapy. A repeat echocardiogram is done at least 6 months after commencing PAH-specific therapy. The timing of repeat RHC varies between PH centers. RHC should be considered in patients with progressive symptoms in spite of therapy, prior to addition of a new PAH specific agent, and many experts routinely repeat RHC after 1 year on therapy, particularly in patients on prostacyclin therapy (Figure 6).

Patients who have inadequate clinical response on mono-therapy, i.e., symptoms progress or do not improve to WHO



Strength of recommendation	WHO class II	WHO class III	WHO class IV
A	Ambrisentan, bosentan, sildenafil	Ambrisentan, bosentan, epoprostenol (intravenous), iloprost (inhaled), sildenafil	Epoprostenol (intravenous)
B	Tadalafil	Tadalafil, treprostinil (SC)	Iloprost (inhaled)
C			Treprostinil (SC)
E/B		Treprostinil (intravenous)	Treprostinil (intravenous), initial combination therapy (see below)
E/C			Ambrisentan, bosentan, sildenafil, tadalafil
Not approved at the time of publication of latest guidelines		Treprostinil (inhaled)	Treprostinil (inhaled)

iPAH, idiopathic pulmonary arterial hypertension; PDE-5i, phosphodiesterase-5 inhibitor; ERA, endothelin receptor antagonist; SC, subcutaneous.

FIGURE 6. Algorithm for the management of pulmonary arterial hypertension. Also consider general measures and supportive therapies as detailed in the text. Drugs within the same grade of evidence are listed in alphabetical order and not order of preference. Not all agents listed are approved or available for use in all countries. Strengths of recommendations: E/B—moderate recommendation on the basis of expert opinion only; E/C—weak recommendation on the basis of expert opinion only. *Adapted from* Barst RJ, Gibbs JS, Ghofrani HA, Hoeper MM, McLaughlin VV, Rubin LJ, et al. Updated evidence-based treatment algorithm in pulmonary arterial hypertension. *J Am Coll Cardiol*. 2009;54(1 Suppl):S78-84, *with permission*.

functional class I or II may benefit from switching PAH specific agents or from a combination of agents. As discussed above, combining PAH specific therapies that affect different pathways make therapeutic sense and are currently under intense investigation. Lastly, invasive therapies like lung transplantation or atrial septostomy may be an option for patients who have progressive symptoms in spite of optimization of medical therapies.

MEDICAL THERAPIES UNDER INVESTIGATION

None of the current therapies for PAH are curative and the search for new treatments continues. With a deeper understanding of the molecular mechanics in PAH, many new treatment options are being explored in humans and animal models.[63-65]

Investigational Drugs Aimed at "Traditional Pathways"

FREEDOM studies (Multicenter, double-blind, placebo-controlled, phase III clinical trials of oral treprostinil for PAH): FREEDOM-M was a 12-week trial that enrolled patients on no PAH specific therapy. FREEDOM-C and C2 were 16-week trials that investigated oral treprostinil adjunctively with an ERA and/or a phosphodiesterase-5 inhibitor. Primary end-point was improvement in 6-MWD. Preliminary analysis of the FREEDOM-C2 trial is that it did not meet the primary end-point of improvement in 6-MWD. The FREEDOM trials have been completed, but final analysis of the data is pending.

GRIPHON study (A multicenter, double blind, placebo controlled, phase III study to demonstrate the efficacy and safety of selexipag in patients with PAH): Selexipag is an oral, selective prostaglandin receptor agonist. This study is event-driven and the primary end-point is time to first clinical worsening. Estimated completion date for this trial is August 2013.

SERAPHIN (Study with an Endothelin Receptor Antagonist in Pulmonary arterial Hypertension to Improve cliNical outcome): Multicenter, double-blind, placebo-controlled, phase III clinical study that is designed to evaluate the safety and efficacy of a new ERA, macitentan. The primary end-point is morbidity and all-cause mortality in patients with symptomatic PAH. Global enrollment was completed in December 2009 with a total of 742 patients. Patients with PAH, on no treatment or sildenafil, were randomized 1:1:1 to receive 2 different doses of macitentan or placebo. The study is event-driven and based on the progress results could become available in the first half of 2012.

PATENT (A Study to Evaluate Efficacy and Safety of Oral BAY63-2521 in Patients With PAH): A 12-week multicenter, double-blind, placebo-controlled, phase III clinical trial to evaluate the efficacy and safety of riociguat (1, 1.5, 2, or 2.5 mg thrice a day) in patients with symptomatic PAH. Patients on no PAH specific therapies, on ERAs, or inhaled prostacyclins are eligible for this study. Riociguat affects the nitric oxide pathway by directly stimulating soluble guanylate cyclase and resulting in the production of cGMP (Figure 1). The primary end-point is 6-MWD. The estimated completion date for this trial is in early 2012.

Investigational Drugs Aimed at "Novel Pathways"

PAH is a disease characterized by excess proliferation and impaired apoptosis in pulmonary artery smooth muscle cells and endothelial cells. Many of the novel therapeutic targets that have been the focus of investigation in the most recent years decrease the proliferation/apoptosis ratio. Most of the studies to date have been in animal models but one phase III clinical study investigating effect of imatinib was just completed.

IMPRES (Imatinib in Pulmonary Arterial Hypertension, a Randomized, Efficacy Study): A 24-week multicenter, double-blind, placebo-controlled, phase III clinical trial evaluating the efficacy and safety of imatinib as an add-on therapy in the treatment of severe PAH. To be eligible for this trial, patients had to be on 2 or more PAH specific therapies. Imatinib is a tyrosine kinase inhibitor that inhibits the platelet derived growth factor receptor (PDGFR). PDGF is a vascular smooth muscle cell mitogen that activates signal transduction pathways associated with smooth muscle hyperplasia. PDGF and PDGFR have been implicated in the pathobiology of pulmonary hypertension in animal studies and in patients with PAH.[66,67] The primary end-point for this study was 6-MWD and preliminary data indicates that this end-point was met, with between-groups treatment difference of 32 m ($p = 0.002$). This study has been completed and publication of results is pending.

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12 CHAPTER

Cardiac Drugs in Pregnancy and Lactation

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INTRODUCTION

Cardiovascular diseases (CVD) complicate 0.2–4% of all pregnancies in Western industrialized countries.[1] In addition, the risk of CVD in pregnancy is expected to increase due to increasing age at first pregnancy and increasing prevalence of cardiovascular risk factors.[2] Since only few medications have specifically been tested for safety and efficacy during pregnancy and lactation, physicians caring for pregnant women have very little information to help them decide whether the potential benefits to the mother outweigh the risks to the fetus.[3] It should be appreciated, however, that current methods to assess teratogenicity consist mainly of pregnancy registries and case-control surveillance studies with very few randomized controlled trials available.

Several factors have to be taken into consideration when prescribing a drug to a pregnant or breastfeeding woman. These factors include, but are not limited to, gestational age of the embryo or fetus, route of drug administration, whether the drug crosses the placenta or is excreted in breast milk, and the necessary effective dose of the drug.[4] Awareness of the unique physiologic changes of pregnancy (increase in cardiac output and glomerular filtration rate, increase in body fat, and decrease in plasma albumin concentration) that affect the pharmacokinetics of medications used by pregnant women is of critical importance in deciding the dosage and frequency of administration and monitoring. A major concern is the potential harm to the fetus or nursing infant, but equally important is the assessment of the potential harm to the mother that withholding a drug can cause.[4] Thus, in these situations, when prescribing a drug, the decision comes down to "Does the benefit of the drug outweigh its risks?"

It is of paramount importance to start by identifying cardiovascular drugs of known teratogenic effects. Drugs that irreversibly alter growth, structure, or function of the developing embryo or fetus are classified as teratogens. Commonly

TABLE 1

Cardiovascular Drugs with Teratogenic Effects	
Drug	*Teratogenic effects*
Inhibitors of the renin angiotensin system	Renal or tubular dysplasia, prolonged renal failure in neonates, ossification disorders of skull, oligohydramnios, growth retardation, lung hypoplasia, contractures, large joints, anemia, and intrauterine fetal death.
Warfarin	Fetal hemorrhage, skeletal and central nervous system defects, Dandy-Walker syndrome*
3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors (statins)	Skeletal malformations

*A congenital brain malformation involving the cerebellum and the fluid filled spaces around it.

CoA, coenzyme A.

TABLE 2

USFDA Pregnancy Risk Category for Medications	
USFDA category	*Definition*
A	No risk in controlled human studies
B	No risk in controlled animal studies; or animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus
C	Small risk in controlled animal studies; or no animal studies have been conducted and there are no adequate and well-controlled studies in pregnant women
D	Strong evidence of risk to the human fetus, but the benefits from use in pregnant women may be acceptable, despite the risk
X	Never to be used in pregnancy; very high risk to the human fetus

used cardiovascular drugs that are classified as teratogens include inhibitors of the renin-angiotensin system, warfarin, and 3-hydroxy-3-methyl-glutaryl-coenzyme A (CoA) reductase inhibitors (Table 1).

To help guide physicians, the USFDA has developed categories of risk of medication-used during pregnancy (Table 2). Categories A and B generally are considered safe in humans. Category C medications have not been definitively shown to be harmful to human fetuses, but reasons exist to be cautious when prescribing them. Category D drugs are those with evidence of human fetal risk based on well-controlled human studies. Finally, category X drugs are very high risk to the human fetus and should never be used in pregnancy.

HYPERTENSIVE DISEASE IN PREGNANCY AND LACTATION

Hypertensive disorders are the most frequent cardiovascular complications during pregnancy, complicating up to 15% of pregnancies and accounting for about a quarter of all antenatal admissions.[5] Hypertension in pregnancy is not a single entity but comprises and is generally classified into 4 different entities, including preexisting hypertension and gestational hypertension (develops after 20 weeks gestation).[6] It remains a major cause of maternal, fetal, and neonatal morbidity and mortality. These women are at higher risk for severe complications, such as abruptio placentae, cerebrovascular accident, organ failure, and disseminated intravascular coagulation, and the fetus is at risk for intrauterine growth retardation, prematurity, and intrauterine death.[2]

Antihypertensive therapy for mild-to-moderate hypertension in pregnancy (defined as systolic blood pressure (SBP) of 140–169 mmHg and diastolic blood pressure (DBP) of 90–109 mmHg) does not seem to decrease the incidence of preeclampsia nor affect maternal or perinatal outcomes.[7] Thus, avoidance of drug therapy is suggested in mild hypertension where nonpharmacological therapies may suffice.[8] Chronic anti-hypertensive therapy can be stopped during pregnancy under close observation and resumed, if necessary. Alternatively, a woman whose arterial pressure was well controlled by antihypertensives before pregnancy may continue with the same agents (except for angiotensin converting enzymes inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and direct renin inhibitors, which are contraindicated). On the other hand, drug treatment of severe hypertension (SBP ≥160–170 mmHg or DBP ≥110 mmHg) in pregnancy is beneficial and is required.

The different antihypertensive medications and their potential usage in pregnancy are listed in table 3. The drug of choice for long-term treatment of hypertension during pregnancy is methyldopa (centrally acting agent leading to a reduction in the sympathetic outflow).[9] Multiple other agents could also be used, such as the α-/β-blocker labetalol, β-adrenoceptor antagonists (metoprolol and propanolol), and calcium channel blockers (nifedipine). Diuretics may decrease blood flow in the placenta and should be avoided for treatment of hypertension.[2] In hypertensive crises, the drug of choice is sodium nitroprusside, given as an intravenous infusion at 0.25–5.0 μg/kg/min.[2] In the case of preeclampsia associated with pulmonary edema, intravenous nitroglycerin infusion (20–200 μg/min) is the drug of choice.[2] Labetalol can also be administered in intravenous form and used for treatment

TABLE 3

Drugs Commonly Used to Treat Hypertension in Pregnancy and Lactation

Drug	*USFDA category*	*Route of administration*	*Placental permeability*	*Reported adverse effects*
Methyldopa	B	Oral	Yes	Mild neonatal hypotension
Labetalol	C	Oral/intravenous	Yes	Intrauterine growth retardation (second and third trimesters), neonatal bradycardia and hypotension (used near term)
Nifedipine	C	Oral	Yes	Tocolytic; potential synergism with magnesium sulfate may induce maternal hypotension and fetal hypoxia
Metoprolol	C	Oral/intravenous	Yes	Bradycardia and hypoglycemia in fetus
Propanolol	C	Oral	Yes	Bradycardia and hypoglycemia in fetus
Nitroglycerin	B	Intravenous	Unknown	Bradycardia, tocolytic
Hydralazine	C	Oral	Yes	Maternal lupus-like symptoms; fetal tachyarrhythmias. Intravenous use is associated with more perinatal adverse effects and is avoided
Hydrochlorothiazide	B	Oral	Yes	Oligohydramnion

of severe hypertension. Intravenous hydralazine use is associated with more perinatal adverse effects than other drugs and is no longer the drug of choice.[2] All antihypertensive agents taken by the nursing mothers are excreted into breast milk; however, most are present at very low concentrations and are considered compatible with breastfeeding. The exceptions are propranolol and nifedipine, whose concentrations in breast milk are similar to those in maternal plasma.[2]

ACUTE CORONARY SYNDROME AND STABLE CORONARY ARTERY DISEASE IN PREGNANCY AND LACTATION

Coronary artery disease (CAD) management during pregnancy has been an increasingly encountered challenge by the physicians because of the increasing maternal age. Acute coronary syndrome (ACS) is rare during pregnancy, but it has devastating consequences with maternal mortality of 5–10%.[2] The spectrum of causes of ACS during pregnancy is different than the general population. Spontaneous coronary artery dissection makes a substantial proportion and is mostly reported around delivery or in the early postpartum period.[10] Thus, coronary angiography with the possibility of coronary intervention (PCI) is the preferred first line therapy for patients presenting with ST-elevation myocardial infarction.[2] PCI in pregnancy can be considered relatively safe, taking into account the minimal risk of radiation exposure to the fetus, especially during the period of organogenesis. On the other hand, thrombolytic therapy should be reserved for life threatening ACS with no access to PCI.[11] Coronary artery bypass surgery can be performed during pregnancy and the maternal mortality equals mortality in nonpregnant cardiac surgery. However, the fetal mortality risk is still high with an incidence of 20%.[12] Drug therapy during pregnancy for patients with ACS is summarized in table 4.

The management of patients with stable CAD aims to reduce the progression of atherosclerosis and prevent anginal symptoms. The classes of medications used include antiplatelet agents, lipid lowering agents, and antianginal drugs (Table 5). In pregnant patients with CAD, aspirin in low doses (<150 mg/day) should be used and is considered safe.[13,14] On the other hand, higher doses are associated with fetal and maternal hemorrhage, premature closure of the ductus arteriosus, and fetal congenital abnormalities. It is well established that reduction in low-density lipoprotein is associated with decrease in the risk of coronary heart disease and all-cause mortality. Statins are the first-line

TABLE 4

Drug Therapy in Pregnancy and Acute Coronary Syndrome

Drug	*USFDA category*	*Maternal considerations*	*Fetal considerations*	*Breastfeeding*	*Comments*
Thrombolytics					
▪ Streptokinase ▪ Recombinant palsminogin activators	C	Hemorrhage risk ~8% (mostly from the genital tract)[15]	▪ Do not cross the placenta in animals (unknown in human) ▪ Causes subplacental bleeding ▪ Fetal loss 6%[16] ▪ Preterm delivery 6%[16]	No data on excretion into human milk.	▪ Relatively contraindicated ▪ Reserved for life threatening ACS with no access to PCI
Antithrombotics					
▪ Unfractionated heparin ▪ Low molecular weight heparin	B	Regular monitoring of therapeutic levels is needed	Does not cross the placenta	Compatible	▪ Because of scarce data, fondaparinux should not be used in pregnancy ▪ Bivalirudin is not recommended during pregnancy due to lack of safety data

(continued)

Table 4 *(continued)*

Drug	*USFDA category*	*Maternal considerations*	*Fetal considerations*	*Breastfeeding*	*Comments*
Antiplatelet agents					
Low-dose aspirin (< 150 mg/day)	B	Large trials demonstrated relative safety during pregnancy	Crosses human placenta	Well tolerated	▪ Higher doses have teratogenic effects ▪ Avoid breastfeeding with high dose
Clopidogrel	C	▪ During pregnancy use only when strictly needed (e.g., after stenting) and for the shortest duration possible (ESC) ▪ Bare metal stents should be the first choice if percutaneous coronary intervention is needed	Unknown	Unknown	The use of glycoprotein of IIb/IIIa inhibitors, prasugrel, and ticagrelor is not recommended during pregnancy given the absence of safety data

TABLE 5

Drug Therapy in Pregnancy and Stable Coronary Artery Disease					
Drugs	*USFDA category*	*Maternal considerations*	*Fetal considerations*	*Excretion in milk*	*Comments*
Antiplatelet agents					
Low-dose aspirin (< 150 mg/day)	B	Large trials demonstrated relative safety during pregnancy	Crosses human placenta	Well tolerated	▪ Higher doses are associated with teratogenic effects ▪ Avoid breastfeeding if using high dose
Antianginal drugs					
Nitrates (Isosorbide dinitrate)	B	Maternal hypotension should be avoided (subsequent fetal hypoperfusion)	Unknown if crosses human placenta	Unknown	Bradycardia; isosorbide mononitrate class C
Calcium channel blockers	C	—	Crosses the placenta	Yes	Diltiazem has teratogenic effects in animals (should not be used)
β-blockers	C	—	Risk of mildly lower birthweight, bradycardia, and hypoglycaemia in fetus	—	Avoid atenolol (USFDA category D)

(continued)

Table 5 *(continued)*

Drugs	*USFDA category*	*Maternal considerations*	*Fetal considerations*	*Excretion in milk*	*Comments*
Lipid Lowering drugs					
Statins	X	Should be started in the postpartum period	Crosses human placenta	Unknown	Causes congenital anomalies
Fenofibrate	C	—	Crosses human placenta	Yes	No adequate human data available
Gemfibrozil	C	—	Crosses human placenta	Unknown	No adequate human data available
Colestipol, cholestyramine	C	—	Unknown	Transfer to breast milk lowering neonatal fat soluble vitamins (e.g., vitamin K)	May predispose to neonatal cerebral bleeding
Ezetimibe	C	—	Unknown	Unknown	Limited data available

therapy for dyslipidemias in the general population, but are contraindicated in pregnancy. They are labeled USFDA category X for possible teratogenic effects (mainly skeletal defects observed in animal studies).[17]

The treatment of angina pectoris in pregnancy follows the same general principles, which include decreasing the myocardial oxygen demand and improving coronary perfusion. β-blockers decrease oxygen demand by slowing down the heart rate. In general, β-blockers are relatively safe with the exception of atenolol (USFDA category X). However, caution should be used as severe bradycardia can lead to uteroplacental hypoperfusion. The use of β-blockers is associated with a mildly lower birth weight, bradycardia, and hypoglycemia in fetus. On the other hand, atenolol use should be avoided as it has been associated with hypospadias (first trimester) and birth defects, low birth weight, bradycardia, and hypoglycemia in fetus (second and third trimesters).[2]

The antianginal effect of nitrates and calcium channel blockers is via vasodilatation. This results in decreased cardiac workload (decreased afterload from peripheral vasodilation) and improved coronary perfusion (coronary vasodilatation). Similar to β-blockers, caution has to be practiced with high doses, which may cause maternal hypotension and subsequent fetal hypoperfusion. Nifedipine appears to be safe and is frequently used during pregnancy for the treatment of hypertension. On the other hand, diltiazem should not be used, as it has teratogenic effects (skeletal abnormalities) in animals, and there is no information about its use in human pregnancy.[18] Diltiazem is also excreted in milk in concentration similar to that in maternal plasma and should be avoided during breastfeeding.

CARDIOMYOPATHIES AND HEART FAILURE IN PREGNANCY AND LACTATION

Cardiomyopathies are rare but serious disease during pregnancy with peripartum cardiomyopathy (PPCM) representing the most common cause of severe complications.[2,19] PPCM is defined as an idiopathic cardiomyopathy that presents with heart failure secondary to left ventricular (LV) systolic dysfunction towards the end of pregnancy or in the months after delivery, in the absence of any other cause of heart failure.[20] When diagnosed during pregnancy, the majority of patients present in third trimester, with a few patients presenting in the second trimester.[21]

In general, the medical management of pregnant or lactating patient with cardiomyopathy should follow the standard drug

therapy for acute and chronic heart failure, except that drug therapy may need to be altered because of potential detrimental effects on the fetus or the lactating infant.[22] The drugs commonly used for the management of patients with cardiomyopathy during pregnancy or lactation are summarized in table 6. It is important to note that ACEIs despite being hallmark for therapy of patients with heart failure, given their effect on ventricular remodeling, are teratogenic in pregnancy and, therefore, should be strictly avoided.[23] Few data are available regarding ARBs in pregnancy, but are also contraindicated in pregnancy because their actions are similar to that of ACEIs.[24] Thus, during pregnancy, the combination of organic nitrates and hydralazine should be used as a substitute for ACEIs or ARBs; and in the acute setting, intravenous nitroglycerin is considered first line for afterload reduction.[22] The ACEIs considered compatible with breastfeeding are benazepril, captopril, and enalapril.[2,25] Currently, there is no data describing the use of other ACEIs or ARBs during human lactation.[8]

The use of aldosterone antagonists should be avoided during pregnancy.[26] Spironolactone (USFDA category D) can be associated with antiandrogenic effects in first trimester. However, it is considered compatible with breastfeeding.[25] Data for eplerenone are lacking, otherwise, most other drugs used for the management of heart failure are compatible with breastfeeding.[22] In addition, a recent study reported that the rate of recovery of LV function was significantly higher in lactating women.[27] Thus, clinically stable women with PPCM should not be discouraged from breastfeeding their infants.[22]

ARRHYTHMIA IN PREGNANCY AND LACTATION

Arrhythmias are divided into 2 categories—bradyarrhythmias and tachyarrhythmias. During pregnancy, there is an increased incidence of maternal cardiac arrhythmias explained in part by the metabolic, hormonal, and hemodynamic changes.[28] In addition, there is an increased number of women with congenital cardiac malformations reaching reproductive age with the advances in cardiac surgery, and these patients are known to be more prone to cardiac arrhythmias.[29]

The most common maternal arrhythmias during pregnancy are simple ventricular and atrial ectopy (reported in 50–60% of pregnant women).[30] Bradyarrhythmias are rare during pregnancy and usually have a favorable outcome in the absence of underlying heart disease.[2] Characteristic arrhythmia in the

TABLE 6

Drugs Commonly Used in the Management of Heart Failure Patients During Pregnancy				
Drug	*USFDA category*	*Route of administration*	*Placental permeability*	*Reported adverse effects*
Inotropy				
Dopamine	C	Intravenous	—	Increased uterine resistance; animal studies demonstrated decrease in newborn survival rate and potential for cataract formation
Dobutamine	B	Intravenous	—	No evidence of harm to the fetus
Milrinone	C	Intravenous	Yes	No teratogenicity in animal studies
Digoxin	C	Intravenous /oral	Yes	Serum levels unreliable
Preload reduction				
Furosemide	C	Intravenous /oral	Yes	Oligohydramnion
Hydrochlorothiazide	B	Oral	Yes	Oligohydramnion
Afterload reduction				
Nitrates	B	Intravenous /oral	Unknown	Bradycardia, tocolytic

(continued)

Table 6 *(continued)*

Drug	*USFDA category*	*Route of administration*	*Placental permeability*	*Reported adverse effects*
Nitroprusside	C	Intravenous	—	Prolonged use associated with thiocyanate toxicity
Hydralazine	C	Oral	Yes	Maternal lupus-like symptoms; fetal tachyarrhythmias. Intravenous use is associated with more perinatal adverse effects and is avoided
β-blockers				
Metoprolol	C	Intravenous /oral	Yes	Bradycardia and hypoglycemia in fetus
Bisoprolol	C	Oral	Yes	Bradycardia and hypoglycemia in fetus

fetus are supraventricular tachycardia (SVT) and atrial flutter.[31] In these cases, the mother is simply the conduit for transplacental administration of the drug.

The major concern regarding the use of antiarrhythmic drugs during pregnancy is their potential adverse effects on the fetus, and all antiarrhythmic drugs should be regarded as potentially toxic to the fetus (Tables 7 and 8).[2] The smallest recommended dose should be used initially and the patient should be monitored regularly with measurement of serum drug levels (when available) along with reassessment for continued need for medication.[31] In the setting of minimally symptomatic simple arrhythmias (such as, premature ventricular or atrial beats), no treatment is necessary. On the other hand, patients with SVT (atrioventricular nodal re-entry tachycardia, atrioventricular re-entry tachycardia, atrial fibrillation, atrial flutter, etc.) and severe symptoms or hemodynamic compromise need medical intervention. Serious ventricular arrhythmias (ventricular tachycardia or fibrillation) are rare during pregnancy but are life-threatening, so prompt treatment is needed.

Patients with SVT and hemodynamic instability require immediate electrical cardioversion (which seems to be safe in all stages of pregnancy).[2] Intravenous adenosine is safe to terminate SVTs in the hemodynamically stable patient, if the vagal maneuver fails, and in the absence of preexcitation (class I: conditions for which there is evidence and/or general agreement that a given procedure is useful and effective). Intravenous metoprolol or propranolol can also be considered for the same purpose (class IIa: weight of evidence/opinion is in favor of usefulness/efficacy). Alternatively, intravenous verapamil can be used (class IIb: usefulness/efficacy is less well established by evidence/opinion).[2] For long-term management, β-blockers (metoprolol or propranolol) and digoxin are drugs of first choice (class I). If these fail, oral sotalol or flecainide should be considered (IIa) and oral propafenone or procainamide may be considered as the last option if other suggested agents fail and before amiodarone is used (IIb). It is important to note that atenolol should not be used for any arrhythmia (USFDA risk category D) because of its known adverse effects on fetal growth. Amiodarone is also fetotoxic and should not be used unless other options fail. There is limited experience with dronedarone (a new antiarrhythmic drug) and should not be used during pregnancy.

Immediate electrical cardioversion is recommended for patients with sustained ventricular tachycardia (VT) and hemodynamic instability (class I). In stable patients with sustained VT, it is also desirable to restore normal sinus rhythm in a timely

TABLE 7

Drugs Commonly Used for Treatment of Supraventricular Tachyarrythmias During Pregnancy and Lactation

Drug	*Drug class**	*USFDA category*	*Placental permeability*	*Breastfeeding considerations*	*Reported adverse effects*
Adenosine	—	C	No	Compatible	No fetal adverse effects reported
Metoprolol	II	C	Yes	Compatible	Bradycardia and hypoglycemia in fetus
Digoxin	—	C	Yes	Compatible	Serum levels unreliable
Diltiazem	IV	C	No	Compatible	Increased risk of birth defects
Verapamil	IV	C	Yes	Compatible	Maternal hypotension, fetal bradycardia, and heart block
Sotalol	III	B	Yes	Compatible	Bradycardia and hypoglycaemia in fetus
Flecainide	Ic	C	Yes	Compatible	Safe in structurally normal hearts
Propafenone	Ic	C	Yes	Unknown	Limited experience
Amiodarone	III	D	Yes	Avoid	Fetal hypothyroidism, hyperthyroidism, goiter, bradycardia, growth retardation, premature birth

*Vaughan Williams classification of antiarrhythmic drugs.

TABLE 8

Drugs Commonly Used for Treatment of Ventricular Tachyarrythmias During Pregnancy and Lactation

Drug	*Drug class**	*USFDA category*	*Placental permeability*	*Breastfeeding considerations*	*Reported adverse effects*
Metoprolol	II	C	Yes	Compatible	Bradycardia and hypoglycemia in fetus
Verapamil	IV	C	Yes	Compatible	Maternal hypotension, fetal bradycardia, and heart block
Sotalol	III	B	Yes	Compatible	Bradycardia and hypoglycaemia in fetus; Torsade de Pointes
Procainamide	Ia	C	Yes	Compatible but long-term therapy should be avoided	Lupus-like syndrome with long-term use, Torsade de Pointes
Flecainide	Ic	C	Yes	Compatible	Safe in structurally normal hearts
Propafenone	Ic	C	Yes	Unknown	Limited experience
Amiodarone	III	D	Yes	Avoid	Fetal hypothyroidism, hyperthyroidism, goiter, bradycardia, growth retardation, premature birth

*Vaughan Williams classification of antiarrhythmic drugs.

fashion.[2] This can be achieved via electrical cardioversion, antitachycardia pacing, or antiarrhythmic drugs.[2] Intravenous sotalol (in the absence of prolonged QT interval) or procainamide should be considered in monomorphic VT (IIa; conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure and the weight of evidence favors usefulness/efficacy). The use of intravenous amiodarone should be reserved for patients with sustained monomorphic VT that is hemodynamically unstable, refractory to conversion, or recurrent despite other agents (IIa).[2] Oral metoprolol, propranolol, or verapamil is recommended for long-term management of idiopathic sustained VT (class I). If these drugs fail, oral sotalol, flecainide, or propafenone should be considered (IIa). For long-term management of the congenital long QT syndrome, β-blocking agents are recommended during pregnancy and also postpartum (class I).[2]

VENOUS THROMBOEMBOLISM AND THROMBOPROPHYLAXIS IN PREGNANCY AND LACTATION

In addition to venous thromboembolism (VTE) that occurs in increased frequency during pregnancy and postpartum period and represents a significant cause of morbidity and mortality, there are multiple other conditions, which need antithrombotic therapy during pregnancy and lactation. The increased thromboembolic risk in atrial fibrillation is assessed with the CHADS2 (C: congestive heart failure (or LV systolic dysfunction); H: hypertension: blood pressure consistently above 140/90 mmHg (or treated hypertension on medication); A: age ≥75 years; D: diabetes; S: prior stroke or transient ischemic attack) score or the CHA2DS2VASC (C: congestive heart failure (or LV systolic dysfunction); H: hypertension: blood pressure consistently above 140/90 mmHg (or treated hypertension on medication); A: age ≥75 years; D: diabetes; S: prior stroke or transient ischemic attack, or thromboembolism; V: vascular disease; A: age 65–74 years; Sc: sex category) score, and thromboprophylaxis is recommended in high-risk pregnant patients.[2] Thromboprophylaxis is also advisable in PPCM patients from the time of the diagnosis until LV function recovers (LV ejection fraction (LVEF) >35%), because of the high incidence of thromboembolism (particularly during pregnancy and the first 6–8 weeks postpartum).[22] Patients with mechanical valves carry the risk of valve thrombosis, which is increased during pregnancy. Thus, anticoagulation therapy (Table 9) in these women is recommended to prevent the

TABLE 9

Commonly Used Anticoagulation Drugs in Pregnancy and Lactation

Drug	*USFDA category*	*Placental permeability*	*Transfer to milk*	*Therapeutic level*	*Reported adverse effects*
UFH	B	No	No	aPTT ratio 1.5–2.5 times the control value*	Osteoporosis (long-term use) and thrombocytopenia
LMWH	B	No	No	4–6 hour peak anti-Xa values of 0.6–1.2 IU/mL*	Osteoporosis (long-term use); markedly less thrombocytopenia than UFH
Warfarin	D	Yes	Yes (well tolerated)	INR 2–3**	Embryopathy (mainly first trimester), bleeding

*Dose-adjusted UFH (a PTT ≥2 times control) or adjusted-dose LMWH (target anti-Xa level 4–6 hours post-dose 0.8–1.2 U/mL) in mechanical valve patients
**In atrial fibrillarion, INR can be kept between 2.0 and 2.5 to minimize the risk.

UFH, unfractionated heparin; LMWH, low-molecular weight heparin; aPTT, activated partial thromboplastin time ratio; INR, international normalized ratio.

occurrence of valve thrombosis and its lethal consequences for both mother and fetus.[2]

The choice of the anticoagulant is made according to the condition being treated and the stage of pregnancy. Low molecular weight heparin (LMWH) has become the drug of choice for the treatment of VTE (pulmonary embolism or deep vein thrombosis) in pregnancy. Because of more risk of thrombocytopenia, osteoporosis, and less convenient dosing when compared with LMWH, unfractionated heparin is favored only in special situations like in patients with renal failure and in the acute treatment of massive pulmonary embolism.[2] On the other hand, multiple studies have shown that heparin therapy is associated with a higher incidence of thrombotic complications when given instead of oral anticoagulants in pregnant patients with mechanical valves.[32]

Thus, in this patient population, low-dose warfarin use throughout pregnancy under strict international normalized ratio (INR) control is the safest approach from the maternal perspective.

The use of warfarin during first trimester has been associated with a risk for embryopathy. However, the absolute incidence is unknown and the risk is dose-related and appears to be very low in patients taking 5 mg/day or less.[33] Thus, continuation of oral anticoagulants should be considered during first trimester if the warfarin dose required for therapeutic anticoagulation is <5 mg/day after discussing the "risk and benefit" potential of this strategy with the patients and obtaining their consent.[2] In patients with a warfarin dose requirement of >5 mg/day, discontinuation of oral anticoagulation between weeks 6 and 12 and replacement by adjusted-dose heparin should be considered.[2]

To minimize the risk of fetal intracranial hemorrhage during delivery, heparin should be restarted at 36th week of gestation.[32] Cesarean delivery is indicated if delivery starts while on oral anticoagulants.[2] There is scarcity of evidence regarding the safety of LMWH during pregnancy in women with mechanical prostheses, and, thus, its use is still controversial.

The regimen for anticoagulation in pregnant patients with atrial fibrillation and high-risk of thromboembolism follow the same rationale like the mechanical valve patients. The only exception is that LMWH is effective and is the drug of choice during first trimester and last month of pregnancy.[34] There is evidence of fetotoxicity with high doses of the new oral thrombin antagonists, such as dabigatran and thus should not be used.[2]

CONCLUSION

In several instances, drug therapy for patients with CVD during pregnancy and lactation is necessary. The risk to mother, fetus, and neonate must be considered and weighed against the benefit. There are general principles that apply to the medical therapy of patient with CVD during pregnancy and lactation. Given the highest risk during first trimester of pregnancy, drug therapy should be avoided during this period, if possible. If needed, drugs with the longest record of safety should be used as first-line therapy and combination drug therapy should be avoided. The lowest effective dose of a medication should be used and short-acting drugs are preferred. Finally, patients should always be informed about the risks and benefits of each medical therapy and should be involved in the decision-making process.

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13 CHAPTER

Future Directions: Role of Genetics in Drug Therapy

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Our contemporary approach of exploring the human genome offers new and exiciting opportunities for improving therapeutic precision in cardiovascular medicine. There are essentially three different genomic methodologies that have been applied to identify specific DNA sequence variations, which are associated with either significant side effects or responsiveness to a drug. All of them are free from hypothesis, representing a major departure from an older era of genomic science when candidate gene variants were typically published and eventually lacked independent replication. But the methodologies of genome-wide association studies (GWAS), exome sequencing, and whole genome sequencing are being successfully applied to many cardiovascular drugs and conditions.

GWAS refers to the scanning of genome with approximately 500,000 to 1 million single nucleotide variants that tag the hundreds of thousands of bins (also known as haplotype blocks or what can be conceived as "zip codes" of linkage disequilibrium). Essentially, this technique identifies the bin(s) of the genome that unequivocally tracks down the clinical condition we are interested in. For example, it has been remarkably useful for determining the principal gene associated with statin-induced myopathy (SCLOB1). Although it has not been applied clinically yet, an individual having two copies of the variant identified in this gene is at a 20-fold increased risk of developing significant myositis, which is the most common side effect for statin therapy. With statins being the most widely prescribed group of medicines, one can make a strong case to screen individuals who are being considered for a new prescription in order to preempt side effects.

Another example in favor of efficacy of GWAS is the analysis of responsiveness of patients receiving clopidogrel, one of the other most widely prescribed drugs in cardiovascular medicine. Clopidogrel is an inert drug that needs to be metabolized in order to affect its target platelet receptor, P2Y12. The main route

of metabolism is via a P450 cytochrome known as CYP2C19. A GWAS study has shown that the principal signal for clopidogrel responsiveness is localized to variations in the CYP2C19 gene. There are multiple loss-of-function alleles in this gene that are commonly present in 30% of individuals of European ancestry and 40–50% of people of African or Asian ancestry. Amongst the patients who undergo coronary stenting, and are only carriers of one of the loss-of-function variants, the risk for stent thrombosis is increased by 300% , manifested either as myocardial infarction or sudden cardiac death. To assure platelet responsiveness of carriers or homozygotes of loss-of-function alleles, rapid point-of-care platelet function studies can be organized which can be helpful in assessing the usage of much higher doses of clopidogrel in such cases or alternative P2Y12 blockers (prasugrel and ticagrelor). This constitutes the prototypic case of pharmacogenomics, since the clinical stakes are high and the genotype information is highly actionable. GWAS also determined the principal gene variants for warfarin responsiveness, but the data has unfortunately not yet influenced clinical practice because of the cost and the time consumed in performing genotyping.

GWAS studies are now giving way to two more informative approaches involving sequencing of the genome rather than just scanning. The diploid human genome is comprised of 2 copies of 3 billion base pairs (A, T, C, G). By only scanning 1 million single nucleotide variants, GWAS has a limited access to only 0.03% of the genome. Now we can readily sequence the exome, the entire set of protein-coding elements of the genome, but still this only accounts for 1.5% of the genome. The fact that the coding elements of the genome ("exome") account for such a small portion of entire genome, is frequently not appreciated. Furthermore, the importance of non-coding elements of the genome has been greatly emphasized by many seminal studies in the past couple of years. Exome sequencing is now being applied to many commonly used drugs in cardiovascular medicine. We have already identified some additional sequence variants that predict clopidogrel responsiveness beyond CYP2C19.

Whole genome sequencing, in which all 6 billion base pairs are determined, is the current method that is receiving considerable attention, for it moves us closer to "full disclosure" of DNA description. In 2012, it has been predicted that whole genome sequencing will be performed within 2 hours at a cost of approximately $1000. The tremendous advances in the technology of sequencing are epitomized by the fact that in

1991 its cost was $10 per base pair; in 2001, it decreased to 10 cents, and in 2011, it dropped down to 0.001 cents!

With the cost of sequencing decreasing so dramatically, and our increasing ability to determine genomic variations that are undeniably linked to efficacy or side effects of the cardiac drugs, the field of cardiovascular pharmacogenomics is set to take off. Once specific genomic variations are identified and replicated, they can be quickly assayed by point-of-care genotyping systems. A handheld device that can perform genotyping in <15 minutes is under experimentation. These advancements have made it easy to envision the cost effectiveness of rapid genotyping of key pharmacogenomics variants in near future and enabling it to become a routine clinical practice. Of particular note, it will be essential in clinical development of all new drugs to incorporate genomic approaches in order to reliably predict major side effects and efficacy. In this way, we can transcend our current "hit or miss" approach to therapeutics and move to a much higher plane of precision in cardiovascular approaches in future.

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