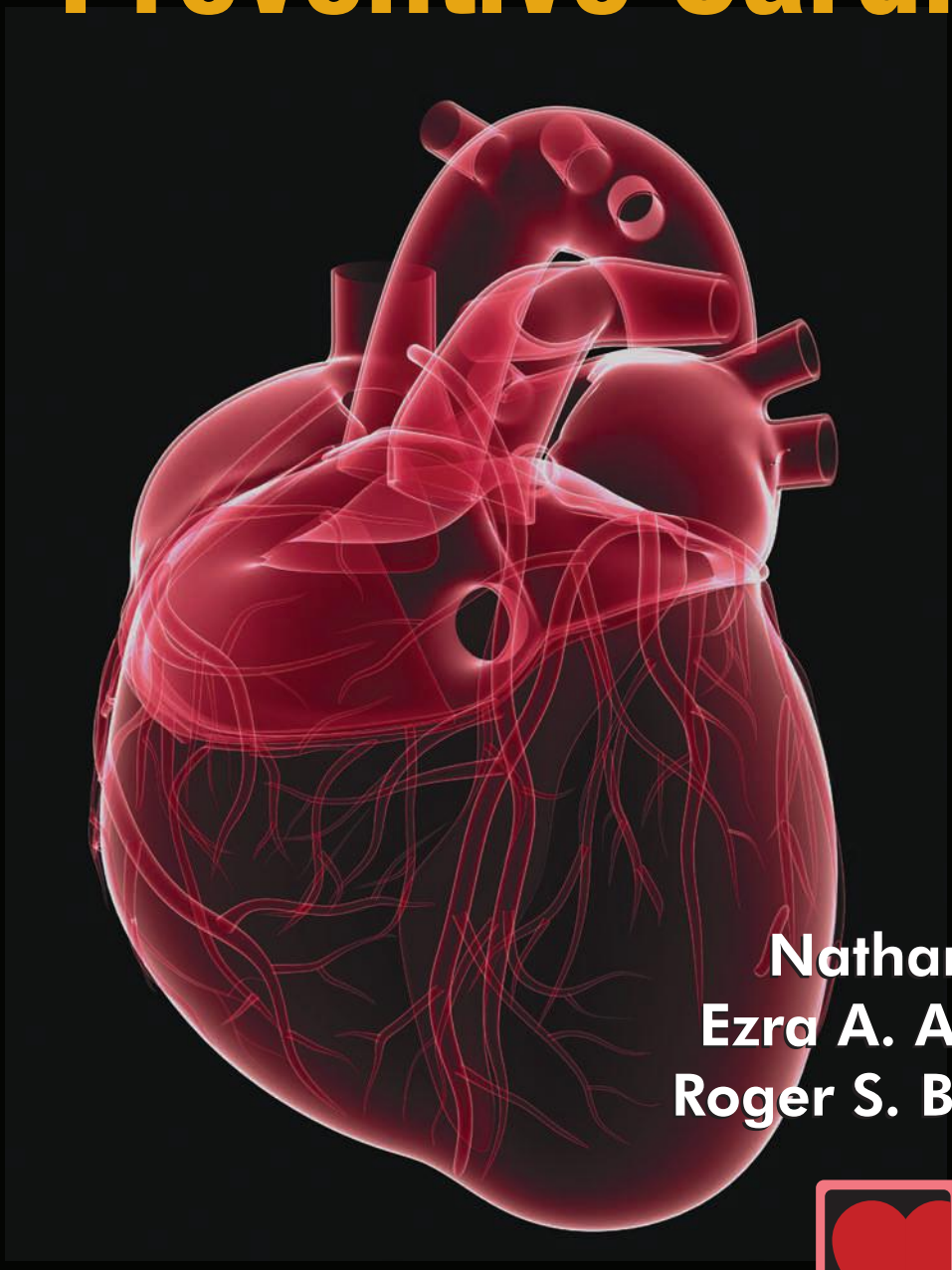
ASPC Manual of Preventive Cardiology



Nathan D. Wong
Ezra A. Amsterdam
Roger S. Blumenthal

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Editors

Nathan D. Wong, PhD, FACC, FAHA, FNLA
Director, UCI Heart Disease Prevention Program
Professor, Department of Internal Medicine
University of California Irvine School of Medicine
Irvine, California
Past President, American Society for Preventive Cardiology

Ezra A. Amsterdam, MD
Distinguished Professor of Medicine
Department of Internal Medicine
Associate Chief (Academic Affairs)
Division of Cardiovascular Medicine
Master Clinician Educator
University of California Davis School of Medicine
Sacramento, California

Roger S. Blumenthal, MD, FACC, FAHA
Director, Johns Hopkins Ciccarone Center for the
Prevention of Heart Disease
Professor, Department of Internal Medicine
The Kenneth J. Pollin Professor of Cardiology
Johns Hopkins Hospital
Baltimore, Maryland

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Contents

†Deceased.

Contributors

Hermelinda G. Abcede, MD
Assistant Clinical Professor
Department of Neurology
University of California, Irvine
Irvine, California

Ahsan Achtchi, DO
Fellow
Division of Cardiovascular Disease
Department of Medicine
Emory University School of Medicine
Atlanta, Georgia

Haitham M. Ahmed, MD, MPH
Cardiology Fellow
Division of Cardiology
Johns Hopkins Hospital
Baltimore, Maryland

Lama Al-Khoury, MD
Clinical Assistant Professor
Department of Neurology
University of California Irvine (UCI) Medical Center
Irvine, California

Ezra A. Amsterdam, MD
Distinguished Professor of Medicine
Department of Internal Medicine
Associate Chief (Academic Affairs)
Division of Cardiovascular Medicine
Master Clinician Educator
University of California Davis School of Medicine
Sacramento, California

M. Dominique Ashen, PhD, CRNP
Nurse Practitioner Coordinator
John Hopkins Ciccarone Center for the Prevention of Heart Disease
Baltimore, Maryland

Stanley Bassin, EdD
Clinical Professor of Medicine
Department of Cardiology
University of California School of Medicine
Irvine, California

Seth J. Baum, MD, FACC, FAHA, FACPM, FNLA
Associate Professor
Miller School of Medicine
University of Miami
Miami, Florida;
Medical Director
Department of Women's Preventive Cardiology
Boca Raton Regional Hospital
Boca Raton, Florida

Jarrett D. Berry, MD, MS
Division of Cardiology
UT Southwestern Medical Center
Dallas, Texas

Neal Kumar Bhatia, MD
Cardiology Fellow
Department of Cardiology
Emory University School of Medicine
Atlanta, Georgia

Roger S. Blumenthal, MD, FACC, FAHA
Director
Johns Hopkins Ciccarone Center for the Prevention of Heart Disease;
Professor
Department of Internal Medicine
The Kenneth Jay Pollin Professor of Cardiology
Johns Hopkins Hospital
Baltimore, Maryland

Javed Butler, MD, MPH
Professor of Medicine
Department of Cardiology
Emory University School of Medicine
Atlanta, Georgia

Dimitri Cassimatis, MD
Director
Emory University Hospital Midtown Coronary Care Unit;
Assistant Professor of Medicine
Division of Cardiology
Emory University School of Medicine
Atlanta, Georgia

Henry G. Cheng, MD
Resident Physician
Department of Medicine
The John Hopkins Hospital
Baltimore, Maryland

Edward Claude Clermont, MD
Resident Physician
Department of Internal Medicine
Emory University School of Medicine
Atlanta, Georgia

Danny J. Eapen, MD
Assistant Professor of Medicine
Division of Cardiology
Emory University School of Medicine
Atlanta, Georgia

William J. Elliott, MD, PhD
Professor of Preventive Medicine
Internal Medicine and Pharmacology
Head of Division of Pharmacology
Chairman of Department of Basic Medical Sciences
Pacific Northwest University of Health Sciences
Yakima, Washington

Mark Fisher, MD
Professor
Department of Neurology
University of California, Irvine
Irvine, California

Nima Ghasemzadeh, MD
Cardiology Fellow
Department of Internal Medicine (Cardiology)
Emory University School of Medicine
Atlanta, Georgia

Ty J. Gluckman, MD, FACC, FAHA
Medical Director
Department of Clinical Transformation
Providence Heart and Vascular Institute
Portland, Oregon

Alan S. Go, MD
Division of Research
Kaiser Permanente Northern California
Oakland, California

Terence Hill, MD
Cardiovascular Medicine Fellow
Department of Cardiovascular Medicine
Cleveland Clinic
Cleveland, Ohio

Ijeoma Isiadinso, MD
Assistant Professor of Medicine
Division of Cardiology
Department of Medicine
Emory University School of Medicine
Atlanta, Georgia

Vivek Jain, MD
Associate Clinical Professor
Department of Neurology
University of California, Davis
Davis, California

Steven R. Jones, MD
Assistant Professor of Medicine
Department of Medicine, Division of Cardiology
Director of Inpatient Cardiology
Director of University Lipid Clinic
Johns Hopkins Ciccarone Center for the Prevention of Heart Disease
Johns Hopkins Hospital
Baltimore, Maryland

C. Tissa Kappagoda, MD, PhD
Professor of Emeritus
Department of Cardiovascular Medicine
University of California Davis School of Medicine
Sacramento, California

Jenna Kay, MD
Chief Resident
Department of Internal Medicine
Emory University School of Medicine
Atlanta, Georgia

Amit Khera, MD, MSc, FACC
Director
Preventive Cardiology Section
Associate Professor
Department of Internal Medicine
UT Southwestern Medical Center
Dallas, Texas

Arthur L. Klatsky, MD
Senior Consultant
Department of Cardiology
Adjunct Investigator
Division of Research
Kaiser Permanente Medical Center
Oakland, California

Peter Kwiterovich, MD[†]
Professor
Department of Pediatrics, Division of Cardiology
Johns Hopkins Children's Center
Johns Hopkins University School of Medicine
Baltimore, Maryland

Russell V. Luepker, MD, MS
Mayo Professor
Department of Epidemiology and Community Health
Professor
Department of Medicine (Cardiology)
University of Minnesota
Minneapolis, Minnesota

Shaista Malik, MD, PhD, MPH
Associate Professor
Department of Medicine
University of California, Irvine
Irvine, California

Seth S. Martin, MD
Pollin Cardiovascular Prevention Fellow
Department of Cardiology
Johns Hopkins University School of Medicine
Baltimore, Maryland

Jessica L. Mega, MD, MPH, FACC, FAHA
Cardiologist
Brigham and Women's Hospital;
Associate Professor
Harvard Medical School
Boston, Massachusetts

Erin D. Michos, MD, MHS
Associate Professor of Medicine
Division of Cardiology
Department of Medicine
Johns Hopkins University School of Medicine
Baltimore, Maryland

Satish Misra, MD
Clinical Fellow
Division of Cardiology
Department of Medicine
Johns Hopkins University School of Medicine
Baltimore, Maryland

Samia Mora, MD, MHS
Associate Physician
Brigham and Women's Hospital;
Assistant Professor
Harvard Medical School
Boston, Massachusetts

Vijay Nambi, MD, PhD
Associate Professor
Michael E. DeBakey Veterans Affairs Medical Center
Section of Atherosclerosis and Vascular Medicine
Section of Cardiology
Department of Medicine
Center for Cardiovascular Prevention
Baylor College of Medicine
Methodist DeBakey Heart and Vascular Center
Houston, Texas

Khurram Nasir, MD, MPH
Director, Center for Prevention and Wellness Research
Department of Wellness Research
Baptist Health South Florida
Miami, Florida

[†]Deceased.

Chiadi E. Ndumele, MD, MHS
Robert E. Meyerhoff Assistant Professor of Medicine
Division of Cardiology
Department of Medicine
Johns Hopkins University
Baltimore, Maryland

Christine L. Nell-Dybdahl, NP-C, MPH, MSN
Nurse Practitioner of Preventive Cardiology
Nurse Clinical Director
Emory Heart Disease Prevention Center
Adjunct Faculty
Emory University School of Nursing
Atlanta, Georgia

Benjamin Oldfield, MD
Resident
Department of Internal Medicine and Pediatrics
Johns Hopkins University School of Medicine
Baltimore, Maryland

Andre R. M. Paixao, MD
Division of Cardiology
UT Southwestern Medical Center
Dallas, Texas

Aalok Patel, MD
Fellow
Division of Cardiovascular Disease
Department of Medicine
Mayo Clinic
Rochester, Minnesota

Rohini J. Patel, MPH
Department of Cardiology
University of California, Irvine
Irvine, California

Donna M. Polk, MD, MPH
Director
Cardiovascular Fellowship Program
Brigham and Women's Hospital
Boston, Massachusetts

Jamal S. Rana, MD, PhD
Division of Cardiology
Department of Medicine
Kaiser Permanente Northern California
Oakland, California

Elizabeth V. Ratchford, MD
Director of the Johns Hopkins Center for Vascular Medicine;
Assistant Professor
Department of Medicine
Division of Cardiology
Johns Hopkins University School of Medicine
Baltimore, Maryland

Alan Rozanski, MD, FACC
Chief
Division of Cardiology
Mt. Sinai St. Luke's and Roosevelt Hospital
New York, New York

Maya J. Salameh, MD
Assistant Professor of Medicine
Division of Cardiology
Department of Internal Medicine
Johns Hopkins University School of Medicine
Baltimore, Maryland

Monika Sanghavi, MD
Assistant Professor
Department of Internal Medicine
UT Southwestern Medical Center
Dallas, Texas

Amil M. Shah, MD, MPH
Assistant Professor of Medicine
Harvard Medical School;
Associate Physician
Division of Cardiovascular Medicine
Brigham and Women's Hospital
Boston, Massachusetts

Geeta Sikand, MA, RDN, FAND, CDE, CLS, FNLA
Associate Clinical Professor of Medicine
Department of Cardiology
Director of Nutrition
Preventive Cardiology Program
University of California Irvine School of Medicine
Irvine, California

Laurence Sperling, MD, FACC, FACP, FAHA
Professor of Medicine (Cardiology)
Director of Emory Heart Disease Prevention Center
Professor of Global Health
Rollins School of Public Health
Emory University School of Medicine
Atlanta, Georgia

Neil J. Stone, MD, MACP, FACC, FAHA
Bonow Professor of Medicine
Department of Medicine (Cardiology)
Feinberg School of Medicine;
Suzanne and Milton Davidson Distinguished
Physician and Medical Director
Bluhm Cardiovascular Institute
Northwestern Memorial Hospital
Chicago, Illinois

Nirmal Sunkara, MD
Fellow in Cardiology
Department of Internal Medicine
University of California Irvine
Irvine, California

Salman Waheed, MD, MPH, MHS
Fellow, Cardiovascular Diseases
Department of Cardiology
University of Kansas Medical Center
Kansas City, Kansas

Eric Y. Yang, MD
Cardiology Fellow
Department of Medicine
Baylor College of Medicine
Houston, Texas

Omair K. Yousuf, MD
Chief Cardiology Fellow
Department of Medicine
Johns Hopkins University
Baltimore, Maryland

Foreword

The publication of this *ASPC Manual of Preventive Cardiology* coincides with the twentieth anniversary of the 1994 publication of the *Primer in Preventive Cardiology* by the American Heart Association (1). As the chair of its editorial committee, I can vouch that the *Primer* and the *ASPC Manual* share the goal of "summarizing the knowledge and experience gained" in the efforts to control this greatest epidemic of the twentieth century. Also shared is the target audience of the publications, namely students and practitioners of medicine, nursing, and other health professions, who will be responsible for translation of that knowledge and experience into better cardiovascular health at the patient, community, and societal levels.

The foreword for the *Primer* (2) was contributed by Dr. Jeremiah Stamler, a member of everyone's Preventive Cardiology Hall of Fame. His remarks emphasized the role of populationwide, primordial prevention, as the main driver of the 50% decline in coronary heart disease mortality since the late 1960s. He also provided a challenge for physicians to contribute to the cardiovascular disease prevention efforts: "physicians should work at three levels: (i) in their practices, with their patients, and with their patients' families; (ii) in their communities, to advance implementation of preventive efforts in neighborhoods, schools, workplaces, and medical centers …, and (iii) at the national level to influence public policy, resource allocation, and national priorities."

The *ASPC Manual* summarizes the considerable progress made in all three of these areas. The *Manual* especially provides practitioners with evidence-based knowledge and tools to reduce the risk of heart attack, stroke, and sudden death. These guidelines have evolved also from those oriented to primary (3) versus secondary prevention (4) to those that consider a continuum of risk and cost effectiveness. Complementary to clinical guidelines, community-level prevention has been re-emphasized in the original "American Heart Association Guide for Improving Cardiovascular Health at the Community Level" in 2003 (5). Its 2013 update provides practitioners and planners alike with community-based strategies focused on improving cardiovascular health rather than reducing cardiovascular risk (6). The policy infrastructure alluded to by Dr. Stamler has also evolved (7), with large initiatives such as the Community Transformation Grant Program focusing on creating environments in which the heart healthy option is the easier and less expensive one. The knowledge, skills, and tools available to practitioners in 2014 dwarf those available in 1994. The *ASPC Manual* assembles these for its readers.

The final chapter of the *Primer* consisted of a "Postscript: Preventive Cardiology in the 21st Century" (8), which I had the pleasure of coauthoring with our late friend and colleague from the American Heart Association, Dr. Mary Winston. In that brief document, we warned: "The continuation of the decline in cardiovascular mortality rate is by no means a foregone conclusion." Indeed, by the late 1990s, there was concern about the slowing of the decline in coronary and stroke mortalities (9). The new epidemics of obesity and diabetes posed real threats to the progress made. Yet, the subsequent data show sizeable and continuing declines in coronary and stroke mortality,

disproving our prediction that "cardiovascular disease will probably remain the leading cause of death in the United States and most Western countries well into the 21st century." Indeed, for a number of states in the United States, coronary heart disease is currently not the leading cause of death for the first time in 100 years. Although community-level and policy initiatives clearly continue to play significant roles, studies of health plan populations have documented large and rapid declines in myocardial infarction incidence and case fatality, coinciding with increased use of individual preventive cardiology interventions such as lipid-lowering and antihypertension therapies (10). This evidence base has led to national programs such as the Million Hearts Initiative to implement the ABCS (Aspirin, Blood Pressure Control, Cholesterol Management, and Smoking Cessation) more widely into the nation's clinics and hospitals (11).

Underpinning these programs is the notion that we have the knowledge and tools to effectively prevent most cases of coronary heart disease and stroke. The next (and final?) challenge then is to implement what we already know into the flow of clinical care, through the use of evidence-based strategies shown to be feasible and effective in a wide variety of contexts. The relatively new area of implementation science has identified a number of strategies that could be implemented at the clinical institution (e.g., hospital, clinic) or the practitioner levels to increase quickly the proportion of eligible patients who are receiving interventions recommended by guidelines.

This *ASPC Manual* is essential to this effort, in providing the knowledge, tools, and the evidence to support the clinical practice of preventive cardiology. In 1994 we wrote (8): "Whatever the 21st century brings, future prevention and treatments will surely be built upon the foundation of knowledge and experience summarized in the publication. It is hoped that this primer will prepare the physician for the exciting times ahead." The *ASPC Manual* clearly continues this tradition. The 20-year perspective might include that, although much remains to be done, we now have expanded confidence that the knowledge, tools, and strategies included in the *Manual* are proven to provide huge benefits to our patients and communities. The apathy and doubts about preventive cardiology as a discipline can be set aside and replaced by its inclusion in all health professional curricula. The *ASPC Manual* should play an important role in this coming-of-age of preventive cardiology.

Thomas A. Pearson, MD, MPH, PhD

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Preface

Preventive cardiology has made substantial contributions to reducing the toll of cardiovascular disease (CVD) during the past 50 years but despite these advances, CVD remains the leading cause of death in the United States, and the global burden of the disease continues to rise. In addition, the epidemic of obesity and the increase in diabetes threaten to reverse the downward trend of CVD. Coronary heart disease (CHD) is the primary etiology of this public health crisis and claims more than one million victims annually in the United States, and stroke, heart failure, and peripheral arterial disease are also major contributors to the burden of CVD. The crucial personal and economic benefits of preventing CVD compared to treatment of advanced atherosclerotic vascular disease have been convincingly demonstrated but optimal application of this evidence into daily practice lags, a deficiency that has gained recognition as the "knowledge–practice gap."

This situation necessitates intensification of efforts to prevent a reversal of past achievements in the struggle against CVD. It has also provided the background and incentive for the development of the *American Society for Preventive Cardiology (ASPC) Manual of Preventive Cardiology.* The editors have devoted their careers to this field in both practice and research and we are gratified that this *Manual* is an official publication of the ASPC.

Although textbooks on preventive cardiology have detailed its science and application, the goals of the *ASPC Manual of Preventive Cardiology* are to address contemporary practical approaches to the most vital aspects of preventing cardiac and vascular disease. Clinical utility for practitioners is foremost and special efforts have been made by the authors and editors to ensure that the content of all chapters is as up to date as possible.

The extent of this field now far exceeds its traditional designation of "preventive cardiology," as reflected by the spectrum of topics in the *ASPC Manual of Preventive Cardiology*. In addition to the time-honored topics of CVD risk factors, we also include chapters on peripheral artery disease, stroke, smoking, contemporary cardiovascular imaging, heart failure, metabolic syndrome, thrombosis, nutrition, special populations, novel risk factors, and psychosocial stress. An important feature is inclusion and expert assessment of the most recent prevention guidelines of the American College of Cardiology and American Heart Association, including those on risk assessment, lifestyle recommendations, blood cholesterol, and obesity as well as the new guidelines on hypertension.

This volume is the first of its kind since the publication of the original *Primer in Preventive Cardiology* in 1994 by the American Heart Association, edited by Dr. Thomas Pearson and colleagues. It is hoped that the expertise and access of current approaches to prevention in this compact *Manual* will promote translation of knowledge into daily practice to stem the tide of CVD worldwide.

Acknowledgments

We wish to acknowledge all those who have dedicated their lives to the prevention of cardiovascular disease, in particular Dr. William B. Kannel, Dr. Jeremiah Stamler, and Dr. Nanette K. Wenger.

I wish to acknowledge my wife Mia, parents Donald and Mew Lun, and friends Dr. David Kurtz, John Yasuda, and Ken Posthuma for their inspiration.

—NDW

I wish to acknowledge my wife, Beulah, for her inspiration, support and understanding during this work.

—EAA

I would like to acknowledge two leaders in preventive cardiology: Irene Pollin (founder of Sister to Sister) and the late Dr. Kenneth L. Baughman for their leadership in the field of preventive cardiology. I am most grateful for the support of my wife Dr. Wendy Post, my parents, Anita and the late Dr. Stanley L. Blumenthal, and my son Ross.

—RSB

Finally we wish to express our appreciation for the tireless efforts of the Demos Medical publishing staff, including Rich Winters, Brian Black and Joe Stubenrauch, and the staff and past and present officers, board, and membership of the American Society for Preventive Cardiology for their efforts and contributions to education, research, and patient care related to preventive cardiology.

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ASPC Manual of Preventive Cardiology

Jamal S. Rana, MD, PhD
and Alan S. Go, MD

1

National Burden of Cardiovascular Disease and Associated Risk Factors

Cardiovascular disease (CVD) and associated contributing risk factors impose a major burden on our society nationally and internationally (1). Despite successful advances over the past several decades in treatment of cardiovascular disease, risk factors such as obesity, lack of physical activity, and diabetes mellitus are all on the rise. In this chapter, we briefly summarize the burden of cardiovascular disease and major vascular risk factors, along with the resulting economic and human costs. Toward this end, the American Heart Association (AHA), in conjunction with the Centers for Disease Control and Prevention, the National Institutes of Health, and other government agencies, brings together the most up-to-date statistics on heart disease, stroke, other vascular diseases, and their risk factors, and presents them in its annual Heart Disease and Stroke Statistical Update (1) which serves as a major resource for highlighting key statistics most pertinent to practicing physicians.

CARDIOVASCULAR DISEASE

CVD includes all diseases of the circulatory system. In general, however, we focus on patients with clinical coronary heart disease (CHD), hypertension, heart failure, stroke, peripheral artery disease (PAD), and diseases of the veins (eg, deep venous thrombosis). Although congenital heart disease is an important form of CVD, it is not typically included in national estimates for total CVD unless otherwise specified (1).

Mortality and Morbidity Attributable to CVD

Overall Cardiovascular Disease

- The 2010 rate of death attributable to CVD was 236 per 100,000 in the United States. The CVD death rate varied by race and gender: 278 per 100,000 for white men, 369 per 100,000 for black men, 192 per 100,000 for white women, and 261 per 100,000 for black women.
- On a positive note, from 2000 to 2010, the death rate attributable to CVD declined a relative 31%, with a decline in the actual number of CVD deaths per year of ≈17%. However, in 2010, 32% of all ≈2.5 million deaths were attributed to CVD, or ≈1 of every 3 deaths in the United States.
- Based on 2010 estimates, >2150 Americans die of CVD each day, representing ≈1 death every 40 seconds. About 150,000 Americans who died of CVD in 2010 were younger than 65 years old. Furthermore, 34% of deaths attributable to CVD occurred before the age of 75 years, which is younger than the current average life expectancy of ≈79 years old.
- In 2010, the age-standardized death rate attributable to CVD was 237 per 100,000 (including congenital heart disease), which is 8.8% lower compared with 2007 (259 per 100,000) (2). However, the overall CVD mortality burden remains high nationally (Figure 1.1).

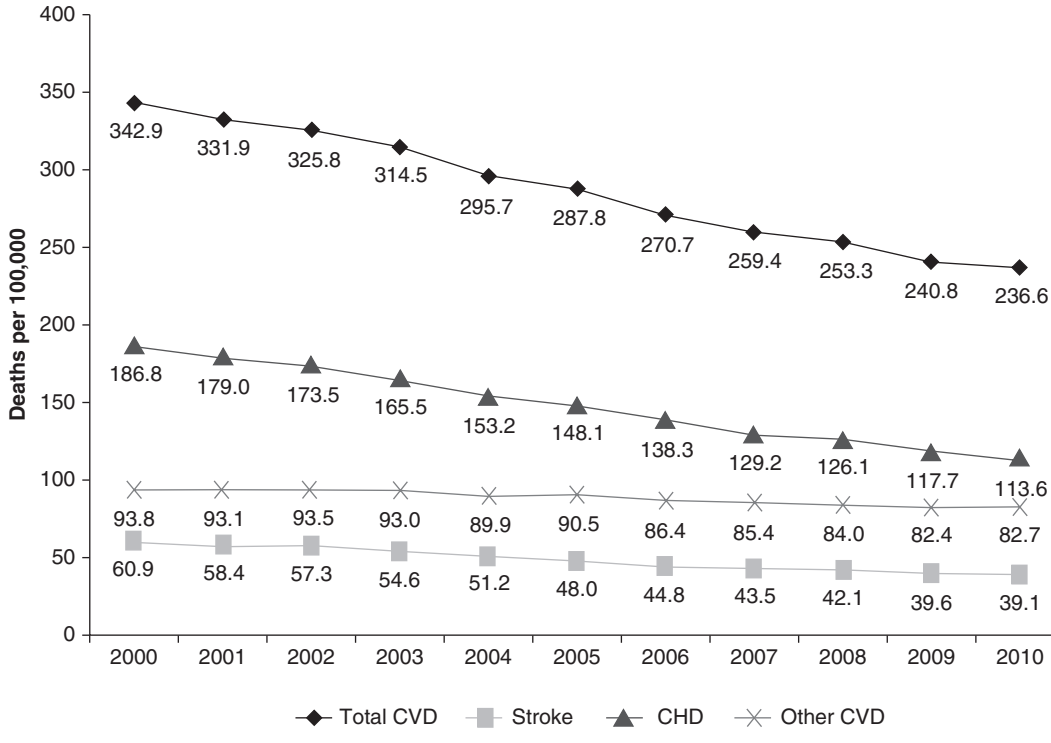

FIGURE 1.1 Age-standardized rate of death attributed to CVD (based on ICD-10 coding used for death certificates) in the United States (2000 to 2010). Based on data from Centers for Disease Control and Prevention and the National Center for Health Statistics.

Coronary Heart Disease

CHD (defined as acute myocardial infarction, other acute coronary syndrome, angina pectoris, and chronic ischemic coronary heart disease) alone caused ≈1 of every 6 deaths in the United States in 2010. In 2010, there were 379,559 deaths in the United States attributed to CHD. Each year, an estimated ≈620,000 Americans experience either a first hospitalized myocardial infarction or die secondary to CHD, and ≈295,000 have a recurrent hospitalized myocardial infarction. Furthermore, it is estimated that an additional 150,000 silent first myocardial infarctions occur each year which is associated with a poorer long-term prognosis. Based on these estimates, approximately every 34 seconds, 1 American has an acute coronary event, and approximately every 1 minute 23 seconds, an American will die of one.

Stroke

From 2000 to 2010, the relative rate of stroke-related death fell by 35.8% and the actual number of stroke deaths declined by 22.8%. Despite this encouraging news, ≈795,000 people continue to experience a new or recurrent stroke (ischemic or hemorrhagic) annually in the United States. Approximately 610,000 of these are first events and 185,000 are recurrent stroke events, with an estimated 85% of all strokes being ischemic. In 2010, stroke caused ≈1 of every 19 deaths in the United States.

- On average, every 40 seconds, someone in the United States experiences a stroke, and someone dies of one approximately every 4 minutes.
- The decline in stroke-related death over the past several decades—a major improvement in population health observed for both sexes and all race and age groups—has resulted from both reduced stroke incidence and lower case fatality rates.

Heart Failure

- In 2010, 1 in 9 death certificates (≈280,000 deaths) in the United States mentioned heart failure. Heart failure was assigned as the underlying cause in ≈58,000 of those deaths in 2010. Of interest, the number of deaths attributable to heart failure was approximately as high in 1995 (≈287,000) as it was in 2010 (≈280,000).
- In addition, annual hospitalizations for heart failure remained stable from 2000 to 2010, with first-listed

discharges of 1,008,000 and 1,023,000, respectively. Unfortunately, heart failure remains the leading cause of hospitalization in Medicare beneficiaries.

Arrhythmias

- Atrial fibrillation is the most common clinically relevant arrhythmia in adults, with an estimated 2.7 to 6 million Americans affected in 2010 and projected 5.6 to 12 million by 2030. Atrial fibrillation independently increases the risk of ischemic stroke by four- to fivefold. Atrial fibrillation was listed as a cause of death in ≈15% of deaths in the United States in 2010.
- Sinus node dysfunction has a prevalence of ≈400–670 per million in the United States, affects 1 in 600 cardiac patients older than 65 years old, and is the responsible for half of the pacemaker implantations in the United States. Approximately 60% of patients develop symptoms and ≈25% will develop syncope within 4 years if untreated, and ≈50% will develop tachy–brady syndrome during their lifetime.
- Wolf–Parkinson–White syndrome (with ventricular pre-excitation or tachyarrhythmias) may affect ≈1 in 1,000 adults and ≈2 in 1,000 adolescents, and is associated with both atrial fibrillation and risk of sudden cardiac death. The average annual risk of sudden cardiac death in persons with Wolf–Parkinson–White syndrome is estimated to be ≈1 per 1,000.

Valvular Disease

- The prevalence of valvular heart disease in the United States has been increasing over time—primarily driven by the aging of the population and more widespread use of echocardiography and other cardiovascular imaging—and affects ≈1 in 40 U.S. adults, with the most common disorders being mitral regurgitation, aortic stenosis, and aortic regurgitation in that order.
- The 5-year risk of death is higher in those with any valvular disease (≈20%) compared with those who do not have known valvular disease (7%).
- Rheumatic fever/heart disease is uncommon in the United States compared with other parts of the world. Temporal trends suggest improving mortality in those with rheumatic fever/heart disease, with a death rate of ≈1 per 100,000 in 2009 but higher in whites compared with other racial/ethnic groups.

Congenital Heart Disease

- Congenital heart defects are thought to affect between 650,000 and 1.3 million Americans currently, with the most common defects in adults being atrial septal defects and tetralogy of Fallot.
- There are more adults than children living with congenital heart defects in the United States, given the declining rate of death in affected children over time. In 2010, ≈3,200 deaths were attributed to congenital heart defects nationally. Between 1999 and 2006, the age-adjusted rate of death declined ≈20–40%, and deaths were more likely to occur at older ages in more recent years.

Cardiovascular Health

In the context of preventive cardiology, it is important to discuss a newly introduced concept of cardiovascular health by AHA. It is characterized by 7 health metrics (Table 1.1) where *ideal cardiovascular health* is defined by the absence of clinical CVD in combination with having optimal levels of all seven metrics, including four health behaviors (not smoking, adequate physical activity, a healthy diet, and normal body weight) and three health factors (optimal total cholesterol, blood pressure, and fasting blood glucose in the absence of drug treatment). Using this approach, one can consider the spectrum of cardiovascular health in terms of each of the health behaviors and health factors and represented as being "ideal," "intermediate," or "poor." Table 1.1 provides the specific AHA definitions for ideal, intermediate, and poor cardiovascular health based on each of the seven metrics.

Age-standardized estimates for poor, intermediate, and ideal cardiovascular health for each of the seven metrics are shown in Figure 1.2. Unfortunately, as the figure illustrates, based on estimates from the 2009–2010 National Health and Nutrition Examination Survey (NHANES), there is very high prevalence of poor indices for healthy diet, physical activity, and obesity in U.S. adults.

What is particularly sobering is that only 0.1% of U.S. adults met all seven criteria at ideal levels in 2009–2010, with only ≈13% of U.S. adults meeting five criteria and ≈4% meeting six criteria. Most U.S. adults (≥65%) have only two, three, or four criteria at ideal cardiovascular health, with ≈1 in 5 adults within each of these categories. There is also significant racial/ethnic variation in achieving ideal cardiovascular health, with blacks and Mexican Americans meeting fewer metrics at ideal levels compared with whites or other races. Approximately 6 in 10 white adults achieved three or fewer metrics at ideal levels, as compared with 7 in 10 black or Mexican American adults.

The AHA as set an ambitious national goal to achieve by the year 2020: to improve the cardiovascular health of all Americans by 20%, while reducing deaths from CVD and stroke by 20% (3). To try to achieve this, an initiative focuses on three major strategies (3):

1. In addition to optimizing the treatment of established CVD, an expanded focus on CVD prevention and promotion of the model of positive "cardiovascular health"

TABLE 1.1 Definitions of Poor, Intermediate, and Ideal Cardiovascular Health Based on AHA Metrics

	Level of Cardiovascular Health for Each Metric		
	Poor	**Intermediate**	**Ideal**
Current smoking			
Adults ≥ 20 y of age	Yes	Former ≥ 12 mo	Never or quit > 12 mo
Children 12–19 y of age	Tried during the prior 30 d	…	Never tried; never smoked whole cigarette
BMI*			
Adults ≥ 20 y of age	≥ 30 kg/m^2	25–29.9 kg/m^2	< 25 kg/m^2
Children 2–19 y of age	> 95th percentile	85th–95th percentile	< 85th percentile
PA			
Adults ≥ 20 y of age	None	1–149 min/wk moderate or 1–74 min/wk vigorous or 1–149 min/wk moderate + 2×vigorous	≥ 150 min/wk moderate or ≥ 75 min/wk vigorous or ≥ 150 min/wk moderate + 2×vigorous
Children 12–19 y of age	None	> 0 and < 60 min of moderate or vigorous every day	≥ 60 min of moderate or vigorous every day
Healthy diet pattern, No. of components†			
Adults ≥ 20 y of age	0–1	2–3	4–5
Children 5–19 y of age	0–1	2–3	4–5
Total cholesterol, mg/dL			
Adults ≥ 20 y of age	≥ 240	200–239 or treated to goal	< 200
Children 6–19 y of age	≥ 200	170–199	< 170
Blood pressure			
Adults ≥ 20 y of age	SBP ≥ 140 mmHg or DBP ≥ 90 mmHg	SBP 120–139 mmHg or DBP 80–89 mmHg or treated to goal	< 120 mmHg/< 80 mmHg
Children 8–19 y of age	> 95th percentile	90th–95th percentile or SBP ≥ 120 mmHg or DBP ≥ 80 mm hg	< 90th percentile
Fasting plasma glucose, mg/dL			
Adults ≥ 20 y of age	≥ 126	100–125 or treated to goal	< 100
Children 12–19 y of age	≥ 126	100–125	< 100

Abbreviations: AHA indicates American Heart Association; BMI, body mass index; DBP, diastolic blood pressure; ellipses (…), data not available; PA, physical activity; and SBP, systolic blood pressure.

*Represents appropriate energy balance, that is, appropriate dietary quantity and PA to maintain normal body weight.

†In the context of a healthy dietary pattern that is consistent with a Dietary Approaches to Stop Hypertension [DASH]–type eating pattern, to consume ≥ 4.5 cups/d of fruits and vegetables, ≥ 2 servings/wk of fish, and ≥ 3 servings/d of whole grains, and no more than 36 oz/wk of sugar-sweetened beverages and 1500 mg/d of sodium.

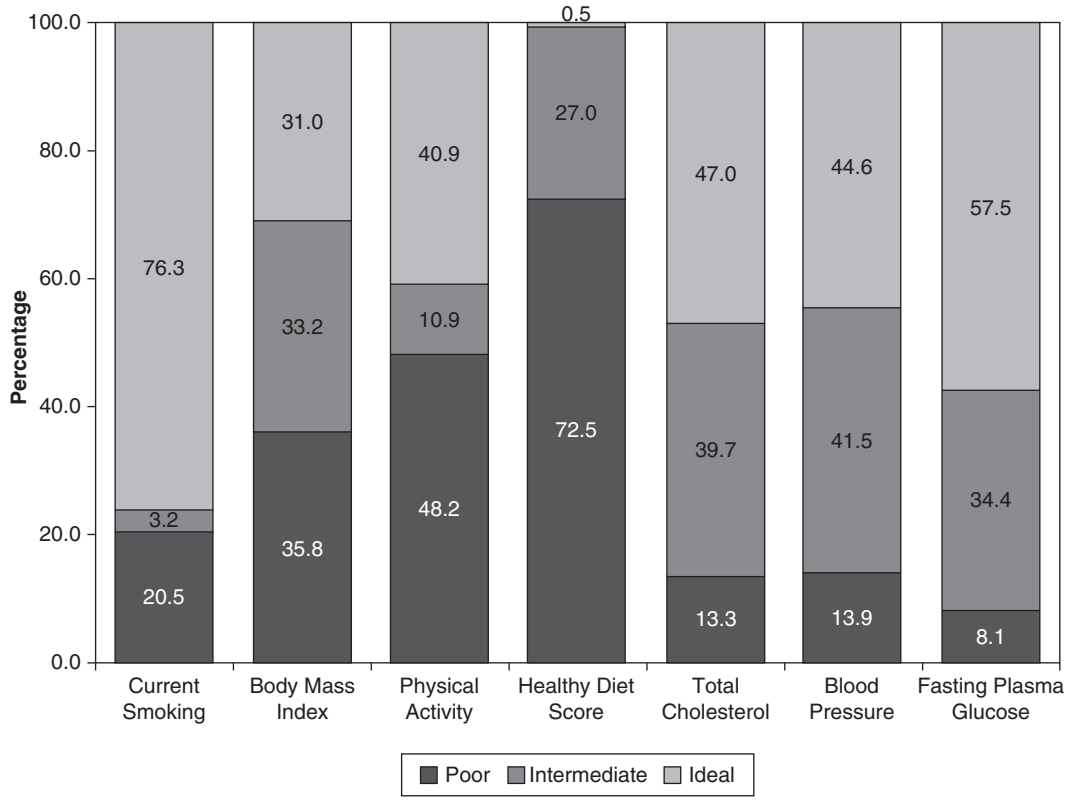

FIGURE 1.2 Age-standardized estimates for poor, intermediate, and ideal cardiovascular health based on AHA metrics using data from the 2009–2010 National Health and Nutrition Examination Survey (NHANES).

2. Increased efforts to promote both healthy biomarker levels (ie, optimal blood lipid, blood pressure, and fasting blood glucose levels) and healthy behaviors (healthy dietary pattern, appropriate energy intake, adequate physical activity, and not smoking) throughout a person's lifetime
3. Population-level health promotion strategies to shift the majority of the public toward greater cardiovascular health, in addition to targeting those individuals at greatest CVD risk

Epidemic of Poor Cardiovascular Health Behaviors

■ Adjusted estimated population attributable fractions for CVD mortality (ie, the proportion of CVD deaths that would be avoided if the adverse risk factor were completely removed) are:

- ≈41% for high blood pressure
- ≈14% for cigarette smoking
- ≈13% for a poor diet
- ≈12% for insufficient physical activity
- ≈9% for abnormal blood glucose levels

■ Despite significant progress over the past four decades, in 2012, among Americans ≥18 years of age, ≈1 in 5 men, and ≈1 in 6 of women continued to be cigarette smokers. In 2011, ≈18% of students in grades 9 through 12 reported current cigarette use.

■ In 2009 to 2010, <1% of American adults met at least four of five healthy dietary goals. In meta-analyses of prospective cohort studies, greater consumption of refined complex carbohydrates, starches, and sugars, as assessed by glycemic index or load, was associated with significantly higher risk of diabetes mellitus and development of CHD. Compared with the lowest category of glycemic load, the highest category of glycemic load is associated with a 40% higher risk of developing diabetes mellitus and a 36% higher risk of CHD (5,6).

■ In 2012, only one third of adults reported engaging in aerobic leisure-time physical activity. Television watching is one of the most common sedentary activities nationally, and two hours of television per day is associated with 20% higher risk of developing type 2 diabetes mellitus, 15% higher risk of a fatal or nonfatal CVD

event, and 13% higher risk of death from any cause: these risks increase with longer television watching (4).
■ The estimated prevalence of overweight and obesity in U.S. adults (≥20 years of age) is ≈155 million, representing more than 68% of all American adults in 2010. Nearly 35% of U.S. adults are obese (body mass index ≥30 kg/m^2). This current and worsening epidemic of overweight and obesity affects men and women of all racial/ethnic groups nationally.
■ Obesity (body mass index ≥30 kg/m^2) is associated with marked excess mortality, but is even more strongly associated with excess morbidity including a substantially higher incidence of diabetes mellitus, CVD end points (including CHD, stroke, and heart failure), and numerous other health conditions, including asthma, cancer, end-stage renal disease, degenerative joint disease, and many others.

Prevalence and Control of Cardiovascular Risk Factors

Family History

■ Among adults ≥20 years of age, ≈13% reported having a parent or sibling with a myocardial infarction or angina before the age of 50 years.
■ Having a paternal history of a premature heart attack is associated with an approximately twofold higher risk of myocardial infarction in men and 70% higher risk in women (6,7).
■ Having a family history of premature angina, myocardial infarction or coronary revascularization is associated with ≈50% higher lifetime risk for both CHD (from ≈9% to ≈14%) and CVD mortality (from ≈14% to ≈21%) (8).

High Blood Pressure

■ Estimates from 2007 to 2010 suggested that ≈1 in 3 U.S. adults ≥20 years of age had hypertension. This translates into a conservative estimate of ≈78 million U.S. adults with hypertension.
■ Although the prevalence of hypertension is similar for men and women, black/African American adults have among the highest prevalence of hypertension (44%) in the world.
■ Prehypertension (120–129/80–89 mmHg) is even more common, affecting more than 1 in 3 U.S. adults who do not have any known cardiovascular disease based on 1999–2006 NHANES data.
■ Data from 2009–2010 NHANES showed that ≈82% of adults with hypertension were aware of their condition. Furthermore, three quarters of hypertension patients reported they were taking prescribed antihypertensive medications. Non-Hispanic black adults (87%) were more aware of their hypertension than Hispanics (≈78%) (12).

Dyslipidemia

■ An estimated 32 million adults ≥20 years of age have total serum cholesterol levels ≥240 mg/dL, representing a prevalence of ≈14% among American adults.
■ An estimated 49 million adults ≥20 years of age had HDL cholesterol levels <40 mg/dL in 2010, representing a prevalence of ≈22% among American adults.
■ Data from NHANES found that treatment of high LDL cholesterol increased from ≈28% of individuals during 1999 to 2002 to ≈48% during 2005 to 2008 (10).
■ As expected, self-reported use of cholesterol-lowering medications increased from ≈8% during 1999 to 2000 to ≈14% during 2005 to 2006 (11).

Diabetes Mellitus

■ In 2010, an estimated ≈20 million Americans had diagnosed diabetes mellitus, representing ≈1 in 12 U.S. adults. An additional 8.2 million had undiagnosed diabetes mellitus, and ≈38% had prediabetes defined as having abnormal fasting glucose levels. Black/African Americans, Mexican Americans, Hispanic/Latino individuals, and other ethnic minorities bear a strikingly disproportionate burden of diabetes mellitus nationally.
■ Unfortunately, the prevalence of diabetes mellitus is increasing dramatically over time and occurring in parallel with the rising prevalence of overweight and obesity nationally.

Chronic Kidney Disease

■ Chronic kidney disease (defined by an estimated glomerular filtration rate <60 ml/min/1.73 m^2 or proteinuria) affects ≈20 million Americans and is an important risk factor for CVD events and death even after accounting for other known risk factors (13).
■ CVD is the leading cause of death among those with chronic kidney disease as well as those with end-stage renal disease, although the specific cardiovascular cause of death may be more likely to be arrhythmic than myocardial infarction, end-stage heart failure, or stroke in those with end-stage renal disease. CVD mortality is 5 to 30 times higher in patients on chronic dialysis compared with age-sex-race-matched persons in the general population (14, 15).

Subclinical Atherosclerosis

Coronary Artery Calcification

■ Among a subgroup of Framingham Heart Study adult participants, the prevalence of any coronary artery calcification was 32% in women and ≈53% in

men; the prevalence of coronary artery calcification was even higher among participants considered at intermediate risk for CHD events per the Framingham risk score (58% of women and 67% of men) (16).

■ Coronary artery calcification is also associated with an increased risk for CHD events. For example, data from 6,722 Multi-Ethnic Study of Atherosclerosis (MESA) participants (39% white, 27% black, 22% Hispanic, and 12% Chinese) followed for a median of ≈4 years showed higher rates of the first CHD event with higher coronary artery calcification (Figure 1.3). Compared with those who had no coronary artery calcification (score = 0), the adjusted rate of a first CHD event was ≈4 times higher for a coronary artery calcification score of 1–100 and ≈7–10 times higher for a coronary artery calcification score of >100 (17).

Ankle-Brachial Index

■ An abnormal (<0.90 or >1.30) ankle-brachial index (ABI) is used for detecting peripheral artery disease and is an independent risk factor for subsequent cardiovascular events and death. Peripheral artery disease also has a major negative impact on a person's functional status and quality of life.

■ Low ABI affects ≈4% of all U.S. adults aged 40 years or older based on 1999–2004 NHANES data (18) and ≈2% of older men and women without known cardiovascular disease (19).

Economic Costs of Cardiovascular Disease

■ The total direct and indirect cost of CVD and stroke in the United States is enormous and was conservatively estimated to be >$315 billion in 2010. This figure includes both health expenditures (ie, direct costs, which include the cost of seeing physicians and other professionals and receipt of hospital services, prescribed medications, home health care, and other medical durables) and lost productivity that results from premature mortality (ie, indirect costs).

■ The total number of inpatient cardiovascular-related operations and procedures increased 28%, from ≈5.9 million in 2000 to ≈7.6 million in 2010 (Figure 1.4). However, in recent years, there has been a downward trend in the rates of cardiac catheterizations, percutaneous coronary interventions, and coronary artery bypass surgeries (NHLBI computation based on NCHS annual data) (Figure 1.4).

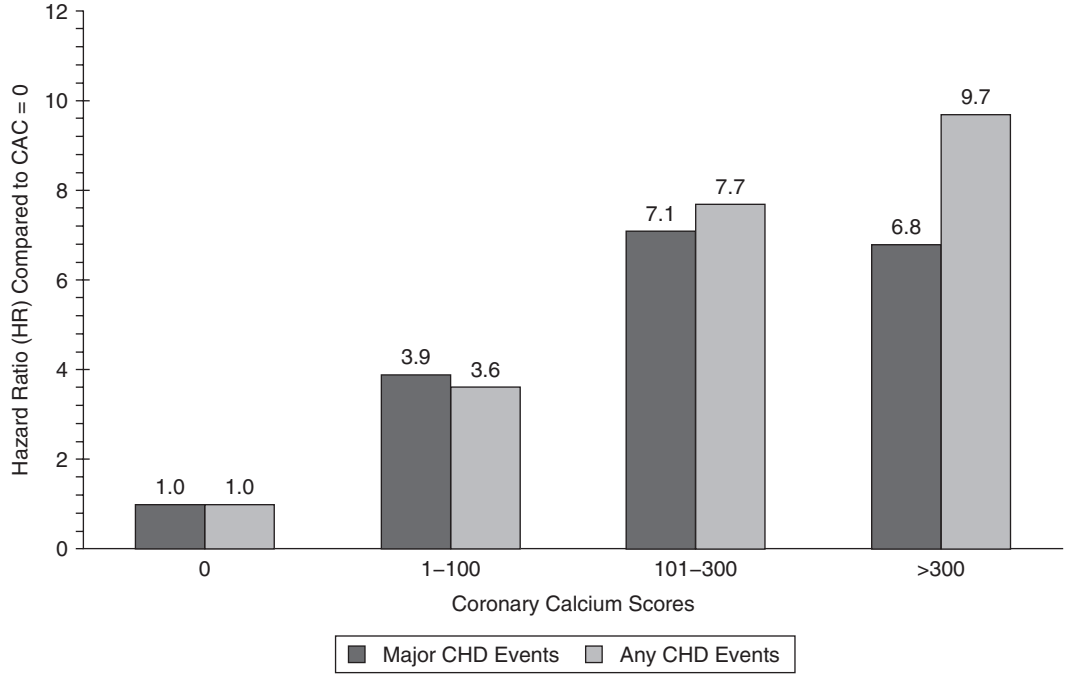

FIGURE 1.3 Adjusted rate of first CHD event associated with coronary artery calcification score among Multi-Ethnic Study of Atherosclerosis (MESA) participants. Major CHD events included myocardial infarction and CHD death; any CHD event included major CHD events in addition to definite angina or definite/probable angina after coronary revascularization. Criqui MH, Denenberg JO, Ix JH, McClelland RL, Wassel CL, Rifkin DE, Carr JJ, Budoff MJ, Allison MA. Calcium density of coronary artery plaque and risk of incident cardiovascular events. JAMA. 2014 Jan 15;311(3):271–8. doi: 10.1001/jama.2013.282535. PMID: 24247483

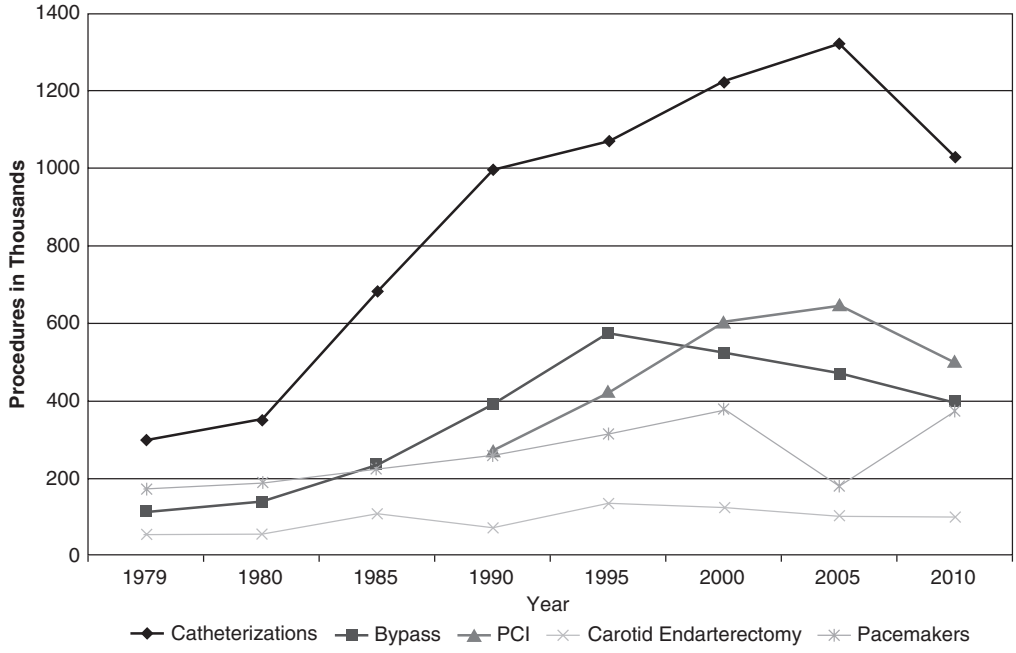

FIGURE 1.4 Temporal trends in the inpatient use of cardiovascular-related procedures in the United States between 1979 and 2010 based on data from the National Hospital Discharge Survey, National Center for Health Statistics, and the National Heart, Lung, and Blood Institute. PCI denotes percutaneous coronary interventions.

■ The projected future costs of care for high blood pressure, CHD, stroke, heart failure, and all other CVD are also staggering (Figure 1.5) (20). By 2030, an estimated ≈44% of the U.S. population is projected to have some form of CVD. Between 2015 and 2030, total direct medical costs of CVD are projected

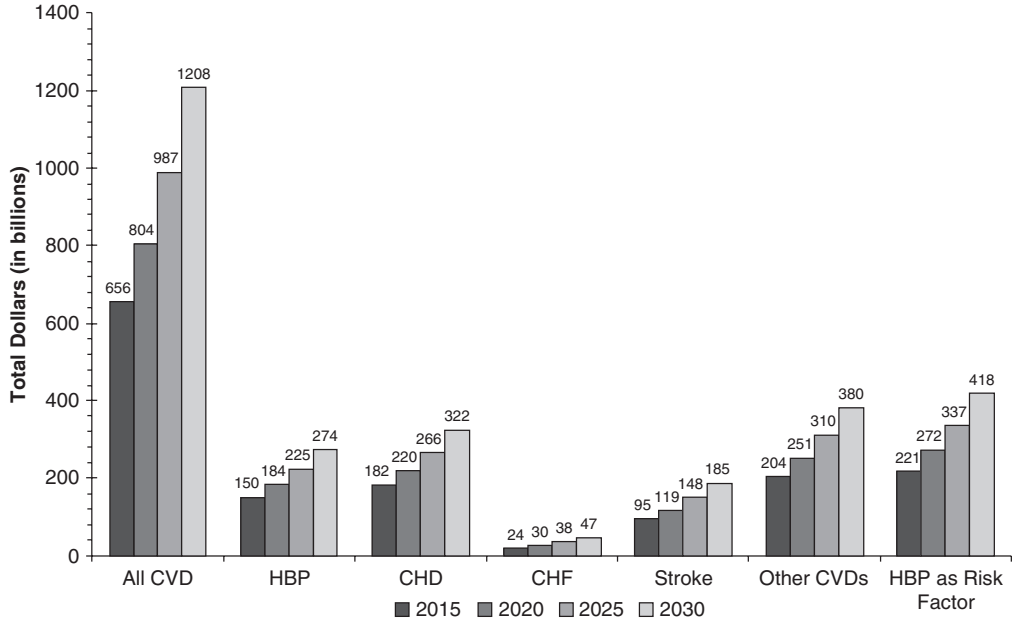

FIGURE 1.5 Total estimated costs related to CVD between 2015 and 2030 in the U.S. HBP = high blood pressure, CHD = coronary heart disease, and CHF = chronic heart failure.

to increase from $396 billion to $918 billion (estimates in 2012 dollars). Of this projected total CVD-related costs, ≈61% is attributable to hospital costs, ≈16% to medications, ≈11% to physician fees, ≈7% to nursing home care, ≈5% to home health care, and ≈1% to other costs. Indirect costs linked to lost productivity for all CVD are estimated to increase from ≈$180 billion in 2015 to nearly $300 billion in 2030 (estimates in 2012 dollars), which represents a relative increase of nearly 60%.

SUMMARY

The goal of achieving an ideal cardiovascular health profile for all Americans is the step in the right direction to reducing the burden of clinical CVD now and in the future. In this era of rapid changes to health care delivery nationally, increasing focus on more cost-effective medicine, and the worsening cardiometabolic profile of the U.S. population, prevention remains the most essential tool in our armamentarium. Toward that end, primary care providers are in the best position to have the greatest impact on promoting and implementing effective methods to optimize primary and secondary prevention of CVD nationally.

ACKNOWLEDGMENTS

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Andre R. M. Paixao, MD
and Jarett D. Berry, MD, MS

2

Cardiovascular Risk Assessment

In the United States alone cardiovascular disease (CVD) is responsible for more than 2,000 deaths each day and accounts for one third of all-cause mortality (1). Furthermore, approximately 90% of coronary events occur in individuals without established CVD (1). Therefore, the identification of individuals at risk for CVD represents an important clinical problem. Over the last two decades, this process has evolved from the use of individual risk factors to the estimation of global cardiovascular risk.

This chapter reviews the context, rationale, and current approach to risk prediction as proposed by currently available clinical practice guidelines. In addition, this chapter also reviews some of the limitations of the current approach to global risk prediction and several potential strategies to address them.

RATIONALE FOR CONTEMPORARY CV RISK PREDICTION

Relative Risk Versus Absolute Cardiovascular Risk

■ Early risk assessment strategies emphasized isolated, individual risk factors and relative risk estimates to guide treatment decisions. However, the impact of elevated cholesterol is highly dependent upon other associated risk factors.

■ Consider the data presented in Figure 2.1, where the association between cholesterol levels and cardiovascular risk is compared across a range of other associated risk factors. For an otherwise healthy 50-year-old woman without any associated CVD risk factors, higher levels of serum cholesterol levels are associated with higher relative risks but only trivial differences in absolute CVD risk. In contrast, in a 60-year-old male with multiple risk factors, the absolute CVD risk is substantially higher and differences in serum cholesterol are associated with dramatic differences in absolute risk for CVD.

■ Although the relative risk of an elevated cholesterol level is similar across all risk factor strata, the absolute risk differences are not.

Treatment Benefit Depends on Absolute Risk Rather Than Relative Risk

The relative risk reduction observed with treatment (ie, lipid-lowering therapy) is similar for patients with both low absolute risk (ie, primary prevention) and high absolute risk (ie, secondary prevention). Consider the examples pictured in Figure 2.2, comparing the observed relative risk and absolute risk differences associated with both low-risk and high-risk patients. Although the effect of lipid-lowering therapy in both scenarios is associated with a similar 24% relative risk reduction, the absolute risk differences are quite different, with substantially higher absolute risk differences in the high risk subgroups.

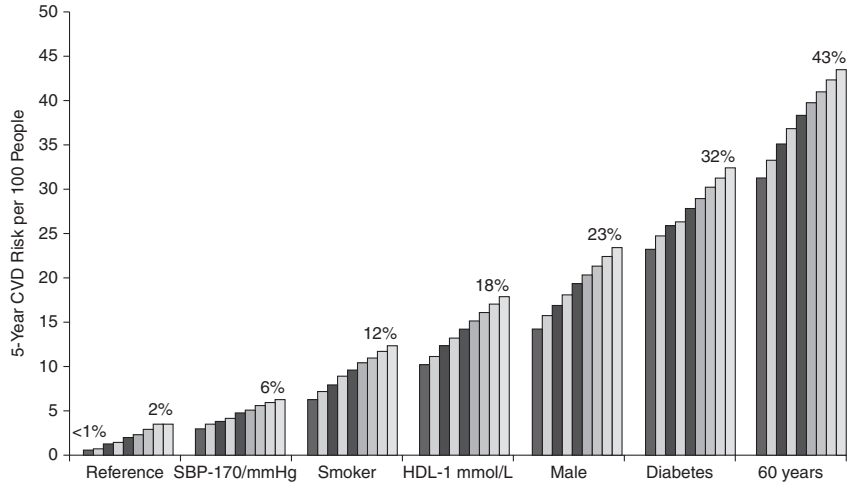

FIGURE 2.1 Absolute risk of cardiovascular disease over 5 years as determined by total cholesterol at specified levels of other risk factors (18). Reference category is a 50-year-old nonsmoker, nondiabetic female with systolic blood pressure of 110 mmHg, HDL of 60 mg/dL. In each of the categories additional risk factors are added consecutively. Different color bars represent increasing levels of total cholesterol. 1 mmol/L of HDL = 39 mg/dL.

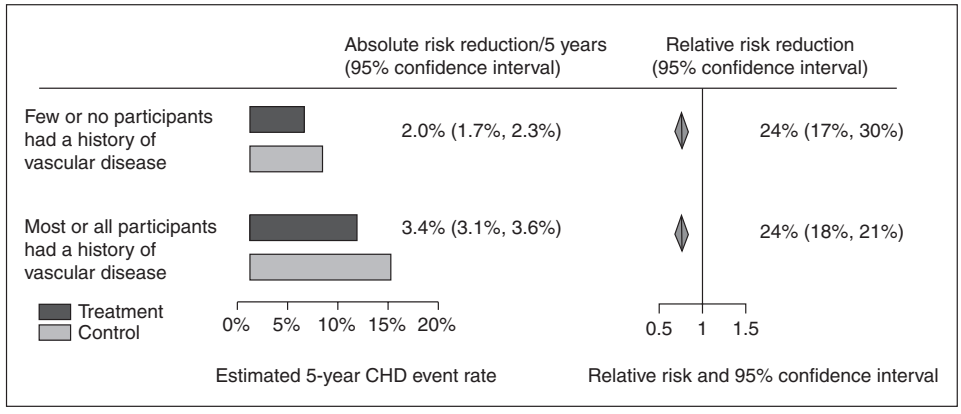

FIGURE 2.2 Absolute and relative treatment effects on coronary heart disease in cholesterol lowering trials by history of vascular disease (19). CHD = coronary heart disease.

Thus, although the relative risk reduction for lipid-lowering and blood pressure therapy are consistent across the risk distribution, the observed clinical benefit depends almost exclusively on the absolute CVD risk. It is for this reason that prevention guidelines have emphasized global CVD risk estimation as a guide to treatment decisions.

Multiple, Online Risk Prediction Tools for CVD Are Widely Available

Several CV risk prediction tools are currently available online (Table 2.1). In general, these tools represent multivariable regression equations derived from prospective cohorts such as the Framingham Heart Study. These tools use established CVD risk factors such as age, sex, blood pressure, cholesterol levels, and smoking in order to estimate the absolute risk for CVD over the next 5 or 10 years. The latest U.S. guidelines propose a novel risk assessment tool developed from several well-established cohorts (2). These Pooled Cohort Equations include the same traditional risk factors included in the Framingham risk score with the addition of diabetes and race. The output of this calculator is the estimated 10-year risk of atherosclerotic CVD (ASCVD) which includes coronary heart disease death, myocardial infarction, and fatal and nonfatal stroke. The performance and calibration of this risk assessment tool in a contemporary

TABLE 2.1 Cardiovascular Risk Prediction Tools

Risk Score	Region	Variables	End Points	URL
Pooled cohort equations	U.S.	Age, sex, TC, HDL-C, SBP, smoking, antihypertensive medications, DM, and race	CHD death, nonfatal MI, fatal and nonfatal stroke	http://my.americanheart.org/professional/StatementsGuidelines/PreventionGuidelines/Prevention-Guidelines_UCM_457698_SubHomePage.jsp
Framingham – ATP III, 2001	U.S.	Age, sex, TC, HDL-C, SBP, smoking, and antihypertensive medications	CHD death and nonfatal MI	http://hp2010.nhlbihin.net/atpiii/calculator.asp
Framingham – Global CVD, 2008	U.S.	Age, sex, TC, HDL-C, SBP, smoking, antihypertensive medications, DM, and known CHD, PAD, or stroke	CVD death, all CHD, stroke, heart failure, and claudication	http://www.framinghamheartstudy.org/risk/gencardio.html
Reynolds (men)	U.S.	Age, TC, HDL-C, SBP, smoking, FHMI, HbA1C, and CRP	CVD death, nonfatal MI, stroke, and coronary revascularization	http://www.reynoldsriskscore.org/
Reynolds (women)	U.S.	Age, TC, HDL-C, SBP, smoking, FHMI, HbA1C, and hsCRP	CVD death, nonfatal MI, stroke, and coronary revascularization	http://www.reynoldsriskscore.org/
SCORE	Europe	Age, sex, TC, HDL-C, SBP, and smoking	CVD death	http://www.heartscore.org/Pages/welcome.aspx

Abbreviations: ATP = National Cholesterol Education Program's Adult Treatment Panel; CVD = cardiovascular disease; SCORE = Systematic Coronary Risk Evaluation; TC = total cholesterol; HDL-C = high density lipoprotein cholesterol; SBP = systolic blood pressure; CHD = coronary heart disease; PAD = peripheral arterial disease; FHMI = family history of myocardial infarction; HbA1C = hemoglobin A1C; CRP = high sensitivity C-reactive protein; MI = myocardial infarction.

population and in ethnic groups other than blacks and whites is still a topic of debate.

CURRENT GUIDELINE RECOMMENDATIONS

Current Clinical Practice Guidelines Suggest That the Indication and Intensity of Treatment Should Be Proportional to the Absolute Risk for CVD

■ As are previous U.S. guidelines, the most recent recommendations are based on the paradigm that the intensity of treatment should be proportional to the absolute CVD risk (ie, in the next 5 to 10 years) (3).

■ Based on the very consistent observation that statin therapy results in a predictable relative risk reduction, treatment with this class of medications is indicated when the baseline risk is high enough that a net benefit can be expected. In other words, moderate- to high-dose statins should be initiated when the absolute risk reduction is expected to surpass the risk of adverse effects.

■ The recommendation for treatment to target LDL and non-HDL levels has been abandoned.

■ Treatment with moderate- to high-dose statins is indicated in four main groups (Figure 2.3):

- Clinical ASCVD
- LDL ≥190 mg/dL (≥21 years old)
- Diabetics (40–75 years old)
- Estimated 10-year risk ≥7.5% according to the Pooled Cohort Equations (40–75 years old)

The definitions of moderate and high doses of the commonly used statins can be found on Table 2.2.

■ Moderate intensity statin therapy is considered *reasonable* in individuals with estimated 10 year risk between 5% to 7.5% (recommendation class IIa, level of evidence B). In individuals not otherwise included in one of the four statin eligible groups, the following

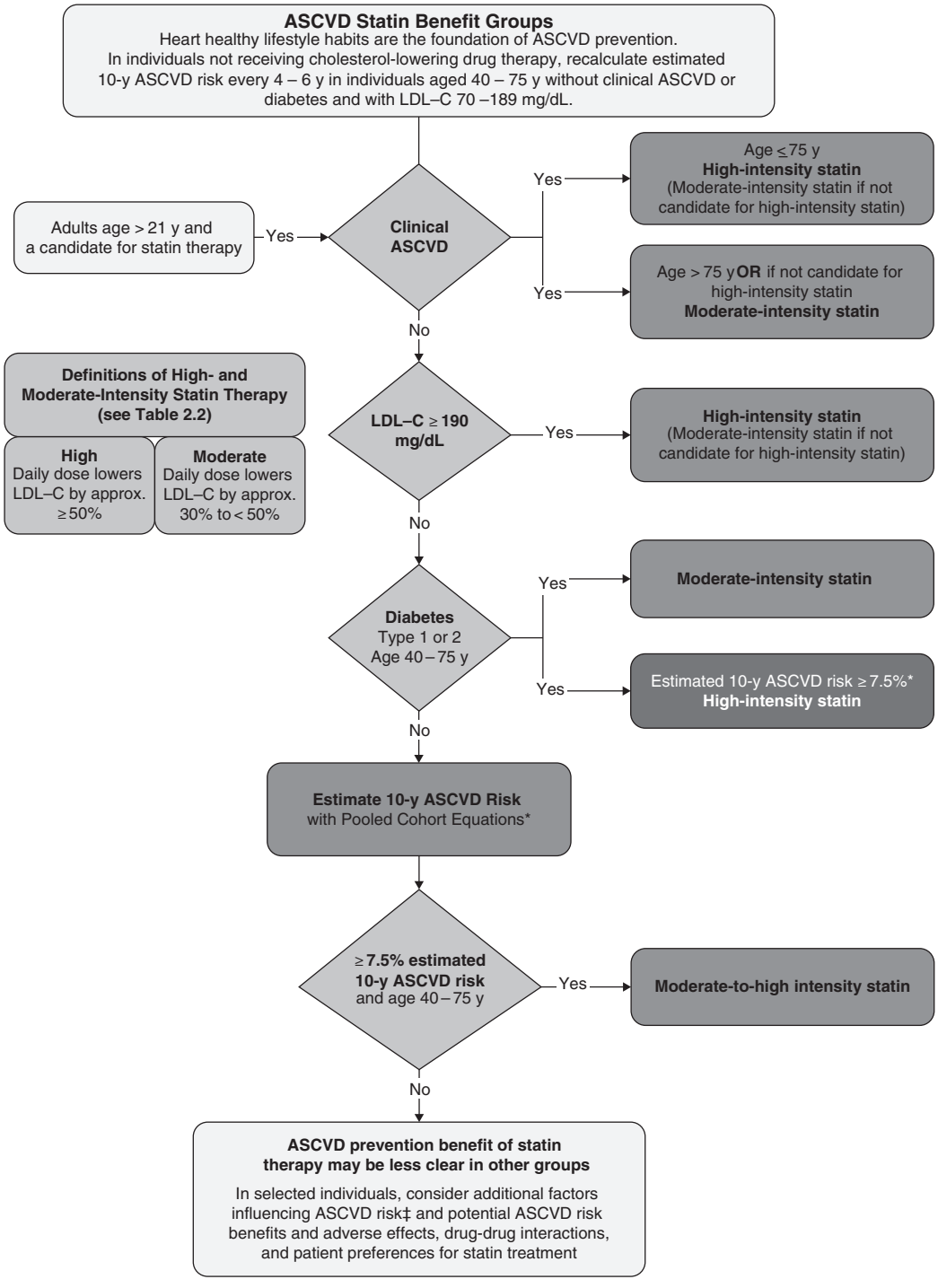

FIGURE 2.3 2013 American College of Cardiology and American Heart Association recommendations on statin therapy for the prevention of ASCVD (3). Colors correspond to the class of recommendations: Dark gray = class one recommendation (should be performed); White on grey = class IIa recommendation (reasonable to perform).
*The Pooled Cohort Equations can be used to estimate 10-year ASCVD risk in individuals with and without diabetes.
‡Primary LDL–C ≥ 160 mg/dL or other evidence of genetic hyperlipidemias, family history of premature ASCVD with onset < 55 years of age in a first degree male relative or < 65 years of age in a first degree female relative, high-sensitivity C-reactive protein > 2 mg/L, CAC score ≥ 300 Agatston units or ≥ 75 percentile for age, sex, and ethnicity, ankle-brachial index < 0.9, or elevated lifetime risk of ASCVD. ASCVD = atherosclerotic cardiovascular disease; CAC = coronary artery calcium; LDL–C = low-density lipoprotein cholesterol.

TABLE 2.2 High-, Moderate-, and Low-Intensity Statin Therapy

High-Intensity Statin Therapy Daily dose lowers LDL–C by approximately ≥50%	Moderate-Intensity Statin Therapy Daily dose lowers LDL–C by approximately 30% to <50%	Low-Intensity Statin Therapy Daily dose lowers LDL–C by <30%
Atorvastatin (40†)–80 mg	Atorvastatin 10–20 mg	Simvastatin 10 mg
Rosuvastatin 20–40 mg	Rosuvastatin 5–10 mg	Pravastatin 10–20 mg
	Simvastatin 20–40 mg	Lovastatin 20 mg
	Pravastatin 40–80 mg	Fluvastatin 20–40 mg
	Lovastatin 40 mg	Pitavastatin 1 mg
	Fluvastatin XL 80 mg	
	Fluvastatin 40 mg bid	
	Pitavastatin 2–4 mg	

† Down-titration if unable to tolerate atorvastatin 80 mg.
bid = twice daily; LDL–C = low-density lipoprotein cholesterol.

factors may be considered in clinical decision making (recommendation class IIb, level of evidence C):

- LDL ≥160 mg/dL or other evidence of genetic lipid disorders
- Family history of premature ASCVD
- C-reactive protein (CRP) >2 mg/dL
- Coronary calcium score (CAC) ≥300 Agatston units or ≥75th age, sex, and race percentile
- Ankle-brachial index (ABI) <0.9
- High lifetime risk

See more on the section on novel cardiovascular risk markers.

■ These recommendations should guide a "risk conversation" in which patient preference should be considered. One should keep in mind that the net benefit expected from statin therapy balances different outcomes (ie, death/stoke/heart attack vs. new onset diabetes) and some patients at lower risk may still choose to start treatment.

■ The European guidelines recommend the use of the Systematic Coronary Risk Evaluation (SCORE) system which is very similar to the Framingham model but provides risk estimates for fatal CVD (4). By considering only fatal outcomes, risk estimates and associated treatment thresholds are numerically lower (eg, high risk = 10 year risk >5%). Similar to U.S. guidelines, the European guidelines emphasize the importance of predicted absolute risk. Emphasis is given to statin treatment in patients in the high and very high categories.

Novel Developments in Global CVD Risk: Considering Alternative CVD Outcomes

Recent Risk Scores Have Been Developed to Estimate Risk for Both Atherosclerotic and Nonatherosclerotic Outcomes

Traditionally, interventions were guided by predicted CHD risk (5). Although recent guidelines have adopted the more comprehensive outcome of atherosclerotic CVD which incorporates fatal and nonfatal stroke, other common CV events such as heart failure and atrial fibrillation have not been included.

Additional iterations of the FRS have been developed to include additional atherosclerotic events (ie, stroke) and nonatherosclerotic CVD events (ie, heart failure). Estimated risks are larger, reflecting the contribution of heart failure. Although this approach is more comprehensive because it provides a more complete picture of the global risk of CVD, this approach has some limitations. In particular, not all of the outcomes included in this risk estimator are sensitive to certain interventions such as lipid-lowering therapy (ie, heart failure).

Novel Developments in Global CVD Risk: Considering Alternative Risk Factors

Additional Risk Markers Are Available and Have Been Proposed as a Supplement to Current Absolute Risk Prediction Equations.

Although currently available risk prediction equations provide reasonable risk estimates, they have some shortcomings. Because only a very small proportion of the population is classified as high risk, the absolute number of events that occur among low- and intermediate-risk individuals is greater than among the high-risk group alone (6). A small single center study suggests that only 12% of young patients presenting with a first MI would have been classified as high risk based on previous guidelines (7).

Although many novel risk markers have been shown to be independently associated with CVD, few have been shown to provide clinically relevant improvements in risk prediction. In brief, a clinically relevant improvement in risk prediction should help the clinician more reliably identify the at-risk patient.

In the literature, this improvement in risk prediction is quantified in two different metrics:

■ *C-statistics or area under the receiver operating characteristics (ROC) curve:* The C-statistic varies from 0.5 to 1.0 and reflects the probability that a novel risk marker will classify individuals with an event as higher risk compared to individuals without an event. A novel marker should produce a statistically significant increase in the C-statistic when added to the baseline model.

■ *Net reclassification improvement (NRI):* The NRI reflects the proportion of individuals who are correctly reclassified (ie, from "low risk" to "intermediate risk") by the addition of a novel marker to the baseline model.

Commonly, novel risk factors that are associated with CVD risk have little to no impact on the C-statistic or the NRI.

Novel Serum Markers

Although Many Biomarkers Are Associated With CVD Risk, Few Have Had Any Clinically Meaningful Impact on CVD Risk Estimation

Promising serum markers studied in recent years include high sensitivity C-reactive protein (CRP), lipoprotein-associated phospholipase A2 (Lp-PLA2), lipoprotein (a), and advanced lipid measures (ie, apoprotein A and B, LDL and HDL particle numbers). Although almost all of these markers have been shown to be independently associated with CVD, their ability to improve risk prediction has not been demonstrated and their use is, in general, discouraged by current guidelines (2).

■ CRP is a marker of inflammation and has a strong independent association with CVD. It has not, however, been shown to consistently improve risk prediction when added to traditional models (8). Nevertheless, recent guidelines gave CRP a class IIb recommendation in individuals not otherwise eligible for statin therapy but in whom treatment decision is still uncertain (2). Of note, CRP has been incorporated into the Reynolds Risk Score and was used as an inclusion criterion for one of the largest primary prevention statin trials (9,10).

The application of individual serum markers in clinical practice is limited by the absence of readily available scores or an online calculator that allows its integration with traditional risk factors.

Novel Imaging Markers

Coronary Artery Calcium Provides Robust Improvements in Risk Prediction

■ Coronary artery calcium (CAC) measured by computed tomography has recently emerged as one of the most powerful predictors of coronary heart disease (CHD). The degree of coronary calcification is proportional to the overall burden of coronary atherosclerosis and is therefore a very intuitive risk marker. When added to traditional risk factor models, CAC produces remarkable improvements in the c-statistic and the NRI. When compared to other novel risk markers, CAC clearly stands out with greater increments in c-statistics and NRI (11). Recent guidelines have given CAC a class IIb recommendation in individuals not otherwise eligible for statin therapy but in whom the treatment decision is still uncertain (2). Although the ability of CAC to improve CHD risk prediction has been very well demonstrated, the impact of CAC on ASCVD risk has not been fully assessed. An online tool to truly integrate CAC scores and traditional risk factors is currently under development and should be available soon.

Other Risk Markers

■ *Genetics:* Multiple common genetic variants with small to modest association with CVD have been reported but, so far, all have failed to improve risk prediction significantly when added to traditional risk factors and family history of MI (FHMI). Therefore, their use is not recommended by the American Heart Association (12).

■ *Family history:* Although not included in the Framingham Risks Score, family history is included in the Reynolds risk score. In recent guidelines, family history of premature ASCVD has received the same class IIb recommendation given to CRP and CAC.

■ *ECG*: Commonly found abnormalities associated with CVD risk among asymptomatic subjects include left ventricular hypertrophy, QRS prolongation, ST-segment depression, T-wave inversion, and pathological Q-waves. At least two large cohort studies have reported modest improvement in c-statistic and IDI when ECG is added to traditional risk factor models (13,14). Recent U.S. guidelines made no recommendations regarding the use of ECG for risk prediction (2).

■ *Ankle-Brachial Index (ABI):* This office-based test requires only a Doppler probe and blood pressure cuff. Ratios under 0.9 correlate well with the presence of obstructive peripheral artery disease but also predict CV risk independently of traditional risk factors. Few studies have formally assessed the addition of ABI to Framingham-based models. In one multiethnic cohort, the resulting changes in discrimination and reclassification measurements were modest at best (15). Recent guidelines have given ABI the same class IIb recommendation given to CRP, CAC, and family history of premature ASCVD (2).

NOVEL DEVELOPMENTS IN GLOBAL CVD RISK: CONSIDERING LONG-TERM OR LIFETIME RISK

Short-term risk prediction models are highly age dependent. For example, a 44-year-old man with hyperlipidemia and hypertension will be classified as low short-term risk by most currently used models. Although this assessment of his short-term risk is likely accurate, based on his risk factor burden, his lifetime risk is actually quite high (>60% in 40 years). Likewise, essentially all women under 65 years of age will be classified as low risk even though their risk factor burden and lifetime risk may vary widely. Lifetime or long-term risk can be estimated based on a simple algorithm or using a 30-year risk model as proposed by Pencina et al. available at www.framinghamheartstudy.org/risk/cardiovascular30.html (16,17). A simple lifetime risk calculator has also been incorporated into the Pooled Cohort Equations.

Recent guidelines now recommend that predicted lifetime risk may be considered in adults 20 to 59 years of age who are not at high short-term risk (recommendation class IIb, level of evidence C) (2). The use of long-term or lifetime risk estimates can be particularly useful for risk communication and lifestyle counseling. Similarly, European guidelines also encourage the consideration of risk-factor–associated relative risks when determining the intensity of lifestyle intervention in younger individuals. They also encourage the use of relative risks as a motivational tool, particularly in young patients with a high risk factor burden.

CONCLUSION

Global cardiovascular risk based on traditional risk factors and calculated with one of the many available equations should guide clinical decision making. Preventive interventions are expected to result in higher absolute risk reductions in individuals with higher baseline risk. Few novel markers have been shown to improve short-term risk prediction and may be used in cases where a clinical decision is not clear. Although the expected net benefit from statin therapy is based on short-term risk, atherosclerosis is a lifelong process and predicted lifetime risk can identify unfavorable trajectories that will result in high long-term event rates. These concepts should be part of a risk conversation that will enable each patient to make an informed decision.

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Neil J. Stone, MD, MACP, FACC, FAHA

The New American Prevention Guidelines: Aligning the Guidelines for Atherosclerotic Cardiovascular Risk Reduction With the Evidence

After more than four years of detailed preparation, new clinical guidelines were released by the American College of Cardiology/American Heart Association (ACC/AHA) on November 12, 2013. They covered Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults (1), Lifestyle Management to Reduce Cardiovascular Risk (2), and Assessment of Cardiovascular Risk (3). A full discussion of obesity and overweight management covered in a fourth clinical guideline is beyond the scope of this chapter so the interested reader is referred to this important document (4).

A NEW APPROACH

These guidelines updated previous guidelines but were different in several ways. First, the workflow was different. Adult Treatment Panel III (ATP III) (5,6) discussed lifestyle management and cardiovascular risk assessment as well as a comprehensive approach to lipid management. The new Cholesterol guideline included components from the risk assessment working group and the lifestyle working group. The Obesity and Overweight guideline was a standalone guideline that was a welcome update to the older Obesity Panel Report published 15 years earlier (7).

Second, the evidence-based process was different. The cholesterol panel, like ATP III, was a diverse panel representing expertise that included primary care, cardiovascular disease, endocrinology and diabetes, nutrition, biostatistics and epidemiology, clinical trials, and medical economics. The new guidelines took several additional steps to reduce bias of all types. The majority of the cholesterol panel disclosed no conflicts of interest during the more than 4 years of deliberations. Only those with no conflicts could vote on the evidence statements and recommendations of the report.

Inasmuch as the cholesterol panel's focus was defined as *treatment* of blood cholesterol to reduce atherosclerotic cardiovascular disease (ASCVD) risk, randomized clinical trials (RCTs) and systematic reviews of RCTs evaluated for quality by an independent contractor chosen by the NHLBI were used to form the guideline's evidence statements and recommendations. The panels and working groups selected critical questions (CQs) that were answered by a strict rule-based process. The panel employed the use of expert methodologists chosen by the NHLBI to be sure the evidence statements and recommendations were supported by the evidence as closely as possible.

Due to the decision by the NHLBI to limit their focus to evidentiary reviews for these guidelines (8), adjudication and implementation were accomplished with the skillful assistance of the ACC/AHA guideline staff (9). The guideline panels in their entirety agreed to continue the process resulting in the ACC/AHA guideline reports. This transfer allowed, however, the panels to include in their review more recent data up until July 2013. The reports underwent extensive internal and external reviews first by the NHLBI and then by the ACC/AHA. This period of "expert" comment

and review lasted more than one year. Interestingly, the Institute of Medicine Report on Clinical Guidelines (10) proposed a structure for clinical guideline reports that had many similarities to the process that was undertaken to create these guidelines.

MAJOR THEMES

The results of this rigorous evidentiary process led to a report that differed in several important ways from prior guidelines.

1. The panel could not find evidence to support either an LDL-C or non-HDL-C goal from their evidence review. This should not have come as a complete surprise. It was pointed out years ago that most RCTs of lipid drugs employed essentially fixed-dose combinations of lipid drugs versus placebo (11). Although later trials looked at higher intensity versus lower intensity cholesterol lowering medications in those at high risk of ASCVD, they did not use a clinical design that would have supported an evidence based "treatment to target" approach.
2. The focus in the cholesterol guideline was on the appropriate intensity of statin therapy because this class of cholesterol-lowering medication had several important features that distinguished it from other cholesterol-lowering medications that were considered. Statins were found to show consistent ASCVD reduction across a wide range of LDL-C values in a large number of high-quality RCTs. For those with ASCVD, those with diabetes ages 40–75 years, with LDL-C 70–189 mg/dL, and those with primary elevations of LDL-C ≥190 mg/dL, the guidelines recommend a consideration of the appropriate intensity of statin to reduce ASCVD in optimal fashion.

In primary prevention, the guidelines urge consideration of statins for those at higher risk who can be shown to benefit based on RCT data. Supporting this decision are high-quality systematic reviews that have shown a mortality benefit for statins in primary prevention (12,13). Of the seven statins, five are available as low-cost generics. This includes statins of both moderate and high intensity. Statins are also safe when taken as recommended in the RCTs. The cholesterol guideline provides useful information to guide the safe use of statins in practice.

3. The new guideline recommends that statins be given thoughtfully especially in those at lower ASCVD risk. Statins were recommended for those in whom a proven clinical benefit was established by RCTs and systematic reviews of RCTs. A real strength of RCT-based evidence is that treatments shown to benefit can have their absolute benefits compared to their absolute risks or safety considerations. This allows for overall or net benefit to be determined.

The guidelines highlight patient groups that especially benefit from lifestyle and statin treatment. In the first three groups, statins are already extensively used. These include those who require secondary prevention of ASCVD, those with diabetes ages 40–75 years with LDL-C 70 to 189 mg/dL, and those with primary LDL-C elevations 190 mg/dL or greater. The latter include most of those with genetic hypercholesterolemia. In these groups at high ASCVD risk, what is new is guidance on the optimal statin intensity if this can be safely achieved. Younger individuals with primary elevations of LDL-C ≥160 mg/dL or who have a family history of premature ASCVD who do not appear to qualify for statin treatment based on a risk calculation, may be included in the treatment algorithm as per clinician judgment as discussed later in this chapter. In those over age 75 who require statins for secondary prevention, the guidelines suggest that a moderate intensity, rather than high intensity, be considered initially. Finally, the cholesterol guideline makes no recommendation for statin initiation in those with heart failure and those with chronic kidney disease on hemodialysis, finding no RCT evidence that established benefit in these groups.

The importance of personalizing the statin prescription in primary prevention is emphasized in the cholesterol guideline. The fourth statin benefit group is defined as those with 7.5% or greater ASCVD risk. However, the guideline report indicates that a statin prescription is given only after a clinician–patient discussion as noted in Figure 4 of the cholesterol guideline report (modified as Figure 3.1 for this chapter) occurs. This discussion is deemed crucial because it initiates the risk modification process.

Many physicians will wish to enter risk factor data into the ASCVD risk calculator (see Figure 3.2) with the patient. This focuses attention on the importance of the patient's own risk factors. This can facilitate understanding and attention to treatable factors such as blood pressure control, tobacco cessation, or blood sugar control, if required. The ASCVD risk calculator doesn't write statin prescriptions. The actual level of ASCVD risk found must be put into context of the individual's personal characteristics that affect both the potential for benefit of statin therapy as well as the potential for safety issues including drug–drug interactions. A vital aspect of this recommendation is the inclusion of patient preferences. The guideline recognizes the importance of shared decision making with the clinician helping the patient prioritize and understand the treatment choices. This was shown in the flow diagram for primary prevention (see Figure 3.1) that is adapted from Figure 4 of the Cholesterol Guideline report.

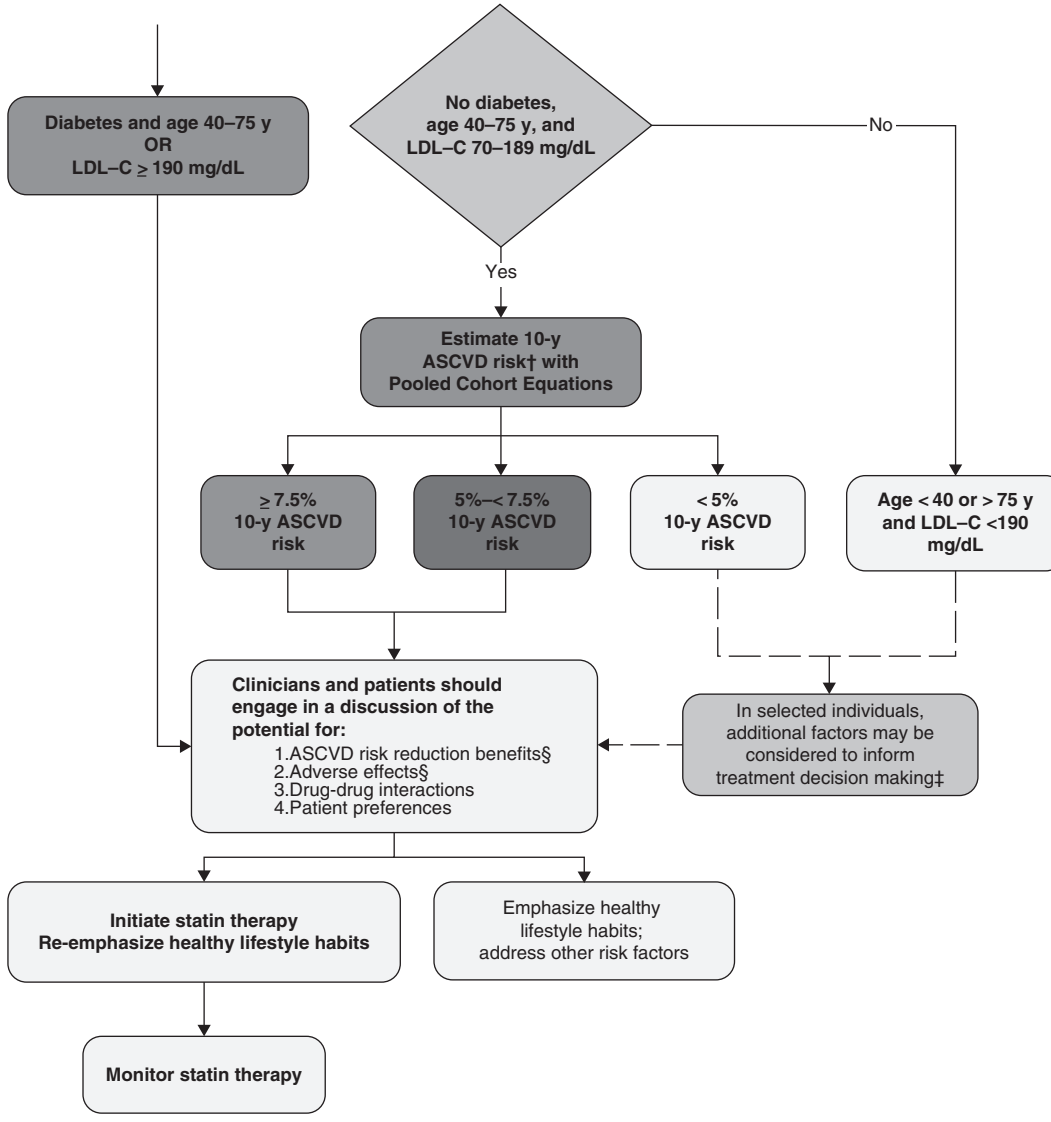

FIGURE 3.1 Flow Diagram for Statin Decisions in Primary Prevention. (Footnote symbols are explained in page 26.)

4. The focus for follow-up is on adherence to maximally tolerated therapy of proven benefit. This can be lifestyle alone or lifestyle and the appropriate intensity of statin therapy. For those who would prefer targets, it is important to note the lack of RCT evidence showing that additional therapies provide incremental benefit to optimal lifestyle and statin therapy. For those on optimal therapy with the appropriate intensity of statin therapy and adherence to a heart-healthy lifestyle, it is difficult to support additional unproven therapy to attain an arbitrary goal level of LDL-C or non-HDL-C that may be slightly lower than the patient's current values.

It is important that lifestyle and statin therapy be viewed as complementary. Both should be evaluated regularly as they were in the RCTs. As in the RCTs, adherence is crucial for optimal statin benefit. Systematic review of RCTs shows that ASCVD reduction with statin therapy is greater in years 2–5 than they are in year 1, highlighting the importance of continued adherence to optimal statin therapy (14). This fact should be shared with patients so they understand the long-term value of statin therapy if it is initiated.

Appropriately, clinicians and patients are concerned that statins elevate blood sugar and increase the risk of type 2 diabetes in individuals at risk for diabetes.

		Enter patient values in this column		
Risk Factor	**Units**	**Value**	**Acceptable range of values**	**Optimal values**
Sex	M (for males) or F (for females)		M or F	
Age	years		20–79	
Race	AA (for African Americans) or WH (for whites or others)		AA or WH	
Total Cholesterol	mg/dL		130–320	170
HDL-Cholesterol	mg/dL		20–100	50
Systolic Blood Pressure	mm Hg		90–200	110
Treatment for High Blood Pressure	Y (for yes) or N (for no)		Y or N	N
Diabetes	Y (for yes) or N (for no)		Y or N	N
Smoker	Y (for yes) or N (for no)		Y or N	N

Your 10-Year ASCVD Risk (%)	This calculator only provides 10-year risk estimates for individuals 40 to 79 years of age Enter M or F Gender Enter WH or AA for race Enter 130–320 for TC value Enter 20–100 for HDL value Enter 90–200 for SBP value Enter Y or N for treatment for hypertension Enter Y or N for Diabetes Enter Y or N for Smoker
10-Year ASCVD Risk (%) for Someone Your Age with Optimal Risk Factor Levels (shown above in column E)	Enter M or F for Gender This calculator only provides 10-year risk estimates for individuals 40 to 79 years of age Enter WH or AA for race
Your Lifetime ASCVD Risk* (%)	This calculator only provides lifetime risk estimates for individuals 20 to 59 years of age Enter M or F for Gender Enter 130–320 for TC value Enter 90–200 for SBP value Enter Y or N for treatment for Hypertension Enter Y or N for Diabetes Enter Y or N for Smoker
Lifetime ASCVD Risk (%) for Someone at Age 50 with Optimal Risk Factor Levels (Shown above in column E)	Enter M or F for gender

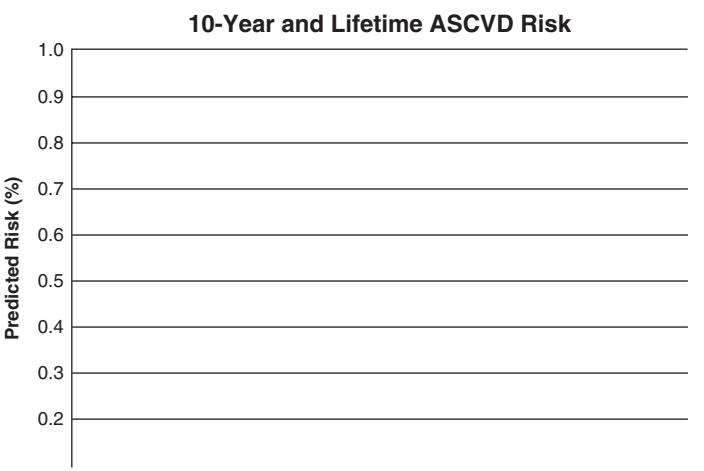

FIGURE 3.2 The new ASCVD Risk Calculator.

This calculator now includes stroke as an endpoint and African-American status as a risk input. It doesn't address those of Hispanic or Asian ancestry whose specific risk characteristics must be taken into account for appropriate risk calibration. For example, it may underestimate risk in South Asians and overestimate risk in Hispanics.

Note: See page 24 for web address to download risk estimator. It is newly designed and includes decision support.

Despite this potential negative, there are several important reasons to utilize statins in those at risk. First, a detailed evidence review of RCTs and systematic reviews of RCTs show that ASCVD risk reduction benefit significantly outweighs the excess risk of type 2 diabetes, especially in the 40- to 75-year-old age range. Second, although there is evidence that improved adherence to lifestyle recommendations can prevent progression to diabetes (15), lifestyle alone is not adequate for ASCVD risk reduction once type 2 diabetes has occurred. Third, those at risk for statin-related new diagnosis of diabetes can be predicted by their clinical characteristics. Although not a part of the cholesterol guideline, clinicians should note that in the JUPITER RCT, an increased risk of new onset of diabetes was predicted by the presence of 1 or more of diabetes risk factors (16). Those who did not have a BMI ≥ 30; FBS ≥ 100 m/gld; A1c ≥ 6.0%; or metabolic syndrome were unlikely to progress to a clinical diagnosis of diabetes. Of note, an optimal lifestyle improves all of the above parameters of diabetes risk and must accompany the statin prescription.

WHAT YOU NEED TO KNOW

Attempting to simplify and apply proper emphasis is an important task for those who summarize guidelines. On the other hand, oversimplification and misplaced emphasis can give rise to misinterpretation. To minimize the latter, the guidelines should be read in full. Because many may not find the time, this chapter reproduces a critical subset of the recommendations so that an appreciation of what the guidelines actually say is obtained.

We begin with a brief summary of the Lifestyle recommendations reproduced from Table 17 of the Lifestyle Guideline report.

A. HEART HEALTHY NUTRITION AND PHYSICAL ACTIVITY BEHAVIORS

The adult population should be encouraged to practice heart healthy lifestyle behaviors including:

1. Consume a dietary pattern that emphasizes intake of vegetables, fruits, and whole grains; includes low-fat dairy products, poultry, fish, legumes, nontropical vegetable oils and nuts; and limits intake of sodium, sweets, sugar-sweetened beverages, and red meats.

a. Adapt this dietary pattern to appropriate calorie requirements, personal and cultural food preferences, and nutrition therapy for other medical conditions (including diabetes mellitus).

TABLE 3.1 High-, Moderate-, and Low-Intensity Statin Therapy (Used in the RCTs reviewed by the Expert Panel and adapted from Table 5 in the Cholesterol Guideline Report)

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy
Daily dose lowers LDL–C, on average, by approximately ≥ 50%	Daily dose lowers LDL–C, on average, by approximately 30% to < 50%
Atorvastatin (40†)–80 mg **Rosuvastatin 20** *(40)* **mg**	**Atorvastatin 10** *(20)* **mg** **Rosuvastatin** *(5)* **10 mg** **Simvastatin 20–40 mg‡** **Pravastatin 40** *(80)* **mg** **Lovastatin 40 mg** *Fluvastatin XL 80 mg* **Fluvastatin 40 mg bid** *Pitavastatin 2–4 mg*

Specific statins and doses noted in bold were evaluated in RCTs analyzed by the panel. All of these RCTs demonstrated a reduction in major cardiovascular events. Statins and doses that are approved by the U.S. FDA but were not tested in the RCTs reviewed are listed in *italics*.

*Individual responses to statin therapy varied in the RCTs and should be expected to vary in clinical practice. There might be a biologic basis for a less-than-average response.

†Evidence from 1 RCT only: down-titration if unable to tolerate atorvastatin 80 mg in one RCT

‡Although simvastatin 80 mg was evaluated in RCTs, initiation of simvastatin 80 mg or titration to 80 mg is not recommended by the FDA due to the increased risk of myopathy, including rhabdomyolysis.

bid indicates twice daily; FDA, Food and Drug Administration; IDEAL, Incremental Decrease through Aggressive Lipid Lowering study; LDL-C, low-density lipoprotein cholesterol; and RCTs, randomized controlled trials.

b. Achieve this pattern by following plans such as the DASH dietary pattern, the USDA Food Pattern, or the AHA Diet.

2. Engage in 2 hours and 30 minutes a week of moderate-intensity, or 1 hour and 15 minutes (75 minutes) a week of vigorous-intensity, aerobic physical activity, or an equivalent combination of moderate- and vigorous-intensity aerobic physical activity. Aerobic activity should be performed in episodes of at least 10 minutes, preferably spread throughout the week. U.S. Department of Health and Human Services. 2008 Physical Activity Guidelines for Americans. Washington, DC: U.S. Department of Health and Human Services, 2008:1–76.

3. Achieve and maintain a healthy weight. Refer to the 2013 Obesity Expert Panel Report for recommendations on weight loss and maintenance (4). AHA indicates American Heart Association; DASH, Dietary Approaches to Stop Hypertension; and USDA, U.S. Department of Agriculture.

B. RECOMMENDATIONS FROM THE RISK ASSESSMENT WORKGROUP WITH THOSE REFLECTING EXPERT OPINION HIGHLIGHTED IN *ITALICS*

1. *The race- and sex-specific Pooled Cohort Equations* to predict 10-year risk for a first hard ASCVD event should be used in non-Hispanic African Americans and non-Hispanic whites, 40 to 79 years of age.*
2. *Use of the sex-specific Pooled Cohort Equations for non-Hispanic whites may be considered when estimating risk in patients from populations other than African Americans and non-Hispanic whites.*
3. If after quantitative risk assessment, a risk-based treatment decision is uncertain, assessment of one or more of the following—family history, hsCRP, CAC score, or ABI—may be considered to inform treatment decision making.
4. The contribution to risk assessment for a first ASCVD event using ApoB, CKD, albuminuria, or cardiorespiratory fitness is uncertain at present. –No recommendation for or against.
5. CIMT is not recommended for routine measurement in clinical practice for risk assessment for a first ASCVD event. –No recommendation for or against.
6. It is reasonable to assess traditional ASCVD risk factors‡ every 4 to 6 years in adults 20 to 79 years of age who are free from ASCVD and to estimate 10-year ASCVD risk every 4 to 6 years in adults 40 to 79 years of age without ASCVD.
7. Assessing 30-year or lifetime ASCVD risk based on traditional risk factors‡ may be considered in adults 20 to 59 years of age without ASCVD and who are not at high short-term risk.

A downloadable spreadsheet enabling estimation of 10-year and lifetime risk for ASCVD and a web-based calculator are available at http://my.americanheart.org/cvriskcalculator and http://www.cardiosource.org/science-and-quality/practice-guidelines-and-quality-standards/2013-prevention-guideline-tools.aspx.
*Derived from the ARIC study (8), CHS (5), CARDIA study (23), Framingham original and offspring cohorts (4,6). †Based on new evidence reviewed during ACC/AHA update of evidence. ‡Age, sex, total and HDL–cholesterol, systolic BP, use of antihypertensive therapy, diabetes, and current smoking.
ABI indicates ankle-brachial index; ACC, American College of Cardiology; AHA, American Heart Association; ApoB, Apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CAC, coronary artery calcium; CKD, chronic kidney disease; CIMT, carotid intima-media thickness; COR, Class of Recommendation; CQ, critical question, ES, evidence statement; HDL–C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LOE, Level of Evidence; and NHLBI, National Heart, Lung, and Blood Institute.

Comments: The accuracy of the ASCVD risk calculator has engendered much discussion due to a *Lancet* editorial published shortly after the guidelines were electronically published (17). The authors felt that the ACC/AHA cholesterol guidelines took "several major steps forward that will simplify and improve care for higher risk patients" but took issue with the new risk prediction algorithm for primary prevention. They felt the ASCVD risk calculator overestimated risk, giving new data from three existing clinical trial populations. They offered their own approach for primary prevention using RCT inclusion criteria.

In a following editorial in response to these comments, Lloyd-Jones et al. (18) noted that the pooled cohort equations presented by the risk assessment guideline represented "a major step forward for risk estimation." Two important features in the new risk calculator were the estimation of stroke as well as heart attack in the risk estimates that were now applicable to African American people. Neither of these was possible with the older Framingham "hard CVD" risk calculator recommended by ATP III. This was not a trivial improvement.

The new risk calculator estimates global cardiovascular disease risk better in women and African Americans, who are more likely to experience stroke before heart attack. It is excellent in rank ordering risk, separating the high risk from the low risk. Moreover, Lloyd-Jones et al. felt that alternative proposed strategies were also prone to error and not necessarily easy to apply in clinical practice. Finally, they responded to the concern that the ASCVD risk calculator greatly overpredicted ASCVD risk. Lloyd-Jones et al. pointed out that the ASCVD risk calculator "was subjected to more intensive validation than any other ASCVD risk equations before their publication."

Using data from the Multi-Ethnic Study of Atherosclerosis (MESA) and Reasons for Geographic and Racial Differences in Stroke (REGARDS) cohorts from the early 2000s, they acknowledged some overestimation of risk, but this occurred mainly in high-risk individuals who had fewer observed events than predicted. This could have occurred due to statin use in these high-risk individuals, some of whom had calcium scores reported to them as part of the study protocol. The editorial also pointed out that an overestimation in those at highest risk is least likely to cause inappropriate statin prescriptions. Moreover, the cholesterol panel chose 7.5% as the level of risk to trigger discussion of statin use, even though RCT evidence

for benefit with statins in primary prevention was seen in those with ASCVD risk down to 5%. Thus, if 7.5% was chosen and there was some overestimation, the patient's actual risk would still fall in a range shown to provide benefit. But the guideline offered an important buffer to statin overprescription by specifying a clinician-patient discussion as noted in both the text and flow diagram (Figure 4 of the report).

Next are the recommendations to reduce ASCVD risk with statin therapy, the statin safety recommendations, and the recommendations regarding monitoring and follow-up of such therapy. The recommendations that relate to nonstatin use are given. However, the safety recommendations regarding nonstatin therapy are not included due to space limitations, and the interested reader is referred to the guideline for this information.

C. GRADED RECOMMENDATIONS FOR STATIN TREATMENT TO REDUCE ASCVD RISK

(*Italics used for Expert Opinion*) From Tables 4, 6, 8, 10 of the Cholesterol Guideline Report

1. High-intensity statin therapy should be initiated or continued as first-line therapy in women and men ≤75 years of age who have *clinical ASCVD**, unless contraindicated.
2. In individuals with *clinical ASCVD** in whom high-intensity statin therapy would otherwise be used, when high-intensity statin therapy is contraindicated† or when characteristics predisposing to statin-associated adverse effects are present, moderate-intensity statin should be used as the second option if tolerated (Table 8 for Safety of Statins, Recommendation 1).
3. *In individuals with clinical ASCVD >75 years of age, it is reasonable to evaluate the potential for ASCVD risk-reduction benefits and for adverse effects, drug-drug interactions and to consider patient preferences, when initiating a moderate- or high-intensity statin. It is reasonable to continue statin therapy in those who are tolerating it.*
4. Individuals with LDL-C ≥190 mg/dL or triglycerides ≥500 mg/dL should be evaluated for secondary causes of hyperlipidemia (Table 6).
5. Adults ≥21 years of age with primary LDL-C ≥190 mg/dL should be treated with statin therapy (10-year ASCVD risk estimation is not required):
    - Use high-intensity statin therapy unless contraindicated.
    - For individuals unable to tolerate high-intensity statin therapy, use the maximum tolerated statin intensity

6. *For individuals ≥21 years of age with an untreated primary LDL-C ≥190 mg/dL, it is reasonable to intensify statin therapy to achieve at least a 50% LDL-C reduction.*
7. *For individuals ≥21 years of age with an untreated primary LDL-C ≥190 mg/dL, after the maximum intensity of statin therapy has been achieved, addition of a nonstatin drug may be considered to further lower LDL-C. Evaluate the potential for ASCVD risk reduction benefits, adverse effects, drug-drug interactions, and consider patient preferences.*
8. Moderate-intensity statin therapy should be initiated or continued for adults 40 to 75 years of age with diabetes mellitus.
9. *High-intensity statin therapy is reasonable for adults 40 to 75 years of age with diabetes mellitus with a ≥7.5% estimated 10-year ASCVD risk|| unless contraindicated.*
10. *In adults with diabetes mellitus, who are <40 or >75 years of age, it is reasonable to evaluate the potential for ASCVD benefits and for adverse effects, for drug-drug interactions, and to consider patient preferences when deciding to initiate, continue, or intensify statin therapy.*
11. *The Pooled Cohort Equations should be used to estimate 10-year ASCVD* risk for individuals with LDL-C 70 to 189 mg/dL without clinical ASCVD|| to guide initiation of statin therapy for the primary prevention of ASCVD.*
12. *Adults 40 to 75 years of age with LDL-C 70 to 189 mg/dL, without clinical ASCVD* or diabetes, and an estimated 10-year ASCVD|| risk ≥7.5% should be treated with moderate- to high-intensity statin therapy.*
13. *It is reasonable to offer treatment with a moderate- intensity statin to adults 40 to 75 years of age, with LDL-C 70 to 189 mg/dL, without clinical ASCVD* or diabetes, and an estimated 10-year ASCVD|| risk of 5% to <7.5%.*
14. Before initiating statin therapy for the primary prevention of ASCVD in adults with LDL-C 70 to 189 mg/dL without clinical ASCVD* or diabetes it is reasonable for clinicians and patients to engage in a discussion that considers the potential for ASCVD risk reduction benefits and for adverse effects, for drug-drug interactions, and patient preferences for treatment.
15. *In adults with LDL-C <190 mg/dL who are not otherwise identified in a statin benefit group, or for whom after quantitative risk assessment a risk-based treatment decision is uncertain, additional factors¶ may be considered to inform treatment decision making. In these individuals, statin therapy for primary prevention may be considered after evaluating the potential for ASCVD risk reduction benefits, adverse*

effects, drug-drug interactions, and discussion of patient preferences.

16. The Expert Panel makes no recommendations regarding the initiation or discontinuation of statins in patients with NYHA class II to IV ischemic systolic heart failure or in patients on maintenance hemodialysis.

Footnotes to this Section (from the Cholesterol Guideline Report)

*Clinical ASCVD includes acute coronary syndromes, history of MI, stable or unstable angina, coronary or other arterial revascularization, stroke, TIA, or peripheral arterial disease presumed to be of atherosclerotic origin.† Contraindications, warnings, and precautions are defined for each statin according to the manufacturer's prescribing information (64–70).
‡Individuals with secondary causes of hyperlipidemia were excluded from RCTs reviewed. Triglycerides >500 mg/dL were an exclusion criterion for almost all RCTs. Therefore, ruling out secondary causes is necessary to avoid inappropriate statin therapy.
§No RCTs included only individuals with LDL-C ≥190 mg/dL. However, many trials did include individuals with LDL-C ≥190 mg/dL and all of these trials consistently demonstrated a reduction in ASCVD events. In addition, the CTT meta-analyses have shown that each 39 mg/dL reduction in LDL-C with statin therapy reduced ASCVD events by 22%, and the relative reductions in ASCVD events were consistent across the range of LDL-C levels. Therefore, individuals with primary LDL-C >190 mg/dL should be treated with statin therapy.
‖Estimated 10-year or "hard" ASCVD risk includes first occurrence of nonfatal MI, CHD death, and nonfatal and fatal stroke as used by the Risk Assessment Work Group in developing the Pooled Cohort Equations.
¶These factors may include primary LDL-C ≥160 mg/dL or other evidence of genetic hyperlipidemias, family history of premature ASCVD with onset <55 years in a first degree male relative or <65 years in a first degree female relative, high sensitivity-C-reactive protein >2 mg/L, CAC score ≥300 Agatston units or ≥75 percentile for age, sex, and ethnicity (for additional information, see http://www.mesa-nhlbi.org/CACReference.aspx), ABI <0.9, or lifetime risk of ASCVD. Additional factors that may aid in individual risk assessment may be identified in the future.
ALT indicates alanine transaminase; ACC, American College of Cardiology; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; AST, aspartate aminotransferase; CAC, coronary artery calcium; CK, creatine kinase; COR, Class of Recommendation; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LOE, Level of Evidence; NHLBI, National Heart, Lung, and Blood Institute; NYHA, New York Heart Association; RCTs, randomized controlled trials; TIA, transient ischemic attack; ULN, upper limit of normal; and—, not applicable.

STATIN SAFETY RECOMMENDATIONS

1. To maximize the safety of statins, selection of the appropriate statin and dose in men and nonpregnant/non-nursing women should be based on patient characteristics, level of ASCVD* risk, and potential for adverse effects. Moderate-intensity statin therapy should be used in individuals in whom high-intensity statin therapy would otherwise be recommended when characteristics predisposing them to statin-associated adverse effects are present.

2. Characteristics predisposing individuals to statin adverse effects include, but are not limited to:

- Multiple or serious comorbidities, including impaired renal or hepatic function.
- History of previous statin intolerance or muscle disorders.
- Unexplained ALT elevations >3 times ULN.
- Patient characteristics or concomitant use of drugs affecting statin metabolism.
- >75 years of age.

Additional characteristics that may modify the decision to use higher statin intensities may include, but are not limited to:

- History of hemorrhagic stroke;
- Asian ancestry.
- CK should not be routinely measured in individuals receiving statin therapy.
- Baseline measurement of CK is reasonable for individuals believed to be at increased risk for adverse muscle events based on a personal or family history of statin intolerance or muscle disease, clinical presentation, or concomitant drug therapy that might increase the risk for myopathy.
- During statin therapy, it is reasonable to measure CK in individuals with muscle symptoms, including pain, tenderness, stiffness, cramping, weakness, or generalized fatigue.

3. a. *Baseline measurement of hepatic transaminase levels (ALT) should be performed before initiating statin therapy.*

   b. *During statin therapy, it is reasonable to measure hepatic function if symptoms suggesting hepatotoxicity arise (eg, unusual fatigue or weakness, loss*

of appetite, abdominal pain, dark-colored urine or yellowing of the skin or sclera).

4. Decreasing the statin dose may be considered when two consecutive values of LDL–C levels are <40 mg/dL.
5. It may be harmful to initiate simvastatin at 80 mg daily or increase the dose of simvastatin to 80 mg daily.
6. Individuals receiving statin therapy should be evaluated for new-onset diabetes mellitus according to the current diabetes screening guidelines. Those who develop diabetes mellitus during statin therapy should be encouraged to adhere to a heart healthy dietary pattern, engage in physical activity, achieve and maintain a healthy body weight, cease tobacco use, and continue statin therapy to reduce their risk of ASCVD events.
7. *For individuals taking any dose of statins, it is reasonable to use caution in individuals >75 years of age, as well as in individuals that are taking concomitant medications that alter drug metabolism, taking multiple drugs, or taking drugs for conditions that require complex medication regimens (eg, those who have undergone solid organ transplantation or are receiving treatment for HIV). A review of the manufacturer's prescribing information may be useful before initiating any cholesterol-lowering drug.*
8. *It is reasonable to evaluate and treat muscle symptoms, including pain, tenderness, stiffness, cramping, weakness, or fatigue, in statin-treated patients according to the following management algorithm:*

■ *To avoid unnecessary discontinuation of statins, obtain a history of prior or current muscle symptoms to establish a baseline before initiating statin therapy.*
■ *If unexplained severe muscle symptoms or fatigue develop during statin therapy, promptly discontinue the statin and address the possibility of rhabdomyolysis by evaluating CK, creatinine, and a urinalysis for myoglobinuria.*
■ *If mild to moderate muscle symptoms develop during statin therapy:*

- *Discontinue the statin until the symptoms can be evaluated.*
- *Evaluate the patient for other conditions that might increase the risk for muscle symptoms (eg, hypothyroidism, reduced renal or hepatic function, rheumatologic disorders such as polymyalgia rheumatica, steroid myopathy, vitamin D deficiency, or primary muscle diseases).*
- *If muscle symptoms resolve, and if no contraindication exists, give the patient the original or a lower dose of the same statin to establish a causal relationship between the muscle symptoms and statin therapy.*
- *If a causal relationship exists, discontinue the original statin. Once muscle symptoms resolve, use a low dose of a different statin.*
- *Once a low dose of a statin is tolerated, gradually increase the dose as tolerated.*
- *If, after 2 months without statin treatment, muscle symptoms or elevated CK levels do not resolve completely, consider other causes of muscle symptoms listed above.*
- *If persistent muscle symptoms are determined to arise from a condition unrelated to statin therapy, or if the predisposing condition has been treated, resume statin therapy at the original dose.*

9. *For individuals presenting with a confusional state or memory impairment while on statin therapy, it may be reasonable to evaluate the patient for nonstatin causes, such as exposure to other drugs, as well as for systemic and neuropsychiatric causes, in addition to the possibility of adverse effects associated with statin drug therapy.*

Footnotes to this Section (from the Cholesterol Guideline Report)

*Based on the presence of clinical ASCVD, diabetes mellitus, LDL–C >190 mg/dL, or level of estimated 10-year ASCVD risk.
†Individuals with elevated ALT levels (usually >1.5 or 2 times ULN) were excluded from RCT participation. Unexplained ALT >3 times ULN is a contraindication to statin therapy as listed in manufacturer's prescribing information.
‡Statin use is associated with a very modest excess risk of new onset diabetes in RCTs and meta-analyses of RCTs (ie, 0.1 excess case per 100 individuals treated 1 year with moderate-intensity statin therapy and 0.3 excess cases per 100 individuals treated for 1 year with high-intensity statin therapy). The increased risk of new onset diabetes appears to be confined to those with risk factors for diabetes. These individuals are also at higher risk of ASCVD due to these risk factors. Therefore, if a statin-treated individual develops diabetes as detected by current diabetes screening guidelines, they should be counseled to adhere to a heart healthy dietary pattern, engage in physical activity, achieve and maintain a healthy body weight, cease tobacco use, and continue statin therapy to reduce their risk of ASCVD events.
ALT indicates alanine transaminase; ACC, American College of Cardiology; AST, aspartate aminotransferase; CK, creatine kinase; AHA, American Heart Association; COR, Class of Recommendation; LDL-C, low-density lipoprotein cholesterol; LOE, Level of Evidence; ASCVD, atherosclerotic cardiovascular disease; NHLBI, National Heart, Lung, and Blood Institute; RCTs, randomized controlled trials; TIA, transient ischemic attack; ULN, upper limit of normal; and —, not applicable.

MONITORING STATIN THERAPY

Adherence to medication and lifestyle, therapeutic response to statin therapy, and safety should be regularly assessed. This should also include a fasting lipid panel performed within 4 to 12 weeks after initiation or dose adjustment, and every 3 to 12 months thereafter. Other safety measurements should be measured as clinically indicated.

OPTIMIZING STATIN THERAPY

The maximum tolerated intensity of statin should be used in individuals for whom a high- or moderate-intensity statin is recommended, but not tolerated.

INSUFFICIENT RESPONSE TO STATIN THERAPY

1. In individuals who have a less-than-anticipated therapeutic response or are intolerant of the recommended intensity of statin therapy, the following should be performed:

- Reinforce medication adherence.
- Reinforce adherence to intensive lifestyle changes.
- Exclude secondary causes of hyperlipidemia.

2. It is reasonable to use the following as indicators of anticipated therapeutic response to the recommended intensity of statin therapy. Focus is on the intensity of the statin therapy. as an aid to monitoring:

- High-intensity statin therapy† generally results in an average LDL-C reduction of ≥ 50% from the untreated baseline;
- Moderate-intensity statin therapy generally results in an average LDL-C reduction of 30 to < 50% from the untreated baseline;
- LDL-C levels and percentage reduction are to be used only to assess response to therapy and adherence. They are not to be used as performance standards.

3. *In individuals at higher ASCVD risk receiving the maximum tolerated intensity of statin therapy who continue to have a less-than-anticipated therapeutic response, addition of a nonstatin cholesterol-lowering drug(s) may be considered if the ASCVD risk-reduction benefits outweigh the potential for adverse effects. Higher risk individuals include:*

- *Individuals with clinical ASCVD‡* < 75 years of age.
- *Individuals with baseline LDL-C* ≥ 190 mg/dL.
- *Individuals 40 to 75 years of age with diabetes mellitus.*

Preference should be given to nonstatin cholesterol-lowering drugs shown to reduce ASCVD events in RCTs.

4. *In individuals who are candidates for statin treatment but are completely statin intolerant, it is reasonable to use nonstatin cholesterol-lowering drugs that have been shown to reduce ASCVD events in RCTs if the ASCVD risk-reduction benefits outweigh the potential for adverse effects. A summary of nonstatin safety features are given in Table 9 of the report.*

Comment: There has been some confusion about the role of nonstatin drugs in the guidelines. The cholesterol guideline stressed that adherence to lifestyle and to statin therapy should be re-emphasized before the addition of a nonstatin drug is considered, as there was not strong RCT evidence to support their routine use. Yet, situations with either a lack of an anticipated response or various degrees of statin intolerance may prompt a consideration of the addition of a nonstatin cholesterol-lowering therapy. The cholesterol guideline indicated that in high-risk individuals such as those with ASCVD, LDL-C ≥ 190 mg/dL, and those with diabetes in the 40 to 75 age range, more intensive approaches to ASCVD risk reduction may be sought. Consistent with the theme of using "proven" therapy, the guideline suggests priority should be given to medications with RCT evidence of overall benefit. Thus, preference would go to those drugs that have been shown in RCTs to provide ASCVD risk-reduction benefits that outweigh the potential for adverse effects, minimize drug-drug interaction, and respect patient preferences. Safety issues are different for nonstatins. Therefore, the guideline section on nonstatin safety as well as prescribers' packaging information and pharmacists should be consulted for safe use.

Footnotes to this Section (from the Cholesterol Guideline Report)

*Several RCTs found that low and low-moderate intensity statin therapy reduced ASCVD events. In addition, the CTT meta-analyses found each 39 mg/dL reduction in LDL-C reduces ASCVD risk by 22%. Therefore, the Panel considered that submaximal statin therapy should be used to reduce ASCVD risk in those unable to tolerate moderate- or high-intensity statin therapy.

†In those already on a statin, in whom baseline LDL-C is unknown, an LDL-C < 100 mg/dL was observed in most individuals receiving high-intensity statin therapy.

‡*Clinical* ASCVD includes acute coronary syndromes, or a history of MI, stable or unstable angina,

coronary or other arterial revascularization, stroke, TIA, or peripheral arterial disease presumed to be of atherosclerotic origin.

This section focuses on frequently asked questions about utilizing the guidelines in clinical practice. Many clinicians note and are concerned about the strong influence of age on ASCVD risk. This prompts concern over a younger patient with either a family history of premature ASCVD or with an LDL-C ≥160 mg/dL or even both as can be the case in familial hypercholesterolemia (19). That's why factors such as family history of premature ASCVD and LDL-C ≥160 mg/dL were among a group of factors that might prove useful to clinicians. Potentially the most important additional ASCVD risk information available is a coronary artery calcium (CAC) score (20). There is strong observational evidence that a CAC score allows clinically useful reclassification when added to risk assessment of asymptomatic intermediate-risk patients. Factors such as cost and radiation exposure are important to consider. Other factors such as hs-CRP ≥2.0 and ankle-brachial index <0.9 are recommended as well. Regardless, whether any of the markers are used to guide treatment decisions, the guidelines note that these decisions will require both sound clinical judgment and shared decision making.

On the other hand, age approximately over 60 years for men and over 70 years for women poses problems where unimpressive risk burdens but for age still lead to an estimated 10 year ASCVD risk of ≥7.5%. Although the data suggest risk benefit with statin therapy, assessment of the the merits of such therapy must be individualized in the mandated clinician–patient discussion. An example is an older patient seen with significant muscular issues and a low risk factor burden except for age. A joint decision to avoid statin therapy acknowledging the patient's fears of potential negative effects on muscular function is not unreasonable in this situation.

It is this author's belief that the U.S. prevention guidelines can be provide guidance on reasonable first steps in ASCVD risk reduction in situations not specifically covered. Systematically reviewing barriers and recommending what it takes to have more optimal adherence to a heart-healthy lifestyle, undertaking global ASCVD risk assessment, and applying sound clinician judgment as to the appropriateness of statin therapy that evaluates benefits as well as negative aspects and risks including drug-drug interactions (especially important for transplant and HIV patients) still make sense for groups not specifically mentioned. In situations such as complex genetic disorders and/or situations where significant drug-drug interactions may be present and require expertise not provided by these guidelines, referral to a more experienced clinician should be considered.

Finally, some may wonder if they should use these guidelines or other prevention guidelines. The risk guideline noted that the "2009 ACCF/AHA Performance Measures for the Primary Prevention of CVD" specifically recommended use of global CVD risk estimation in clinical practice (21). Moreover, prevention guidelines in Europe (22) and Canada (23,24) as well as the ATP III guidelines (5) concurred in their use of absolute risk assessment for adjudicating the appropriate intensity of lifestyle and drug therapy interventions. The European guidelines recommend the SCORE (Systemic Coronary Risk Estimation) because it was based on large, representative European cohort data sets.

The 2012 update of the Canadian Cardiovascular Society guidelines for the diagnosis and treatment of dyslipidemia for the prevention of cardiovascular diseases in the adult recommended the total cardiovascular disease Framingham Risk Score (FRS), modified for a family history of premature coronary disease for risk assessment. Whereas U.S. prevention guidelines as noted above have abandoned LDL-C as a target of intervention, the European and the Canadian guidelines continue with LDL-C as the primary target of treatment. The European guidelines consider non-HDL-C along with apo B as a secondary target in combined hyperlipidemia, diabetes, the metabolic syndrome or chronic kidney disease. The Canadian guidelines have added non-HDL-C to apo B as an alternate target. Note that there seems to be consensus of moving toward a strong evidence base for treatment recommendations.

CONCLUSIONS

The challenge for all the guidelines will be in promoting better adherence to lifestyle change in the respective populations. This could reduce major risk factors for ASCVD in a substantial way. In those for whom lifestyle change is not found to be associated with substantial ASCVD risk reduction, these prevention guidelines focusing on the appropriate intensity of statin therapy should have a clear impact on ASCVD outcomes. Despite controversies that have surfaced with the new U.S. prevention guidelines, the evidence-based principles presented should allow for a simpler and more effective management of ASCVD risk in clinical practice.

Less-publicized features such as the clinician–patient discussion in asymptomatic primary prevention have the potential to add value to sound clinician judgment and informed patient preference in clinical

decision making. Although there are numerous gaps in our knowledge, not the least of which is the optimal ASCVD risk reduction therapy for those with varying degrees of statin intolerance, continued research should begin to fill those gaps. The new U.S. prevention guidelines are worth reviewing in detail as they can help clinicians approach ASCVD risk reduction with in a systematic, evidence-based manner.

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William J. Elliott, MD, PhD

Management of High Blood Pressure

High blood pressure (or "hypertension") is one of the most important (if not the number one) major modifiable risk factor for heart disease, stroke, peripheral arterial disease, chronic kidney disease, end-stage renal disease, and vascular dementia in the United States, and is growing in importance worldwide (1,2). Because of worldwide variations in the prevalence of hypertension, availability and acceptability of lifestyle modifications, vastly different drug formularies, and widely disparate health care delivery systems (and insurance programs to pay for them), many different sets of guidelines have been promulgated regarding the prevention, diagnosis, and management of high blood pressure (3), some of which have been recently updated (4–8). This renewed spotlight on hypertension is timely, inasmuch as hypertension is currently the most common chronic condition for which Americans see a health care provider (according to the most recent National Ambulatory Care Survey), accounts for the most preventable deaths in the United States if it could be better controlled (according to the National Committee on Quality Assurance), and has recently increased in prevalence (presumably due to aging of the U.S. population and the growing problem of obesity).

EPIDEMIOLOGY OF HYPERTENSION

Many longitudinal population-based studies across the world have shown a clear, continuous, positive, and graded relationship between often occasional measurements of blood pressure and the risk of stroke, coronary heart disease, kidney failure, and cardiovascular death, beginning at about 115/75 mmHg. In perhaps the best example, mortality data compiled from 61 observational studies involving nearly 1 million subjects worldwide, followed for an average of 13.3 years showed that, at every age, an increase in blood pressure of 20/10 mmHg was associated with a doubling of the risk of cardiovascular death (9). The importance of systolic blood pressure increases in older individuals, both because they are at higher absolute risk of adverse sequelae of hypertension than younger people and because diastolic blood pressure often decreases after 55 years of age (presumably due to stiffening of medium-sized arteries). Hypertension is also more of a public health problem in blacks, both because of an earlier age of onset, greater severity when diagnosed, and possibly a greater sensitivity to dietary sodium, which results in large black:white disparities in age-adjusted risk of stroke, myocardial infarction, and end-stage renal disease (1). Some hypertension treatment guidelines now stratify initial drug therapy, based on race/ethnicity, in an attempt to capitalize on small differences in average blood pressure response to specific antihypertensive drug therapies (4,7,8), despite the fact that adding a second blood pressure–lowering drug nearly always equalizes the blood pressure response across racial/ethnic groups.

DEFINITION AND CLASSIFICATION OF HYPERTENSION

Most major recent guidelines define hypertension at a threshold of ≥140/90 mmHg, and suggest intervention (lifestyle modifications and/or drug therapy) for individuals whose blood pressure exceeds this level (3-6,8). Traditionally in the United States, BP is measured in triplicate by a trained health care provider in the office, after emptying the urinary bladder, after at least 5 minutes of quiet rest in the seated position, and at least 30 minutes after smoking or consuming a caffeinated substance (11). Automated BP monitors (using an appropriately sized arm cuff) improve the accuracy and reproducibility of BP measurements, but cannot substitute for proper technique (including preparation of the patient). Most guidelines recommend serial measurements of BP (typically separated by a week) before confirming a diagnosis of hypertension (except when BP is very high or target organ damage is already present). Similarly, most guidelines now recommend a standing BP measurement, especially in older patients (11); current U.S. Healthplan Employer Data Information Set procedures accept the lowest systolic and diastolic BPs (taken in any position, in any sequence) as the "BP for that visit." In a bold departure from past recommendations, the panel members appointed to JNC 8 (hereinafter "JNC 8") noted that there was scant evidence from high-quality randomized multicenter clinical trials involving more than 2,000 subjects that could justify a systolic BP threshold of 140 mmHg for individuals over age 60 years, because, especially in the last millennium, treatment decisions were traditionally based on diastolic BP alone. Officially, JNC 8 did not formally address the definition of hypertension (7), but some have suggested that, inasmuch as drug treatment has not been proven beneficial (in clinical trials of people past their 60th birthday) for systolic BPs between 140–150 mmHg, older people should not be diagnosed with hypertension (and treated with drug therapy) until and unless their systolic BP is ≥150 mmHg (7). Interestingly, JNC 8 recommended a systolic BP treatment threshold of 140 mmHg for people younger than 60 years, on basis of "expert opinion" (ie, not supported by clinical trial evidence) (7).

Traditionally, the classification of hypertension in Europe has always been more complex than in the United States, as Europeans continue to use more grades or stages of hypertension, and consider "isolated systolic hypertension" as a separate entity (5). The straightforward, 4-category staging system of JNC 7 (see top section of Table 4.1) was controversial when it was released in 2003, but has been retained in at least one recent U.S. guideline (8). Recent meta-analyses have documented the prognostic importance of both "white-coat" and "masked" hypertension. These conditions are properly diagnosed by ambulatory BP monitoring, which is not routinely reimbursed in the United States by the Centers for Medicare and Medicaid Services. However, this procedure was recommended by the 2011 NICE guidelines for all British subjects with elevated in-office BPs, before starting treatment for hypertension (4). The most recent European guidelines highlight the cost and inconvenience of this procedure for large segments of the adult population, which would be an economic burden for many countries (probably including the United States) (5,7,8).

TABLE 4.1 Classification of Blood Pressure

Term	In-Office Systolic Blood Pressure (mmHg)		In-Office Diastolic Blood Pressure (mmHg)		24-Hour Ambulatory Blood Pressure (Average)
"Normal"	<120		<80		—
Prehypertension	120–139	Or	80–89		—
Stage 1 hypertension	140–159	Or	90–99		—
Stage 2 hypertension	≥160	Or	≥100		—
"White-coat" hypertension	≥140	Or	≥90	AND	<135/85
"Masked" hypertension	<140	And	<90	AND	≥135/85

Columns heads are adapted from JNC 7 (2). If the systolic and diastolic blood pressures are classified in different stages, the higher Stage is used. Distinct diagnostic criteria for ambulatory blood pressure monitoring for these conditions have not been issued by U.S. hypertension guideline committees, but these are taken from other guidelines and are widely used in research.

INITIAL EVALUATION OF THE PATIENT

In addition to a complete history and physical examination, the initial encounter usually includes an evaluation of concomitant cardiovascular risk factors (obesity—including body-mass index and waist circumference, dyslipidemia, diabetes, tobacco use, family history, known complications of hypertension—including stroke, transient ischemic attack, coronary heart disease, heart failure, chronic kidney disease, peripheral arterial disease, symptoms and/or signs suggestive of secondary hypertension), proper BP measurement—initially in both arms, directed neurological examination, direct ophthalmoscopy (although its value is reduced among inexperienced observers), urinalysis (both dipstick and microscopy, and an early morning urinary albumin/creatinine ratio), and fasting blood tests (for electrolytes, fasting glucose, serum blood urea nitrogen with creatinine—and estimated glomerular filtration rate, lipid panel), and an electrocardiogram (3–6,8). A complete blood count and liver function tests are often obtained at the initial visit as a "baseline," as some antihypertensive drugs can affect these parameters.

THRESHOLDS FOR INITIATING THERAPY

Most guidelines now agree that individuals with prehypertension (see Table 4.1) should be advised about lifestyle modifications (see discussion below and Table 4.2) that are likely to reduce blood pressure, rather than prescribed antihypertensive drug therapy. The threshold BPs for beginning pharmacotherapy for hypertension, which are identical to BP targets (discussed in detail below), were extensively reviewed in an "evidence-based fashion" in JNC 8; these and recommendations from other guideline committees are summarized in Table 4.3 (3–8,12,13).

The traditional view, originally based on data from life insurance companies in the pre-antihypertensive drug therapy era (1890–1940s), was that blood pressures ≥140/90 mmHg were associated with increased mortality. Post hoc analyses of several placebo-controlled clinical trials (SHEP, Syst-Eur, HYVET; see Legend to Table 4.4 for expansion of trial acronyms) have suggested that "early" institution of therapy (rather than placebo for 1–5 years) had significant cardiovascular and/or long-term mortality benefits. In none of these trials, however, was 140/90 mmHg the BP threshold for enrollment, as all three trials targeted older patients, with baseline systolic BPs in the 160–209 mmHg range. There is growing awareness, in all recent guidelines (3–8) that the clinical trials' evidence base for drug therapy of uncomplicated patients with BPs in the 140–159/90–99 mmHg range is much less robust than it is for those with higher BPs or coexisting cardiovascular risk factors or diseases. This was presumably the impetus for JNC 8 to increase the threshold for initiating drug therapy in people with 60 or more birthdays to 150/90 mmHg (7). In the last decade, much work has been done with home (or self) monitoring of BP (usually resulting in readings that are about 5/5 mmHg lower than in-office readings), which is not only much less expensive than, but also nearly as useful in predicting cardiovascular risk as, ambulatory BP monitoring. Several guidelines committees and health care financing authorities

TABLE 4.2 Lifestyle Modifications for Lowering Blood Pressure

Modality	Lowering of Systolic Blood Pressure (95% Confidence Interval)	Prevents Long-Term Cardiovascular Events in Clinical Trials?
Weight Loss	5–20 mmHg (per 10 kg lost)	Not proven
Dietary Approaches to Stop Hypertension Eating Plan	8–14 mmHg	Not proven
Dietary Sodium Restriction	2–8 mmHg	Shown in follow-up of Trials of Hypertension Prevention (6)
Increased Physical Activity	4–9 mmHg	Not proven, may be confounded by weight loss
Moderation of Ethanol Consumption	2–4 mmHg	Not proven

Source: Adapted from JNC 7 (Ref. 2). World Health Organization. A global brief on hypertension: Silent killer, global public health crisis. Geneva, Switzerland: World Health Organization. 2013, pp. 1-40. WHO document number WHO/DCQ/ WHD/2013.2, available on the Internet at: http://www .apps.who.int/iris/bitstream/10665/79059/1/WHO_ DCO_WHD?2013.2_eng.pdf, accessed 07 JAN 14.

TABLE 4.3. Threshold Blood Pressures for Initiating Antihypertensive Drug Therapy, and Target Blood Pressures, Recommended by Various Guideline Committees

	Critical Blood Pressure Level (mmHg)						
Population	JNC 8 (7)	ASH/ISH (8)	ADA (12)	NKF (13)	ESH/ESC (5)	NICE (4)	CHEP (6)
Age ≥80 years*	150/90	150/90	N.A.	N.A.	150/90	150/90	150/90
Age ≥60 years*	150/90	140/90	N.A.	N.A.	140–150/90	140/90	140/90
Age 18–59 years*	140/90	140/90	N.A.	N.A.	140/90	140/90	140/90
Diabetics	140/90	140/90	140/80§	N.A.	140/85¶	140/90	130/80
Chronic Kidney Disease	140/90	140/90	N.A.	140/90†	140/90	140/90	140/90

*Presumes no diabetes or chronic kidney disease; §a lower target (eg, <130/80 mmHg) may be acceptable for some, especially younger and healthier patients, if it is well tolerated; ¶diastolic BPs between 80–85 mmHg are safe and well tolerated; †a lower target (eg, <130/80 mmHg) was "suggested" for individuals with more than "normal to moderately increased albuminuria" (albumin/creatinine ratios >30 mg/gm in a morning spot urine sample).
Abbreviations: N.A. = not applicable. JNC 8 = Eighth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (7); ASH/ISH = American Society of Hypertension/International Society of Hypertension (8); ADA = American Diabetes Association (12); NKF = National Kidney Foundation (13); ESH/ESC = European Society of Hypertension/European Society of Cardiology (5); NICE = National Institute for Health and Clinical Excellence (4); CHEP = Canadian Hypertension Education Program (6).

currently advocate home (or self) BP monitoring, yet U.S. and British health care providers are currently not paid for the evaluation of out-of-office BP measurements, but only for the proportion of their patients whose in-office BPs are below treatment goals.

LIFESTYLE MODIFICATIONS

The JNC 8 guidelines did not update JNC 7's recommendations for nonpharmacological therapies that lower BP (Table 4.2), especially those related to diet and exercise (14). However, the recent ACC/AHA Guideline on Lifestyle Management to Reduce Cardiovascular Risk suggests advising adults who could benefit from blood pressure lowering to consume no more than 2,400 mg of sodium/day and that a further reduction of sodium intake to 1,500 mg/day can result in even greater reduction in BP. It is noted that even without achieving these goals, reducing sodium intake by at least 1,000 mg/day lowers blood pressure (45). Weight loss remains the most effective short-term lifestyle modification for lowering BP, but it is difficult for many patients to maintain in the long term, even with two recently FDA-approved agents for obesity. The Dietary Approaches to Stop Hypertension (DASH) diet has become the most common download from the NHLBI website, and its efficacy in lowering BP has been demonstrated in two NHLBI-sponsored feeding trials of 8 weeks' duration. Several recent studies support dietary sodium restriction, which not only lowered BP over 5 years, but also was associated with a significant reduction in cardiovascular events over 12–16 years in the Trials of Hypertension Prevention (15). The evidence for other nonpharmacological therapies has recently been summarized by an American Heart Association Scientific Statement (16).

INITIAL DRUG THERAPY

In 1997, U.S. hypertension guidelines recognized, for the first time, that a "compelling indication" exists when a specific type of antihypertensive drug has not only lowered BP, but also improved outcomes in patients with specific diagnoses (eg, an angiotensin receptor blocker [ARB] in type 2 diabetic nephropathy, an angiotensin-converting enzyme [ACE]-inhibitor in proteinuric nondiabetic renal disease). Table 4.4 contains a list of such conditions, several of which have not been officially recognized by either the U.S. Food and Drug Administration or recent hypertension guidelines.

Recommendations about a free choice of initial antihypertensive drug (or drug class) vary across many current guidelines. Since 2003, ESH/ESC guidelines have consistently concluded that effective BP lowering is more important than which agent is chosen to begin the process, particularly because most patients will require more than a single drug to achieve their BP targets (5). This perspective is supported by

meta-analyses from the Blood Pressure Lowering Trialists' Collaboration (which prospectively included all randomized clinical trials since the mid-1990s) (17) and a larger set of meta-analyses (which included many trials of antihypertensive agents that enrolled subjects with other conditions, e.g., postmyocardial infarction) (18). These and other, more recent meta-analyses have shown very few significant differences across antihypertensive drug classes with regard to prevention of most cardiovascular endpoints. The British NICE guidelines, based on pharmacoeconomic analyses specific to their countries, recommend an ACE-inhibitor for young, white hypertensive patients, but a dihydropyridine calcium antagonist otherwise, unless the patient's risk of heart failure is so great that a diuretic would be more appropriate (5). For patients with systolic or diastolic hypertension, the 2014 Canadian guidelines recommended an initial thiazide (as Grade A) or a beta-blocker for patients <60 years of age, an ACE-inhibitor in non-black patients, a long-acting calcium antagonist, or an ARB (all Grade B), with consideration of an initial combination if the BP is >20/10 mmHg above the treatment target (6). For individuals with isolated systolic hypertension, a thiazide or long-acting dihydropyridine calcium antagonist (both Grade A) or an angiotensin receptor blocker (Grade B) was recommended (6).

Since 1973, U.S. hypertension guidelines have consistently favored an initial diuretic for uncomplicated hypertension; a beta-blocker lost this position in 2003 (3). The largest U.S. clinical trial in hypertension, the Antihypertensive and Lipid-Lowering [treatment to prevent] Heart Attack Trial (ALLHAT) compared initial therapy with chlorthalidone, lisinopril, amlodipine, and doxazosin in high-risk hypertensive patients over 55 years of age, and concluded that, "Because of the superiority of thiazide diuretics in preventing one or more forms of cardiovascular disease, and their lower cost, they should be the drugs of choice for first-step antihypertensive drug therapy" (19). Many subsequent meta-analyses of randomized clinical trials have shown better prevention of heart failure (a controversial endpoint in ALLHAT) with an initial diuretic (20), especially chlorthalidone (21). Even if the controversial ALLHAT data are arbitrarily excluded (eg, in a "sensitivity analysis"), however, an initial thiazide was still significantly more effective than other antihypertensive agents in preventing heart failure in hypertensive subjects in clinical trials (21).

The treatment algorithm recommended by JNC 8 is shown in Figure 4.1 (7); it is remarkably similar to the one recently proposed by the American Society of Hypertension/International Society of Hypertension (8), and incorporates, for initial therapy, the stratification on racial/ethnic grounds that had been proposed by older British guidelines: an initial diuretic or calcium antagonist is now recommended for black patients, whereas an ACE-inhibitor or an ARB are additional options for all others. The ACE-inhibitor, lisinopril, was associated with significantly less BP lowering and higher stroke rates in black patients in ALLHAT (19), but ramipril was beneficial in blacks with nondiabetic chronic kidney disease (22).

Unfortunately, JNC 8 provided little guidance beyond the initial drug choice (see Figure 4.1), presumably because so few trials have been done of second-line therapy. Except for inferring from the order of the recommended titration strategies, JNC 8 did not explicitly favor any option: (1) maximizing the dose of the initial medication; (2) adding a second medication before reaching the maximum dose of the initial medication; or (3) starting with a combination (either as a single pill or separate prescriptions). There are now a large number of generic single-pill combinations available across nearly the entire dose range of many popular BP drugs, which have at least additive BP-lowering efficacy; some offer a synergism for reducing adverse effects (eg, diuretic + renin-angiotensin system blocker on serum potassium; dihydropyridine calcium antagonist + renin-angiotensin system blocker on pedal edema). The FDA has approved more single-pill combinations as initial treatment options in the last 5 years than in the prior 3 decades. Single-pill antihypertensive combinations have recently been touted as one important aspect of a successful systemwide strategy to improve BP control (23), and recommended for people with Stage 2 hypertension by a Science Advisory from the American Heart Association, American College of Cardiology, and Centers for Disease Control and Prevention (24). Combining an ACE-inhibitor + an ARB, or a direct renin inhibitor + either an ACE-inhibitor or an ARB in diabetics is not recommended, due to a significantly increased risk of adverse experiences (especially hyperkalemia and increased serum creatinine) seen in several randomized clinical trials.

GOAL BLOOD PRESSURE FOR "UNCOMPLICATED" HYPERTENSIVE PATIENTS

Until 2013, the in-office BP target for uncomplicated hypertensive patients has traditionally been <140/90 mmHg, but the evidence supporting this is based mostly on epidemiological studies and a few post hoc analyses of clinical trials. In the last millennium, the open-label Hypertension Optimal Treatment (HOT) trial randomized 18,790 hypertensive subjects to diastolic BP targets of ≥80, ≥85, or ≥90 mmHg, but

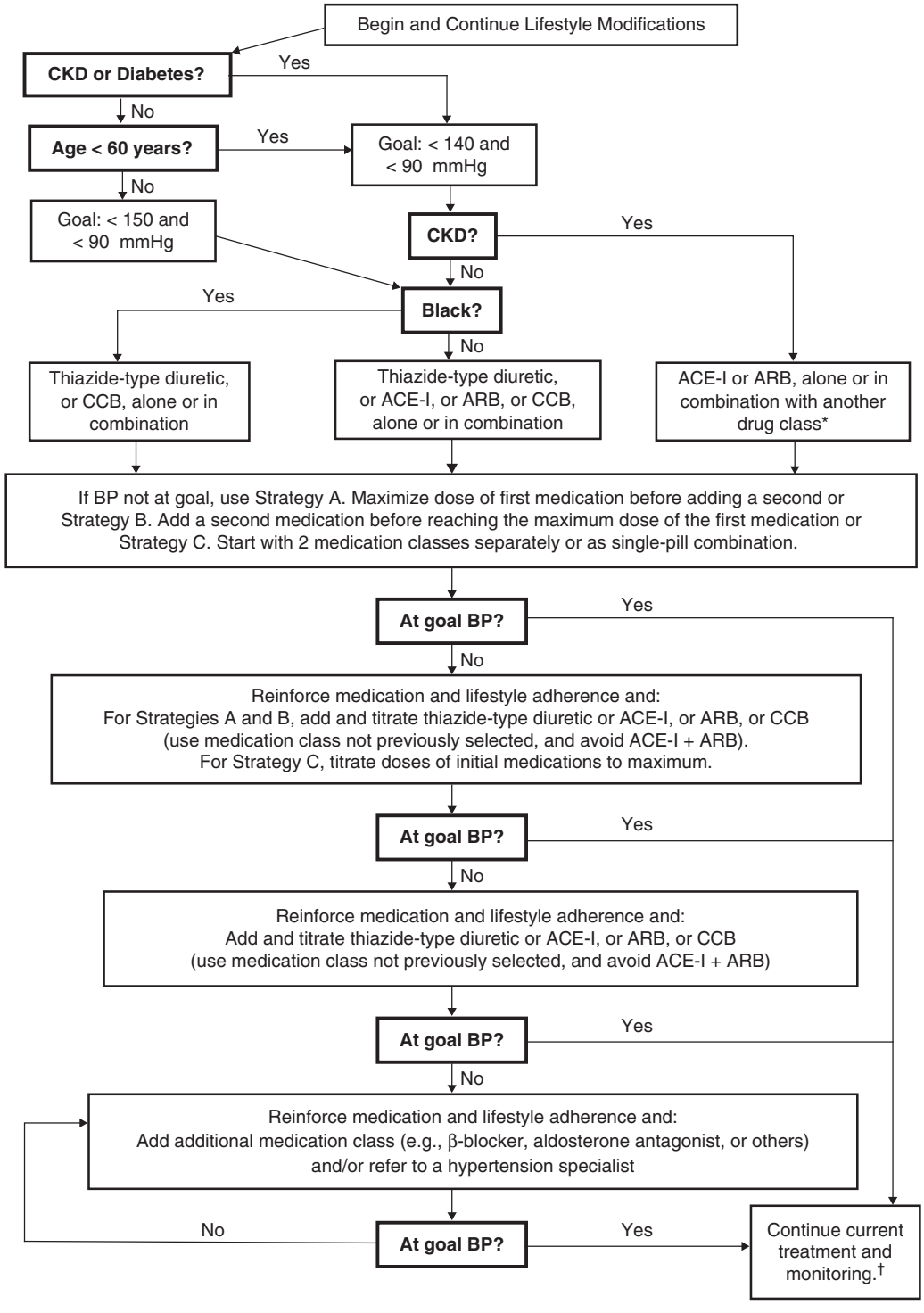

FIGURE 4.1 2014 Hypertension Management Algorithm

Abbreviations: CKD = chronic kidney disease; BP = blood pressure; ACE-I = angiotensin converting-enzyme inhibitor; ARB = angiotensin receptor blocker; CCB = calcium channel blocker.

*The combination of an ACE-inhibitor + ARB is not recommended.

†If the blood pressure is not maintained at or below goal, re-enter the algorithm, where appropriate, based on the current treatment plan.

Source: Adapted from JNC 8 Ref. (7). James PA, Oparil S, Carter BL, et al. 2014 Evidence-based guidelines for the management of high blood pressure in adults: Report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA*. 2014;311:507–520.

showed no significant difference in stroke, myocardial infarction, or cardiovascular death across the three groups (25). Some believe the lack of a significant outcome difference could be attributed to the fact that the achieved diastolic BPs differed by only about 2 (vs. the planned 5) mmHg. A more recent Italian open-label clinical trial randomized 1,111 nondiabetic hypertensive subjects to in-office systolic BPs <140 or <130 mmHg, and followed them for a median of 2 years for development of left ventricular hypertrophy by electrocardiography (26). Significant differences were seen not only in this (primary) endpoint (82 vs. 55, $p < 0.02$), but also in the first secondary endpoint, composite cardiovascular events (52 vs. 27, $p = 0.003$), with those randomized to the lower BP target having significantly lower risk. In addition to issues with the open-label nature and the prespecified, yet secondary, outcome of the trial, the average achieved BP difference between the two randomized groups was only 3.8/1.5 mmHg, much lower than planned; these may be some of the reasons this trial was not included in the database used by JNC 8.

All current hypertension guidelines agree that a diastolic BP target of <90 mmHg can be recommended for uncomplicated hypertensive patients. There is less uniformity about the systolic BP target, both for various ages and across recent guidelines. All guidelines recommend a systolic BP <150 mmHg for people older than 80 years of age (presumably based on HYVET) (27) and <140 mmHg for people between 18 and 59 years of age. JNC 8 broke with tradition in recommending <150 mmHg for fit and otherwise healthy people aged ≥60 years, although such individuals whose systolic BP is currently <140 mmHg are specifically encouraged to continue to maintain their effective treatment and this lower goal (7). European guidelines recommend a systolic BP between 140 to 150 mmHg for people between 60–79 years of age whose initial systolic BP is ≥160 mmHg (5). Current English, Canadian, and ASH/ISH guidelines agree on a systolic BP target of <140 mmHg for all adults in the 60 to 79 year age group (4,6,8). One reason for this disagreement is the lack of clinical trials directly comparing systolic BP targets in this population, as nearly all treatment protocols (including new drug applications to the U.S. FDA) targeted diastolic BP until quite recently.

GOAL BLOOD PRESSURE FOR HYPERTENSIVE PATIENTS WITH OTHER HIGH-RISK CONDITIONS

Recently, guidelines have moved away from a basic precept of preventive medicine that dictated higher-risk patients should be treated more intensively, usually to lower goals of surrogate endpoints. This had been formerly accepted for postexposure prophylaxis for human immunodeficiency virus and low density-lipoprotein (LDL)-cholesterol levels, but now convenience and acceptance of only "evidence-based" treatment algorithms have led to revision of both of these strategies (28,29). Similarly, prior to 2010, many organizations and expert panels had recommended a lower on-treatment BP target (typically <130/80 mmHg) for patients with diabetes mellitus, chronic kidney disease, or established heart disease. In each of these cases, the clinical trial evidence to support the lower target was far from robust, leading guideline panels with mandates to recommend only "evidence-based" strategies to raise these goals.

For diabetics, two clinical trials supported a lower-than-usual BP goal; both were reported in the last millennium. The HOT study enrolled 1,501 diabetics, and found a significant 51% reduction in stroke, myocardial infarction, or cardiovascular death in those randomized to a diastolic BP ≥80 versus ≥90 mmHg, but the systolic BPs were not reported (25). The United Kingdom Prospective Diabetes Trial reported significantly fewer complications (of all types) in 1148 newly diagnosed diabetics randomized to "tight BP control" (defined in the mid-1980s in England as ≥150/85 mmHg, with an average achieved BP of 144/82 mmHg), compared to those randomized to "less tight control" (≥180/105 mmHg, average achieved BP of 154/87 mmHg) (30). A 2005 prospective meta-analysis from the Blood Pressure Lowering Trialists' Collaboration involving 27 trials (enrolling 33,395 diabetics and 125,314 nondiabetics) observed a significant benefit of a lower BP target for diabetics regarding major cardiovascular events ($p = .03$) and cardiovascular death ($p = 0.02$), but not all-cause mortality ($p = 0.06$) (31).

More recently, the National Institutes of Health–sponsored Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial-BP arm randomized 4,733 type 2 diabetics to systolic BPs of <120 or <140 mmHg (32). After 4.7 years, the primary endpoint (a composite of stroke, myocardial infarction, or cardiovascular death) was reduced by a nonsignificant 12% ($p = 0.20$) in those randomized to the lower BP target (achieved: 119 mmHg), compared to the traditional target (achieved: 134 mmHg). Because of the nonsignificant result and a higher risk of hypotension and other adverse effects, the authors concluded that a lower BP target for diabetics should not be implemented. A 2011 systematic review and meta-analysis of 31 trials involving 73,913 diabetics and 295,652 patient-years of follow-up found a significant 31% reduction in stroke risk, but a nonsignificant 13% reduction in myocardial infarction risk, among subjects

randomized to a lower-than-usual BP target (33). A more recent and more focused systematic review and meta-analysis included just five randomized trials that directly compared BPs of 140–160/85–100 mmHg and <130/80 mmHg (34).The lower BP target was associated with a significant 35% reduction in stroke, but nonsignificant reductions in myocardial infarction (7%) and mortality (24%) (34), essentially confirming an earlier report showing significant benefit only in stroke, but not major cardiovascular events, heart failure, or cardiovascular death (35). The 2014 Canadian Hypertension Education Program guidelines persist in recommending a BP target of <130/80 mmHg (6), but those from Great Britain recommend this target only if there is evidence of kidney, eye, or cerebrovascular disease (4). The 2014 Standards of Medical Care in Diabetes promulgated by the American Diabetes Association continued to recommend a BP <140/80 mmHg, with the caveat that a systolic target of <130 mmHg may be appropriate for some (especially younger and healthier) diabetics (12). The 2013 ESH/ESC guidelines recommended a BP target of <140/85 mmHg for diabetics, with a footnote that diastolic BPs between 80 and 85 mmHg are safe and well tolerated (5). Rejecting the conclusions of both HOT (as a post hoc analysis of just 8% of the enrolled population) and UKPDS (because the "intensive" target BP was <150/85 mmHg), JNC 8 cited the ACCORD-BP conclusions to recommend a BP target of <140/90 mmHg for all diabetics (7), in agreement with the ASH/ISH guidelines (8).

The situation is somewhat similar for patients with chronic kidney disease (CKD). In 1997, U.S. hypertension guidelines recommended, for the first time, two lower-than-usual BP targets for CKD patients: <130/85 mmHg or <125/75 mmHg, for those without or with >1 gm of proteinuria/day, respectively. In 2003, JNC 7 simplified these targets to <130/80 mmHg (3), but several subsequent meta-analyses pointed out that the clinical trial evidence for this target was sparse. The most recent systematic review (36) found only three trials that compared outcomes in CKD patients randomized to a lower BP target: a 2005 European trial that randomized 338 subjects taking a low-dose ACE-inhibitor to either placebo or a dihydropyridine calcium antagonist (rather than two specific BP targets), and two National Institutes of Health-sponsored trials from the last millennium that compared outcomes in subjects randomized to a mean arterial pressure ≤102–107 mmHg (about 140/90 mmHg) versus ≤92 mmHg (about 125/75 mmHg): Modification of Diet in Renal Disease (that oversampled subjects with polycystic kidney disease among its 890 subjects) and the African American Study of Kidney Disease and Hypertension (which enrolled 1,094 hypertensive but nondiabetic subjects). Meta-analyses of these trials did "not prove that a blood pressure target of less than 130/80 mmHg improves clinical outcomes more than a target of less than 140/90 mmHg in adults with CKD," although 7 of 11 subgroup analyses were suggestive of a benefit in subjects with proteinuria >300 mg/d (36). A recent nationwide U.S. epidemiological study of 16,129 participants with Stage 3 CKD in the Kidney Early Evaluation Program also showed no benefit of a BP <130/80 mmHg, compared to <140/90 mmHg in preventing end-stage renal disease (37). The previously recommended lower BP target for patients with nondiabetic CKD has been abandoned by British NICE guidelines in 2008, ESH guidelines in 2009, ESH/ESC guidelines of 2013 (5), the 2013 Canadian Hypertension Education Program (6), JNC 8 and ASH/ISH guidelines in 2013 (7,8) but the Kidney Disease: Improving Global Outcomes Work Group has "suggested" a BP target of <130/80 mmHg for people with CKD and urinary albumin excretion of ≥30 mg/24 hours (or equivalent), while recognizing that this "suggestion" is not based on randomized clinical trials (13,38).

A 2007 Scientific Statement from the American Heart Association regarding treatment of hypertension in patients with heart disease also recommended lower-than-usual BP targets (39). The recommendation for those with coronary heart disease was based primarily on a post hoc analysis of a single clinical trial that used progression of coronary atherosclerosis by intravascular ultrasound as its primary endpoint. The 2014 update of this document discusses the limits of current data, the potential benefits of a lower BP target, concerns about the "J-shaped curve" of achieved diastolic BP and all-cause mortality, and many other issues, and takes a more moderate and patient-centered position about goal BP for patients with heart disease (40).

OTHER ISSUES

Essentially all of the other recommendations made by JNC 7 have not been revised (or even considered) by JNC 8 (7), although the ASH/ISH guidelines are much broader (8). Since 2003, however, other reviews and position papers have provided useful information about measurement of blood pressure (both in and out of the medical office setting) (11), resistant hypertension (41), evaluation for secondary hypertension (see Table 4.5 for a list of commonly used screening tests), hypertension at the extremes of age (42,43), and hypertension in pregnancy (44). Although the new hypertension guidelines are a welcome addition, they leave many important topics available for further updates and revisions to current guidelines' recommendations.

TABLE 4.4 Compelling Indications for Antihypertensive Drugs

Condition	Drug Class	Prevents	Supportive Clinical Trial(s)*
After recent myocardial infarction (MI)	Beta-blocker	Death or recurrent MI	ISIS, etc.
Heart failure with diminished left ventricular function	ACE-inhibitor	Death or hospitalization	CONSENSUS, SAVE, etc.
	Beta-blocker	Death or hospitalization	MERIT-HF, etc.
	Aldosterone antagonist	Death	RALES
	Angiotensin II receptor blocker	Death or hospitalization	Val-HeFT, CHARM
Diminished left ventricular function after MI	ACE-inhibitor	Death or hospitalization	SAVE, TRACE, etc.
	Aldosterone antagonist	Death or hospitalization	EPHESUS
	Angiotensin II receptor blocker	Death or hospitalization	VALIANT
Left ventricular hypertrophy (strict criteria)	Angiotensin II receptor blocker	Stroke	LIFE
Prior stroke or transient ischemic attack	ACE-inhibitor + diuretic	Recurrent stroke, cardiovascular events	PROGRESS
Older hypertensive persons	Diuretic	Stroke (or death)	SHEP (or HYVET)
	Calcium antagonist	Stroke	Syst-Eur, Syst-China
High cardiovascular risk (and age >55 years)	ACE-inhibitor	CV events	HOPE
	Angiotensin II receptor blocker	CV events	ONTARGET
Type 2 diabetics	ACE-inhibitor	CV events	MICRO-HOPE
Type 1 diabetic nephropathy	ACE-inhibitor	Doubling of serum creatinine, dialysis or transplant	Captopril Cooperative Study Group
Type 2 diabetic nephropathy	Angiotensin II receptor blocker	Doubling of serum creatinine, end-stage renal disease or death	IDNT, RENAAL
	ACE-inhibitor	Albuminuria	MICRO-HOPE
		Progression of renal disease	DETAIL

(*continued*)

TABLE 4.4 Compelling Indications for Antihypertensive Drugs (*continued*)

Condition	Drug Class	Prevents	Supportive Clinical Trial(s)*
Type 2 diabetic nephropathy (*cont.*)	Angiotensin II receptor blocker	Albuminuria	IRMA-2
Nondiabetic chronic kidney disease	ACE-inhibitor	Progression of nephropathy	REIN, AIPRI, AASK

CV = cardiovascular; ISIS = International Study of Infarct Survival (*Lancet.* 1986;**2**:57-66); CONSENSUS = COoperative North Scandinavian ENalapril SUrvival Study (*N Engl J Med.* 1987;316:1429-35); SAVE = Survival And Ventricular Enlargement study (*N Engl J Med.* 1992;327:669-77); MERIT-HF = MEtoprolol Randomized Intervention Trial in congestive Heart Failure (*JAMA.* 2000;283:1295-302); RALES = Randomized Aldactone® Evaluation Study (*N Engl J Med.* 1999;341:709-17); Val-HeFT = Valsartan Heart Failure Trial (*N Engl J Med.* 2001;345:1667-75); CHARM = Candesartan in Heart failure: Assessment of Reduction in Morbidity and mortality (*Lancet.* 2003;362:759-66); TRACE = TRAndolapril Cardiac Evaluation (*N Engl J Med.* 1995;333:1670-6); EPHESUS = Eplerenone Post-myocardial infarction Heart Failure Efficacy and Survival Study (*N Engl J Med.* 2003;348:1309-21); VALIANT = VALsartan In Acute myocardial iNfarcTion (*N Engl J Med.* 2003;349:1893-906; LIFE = Losartan Intervention for Endpoint Reduction (*Lancet.* 2002;359:995-1003); PROGRESS = Perindopril pROtection aGainst REcurrent Stroke Study (*Lancet.* 2001;358:1033-41); SHEP = Systolic Hypertension in the Elderly Program (*JAMA.* 1991;265:3255-64); HYVET = Hypertension in the Very Elderly Trial (*N Engl J Med.* 2008;358:1887-98); Syst-Eur = Systolic Hypertension in Europe trial (*Lancet.* 1997;360:757-64); STOP-2 = Swedish Trial in Old Patients with hypertension #2 (*Lancet.* 1999;354:1751-6); Syst-China = Systolic Hypertension in China trial (*J Hypertens.* 1998;16:1823-9); SCOPE = Study on Cognition and Prognosis in the Elderly (*J Hypertens.* 2003;21:875-86); HOPE = Heart Outcomes Prevention Evaluation (*N Engl J Med.* 2000;342:145-53); EUROPA = EUropean Reduction Of cardiac events with Perindopril in stable coronary Artery disease (*Lancet*, 2003;362:782-8); ONTARGET = ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (*Lancet.* 2008;358:1547-59); MICRO-HOPE = MIcroalbuminuria, Cardiovascular and Renal Outcomes substudy of the Heart Outcomes Prevention Evaluation (*Lancet.* 2000;355:253-9); LIFE Diabetes substudy (*Lancet.* 2002;359:1004-10); ASCOT = Anglo-Scandinavian Cardiac Outcomes Trial (*Lancet.* 2005;366:895-906); ACTION = A Coronary disease Trial Investigating Outcome with Nifedipine GITS (*J Hypertens* 2005;23:641-8); CCSG = Captopril Cooperative Study Group (*N Engl J Med.* 1993; 323:1456-62); IDNT = Irbesartan Diabetic Nephropathy Trial (*N Engl J Med.* 2001;345:841-60); RENAAL = Reduction of Endpoints in Non-Insulin Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan (*N Engl J Med.* 2001;345:861-9); DETAIL = Diabetics Exposed to Telmisartan And EnalaprIL (*N Engl J Med.* 2004;351:1952-61); IRMA-2 = Irbesartan Microalbuminuria study #2 (*N Engl J Med.* 2001;345:870-8); MARVAL = MicroAlbuminuria Reduction with VALsartan (*Circulation.* 2002;106:672-8); REIN = Ramipril Evaluation In Nephropathy (*Lancet.* 1998;352:1252-6); AIPRI = Angiotensin-converting-enzyme Inhibition in Progressive Renal Insufficiency (*Kidney Int.* 1997;Suppl. 63:S63-7); AASK = African American Study of Kidney disease and hypertension (*JAMA.* 2002;288:2421-31);.

*Note that some of these drugs have NOT been approved by the U.S. FDA for the specific indication listed, and therefore should be considered "off-label" uses of these drugs.

TABLE 4.5 Screening Tests for Secondary Forms of Hypertension

Diagnosis	Preferred Screening Test(s)	Other Tests
Intrinsic renal disease	Serum creatinine with eGFR ($15), urinalysis ($30)	First-morning urine for albumin/creatinine ratio ($30); 24-hour urine for creatinine clearance, protein, sodium, potassium ($40)
Renovascular hypertension	Doppler ultrasound of renal arteries ($250)	Magnetic resonance angiography ($2900), renal angiogram ($8000)
Mineralocorticoid excess states	plasma aldosterone/renin ratio ($125)	24-hour urinary aldosterone during salt loading ($95); computed tomographic scan with thin cuts through the adrenals ($1700)
Pheochromocytoma	24-hour urine for vanillylmandelic acid (VMA) and metanephrines ($175)	Plasma metanephrines ($250), plasma catecholamines ($250), T_2 weighted magnetic resonance imaging ($2750)
Sleep apnea	Berlin Questionnaire ($2?)	Formal sleep study ($900)
Cushing's Syndrome	8 a.m. plasma cortisol ($35)	Dexamethasone suppression test(s) ($120 each)
Hypothyroidism	Ultrasensitive thyroid-stimulating hormone (TSH, $55)	

†Costs vary over time and from institution to institution. These estimates are approximate.

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5

Russell V. Luepker, MD, MS

Smoking and Passive Smoking

Cigarette smoking is the leading preventable cause of many chronic diseases. In wealthy countries, smoking contributes more to the number of years of life lost to disability and death than any other factor (1). In low- and middle-income countries, it is a growing problem as more individuals assume the smoking habit (1). In the United States, it is estimated that smoking directly contributes to 433,000 deaths/year from a variety of cardiovascular, lung, and other diseases (2) (Figure 5.1). Approximately 20% of American adults currently smoke and, as they die, their places are taken by new teenage and young adult smokers (3). Many smokers have quit; however, those who continue the practice are frequently the most addicted and resistant to change.

The health impact of smoking is not isolated to the smokers. Nonsmokers who are exposed to environmental tobacco smoke face increases in chronic disease risk (4). The association of smoking and increased mortality and morbidity from chronic diseases in smokers and those exposed to secondhand smoke has led to widespread calls for prevention of tobacco uptake by teens, cessation among adult smokers, and a regulation of smoking in public places. This chapter discusses the scientific evidence relating active and passive tobacco smoking to cardiovascular risks, trends in cigarette use, and strategies for prevention and cessation of smoking.

SMOKING AND CARDIOVASCULAR DISEASE

Over the past six decades, extensive research has linked cigarette smoking to major cardiovascular diseases including myocardial infarction, sudden death, stroke, and peripheral vascular disease (5,6). Smoking cessation has been shown to reduce these disease outcomes. These associations affect all age, gender, and ethnic groups.

In 1962, epidemiologic studies in Framingham, Massachusetts, and Albany, New York, found an association between coronary heart disease and smoking among men (7). These same findings were later confirmed among women and those with other cardiovascular diseases (7).

Data from the Multiple Risk Factor Intervention Trial (MRFIT) of 316,099 men found a graded relationship between the number of daily cigarettes and relative risk of coronary heart disease death. The relative risk for 1 to 25 cigarettes per day was 2.1 and rose to 2.9 for cigarette consumption above 25 cigarettes per day (8). MRFIT and other studies demonstrated that quitting smoking reduces incident cardiovascular disease morbidity and mortality (7,9). The interaction of cigarette smoking with other known risk factors is well studied. Some suggest that the effect is additive, whereas others find a multiplicative effect. Regardless, cigarette smoking adds to an individual's cardiovascular risk with obesity, diabetes, hypertension, oral contraceptive use, and electrocardiogram

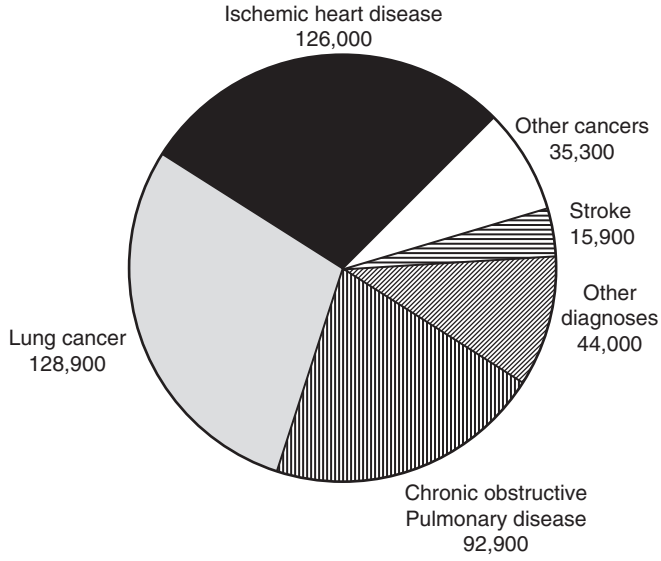


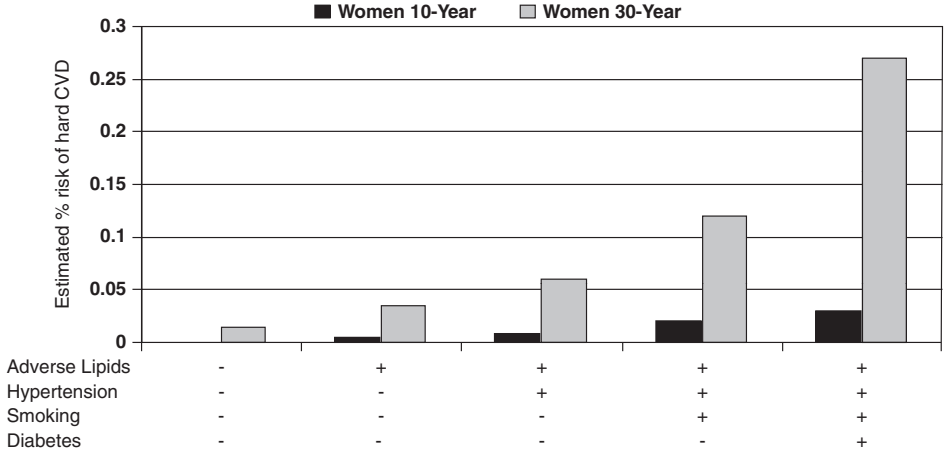
FIGURE 5.1 About 443,000 U.S. deaths each year to cigarette smoking. Average annual number of deaths, 2000–2004. *Source:* cdc.gov

abnormalities (10–12). For example, when cigarette smoking is added to other cardiovascular risk factors, the overall risk of cardiovascular disease increases, as shown for women in Figure 5.2. Smokers who continue the habit after acute myocardial infarction have significantly higher rates of recurrent events and death compared to those who quit (12).

The mechanisms by which smoking affects cardiovascular disease both acutely and chronically are well characterized through laboratory and human experiments. Nicotine has many pharmacologic effects including sympathetic stimulation and coronary vasoconstriction. Inhaled carbon monoxide from burning tobacco decreases oxygen availability in the blood. Other gases in smoke lead to increases in thrombotic factors including platelet activation. Finally, the wide variety of toxic chemicals found in cigarette smoke lead to enhanced inflammation, endothelial dysfunction, and a prothrombotic state (13,14).

SECONDHAND SMOKE

In recent years there has been an increased focus on the harmful effects of cigarette smoke on nonsmoking individuals who are exposed by being around



No risk factors profile: total cholesterol = 150 mg/dL; HDL cholesterol = 60 mg/dL; untreated SBP = 110 mm Hg; nonsmoker; nondiabetic. Adverse lipids: total cholesterol = 260 mg/dL; HDL cholesterol = 35 mg/dL. Hypertension: SBP = 160 mm Hg, untreated.

FIGURE 5.2 Ten- vs 30-year risk of hard CVD for 25-year-old women with different risk profiles. *Source*: Pencina MJ, D'Agostino RB, Larson MG, Massar JM, Vasan RS. Predicting the 30-Year Risk of Cardiovascular Disease: The Framingham Heart Study. *Circulation.* 2009;3078–3084.

smokers. This growing body of information is summarized in the 2006 Surgeon General's Report, The Health Consequences of Involuntary Exposure to Tobacco Smoke (4). These data find that cardiovascular diseases are increased by environmental tobacco smoke as are cancer and respiratory diseases. A meta-analysis of home-based and worksite studies found an overall increase risk of cardiovascular diseases associated with environmental smoke (RR = 1.49, 95% CI, 1.29–1.72) and suggested relative risk from workplace exposure was similar to that of home-based exposure (15).

The mechanism by which secondhand smoke affects individuals is still debated but there is a growing body of available information. Mainstream smoke, inhaled by the smoker, differs from sidestream smoke released directly into the environment (4). Sidestream smoke may be more toxic. Nonsmokers who are exposed regularly to cigarette smoke develop a number of physiologic changes including lower high-density lipoprotein cholesterol, increased fibrinogen, and platelet abnormalities (4). Exposed nonsmokers also have acute effects including endothelial dysfunction and lower exercise tolerance. All of these factors are associated with cardiovascular disease. In addition, there are significant pulmonary effects of secondhand smoke.

TRENDS IN CIGARETTE SMOKING

Cigarette smoking became widespread in the United States following World War II. During this era, cigarette smoking was explicitly encouraged. As part of food rations (K-rations) used by the army, each soldier received 4 cigarettes for each meal equaling 12 cigarettes per day (7). Women gradually attained equivalency with men in smoking rates. By 1965, smoking was a habit of 42.4% of adults (16). Since 1965, the prevalence of cigarette smoking has decreased and more individuals never acquire the habit resulting in a substantial decline in national smoking rates to approximately 20% as reported in 2009. In a 2010 survey of current smokers, 69% responded that they had an interest in quitting and 52% attempted to quit over the past year whereas only 6% were successful (17).

PREVENTION AND REDUCTION OF TOBACCO USE AMONG YOUTH

Smoking begins with experimentation in middle school and becomes regular in high school where 23% of students report that they have smoked in the last 1 to 2 days (3). Smokers become addicted as they grow older and more liberated from the constraints of home and school. The current group with the highest smoking rate is young adults aged 18 to 25. Their smoking rate is 34%, and they have become a target of tobacco companies, which are limited in their ability to approach those under age 18 by regulations and lawsuits (3).

There is a large and substantial literature on the reduction of cigarette smoking among youth. Initially described in the 1994 Surgeon General's Report on Preventing Tobacco Use Among Young People, new research is summarized in the recent 2012 Surgeon General's Report (3). The most effective strategy is the utilization of mass media messaging targeted to appeal to youth and presented multiple times over media channels and social venues accessed by this age group (3).

Several regulatory approaches have also been effective. The enactment of increased cigarette prices has been particularly effective at reducing smoking among youth as they are more price sensitive than older groups. These have the effect of both preventing the onset of cigarette smoking and reducing the number of cigarettes smoked. Youth, as well as adults, are also affected by environmental laws restricting the use of tobacco in public places. The limiting of cigarette advertising or outright banning of cigarette advertisements in the vicinity of schools has been an important adjunct (3). Among junior high youth, school-based programs for smoking prevention are also useful as they are found to have short-term effects. Some have resulted in long-term tobacco avoidance (3). The combination of mass media outreach, regulations restricting public smoking, and prevention programs in schools have been shown to be effective at reducing cigarette smoking among youth as shown by the steadily declining patterns of cigarette use in this age group (16).

PREVENTION AND CESSATION PROGRAMS FOR ADULTS

There has been an overall decline in the prevalence of cigarette smoking; however, this trend has not translated to the young adult demographic. Young adults between the ages of 18 to 25 are the fastest growing group of smokers (16). The tobacco industry has increasingly focused on this demographic group following a court tobacco settlement that limited their access to younger ages. For this group, which has not yet started smoking, school-based programs are rare, although some universities have made initial attempts (3). Health policy and community-based programs are likely to have a more important role in preventing

smoking among 18- to 25-year-old young adults. Sensitivity to tobacco prices, limitations on sites available for public smoking, and other environmental approaches may be very helpful in reducing the prevalence of smoking. For example, over 700 university campuses have banned smoking anywhere on campus.

CESSATION STRATEGIES FOR INDIVIDUALS

Behavioral Treatments

Despite the addictive properties of nicotine, behavioral approaches to smoking cessation are still critical tools. The successful programs, including those utilizing nicotine replacement or other medication strategies, are most successful when they have behavioral treatment components. A number of specific behavioral components included aversive smoking, intratreatment social support, problem solving/skills training, setting a quit date, extra-treatment social support, weight control, nutrition, exercise, contingency contacts, relaxation techniques, and cigarette fading. Many of these individual treatments are not effective when used alone; however, they serve in combination with other approaches. These help programs include the CDC "I'm Ready to Quit" (http://www.cdc.gov/tobacco/campaign/tips/quit-smoking/), a quitting library of local programs (http://www.quitnet.com/library/programs/), and others.

Pharmacologic Interventions

There are social cues and triggers to cigarette smoking for all smokers, which can be confronted by behavioral programs. For the chronic smoker, however, nicotine addiction is the common denominator (18). A number of pharmacologic products have been recognized as effective by the FDA and approved for use. Most of the aids involve some form of nicotine replacement: nicotine gum, nicotine inhaler, nicotine lozenge, nicotine nasal spray, and the nicotine patch. Each of these products has advantages and disadvantages, but all have the potential to result in a new dependence by some smokers.

The nicotine patch is easy to use and needs to be applied once each day. However, it does not allow flexible dosing once it is placed on the skin and delivery of nicotine is relatively slow. Nicotine gum allows more flexible dosing but can be more difficult to use correctly. Many gum users do not adequately dose with this medication. Nicotine nasal spray has the advantage of flexible dosing in addition to providing faster delivery of nicotine. For many users, eye and nose irritation is a problem as is the frequent usage needed to build adequate nicotine levels. A nicotine inhaler allows more flexible dosing and mimics the hand-to-mouth behavior of smoking. The inhaler also has fewer side effects. The nicotine lozenge is convenient and allows flexible dosing. Nicotine replacement therapy has been found to be effective in randomized trials (19).

Bupropion hydrochloride (trade name: Zyban) is approved by the FDA for smoking cessation and is available in tablet form. It appears to act on brain chemistry to mimic the effects of nicotine among smokers although its actions are not fully understood. There is evidence to suggest that a combination of a nicotine patch and bupropion may be more effective than either alone (20). Buproprion has been available for many years as an antidepressant, but works well in smokers without symptoms of depression. It has all the potential side effects of antidepressants including suicidality, depression, anxiety, panic attacks, insomnia, and irritability, and seizures are a particular problem with doses above 300 mg/day. Monitoring for these symptoms is recommended along with social support for cessation.

There are several nicotine receptor partial agonists for smoking cessation. These stimulate nicotine receptors more weakly than nicotine itself but help reduce the craving. Only one is approved by the FDA in the United States: varenicline (trade name: Chantix). It is a pill and is available only through prescription. Varenicline should not be used with other quit smoking products. Common side effects include nausea and insomnia but serious behavioral side effects are also observed. Varenicline received a black box warning in 2009 because of behavioral side effects including agitation, depression, and suicidality (22). There is also some early evidence of increased cardiovascular disease risk but these observations are not yet confirmed (21).

Recent clinical trials tested cytisine and found it effective compared to placebo (23). However, cytisine has not yet been approved for use in the United States as of this review.

Clinical Approaches

Clinicians have multiple opportunities to help their patients quit smoking. The first is in the hospital where smoking cessation is obligatory and there is an opportunity to maintain that behavior after discharge. The individual's acute illness, such as cardiovascular disease, may provide a unique opportunity to

TABLE 5.1 Smoking Cessation Clinical Guideline Recommendations for Adults

1. Tobacco dependence is a chronic disease that often requires repeated intervention and multiple attempts to quit. Effective treatments exist, however, that can significantly increase rates of long-term abstinence.

2. It is essential that clinicians and health care delivery systems consistently identify and document tobacco use status and treat every tobacco user seen in a health care setting.

3. Tobacco dependence treatments are effective across a broad range of populations. Clinicians should encourage every patient willing to make a quit attempt to use the counseling treatments and medication recommended.

4. Brief tobacco dependence treatment is effective. Clinicians should offer every patient who uses tobacco at least the brief treatments shown to be effective.

5. Individual, group, and telephone counseling are effective, and their effectiveness increases with treatment intensity. Two components of counseling are especially effective, and clinicians should use these when counseling patients making a quit attempt:
   a. Practical counseling (problem solving/skills training)
   b. Social support delivered as part of treatment

6. Numerous effective medications are available for tobacco dependence, and clinicians should encourage their use by all patients attempting to quit smoking, except when medically contraindicated or with a specific population for which there is insufficient evidence of effectiveness (ie, pregnant women, smokeless tobacco users, light smokers, and adolescents).
   a. Seven first-line medications (5 nicotine and 2 non-nicotine) reliably increase long-term smoking abstinence rates:
      i. Bupropion SR
      ii. Nicotine gum
      iii. Nicotine inhaler
      iv. Nicotine lozenge
      v. Nicotine nasal spray
      vi. Nicotine patch
      vii. Varenicline
   b. Clinicians also should consider the use of certain combinations of medications identified as effective.

7. Counseling and medication are effective when used by themselves for treating tobacco dependence. The combination of counseling and medication, however, is more effective than either alone. Thus, clinicians should encourage all individuals making a quit attempt to use both counseling and medication.

8. Telephone quitline counseling is effective with diverse populations and has broad reach. Therefore, clinicians and health care delivery systems should both ensure patient access to quitlines and promote quitline use.

9. If a tobacco user currently is unwilling to make a quit attempt, clinicians should use the motivational treatments shown in the guideline to be effective in increasing future quit attempts.

10. Tobacco dependence treatments are both clinically effective and highly cost effective relative to interventions for other clinical disorders. Providing coverage for these treatments increases quit rates. Insurers and purchasers should ensure that all insurance plans include the counseling and medication identified as effective as covered benefits.

TABLE 5.2 Counseling: Five As

Ask: Systematically identify all tobacco users at every visit
Advise: Strongly urge all smokers to quit
Attempt: Identify smokers willing to try to quit
Assist: Aid the patient in quitting
Arrange: Schedule follow-up contact

encourage and maintain cessation. A recent Cochrane review on interventions for smoking cessation in hospitalized patients made a number of important observations (24). High-intensity behavioral interventions such as individual counseling, self-help materials, and group therapy beginning during a hospital stay and continuing at least one month after discharge were successful in smoking cessation. They found no effect for interventions of lower intensity or shorter duration eg, brief advice). It was also observed that the addition of nicotine replacement therapy significantly increased cessation rates over counseling alone. They found no data to suggest that the addition of bupropion or varenicline to intensive counseling increased cessation rates over what was achieved by counseling alone (24).

Although most smokers are observed to quit "on their own," there are numerous opportunities in the outpatient clinical setting to advance smoking cessation. An overall strategy is outlined in Table 5.1. Clinicians have a far greater ability to actualize smoking cessation than most believe. Five hints for smoking cessation counseling by physicians are shown in Table 5.2. The amount of time required to do this is minimal and the potential for change is great (25).

CONCLUSIONS

Evidence linking tobacco use to cardiovascular disease causation is indisputable. Approximately a half million deaths annually are attributed to cigarette smoking in the United States. The economic burden from medical expenses and indirect costs is enormous, but the human cost in suffering exceeds these. Environmental smoke is also an important cause responsible for up to 40,000 deaths from heart disease annually. Preventing cigarette smoking among youth includes a variety of initiatives. For adults, behavioral treatments, self-help approaches, and pharmacologic therapy are readily available. These, in combination with community and public health approaches, provide the potential for eliminating one of the greatest health-impairing behaviors affecting humankind.

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Nirmal Sunkara, MD and
Shaista Malik, MD, PhD, MPH

6

Metabolic Syndrome

The Metabolic Syndrome (MetS), an integrative epidemiologic concept, is a clustering of metabolic risk factors including visceral obesity, dyslipidemia, hypertension, and hyperglycemia, each important risk factors for developing diabetes and atherosclerotic cardiovascular disease (ASCVD). As early as 1923, Kylin, a Swedish physician, described the clustering of cardiovascular risk factors such as hypertension, obesity, and gout (1). Later, a constellation of insulin resistance, hyperglycemia, hypertension, low HDL-cholesterol, and high VLDL-triglycerides was described by Reaven as Syndrome X (2). This clustering since has taken different names including insulin resistance syndrome, dysMetS, hypertriglyceridemic waist, obesity syndrome, and finally settled on MetS.

Genetic predisposition, lack of exercise, and body fat distribution all affect the likelihood that a given obese subject will become overtly diabetic or develop cardiovascular disease (CVD). The evidence for the association between MetS and subsequent development of type II diabetes (fivefold increase) and CVD (twofold increase) is very strong. In addition, individuals with MetS seemingly are susceptible to other conditions, notably polycystic ovary syndrome, fatty liver, cholesterol gallstones, asthma, sleep disturbances, and some forms of cancer. Once CVD or diabetes develops, the presence of MetS and the number of components of the MetS contribute to disease progression and risk. However, the MetS is not an absolute risk indicator, as it does not contain many of the factors that determine absolute risk, for example, age, sex, cigarette smoking, and low-density lipoprotein cholesterol levels. Cross-sectional surveys indicate that in the United States, one-third of adults and an alarming proportion of youth have the MetS (3).

HISTORY, PREVALENCE, AND EPIDEMIOLOGY

In 1998, The WHO proposed criteria (Table 6.1) for defining MetS that included insulin resistance as a defining criterion. It was validated in 2001, with its own ICD-9 code by the American Association of Clinical Endocrinologists and then by the release of the Third Adult Treatment Panel of the National Cholesterol Education Program definition of MetS. Similar criteria proposed later by the International Diabetes Federation identified abdominal obesity to be one of the three criteria required to diagnose the MetS and focused on its ethnic variations. Central adiposity was the central theme of all the definitions and was represented by waist circumference.

Prevalence differs based on the population studied and definition used (4). The Centers for Disease Control and Prevention (CDC) places the official prevalence of MetS at 34% among U.S. adults 20 years and older, based on the ATP III definition and NHANES 2003 to 2006 data (5). Based

TABLE 6.1 WHO Criteria for Metabolic Syndrome (3 or More of the Criteria Below)

Components	WHO Criteria
Insulin Resistance	1 of the following • Type 2 diabetes • Impaired fasting glucose • Impaired glucose tolerance
HTN	On HTN meds or ≥ 140/90 mmHg
Triglycerides	≥ 150 mg/dL
HDL-C	< 35 mg/dL
BMI	30 kg/m^2 or W/H ratio > 0.9 in men and > 0.85 in women
Urine albumin	> 20 µg/min or albumin: creatinine ratio ≥ 30 mg/g

on the most recent data from NHANES 1999 to 2010 (65), 22.9% of U.S. adults using the NCEP/ATP III guidelines criteria have MetS in 2009 to 2010, which has decreased from 25% in 1999 to 2000 (7), predominantly driven by decreases in prevalence of hypertriglyceridemia and elevated blood pressure. During the same period, the prevalence of abdominal obesity has increased to 56% from 45%, especially prominent in women. There are ethnic variations in prevalence: MetS is shown to be most prevalent among Mexican Americans; among African Americans, in particular males, and prevalence was lower than in whites (7,8).

The prevalence among U.S. adolescents has been shown to be rising from 4.2% in 1988 to 1992, 6.4% in 1999, and 10.8% in males and 6.1% in females based on the National Health and Nutrition Examination Surveys 2001 to 2006 (9). Non-white teens were more likely to have MetS defined by WHO criteria (4). A recent review on the prevalence of MetS in children and adolescents found ranged from 1.2% to 22.6% with rates of up to 60% observed in the overweight and obese, using 36 studies using the general population and community-based sampling (10).

DEFINITION

The WHO consultation group proposed criteria for defining MetS that included insulin resistance as a defining criterion, and also included diabetes as a defining criterion (11) (Table 6.1). The European Group for Study of Insulin Resistance (EGIR) proposed a modification of the WHO definition, using the term insulin resistance syndrome rather than MetS and focused more on abdominal obesity than did the WHO; in contrast to the WHO, it excluded patients with type 2 DM from their syndrome because insulin resistance was viewed primarily as a risk factor for diabetes (5). The American Association of Clinical Endocrinologists (Table 6.2) released a definition with lower BMI and blood pressure cutoffs.

In 2001, the Third Adult Treatment Panel of the National Cholesterol Education Program definition of MetS was released which provided easy-to-use criteria (12) (Table 6.3). Later, in a global consensus definition, the International Diabetes Federation, identifying abdominal obesity to be one of the three criteria required to diagnose the MetS, focused on its ethnic and gender-specific variations (13). The IDF consensus group also recommended additional criteria that should be part of further research into MetS, including: tomographic assessment of visceral adiposity and liver fat, biomarkers of adipose tissue (adiponectin, leptin), apolipoprotein B, LDL particle size, formal measurement of insulin resistance and an oral glucose-tolerance test, endothelial dysfunction, urinary albumin, inflammatory markers (C-reactive protein, tumor necrosis factor α, interleukin 6), and thrombotic markers (plasminogen activator inhibitor type 1, fibrinogen). Central adiposity, the central theme of these definitions is represented by waist circumference.

TABLE 6.2 American Association of Clinical Endocrinologists Criteria for Metabolic Syndrome

Components	AACE Criteria
Overweight/Obesity	BMI ≥ 25 kg/m^2
Triglycerides	≥ 150 mg/dL
Low HDL	Men < 40 mg/dL Women < 50 mg/dL
HTN	≥ 130/85 mmHG
2-hour post glucose challenge	≥ 140 mg/dL
Fasting glucose	110–126 mg/dL
Other	• Family h/o DMT2, HTN, CVD • PCOS • Sedentary lifestyle • Advancing age • Ethnic groups with high risk for type 2 diabetes

TABLE 6.3 Modified ATP III Criteria for Diagnosis of Metabolic Syndrome (3 or More of the Criteria Below)

Components	ATP III Modified
Abdominal Obesity	Men > 102 cm Female > 88 cm
Triglycerides	≥ 150 mg/dL or on therapy to lower triglycerides
HDL–C	< 40 mg/dL in men and < 50 mg/dL in women or on therapy to raise HDL-C
Blood Pressure	≥ 130/85 mmHg or on therapy for elevated blood pressure
Fasting glucose	≥ 100 mg/dL or on therapy for elevated glucose

In 2005 an update to the NCEP-ATP III definition brought it more in line with the IDF definition, specifically using the lower cutpoint of impaired fasting glucose to (100 mg/dL) and comments on possible ethnic differences and that lower waist values may be adopted in certain ethnic groups, such as those recommended by the IDF (14). In 2009, a joint statement by the IDF, NHLBI, AHA, WHF, International Atherosclerosis Society, and International Association for the Study of Obesity proposed a set of criteria incorporating ethnic and gender-based cutoffs for waist circumference which is still considered the preliminary screening tool (15) (Table 6.4).

The utility of MetS in predicting CV risk beyond its individual components, and the role of insulin resistance as the cause of the syndrome, have always been debated (16). Moreover, inclusion of diabetes as a defining criterion (when MetS itself acts as an identifier for people at higher risk for diabetes) has also put to question the existence of MetS. However, supporters of the syndrome as a diagnostic entity argue that the recognition of MetS promotes lifestyle therapies that will reduce all of the metabolic risk factors simultaneously (17–20).

TABLE 6.4 2009 Joint Scientific Statement Criteria for Diagnosis of Metabolic Syndrome (Central Obesity Essential Component Plus Any Two of the Other Four Components)

Components	Categorical Cut Points
Elevated waist circumference	Population- and country-specific definitions*
Reduced HDL-C (drug treatment for reduced HDL-C is an alternate indicator)	< 40 mg/dL (1.0 mmol/L) in males; < 50 mg/dL (1.3 mmol/L) in females
Elevated blood pressure (antihypertensive drug treatment in a patient with a history of hypertension is an alternate indicator)	Systolic ≥ 130 and/or diastolic ≥ 85 mmHg
Elevated fasting glucose (drug treatment of elevated glucose is an alternate indicator)	≥ 100 mg/dL
Elevated triglycerides (drug treatment for elevated triglycerides is an alternate indicator)	≥ 150 mg/dL (1.7 mmol/L)

*The writing group agreed that varying definitions of waist circumference cutoff values exist and recommended that cutoff values be based on local group recommendations and suggested that further evidence is needed to assess the waist circumference thresholds and associated risk. Meanwhile the available criteria suggested by the WHO and NHLBI should be used. The WHO identifies 2 levels of abdominal obesity in Europids depending on risk for metabolic complications. An increased risk occurs at waist circumferences of ≥ 94 cm in men and ≥ 80 cm in women, but risk is substantially higher at ≥ 102 cm in men and ≥ 88 cm in women. In the Asian population thresholds suggested are ≥ 90 cm for men and ≥ 80 cm for women, although several newer studies suggested different values for Japanese, Chinese, and Indian populations.

PATHOPHYSIOLOGY

Insulin is needed to facilitate glucose uptake in adipocytes, hepatocytes, and skeletal muscle cells, and it also regulates hepatic glucose production and lipolysis. The central feature of MetS pathophysiology is insulin resistance. It is a genetic and acquired defect in metabolism that is defined as decreased responsiveness of target tissues to normal levels of circulating insulin, resulting in hyperinsulinemia. Hyperinsulinemia is associated with adrenergic overactivity, antinatriuresis, leading to increased cardiac output and urinary catecholamine excretion and plasma volume expansion, thus causing hypertension (2). Chronic sympathetic nervous system overactivity contributes to a further decline of insulin sensitivity and creates a vicious circle that may contribute to the development of hypertension and of the MetS and favor cardiovascular and kidney disease.

Expanded adipose tissue mass releases free fatty acids (FFA), which in addition to reducing insulin sensitivity in muscle and liver, also causes increased production of glucose and triglycerides and secretion

of very low density lipoproteins (VLDL), leading to reduced glycogen stores and increased lipid accumulation in triglycerides (TG) (21). The elevation in FFA and TNF-α and decrease in adiponectin adversely affect endothelial function and promote atherogenesis (22).

The excess adipose tissue observed in the MetS results in overproduction of inflammatory cytokines TNF-α, IL-6, and C-reactive protein (CRP). Also noticed is the increase in plasminogen activator inhibitor type 1 (PAI-1) which is the most potent inhibitor of fibrinolysis in the body and is produced from the increased adipose tissue mass. Central obesity was significantly and positively correlated with PAI-1 levels, levels of insulin, and elevated BP, and being negatively correlated with HDL-C and waist circumference was found to predict PAI-1 levels (23).

CARDIOVASCULAR RISK IN PERSONS WITH METS

Prediction of Diabetes

Several studies examined the risk of developing diabetes in MetS based on NCEP/ATP III definition (relative risk of 2.99 [95% CI 1.96–4.57]) and modified WHO definitions (unadjusted fixed-effects estimate was 6.08 [95% CI 4.76–7.76]) (24). The relative risk of developing diabetes, in those with MetS, based on data from the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) study and the British Regional Heart Study (BRHS) is between 3 and 11 (25). MetS predicted an increased risk of diabetes in PROSPER participants, HR = 4.41 (95% CI = 3.33–5.84) and an even stronger association was observed in BRHS participants, HR = 7.47 (4.90–11.46) (25). The San Antonio Heart Study (n = 2,559) showed that the MetS predicted diabetes beyond glucose intolerance alone and that the NCEP/ATP III definition performed better than the modified WHO definition (26).

Prediction of Cardiovascular Events and Mortality

The combination of both diabetes and MetS is associated with a much higher prevalence of CHD and even those with MetS in the absence of diabetes have a higher prevalence of CHD than those with diabetes who do not have MetS (27).

We demonstrated in the U.S. population of men and women a twofold greater risk of mortality from CHD and CVD in persons with MetS; even those with MetS but without diabetes and those with only one or two MetS risk factors were at an increased risk of death from CHD and CVD. Increased risks associated with MetS held similarly for men as they did for women. Those with both diabetes and pre-existing CVD had the highest risk (28).

In 2,175 elderly subjects in the Cardiovascular Health Study, MetS defined by the ATP III but not WHO criteria was associated with a significant 38% increased risk (hazard ratio 1.38, 95% CI = 1.06–1.79) of coronary or cerebrovascular events (29). Some studies have, however, questioned the utility of MetS when adjustment for cardiorespiratory fitness resulted in associations being no longer significant; in this large, primarily healthy cohort of 19,223 men who received a clinical examination and fitness examination, adjusted relative risks for all-cause and cardiovascular mortality were 1.29 (1.05–1.57) and 1.89 (1.36–2.60), respectively, among those with versus without MetS (30).

In a meta-analysis of risks for all-cause mortality, CVD, and diabetes, Ford et al. noted that among studies using the exact NCEP definition of the MetS, relative risks (and 95% confidence intervals) associated with the MetS were 1.27 (0.90–1.78) for all-cause mortality, 1.65 (1.38–1.99) for cardiovascular disease, and 2.99 (1.96–4.57) for diabetes (24). For the WHO definition, corresponding estimates were 1.37 (1.09–1.74), 1.93 (1.39–2.67), and 2.60 (1.55–4.38), respectively. The authors concluded population-attributable fractions of the MetS to be 6–7% for all-cause mortality, 12–17% for cardiovascular disease, and 30–52% for diabetes.

The association between MetS and CVD events may be attenuated in certain population subgroups. In a study looking at the predictive value of MetS in the elderly, Mozaffarian et al. used data from the Cardiovascular Health Study (CHS) and examined data from 4,258 U.S. adults (31). Although those with MetS had a 22% higher mortality risk (RR, 1.22; 95% confidence interval CI, 1.11–1.34), when looking at the population-attributable risk fraction (PAR %), higher proportions of death were attributable to elevated fasting glucose (EFG) and hypertension (PAR, 22.2%) than to MetS (PAR, 6.3%). This study reinforces the concept that there is limited short-term risk assessment value in using MetS. In general, the MetS may help identify younger cohorts who face a high long-term cardiovascular risk.

Finally, there was a large meta-analysis of the risk of incident cardiovascular events and death associated with MetS analyzed data from 37 studies and 172,573 individuals. MetS in this analysis had a much stronger association with cardiovascular events and death with a relative risk of 1.78 (95% CI = 1.58–2.00). This relationship was stronger in women and remained significant after adjusting for traditional cardiovascular risk factors (32).

Prediction of Stroke

MetS is reported to increase the odds of ischemic stroke by 1.49-fold among patients with known CHD compared to 2.49-fold in diabetic subjects with CHD (33). Similar increased risk was also reported in case controls studies of stroke survivors from Japan (3.1-fold) and Greece (2.6) (34,35).

MetS Risks Among Subjects With Known Cardiovascular Disease

The presence of MetS confers an additional 29% risk of death and 23% risk of major cardiovascular events (36) as seen in the GISSI-Prevenzione Trial among 11,232 patients with a prior MI, and a hazard ratio of 1.49 for death and recurrent MI (37) as seen in the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial. This increased risk was more pronounced in diabetic patients.

Global Risk Assessment of MetS

The recently released ACC/AHA guidelines (38) recommended using a pooled cohort estimate to estimate more closely the total burden of ASCVD, for a comprehensive assessment of the estimated 10-year risk for an ASCVD event that includes both CHD and stroke. The new Pooled Cohort Risk Assessment Equations developed by the Risk Assessment Work Group estimate the 10-year ASCVD risk (defined as first occurrence nonfatal and fatal MI, and nonfatal and fatal stroke) for the identification of candidates for statin therapy. These estimates are to be used to predict stroke as well as CHD in non-Hispanic Caucasian and African American women and men aged 40 to 79 years with or without diabetes and who have LDL-C between 70–189 mg/dL.

These final pooled cohorts were derived from trials that included participants from several large, racially and geographically diverse, modern NHLBI-sponsored cohort studies, including the ARIC (Atherosclerosis Risk in Communities) study, Cardiovascular Health Study, and the CARDIA (Coronary Artery Risk Development in Young Adults) study, combined with applicable data from the Framingham Original and Offspring Study cohorts. These included Caucasian and African American populations and there is a need for validation of these estimates in the various ethnic groups as when compared with nonHispanic whites, estimated 10-year risk for ASCVD is generally lower in Hispanic American and Asian American populations and higher in American Indian populations (39).

Utility of Novel Biomarkers for Additional Risk Assessment in MetS

Once global risk assessment is done utilizing the population-based scores, additional information about the CVD risk for a given individual can then be found with information obtained from the novel biomarker. For example, there has been interest as to whether the addition of risk factors, such as high sensitivity C-reactive protein (hsCRP), fibrinogen, and small dense LDL, will further add to predicting risk in persons with MetS. It has been shown that hsCRP levels add predictive value for cardiovascular risk among individuals with MetS. As shown in the Nurses Health Study and by the Framingham investigators, hsCRP levels of 3 or more have an additive effects for predicting CV risk (40). In addition, the authors have published in the National Health and Nutrition Examination Survey (NHANES) 1999 to 2000 sample that participants with increased CRP levels and MetS have similar odds of CVD to those with diabetes who have low CRP levels, and that those with diabetes and high CRP levels had the highest odds of CVD (41).

It is important to note that the JUPITER trial has shown that screening for C-reactive protein can identify within the primary prevention setting a subset of patients (those with elevated CRP levels) most likely to benefit from preventive therapy with a statin. Both patients with and without MetS, all of whom had CRP levels >2 mg/L benefited from treatment (42). Disputing the relative importance of CRP, a recent comprehensive meta-analysis from the Emerging Risk Factors Collaboration (ERFC) examined data from 54 studies and 160,309 participants and found that statistical adjustment for conventional cardiovascular risk factors resulted in attenuation of the linear relationship between hsCRP concentration and CHD, stroke, and other vascular mortality. The role of other novel risk markers, such as fibrinogen, interleukin (IL-1, IL-6) ApoB, albuminuria, GFR, or cardiorespiratory fitness is of uncertain value, and adiponectin levels have been recommended as of uncertain value in providing additive risk stratification in persons with MetS.

Screening for Subclinical Atherosclerosis

If, after quantitative risk assessment based on a population model (pooled cohort estimate), uncertainty remains in an individual patient, it is considered reasonable to check family history, hsCRP, CAC score, or ABI to help in decision making.

Ingelsson et al. evaluated the incidence of CVD associated with MetS and diabetes according to the

presence or absence of subclinical disease, which was categorized based on any abnormalities on carotid ultrasound or ankle-brachial blood pressure as well as left ventricular hypertrophy on an echocardiogram or an electrocardiograph, or abnormal urinary albumin using data from the Framingham Offspring Study (43). The authors found that participants who had MetS and exhibited subclinical disease had a risk of CVD that was 2.5-fold higher (HR 2.67, 95% CI 1.62–4.41) than those without MetS or subclinical disease. The association of MetS and CVD was attenuated in those without subclinical disease (HR 1.59, 95% CI 0.87–2.90).

Coronary Artery Calcification (CAC)

The presence and extent of CAC strongly correlates with the overall magnitude of the coronary atherosclerosis plaque burden and with the development of subsequent coronary events (44). The authors have previously demonstrated the presence of MetS to be independently associated with an increased likelihood of CAC (compared with those without MetS), and those with diabetes to have the highest likelihood of CAC (45). Moreover, the prevalence of calcium among women with MetS was as high as in those with diabetes. CAC has been deemed a class IIb recommendation in the 2013 ACC/AHA guidelines for the purpose of risk-based treatment decision making when formal risk estimates are uncertain.

TREATMENT

The recently released 2013 ACC/AHA guidelines for prevention of cardiovascular disease provide guidance on treatment of cholesterol, obesity, and lifestyle changes for cardiovascular risk reduction (46). Also, the recently released 2013 guidelines for HTN authored by a panel convened by the Joint National Committee 8 provide guidance on blood pressure management (47).

Lifestyle modification is the mainstay therapy for MetS. The goals for lifestyle risk factor management based on recommendations by the ACC/AHA guidelines on prevention include dietary, exercise, and weight loss recommendations (48).

Diet Recommendations for LDL Cholesterol Lowering

The ACC/AHA recommend adapting a dietary pattern to appropriate caloric requirements and personal and cultural preferences for continued adherence and benefit. Any diet that incorporates the above and emphasizes intake of vegetables, fruits, and whole grains; includes low-fat dairy products, poultry, fish, legumes, nontropical vegetable oils and nuts; and limits intake of sweets, sugar-sweetened beverages, and red meats is recommended. This can be achieved by following diet plans such as the DASH dietary pattern, the USDA Food Pattern, or the AHA Diet. The aim in addition to caloric restriction is for a dietary pattern that achieves 5% to 6% of calories from saturated fats (71).

When food was supplied to adults with a total cholesterol level <260 mg/dL, LDL-C <160 mg/dL, and body weight was kept stable, the DASH dietary pattern, when compared to a typical American diet of the 1990s, lowered LDL-C by 11 mg/dL, lowered HDL–C by 4 mg/dL, and had no effect on TG (48).

Diet Recommendations for Blood Pressure Lowering

In addition to the dietary goals and recommendations above, the goal is to restrict sodium in the diet to no more than 2,400 mg/day and achieve a reduction of sodium in a diet of at least 1,000 mg/day for lowering blood pressure (71). Additional restriction to less than 1,500 mg/day is associated with further reductions in blood pressure. The DASH diet when regularly consumed lowers blood pressure by 5–6/3 mmHg. A low sodium diet has been shown to work in all patients, regardless of ethnic groups. There is insufficient evidence from RCTs to determine whether reducing sodium intake plus changing dietary intake of any other single mineral (eg, increasing potassium, calcium, or magnesium) lowers BP more than reducing sodium intake alone.

Exercise Recommendations by ACC/AHA for Cholesterol and Blood Pressure Lowering

At all BP levels, including individuals with HTN, aerobic physical activity has been shown to decrease systolic and diastolic BP, on average, by 2 to 5 mmHg and 1 to 4 mmHg, respectively.

Typical interventions shown to be effective for lowering BP include aerobic physical activity of, on average, at least 12 weeks' duration, 3 to 4 sessions per week, lasting on average 40 minutes per session, and involving moderate-to-vigorous intensity physical activity.

Aerobic exercise has also been shown to reduce LDL cholesterol by 3–6 mg/dL and non-HDL cholesterol by 6 mg/dL. It did not have any consistent effects on HDL-C and triglycerides.

Type of Exercise

When resistance training is compared to aerobic exercise, it resulted in beneficial effects on systolic blood pressure; however, no consistent effects on diastolic pressure were seen. The combined effect of both aerobic and resistance training is not known. The ACC/AHA guidelines currently recommend aerobic exercise for weight reduction.

Weight Loss Recommendations

Approximately 78 million adults in the United States are obese, which places them at risk for morbidity from a variety of conditions including diabetes, coronary heart disease, and stroke.

Waist circumference, height, weight, and BMI need to be measured at least annually, or more frequently, in patients who are at higher risk. The recent ACC/AHA guidelines did not change the recommended cutoff values for waist circumference previously established by IDF and NCEP/ATP III. These patients with high BMI need to be counseled at every visit about their risk for developing diabetes that even modest weight loss (3–5% of body weight) can result in clinically meaningful benefits for triglycerides, blood glucose, glycated hemoglobin, and development of diabetes (type 2). Greater weight loss (>5%) can further reduce blood pressure, improve lipids (both low-density lipoprotein and high-density lipoprotein cholesterol), and reduce the need for medications to control blood pressure, blood glucose, and lipids. Weight loss is to be achieved using lifestyle modifications and physical activity.

To achieve weight loss, a 1200 to 1500 kcal/diet for women and a 1500 to 1800 kcal/day diet for men with an energy deficit of 500 kcal/day or 750 kcal/day, respectively, is recommended.

Sustained weight loss of 3% to 5% is likely to result in clinically meaningful reductions in triglycerides, blood glucose, HbA1C, and the risk of developing type 2 diabetes.

For weight loss maintenance, prescribe face-to-face or telephone-delivered weight loss maintenance programs that provide regular contact (monthly or more frequently) with a trained interventionist who helps participants engage in high levels of physical activity (ie, 200–300 minutes/week), monitor body weight regularly (ie, weekly or more frequently), and consume a reduced-calorie diet.

Very low calorie diets (less than 800 kcal/day) are to be recommended only as part of a high-intensity lifestyle intervention under the close observation of a trained provider.

Adults with a BMI ≥40 or BMI ≥35 with obesity-related comorbid conditions who are motivated to lose weight and who have not responded to behavioral treatment with or without pharmacotherapy with sufficient weight loss to achieve targeted health outcome goals that bariatric surgery may be an appropriate option, it is reasonable to refer for bariatric surgery.

In a meta-analysis of RCTs examining lifestyle modification for individuals with MetS, lifestyle modification was more likely than conventional education to result in resolution of MetS.

Diets that foster adherence in the long run, such as those modeled after the Mediterranean diet, not only improve risk factors but also reduce coronary mortality after myocardial infarction, improve endothelial function, and increase longevity (49,50). In a study using data from the third National Health and Nutrition Examination Survey (NHANES III), participants diagnosed with MetS had a lower consumption of fruit, vegetables, and antioxidants than those without MetS (51). The Coronary Artery Risk Development in Young Adults Study (CARDIA) showed that consumption of dairy products was associated with a significantly reduced risk of MetS (52). The Framingham Offspring Study showed whole grain and cereal fiber intakes were associated with reduced risk of MetS (53). Weight reduction and increased physical activity slows progression to type 2 diabetes in individuals with MetS (54,55).

Lifestyle and behavior modification can be difficult. O'Malley et al. examined the effect of case management on the development of the MetS (56). In a randomized control trial with 450 patients, they were able to demonstrate greater improvement in motivation to change behavior and lower prevalence of MetS in 6 months after intervention with a cardiovascular case management program.

However, in severely obese patients where lifestyle measures are not sufficient to adequately address the problem, pharmacologic therapy for weight loss can be recommended as an adjunct.

Pharmacological Treatment

When lifestyle modification fails and in high-risk patients, medications that target individual risk factors are recommended (eg, antihypertensives, lipid-lowering drugs, hypoglycemic drugs, antiplatelet drugs, and weight-loss drugs). Specific therapeutic targets focus on atherogenic dyslipidemia, elevated blood pressure, elevated glucose, and prothrombotic and proinflammatory states.

Dyslipidemia

The newly released ACC/AHA guidelines for blood cholesterol management no longer recommend treatment to a goal of LDL as there are no randomized studies comparing specific LDL-C targets and on treatment non-HDL levels (46).

These guidelines recommend high-intensity statin (Table 6.5) therapy to be initiated in individuals with LDL-C ≥190 mg/dL for primary prevention. If these patients are unable to tolerate a high-intensity statin, the maximum tolerated statin intensity is recommended. For primary prevention for LDL ≥190 mg/dL, it is reasonable to intensify statin therapy to achieve at least a 50% reduction in LDL-C levels. The addition of a nonstatin drug to further lower LDL after maximum intensity of statin is achieved was given a level of evidence E citing lack of supporting evidence from RCTs for these drugs.

In patients 40 to 75 years old, with diabetes and LDL between 70 and 189, a moderate intensity statin is recommended; however, if the pooled cohort 10-year risk of ASCVD is calculated to be at least 7.5%, then a high-intensity statin is recommended. In patients 40 to 75 years old, without diabetes and LDL-C between 70 and 189, the 10-year atherosclerosis related cardiovascular disease risk based on pooled cohort equations should be calculated and therapy initiated if 10-year risk ≥7.5%; this will be the case for many persons with MetS.

The Pooled Cohort Equations should be used to estimate 10-year ASCVD risk for individuals with LDL-C 70 to 189 mg/dL without clinical ASCVD to guide initiation of statin therapy for the primary prevention of ASCVD.

Treatment of dyslipidemia associated with MetS with fibrates or niacin, especially in combination with statins, has been shown to be effective. Post hoc analysis of several of the fibrate studies show that those with MetS derive a disproportionately large reduction in cardiovascular events when treated with these agents (57). A meta-analysis of the Familial Atherosclerosis Treatment Study (FATS), the HDL-Atherosclerosis Treatment Study (HATS), and the Armed Forces Regression Study (AFREGS) showed patients with MetS had 50% more rapid coronary stenosis progression than those without MetS and combination of lowering LDL cholesterol plus increasing HDL-cholesterol resulted in added benefit (58). Combination therapy with a statin and fibrate or niacin resulted in a 54% decrease in cardiovascular events in those with MetS; each 10% decrease in LDL cholesterol or 10% increase in HDL cholesterol was associated with 11% or 22% event risk reduction.

Although the recent trials on niacin targeting HDL cholesterol were negative, design limitations in both these trials preclude generalization and a death sentence for niacin (59,60). The VA-HIT study established that a 6% increase in HDL and a 31% decrease in triglycerides were associated with a 29% lower incidence of death/MI/stroke in the absence of statin therapy (61). Subgroup analysis from the AIM-HIGH trial showed that in patients with the upper tertile TG (>=198 mg/dL) and lowest tertile HDL-C (<33 mg/dL), there was an almost significant ($p = 0.07$) reduction in events (HR 0.74) (62). The generalizability of results from HPS2-THRIVE is under question as the average study subject had a LDL-C level of 63 mg/dL and a triglyceride level of 125 mg/dL and that to begin with this study population had no indication for niacin therapy (59). This suggests that rising HDL may be beneficial in targeted patients, and the ongoing HPS3-TIMI 55 may provide additional evidence. The safety of combination lipid therapy is better established, with fenofibrate lacking the well-known strong interaction of statins with gemfibrozil. The evidence supports treatment of dyslipidemia associated with MetS beyond statin treatment for LDL cholesterol,

TABLE 6.5 Intensity of Statin Therapy Based on Statin Type and Dose

High Intensity	Moderate Intensity	Low Intensity
Daily dose lowers LDL-C by ≥50%	Daily dose lowers LDL-C by ≥30% and <50%	Daily dose lowers LDL-C by <30%
Atorvastatin 40 mg, 80 mg Rosuvastatin 20 mg, 40 mg	Atorvastatin 10 mg, 20 mg Rosuvastatin 5 mg, 10 mg Simvastatin 20 mg, 40 mg Pravastatin 40 mg, 80 mg Lovastatin 40 mg Fluvastatin XL 80 mg Fluvastatin 40 mg bid Pitavastatin 2–4 mg	Simvastatin 10 mg Pravastatin 10–20 mg Lovastatin 20 mg Fluvastatin 20–40 mg Pitavastatin 1 mg

to include fibrates or niacin, used in combination with statins to improve incrementally HDL cholesterol and triglycerides in addition to LDL-cholesterol.

Elevated Glucose

The goal for patients with impaired fasting glucose (IFG) is to delay progression to type 2 diabetes, and if diabetic to reduce the HbA1c to <7.0% (although recent guidelines have suggested less stringent guidelines for those with long-standing diabetes or diabetes complicated by other comorbidities including CVD). Weight reduction and increased physical activity remain the primary intervention for persons with IFG, and in those with diabetes, pharmacotherapy should be supplemented as needed to reach HbA1c goals (Table 6.3).

Metformin improves insulin sensitivity and decreases hepatic glucose output and is a biguanide. The DPP demonstrated that metformin was effective at slowing onset of diabetes in those with impaired glucose tolerance. In the Diabetes Prevention Program trial, participants taking metformin did not have significant resolution of MetS compared to those on placebo (63).

Currently, only metformin is recommended as an option for therapy in persons with impaired fasting glucose; there are no such recommendations for TZDs or other antidiabetic agents at present. Drugs that could potentially target insulin resistance include weight-loss drugs, peroxisome proliferators-activated receptor (PPAR)-alpha agonists (fibrates), PPAR-gamma agonists (thiazolidinediones [TZDs]).

In persons with diabetes, fibrates and thiazolidinediones have also been shown to have benefits. In the recent PROACTIVE clinical trial, although the primary composite endpoint was not reduced significantly in those on pioglitazone, the principal secondary endpoint of myocardial infarction, stroke, or cardiovascular disease death was significantly reduced in the group on pioglitazone (64). Also, in the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, although the effect of fenofibrate on CVD events in the entire trial was not significant, there was a reduction in CVD events in those with low HDL cholesterol or hypertension (65). The TZDs lessen insulin resistance and modestly improve various metabolic risk factors. Moreover, among patients with prediabetes, in the Diabetes Reduction assessment with Ramipril and Rosiglitazone Medication (DREAM) trial, and in the ACT-NOW study, the TZD pioglitazone administered to subjects with prediabetes each showed significant reductions in the onset of diabetes (66,67).

Elevated Blood Pressure

JNC 8 released recently recommended less-intensive blood pressure goals, including a goal of less than 150/90 mmHg in those 60 years or older, hypertensive persons age 30 to 59 years to have diastolic goal of less than 90 mmHg, and a goal of less than 140/90 mmHg for most other individuals.

Initiation of therapy with an ACE inhibitor or angiotensin receptor blocker (ARB) has been recommended in those with diabetes (47). A recognized effect of ACE inhibitors and ARBs is an improvement in insulin sensitivity as has been shown by blockage of the RAS using ramipril (Heart Outcomes Prevention Evaluation [HOPE] study) and losartan (Losartan Intervention For Endpoint [LIFE]) reduction in hypertension study (68) and a consistent reduction in the incidence of new-onset diabetes among patients with essential hypertension. Thus, pharmacological blockade of the renin–angiotensin system, in addition to having proven benefits in reducing cardiovascular events, may also be able to prevent the development of diabetes. Elucidation of the mechanism(s) by which these drugs prevent or delay diabetes (2,25) might open the door to new therapeutic strategies.

Other clinical studies have shown that inhibition of RAS with either ACEI or ARBs results in increasing levels of adiponectin, which is associated with improved insulin sensitivity (69). Results from the Diabetes Reduction assessment with ramipril and rosiglitazone medication (DREAM) trial concluded that among persons with impaired fasting glucose levels or impaired glucose tolerance, the use of rampril did not significantly reduce the incidence of diabetes or death, but did improve normoglycemia (70).

The expert writing group for JNC 8 recommended relaxing of the more aggressive JNC 7 target blood pressures and treatment-initiation thresholds in elderly patients and in patients under age 60 with diabetes and kidney disease. JNC 8 also backs away from the recommendation that thiazide-type diuretics should be the initial therapy in most patients, suggesting an ACE inhibitor, angiotensin-receptor blocker (ARB), calcium-channel blocker (CCB), or thiazide-type diuretic are reasonable choices (47).

Prothrombotic and Proinflammatory States

To reduce thrombotic risk, low-dose aspirin therapy should be initiated or continued in moderately high risk or high risk patients and in those with CVD; consider clopidogrel if aspirin is contraindicated. For

proinflamatory states, there are no specific recommended therapies beyond lifestyle modifications,

CONCLUSIONS

MetS, an integrated epidemiologic concept, is a constellation of risk factors that when present results in increased risk for developing diabetes, CVD, and stroke. When present in subjects with diabetes and CVD, it confers additional risk compared to people without MetS. Central obesity is considered the main component of MetS and the recommended screening tool is waist circumference. Treatment is mainly focused on lifestyle modifications and treatment of the components. New guidelines released provide recommendations on treatment of blood cholesterol, cardiovascular risk assessment, and lifestyle modifications including diet, exercise, and weight management.

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7

Donna M. Polk, MD, MPH

Diabetes Management Guidelines

Type 2 diabetes now affects 25.8 million people (8.3% of the U.S. population) and with the escalating incidence of obesity, it will likely continue to increase both in the United States and around the world (1). The majority of patients with diabetes have type 2 diabetes and are at risk for both microvascular and macrovascular complications. There is often a lag time from the onset of the disease and recognition that contributes to the progression of disease. One-third of persons with diabetes may be unrecognized with the diagnosis made at the time of an acute event such as a myocardial infarction (2). Although microvascular complications are common in patients with diabetes, cardiovascular disease (CVD) accounts for two-thirds of all deaths (3).

Aggressive modification of cardiovascular risk factors in patients with diabetes can reduce both microvascular and macrovascular events and mortality, as seen in the STENO-2 trial (4). In this group with evidence of microalburinuria, those treated with intensive therapy of diet, exercise, smoking cessation, ACE inhibitor, multivitamin, aspirin, HgA1C <7%, BP and lipids at goal showed an absolute risk reduction of 20% for mortality and 29% in cardiovascular events as compared to those receiving conventional therapy (4). Thus, identification and treatment of risk factors in those with diabetes can help reduce the increasing burden of cardiovascular disease in this patient population.

DIAGNOSIS

Diabetes can be categorized into four clinical classes including type 1 diabetes (B-cell destruction and insulin deficiency), type 2 diabetes (insulin resistance and worsening insulin secretion), gestational diabetes, and diabetes secondary to genetic defects, drugs, or other diseases such as cystic fibrosis (5). Traditionally the diagnosis of diabetes has been made from random glucose levels and symptoms, elevated fasting glucose levels, or an abnormal glucose tolerance test (6). Recently the American Diabetes Association (ADA) expanded the diagnostic criteria to include HgA1c> 6.5% (Table 7.1). It is important to recognize the opportunity to make a diagnosis not only in patients with cardiovascular disease but those at-risk individuals (Table 7.2).

PREVENTION OF TYPE 2 DIABETES

Early recognition of individuals at risk for diabetes and sustained efforts aimed at lifestyle modification are important in preventing or delaying the onset of diabetes in high-risk individuals. Those with impaired fasting glucose between 100 mg/dL and 126 mg/dL, 2-hr oral glucose tolerance test of 140 to 199 mg/dl, or an A1C of 5.7% to 6.4% are considered prediabetic and therefore at-risk individuals. Several studies such as the Diabetes Prevention Program showed that lifestyle modification

TABLE 7.1 Criteria for the Diagnosis of Diabetes

Criteria for the Diagnosis of Diabetes
1. Fasting plasma glucose ≥126 mg/dL. (Fasting is defined as no caloric intake for at least 8 hours)*
2. 2-hr plasma glucose ≥200 mg/dL during an oral glucose tolerance test*
3. Random plasma glucose ≥200 mg/dL with classic symptoms of hyperglycemia or hyperglycemia crisis
4. HgA1c ≥6.5%*

*Should be confirmed by repeat testing unless unequivocal hyperglycemia.
Source: Adapted from Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care*. 2010;33:S62–S69.

TABLE 7.2 Criteria for Testing for Diabetes in Asymptomatic Adult Individuals

Criteria
1. Testing should be considered in all adults who are overweight (BMI ≥ 25 kg/m^2*) and have additional risk factors. • Physical inactivity • First-degree relative with diabetes • Members of a high-risk ethnic population (eg, African American, Latino, Native American, Asian American, Pacific Islander) • Women who delivered a baby weighing >9 lb or were diagnosed with GDM • Hypertension (≥140/90 mmHg or on therapy for hypertension) • HDL cholesterol level <35 mg/dL and/or a triglyceride level >250 mg/dL • Women with polycystic ovary syndrome • A1C >5.7%, impaired glucose tolerance, or impaired fasting glucose on previous testing • Other clinical conditions associated with insulin resistance (eg, severe obesity, acanthosis nigricans)
2. In the absence of the above criteria, testing should begin at age 45 years.
3. If results are normal, testing should be repeated at least at 3-year intervals, with consideration of more frequent testing depending on initial results and risk status.

*At risk BMI may be lower in some ethnic groups.
Source: Adapted from Standards of Medical Care in Diabetes-2013. *Diabetes Care*. 2013;36:S11–S66.

significantly reduced the subsequent diagnosis of diabetes in patients with insulin resistance (7). In particular patients were randomized to lifestyle, metformin, or placebo. Those individuals randomized to lifestyle changes including 150 minutes/week of exercise and ≥7% weight loss had a 58% reduction in the development of diabetes as compared to placebo over a 3-year follow-up (7). Those individuals who received the insulin sensitizer metformin had a 31% reduction in diabetes. Other studies have also shown reductions in the diagnosis of diabetes in insulin-resistant individuals with lifestyle modification (8,9) and pharmacologic therapies such as ascarbose (10) in the STOP-NIDDM trial, and rosiglitazone in the DREAM trial (11). Most recently, the Look AHEAD trial, an intensive lifestyle intervention in overweight or obese type 2 diabetics, was halted early because of lack of impact on the cardiovascular outcomes despite greater weight loss and improved glycemic control (11a). Despite the lack of reduction in cardiovascular outcomes, those who maintained weight loss during the nearly 10 years of follow-up had improved quality of life, reduced depression, better mobility and fitness, and reduced urinary incontinence and sleep apnea.

Recommendations from the American Diabetes Association (ADA) are summarized below (5,6).

- At risk individuals should be referred for support program for weight loss
- Weight loss goals of 7% to 15% of body weight
- Dietary fiber (14 g/1,000 kcal)
- Moderate activity of at least 150 min/week
- Follow-up counseling to insure adherence to lifestyle modifications
- Consideration of therapy with metformin in high-risk individuals
- Yearly monitoring for development of diabetes
- Evaluation of and treatment of modifiable CVD risk factors

CARDIOVASCULAR RISK FACTORS

Lipids

Treatment of dyslipidemia in patients with diabetes offers an opportunity to significantly affect cardiovascular mortality in this high-risk population. The lipid profile in patients with diabetes and insulin resistance is characterized by low HDL-C, high triglycerides, and a modest increase in LDL-C which are predominantly small dense particles. These small dense LDL particles are more easily oxidized, enter the arterial wall more readily, are cleared more slowly, and thus are considered more atherogenic. Lifestyle modifications including weight loss and exercise can have a positive effect on lipids, particularly triglyceride and HDL-C levels. LDL-C lowering can be achieved with dietary modifications such as reductions in fat, increased fiber intake, addition of stanol/sterol esters, and pharmacologic therapy. LDL-C lowering remains the primary goal of therapy and statins are the first-line agents used to achieve this goal. Additional agents may be added to achieve LDL-C goals, but data in diabetics are limited. There is an increased risk of complications with combination therapy, particularly with fibrates, and with recent evidence of lack of efficacy in a diabetic population, combination therapy should be used with caution in this patient population (12). Often improved glycemic control can improve secondary targets such as triglycerides and non-HDL-C. The treatment recommendations from the ADA are more aggressive and recommend statins be given to all patients with diabetes regardless of the LDL-C level, and that low HDL-C be a treatment goal. Recent ACC/AHA guidelines recommend that all persons with diabetes without evidence of atherosclerotic cardiovascular disease between the ages of 40 and 75 with LDL levels of 70–189 mg/dL be treated with moderate dose statin therapy (13). This is the equivalent of 10–20 mg of atorvastatin, 5–10 mg rosuvastatin, 40–80 mg pravastatin, or 20–40 mg of simvastatin with the aim to reduce LDL-C by 30–50%. Patients with evidence of atherosclerotic cardiovascular disease, LDL levels ≥ 190 mg/dL, or those with a 10-year risk greater than 7.5% should receive high doses statins with the goal of LDL reduction >50%. High-dose statin therapy is considered 40–80 mg atorvastatin or 20–40 mg of rosuvastatin. The following are goals and treatment recommendations from ADA and ACC/AHA (5,13):

- Fasting lipid profile at least annually (every 2 years for low-risk lipid profiles)
- Moderate dose statin for diabetics aged 40–75 without diagnosed CVD and LDL levels of 70–189 mg/dL
- High-dose statin in persons with diabetes with diagnosed CVD
- High-dose statin with LDL levels ≥ 190 mg/dL
- High-dose statin with 10-year risk greater than 7.5%
- Statins should be prescribed for (ADA)
  - Patients with diabetes and CVD regardless of baseline LDL-C level
  - Patients with diabetes over the age of 40 with at least one additional cardiovascular risk factor

Hypertension

The majority of patients with diabetes also have hypertension with 57.3% in a recent NHANES survey and only 56.9% at blood pressure goal (14). Appropriate treatment of hypertension is essential to reduce microvascular complications such as renal function, but also is an opportunity for significant cardiovascular risk reduction. The recent ACCORD trial in persons with diabetes showed that the group achieving intensive blood pressure control (199/64 mmHg vs. 133/70 mmHg) had no improvement in the composite endpoint of fatal and nonfatal MI and nonfatal stroke (although stroke alone did show benefit), but increased serious adverse events such as syncope and hyperkalemia (15). This has called into question whether tight blood pressure control is appropriate in all diabetics. The following are recommendations from the ADA /AHA and JNC 8 (5,16,17,30):

- Blood pressure goal < 140/80 (ADA and ESH).
- Blood pressure goal < 130/< 80 mmHg for certain individuals such as younger patients (ADA).
- Diastolic BP goal < 80 mmHg (ADA).
- Lifestyle modifications for 3 months in individuals with systolic BP ≥ 120/80 mmHg.
- Lifestyle modifications include: increased physical activity, weight loss, moderation of alcohol consumption, and diet rich in potassium and low in sodium such as DASH diet (18).
- Most patients will require at least 2 agents to meet BP goals.
- If BP goals not met with 3 agents including a diuretic, consider secondary causes of hypertension.
- Initial therapy should include ACE inhibitor or ARB.

Tobacco Use

The concomitant use of tobacco in patients with diabetes further increases their risk of microvascular and macrovascular diseases. Uniform identification of all tobacco users should be performed at each encounter, and smoking cessation counseling should be given to all patients (19).

■ Tobacco use should be identified at all health care encounters.
■ All patients should be advised not to smoke.
■ Willingness to quit should be assessed.
■ Provider should provide assistance or referral for assistance for smoking cessation.

Exercise

Physical activity is considered integral in weight loss, weight maintenance, and glycemic control as well as for improvement in cardiovascular risk factors such as high blood pressure and lipids. Aerobic exercise improves insulin resistance and can be very helpful in glycemic control. Improvements are also seen in the lipid profile, particularly with triglyceride lowering, smaller increases in HDL-C, and little change in LDL-C levels (20). Resistance training can improve body composition and potentially improve glycemic control (21). A combination of cardiorespiratory and resistance exercise is recommended for patients with diabetes and is summarized in Table 7.3 (21). Initially patients should start with low intensity exercise and then increase duration and intensity.

The following restrictions should be considered in patients with diabetic complications (5,21):

■ Diabetic retinopathy: Vigorous exercise may increase risk of vitreous hemorrhage or retinal detachment in patients with proliferative diabetic retinopathy or severe nonproliferative diabetic retinopathy.
■ Peripheral neuropathy: Proper footwear, vigilant surveillance for foot or skin injury, and non-weight-bearing activities for those with injuries or sores.
■ Autonomic neuropathy: Patients with symptoms of autonomic neuropathy are at increased cardiovascular risk and should undergo cardiac evaluation prior to significantly intensifying their exercise regime.
■ Hyperglycemia: Patients with evidence of ketosis should avoid vigorous exercise. Otherwise patients may exercise.
■ Hypoglycemia: If pre-exercise glucose levels are < 100 mg/dL in patients taking insulin or insulin secretagogues, they should ingest additional carbohydrates prior to exercise.

Nutrition

Nutrition can play a key role in both the prevention and treatment of type 2 diabetes. Patients with prediabetes or diabetes should be referred to a registered dietician for medical nutrition therapy. Reductions in HgA1c and LDL-C are seen in patients receiving medical nutrition therapy and are particularly successful when performed over a longer period of time and in a multidisciplinary setting. The following are recommendations for individuals with diabetes (5,22):

■ Patients with diabetes or prediabetes should receive medical nutrition therapy.
■ Weight loss for those overweight or obese.
■ For weight loss low carbohydrate or low fat calorie restricted diets may be used (up to one year).
■ For patients on low carbohydrate diets, monitor lipid profiles, renal function, and protein intake (in patients with nephropathy) and adjust hypoglycemic therapy as needed.
■ Fat intake should be limited to:
  - Saturated fat < 7% of total calories
  - Dietary cholesterol < 200 mg/day
  - Minimal *trans* fat

TABLE 7.3 Exercise Prescription for Patients with Type 2 Diabetes (20)

Mode of Exercise	Frequency	Intensity	Duration	Class and Level of Evidence
Cardiorespiratory (large-muscle activities)	3–7 d/week	Moderate intensity OR:	150 min/week	1 (A)
Cardiorespiratory (large-muscle activities)	3 d/week	Vigorous intensity	90 m/week	1 (A)
Resistance (large muscle group, multijoint exercises)	3 d/week	Moderate to high intensity: 2–4 reps of 8–10 reps at a weight that cannot be lifted > 8–10 times, with 1–2-minute rest periods between sets		

Source: Adapted from Marwick TH, Hordern MD, Miller T, et al. Exercise Training for Type 2 Diabetes Mellitus Impact on Cardiovascular Risk. A Scientific Statement from the American Heart Association. *Circulation*. 2009;119:3244–3262.

- Two or more servings of fish per week.
- No protein restriction in patients with diabetes and normal renal function (high-protein diets are not recommended).
- Diet should include fruits, vegetables, whole grains, legumes, and low-fat milk.
- Monitoring carbohydrate intake which may include utilizing glycemic index or carbohydrate counting.
- Limit alcohol to ≤1 per day for women and ≤2 for men.
- No evidence for supplementation with vitamins, minerals, or chromium.

Glucose Control

Although the incidence of cardiovascular events increases as the A1C increases (18% increase in events for each 1% increase in HgA1c), tight glycemic control has not been shown to reduce macrovascular complications significantly in patients with type 2 diabetes (2,23). Microvascular complications such as nephropathy, neuropathy, and retinopathy are improved with improved glycemic control (2,24). Macrovascular complications in patients with type 1 diabetes, however, are improved with tighter glycemic control (25). Several societies including the ACC, AHA, and ADA have advocated for a target HgA1c of <7% in patients with type 2 diabetes. Tighter control may be appropriate for certain populations such as young or newly diagnosed patients and less stringent control such as <8% may be suitable for those with multiple comorbidities such as cardiovascular disease or those at risk for hypoglycemia.

There are a host of agents used to treat type 2 diabetes as noted in Table 7.4. Metformin is considered the first-line pharmacologic agent in the treatment of type 2 diabetes, but second- and third-line agents should be individualized based on the risk/benefit of each of the medications. Thiazolidinediones (TZDs) include rosiglitazone and pioglitazone. In addition to improved glycemic control, these agents also can increase HDL-C, lower triglycerides, and, although the LDL levels may increase, they appear

TABLE 7.4 Antiglycemic Medications

Drug/Class	Mechanism	Side Effects
Sulfonylureas	• Stimulate insulin secretion	• Hypoglycemia • Weight gain
Metformin (biguanide)	• Decreases hepatic production of glucose • Improves insulin sensitivity	• Risk of lactic acidosis (serum creatinine >1.5 mg/dL) • Avoid at time of iodinated contrast • GI side effects especially diarrhea • No weight gain
Thiazolidinediones (TZDs)	• Peroxisome proliferator-activated receptor agonists • Sensitize peripheral tissues to insulin • Improved lipid profile	• Heart failure • FDA restrictions for use of rosiglitazone
A-Glucosidase Inhibitors (eg, Acarbose)	• Slows down absorption of glucose from intestine	• GI especially flatulence • No hypoglycemia
Glinides (eg, repaglinide)	• Increases insulin secretion	• Hypoglycemia • Weight gain
Dipeptidyl Peptidase 4 Inhibitors (DPP-4 inhibitors) (eg, sitagliptin)	• Increased incretin action (increases insulin, decreases glucagon)	• Low risk of hypoglycemia • No weight gain
Glucagon-Like Peptide-1 Agonists (GLP-1 receptor agonists) (eg, Exenatide)	• Increased incretin action (increases insulin, decreases glucagon) • Delays gastric emptying	• Low risk of hypoglycemia • Weight loss • GI especial initial nausea and vomiting
Colesevelam	• Bile acid sequestrant	• Can increase triglycerides • Constipation

to be larger and less dense. Most recently, the FDA relaxed the prescribing and monitoring restrictions that had been placed on rosiglitazone because of concerns for increased cardiovascular risk. Patients on these drugs do need to be monitored for increase in edema. Alpha glucosidase inhibitors such as acarbose lower postprandial hyperglycemia and often cause weight loss. Meta-analysis of trials in patients with cardiovascular disease treated with acarbose showed significant reduction in cardiovascular events (25a). Most recently, incretin therapies including glucagon-like peptide-1 (GLP-1) and dipeptidyl peptidase IV (DPP IV) inhibitors have been used for improved glycemic control. Weight loss is seen with use of GLP-1 agonists, and improved lipid profiles and blood pressure are seen with GLP-1 and DPP IV therapies. Long-term cardiovascular benefits of these drugs are being evaluated in ongoing trials. Recommendations for glycemic control (5):

- Hg A1C <7%.
- HgA1C <6.5 may be reasonable in patients without significant hypoglycemia, particularly with short duration of type 2 diabetes, long life expectancy, and no significant CAD.
- HgA1C <8% in those with history of severe hypoglycemia, short life expectancy, advances micro-or macrovascular complications, or extensive comorbidities.

RISK STRATIFICATION

In the DIAD study, there was evidence of occult CAD when asymptomatic diabetics were screened, but identification of these individuals by noninvasive testing with myocardial perfusion scanning did not alter outcomes (26). This highlights the dilemma of when asymptomatic patients with diabetes should undergo evaluation for CAD. The guidelines for risk stratification in asymptomatic diabetics vary by society's recommendations. Evaluation for subclincial disease with coronary calcium scoring is considered a IIa indication in asymptomatic adults with diabetes 40 years of age and older (27). The evidence supporting performing stress testing in asymptomatic patients with diabetes is less strong, receiving a class IIb indication. There are special circumstances such as when patients with diabetes beginning a vigorous exercise program that may warrant further evaluation. Guidelines for stress testing before exercise training in asymptomatic patients with diabetes are shown in Table 7.5 (21). Exercise, as opposed to pharmacologic, stress testing is the preferred mode when possible because of the additional prognostic data obtained, as well as the opportunity to provide the patient with an exercise prescription.

TABLE 7.5 Stress Testing Before Exercise in Asymptomatic Patients with Type 2 Diabetes

Stress Testing Not Necessary (All Criteria Should Be Present)	Stress Testing Recommended (if ≥1 Criterion Present)
No clinical history of CAD	History of CAD; no stress test within past 2 years
Asymptomatic	Symptoms of chest discomfort or dyspnea
No evidence of PAD or CVD	Clinical or laboratory evidence of PAD or cerebrovascular disease
ECG normal	ECG evidence of infarction or ischemia
Light to moderate exercise program	Vigorous exercise program

Source: Marwick TH, Hordern MD, Miller T, et al. Exercise Training for Type 2 Diabetes Mellitus Impact on Cardiovascular Risk. A Scientific Statement from the American Heart Association. *Circulation*. 2009;119:3244–3262.

OTHER THERAPIES/INTERVENTIONS

Antiplatelet Therapy

As with any therapy, the risk and benefits of the intervention should be evaluated for each patient. More recent evidence suggests that aspirin is not recommended for primary prevention in low-risk individuals. The ADA/AHA/ACCF have recommended the following (5,28):

- Aspirin for primary prevention (75–162 mg)
  - 10-year CVD risk ≥10% (includes most men ≥50 years and women ≥60 years with one additional risk factor including family history of CVD, hypertension, tobacco use, dyslipidemia, or albuminuria)
  - Not recommended for low-risk patients (10-year CVD risk less than 5%)
  - May be considered for those with diabetes at intermediate risk until further research is available
- Aspirin for secondary prevention in all diabetics
- Clopidogrel 75 mg daily in patients with CAD and documented aspirin allergy
- Combination therapy with aspirin (75–162 mg/day) and clopidogrel (75 mg/day) for up to a year after acute coronary syndrome

Immunizations

The following are recommendations for patients with diabetes (5):

- Influenza:
  - Annual vaccination in all patients with diabetes over the age of 6 months
- Pneumococcal:
  - All diabetic patients 2 years of age or older
  - Revaccination for individuals aged ≥ 65 if they were vaccinated before age 65 or if vaccination was more than 5 years ago
  - Revaccination in patients with nephrotic syndrome, chronic renal disease, or transplantation
- Hepatitis B:
  - All diabetic patients aged 19–59 years
  - Consider in patients ≥60 years

Bariatric Surgery

In a recent meta-analysis, there is normalization of glucose levels in 78% of patients undergoing bariatric surgery and therefore may be an alternative in those unable to attain weight reduction with lifestyle changes (29). Bariatric surgery is an option in patients with diabetes and significant obesity (≥35 kg/m^2) when lifestyle and pharmacologic therapies are not adequate (5).

SUMMARY

With the increasing incidence of diabetes and the higher risk of cardiovascular disease in patients with diabetes, there are ample opportunities for the health care provider to improve outcomes in these at-risk patients. As seen in the STENO-2 trial, aggressive treatment of diabetes and cardiovascular risk factors including hypertension and dyslipidemia resulted in a significant reduction in cardiovascular morbidity and mortality. Identification and treatment of risk factors, lifestyle counseling including exercise and nutrition therapy, and close follow-up of patients with diabetes are keys to reducing cardiovascular events. In addition, identification of prediabetics with a focus on lifestyle changes and risk factor modification can help reduce the increasing burden of diabetes.

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Rohini J. Patel, MPH and
Stanley Bassin, EdD

8

Assessment and Management of Obesity

The United States remains in the grip of a growing obesity epidemic. In 1962, 13% of the population was overweight; within 50 years the number had increased to 33%. Being overweight or obese is the second leading preventable cause of death in the United States, and can be attributed to at least 4% of deaths annually. Physical activity is the most important tool in losing and/or maintaining healthy weight. It is important for patients to not only exercise in the traditional sense (eg, going to the gym) but to increase their daily incidental physical activity (eg, walking or climbing stairs) whenever possible. Even today, there remain countless societal barriers and misconceptions about physical activity and exercise. It is important for physicians to recognize what barriers are present in each individual's everyday life and work with them to develop a routine of physical activity that promotes weight loss and improves his lifestyle.

The heaviest Americans continue to grow heavier and more join their ranks. According to the 2009–2010 National Health and Nutrition Examination Survey (NHANES), 35.7% of U.S. adults were obese and over 30% were overweight (22). These numbers are staggering; half of our country's population lies in the unhealthy weight range. Even more shocking are the numbers for children (Table 8.1), showing that children are headed down the same path to obesity as their parents, with half of the country's children being overweight or obese (23). Evidence shows that obese children are more likely to be obese adults than children of normal weight. Once a rare occurrence, more and more children are being diagnosed with prediabetes and type 2 diabetes and many go undiagnosed.

Over the past century and especially the past 50 years, an accrual of epidemiological evidence has established that the unintended consequence of humankind's predilection for labor-saving is an epidemic of hypokinetically induced cardiovascular disease, morbidity, and mortality. Recommendations for both casual and arranged physical activity (duration, intensity, and frequency) are outlined with a focus on simulating the routine physical activities and increasing energy expenditure similar to our ancestors, whose genome we still largely share today. Furthermore, this chapter reviews the evolution and epidemiology of obesity and current ACC/AHA guidelines for the evaluation and management of obesity.

EVOLUTION OF OBESITY

A large proportion of the chronic diseases beleaguering modern cultures are because of daily physical activity patterns that are profoundly different from those for which we are genetically adapted. The ancestral natural environment in which our current genome was forged via natural selection called for a large amount of daily energy expenditure for living. The environmental demands of survival necessitated

TABLE 8.1 Prevalence of Childhood Overweight and Obesity in the United States

%	Overweight	Obese
Total Sample	33.6	17.1
White	33.5	16.3
Black	35.1	20.0
Hispanic	37.0	19.2

Note: Data collected in 2006, current data reflects similar findings
Sources: Ogden CL, Carroll MD, Curtin LR, et al. Prevalence of high body mass index in US children and adolescents, 2007–2008. JAMA. 2010;303:249–9.

prodigious amounts of physical exertion. Twenty-first century humans are now immersed within an environment explicitly designed to eliminate physical labor through labor-saving devices such as household appliances, elevators instead of stairs, and high technology communication.

Table 8.2 demonstrates that obesity does not affect every American in the same way. The most obese states are in the South and Midwest while the least obese states are in the Northeast and West. Evidence also shows that obesity prevalence is disproportionately greater in blacks, Hispanics, and the socioeconomically disadvantaged compared to whites, Asians, and the wealthy (24). Nevertheless, 49 of 50 states have over 20% obesity and the problem continues to grow across the board (Figure 8.1) (31).

Although obesity is a risk factor for insulin resistance and type 2 diabetes, and a significant risk factor for CVD, not every obese patient is insulin resistant or at high risk of diabetes and CVD (32). This explains why obesity has been an ill-defined modifiable CVD risk factor compared with others such as hypertension, smoking, and cholesterol (high low-density lipoprotein [LDL]/low HDL). But, for any given amount of total body fat, the subgroup of individuals with a selective excess of intra-abdominal, or visceral, adipose tissue is at substantially higher risk of being characterized by insulin resistance and by the features of metabolic syndrome (33–34).

TABLE 8.2 Top and Bottom 10 U.S. States by Obesity

2011 Rank	State	% Obese
Top States		
1	Mississippi	34.5
2	Alabama	33.0
3	West Virginia	32.9
4	Tennessee	31.7
5	Kentucky	31.8
6	Louisiana	31.7
7	Oklahoma	31.3
8	South Carolina	32.0
9	Arkansas	30.9
10	Michigan	31.7
Bottom States		
42	Rhode Island	26.0
43	New Jersey	24.8
44	Montana	23.5
45	Vermont	23.9
46	Utah	23.0
47	Hawaii	23.1
48	Massachusetts	23.6
49	Connecticut	23.0
50	District of Columbia	23.7
51	Colorado	21.4

Note: Geographical data demonstrates obesity linkage to Stroke Belt States
Source: Healthiest State Rankings: Hawaii Tops 2013 List. 2013. http://www.huffingtonpost.com/2013/12/11/healthi-eststate- rankings_n_4412574.html

THE COST OF OBESITY

Overweight and obese individuals are more likely to develop chronic disease risk factors, such as high blood pressure and dyslipidaemia, which develop into chronic diseases, such as type 2 diabetes, heart disease, osteoarthritis, and some cancers (9). Furthermore, overweight or obese individuals can experience complications during pregnancy and even die at an earlier age (9). Medicare and Medicaid paid for approximately one-half of obesity-attributed medical expenditures in 2003 (4). If rates continue to increase at their current levels, health care costs attributable to obesity are expected to be $344 billion in 2018 or over 11% of the gross domestic product. Health care is

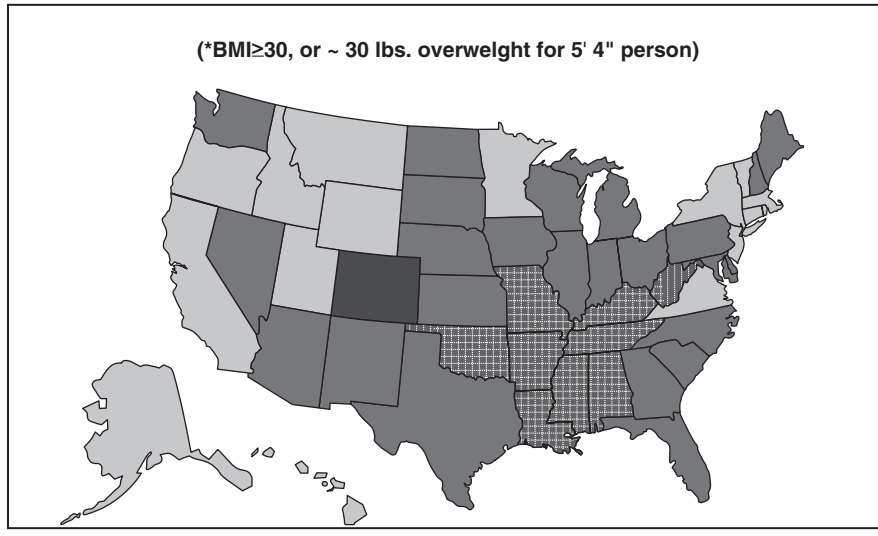

FIGURE 8.1 Obesity prevalence in U.S. adults 2009 dark gray: 15%–19%, light gray: 20%–24%, medium gray: 25%–29%, cross-hatch: ≥30%.
Source: Ogden CL Carroll MD, Kit BK, et al. Prevalence of Obesity in the United States, 2009–2010. NCHS Data Brief No, 82. January 2012.

TABLE 8.3 Top 10 Obesity Costs for U.S. Metro Areas

Metropolitan Area	% Obese	Obesity Cost
New York, NY	21.5	$5,858,908,774
Los Angeles, CA	20.3	$3,734,811,237
Chicago, IL	24.8	$3,395,276,300
Dallas, TX	25.9	$2,386,333,235
Houston, TX	26.1	$2,188,391,505
Philadelphia, PA	25.0	$2,132,158,027
Atlanta, GA	23.2	$1,815,186,415
Detroit, MI	27.0	$1,698,978,098
Boston, MA	21.0	$1,377,016,981
Baltimore, MD	27.4	$1,053,605,650

Source: More Than 15% Obese in Nearly All U.S. Metora Areas. 2012. http://www.gallup.com/poll/153143/obese nearly-metro-areas.aspx

TABLE 8.4 Obesity Attributable Health Care Spending ($/Adult) Top and Bottom Five U.S. States

State	2008 Cost
Least Cost	
Colorado	$235
Connecticut	$279
Virginia	$327
Massachusetts	$296
Rhode Island	$293
Most Cost	
Oklahoma	$417
Ohio	$433
Kentucky	$433
Mississippi	$441
Missouri	$450

Source: Cost of Obesity Report. http://www.fightchronicdisease.org/sites/fightchronicdisease.org/files/docs/CostofObesityReport-FINAL.pdf

rising at a rate of 2.1% greater than the average annual national GDP growth.

Table 8.3 illustrates how much money metropolitan areas could be saving if we reduced the rate of obesity (30). Obesity costs more in areas with higher costs of living, even if the relative prevalence of obesity is low. Table 8.4 demonstrates that the leaner states spend the least on obesity per capita, whereas the weightier states spend almost twice as much (30).

WEIGHT lbs	100	105	110	115	120	125	130	135	140	145	150	155	160	165	170	175	180	185	190	195	200	205	210	215
kgs	45.5	47.7	50.0	52.3	54.5	56.8	59.1	61.4	63.6	65.9	68.2	70.5	72.7	75.0	77.3	79.5	81.8	84.1	86.4	88.6	90.9	93.2	95.5	97.7
WEIGHT in/cm	Underweight					Healthy					Overweight					Obese				Extremely obese				
5'0" - 152.4	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42
5'1" - 154.9	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	36	37	38	39	40
5'2" - 157.4	18	19	20	21	22	22	23	24	25	26	27	28	29	30	31	32	33	33	34	35	36	36	37	38
5'3" - 160.0	17	18	19	20	21	22	23	24	24	25	26	27	28	29	30	31	32	32	33	34	35	36	37	38
5'4" - 162.5	17	18	18	19	20	21	22	23	24	24	25	26	27	28	29	30	31	31	32	33	34	35	36	37
5'5" - 165.1	16	17	18	19	20	20	21	22	23	24	25	25	26	27	28	29	30	30	31	32	33	34	35	35
5'6" - 167.6	16	17	17	18	19	20	21	21	22	22	24	25	25	26	27	28	29	29	30	31	32	33	34	34
5'7" - 170.1	15	16	17	18	18	19	20	21	22	22	23	24	25	25	26	27	28	29	29	30	31	32	33	33
5'8" - 172.7	15	16	16	17	18	19	19	20	21	22	22	23	24	25	25	26	27	28	28	29	30	31	32	33
5'9" - 175.2	14	15	16	17	17	18	19	20	20	21	22	22	23	24	25	25	26	27	28	28	29	30	31	31
5'10" - 177.8	14	15	15	16	17	18	18	19	20	20	21	22	23	23	24	25	25	26	27	28	28	29	30	30
5'11" - 180.3	13	14	15	16	16	17	18	18	19	20	21	21	22	23	23	24	25	25	26	27	28	28	29	30
6'0" - 182.8	13	14	14	15	16	17	17	18	19	19	20	21	21	22	23	23	24	25	25	26	27	27	28	28
6'1" - 185.4	13	13	14	15	15	16	17	17	18	19	19	20	21	21	22	23	23	24	25	25	26	27	27	28
6'2" - 187.9	12	13	14	14	15	16	16	17	18	18	19	19	20	21	21	22	23	23	24	25	25	26	27	27
6'3" - 190.5	12	13	13	14	15	15	16	16	17	18	18	19	20	20	21	21	22	23	23	24	25	25	26	26
6'4" - 193.0	12	12	13	14	14	15	15	16	17	17	18	18	19	20	20	21	22	22	23	23	24	25	25	26

FIGURE 8.2 Body mass index calculator.
Source: J.S. Garrow and W. J. Quetelet's index (W/H2) as a measure of fatness. International Journal of Obesity 1985;9:147–153.

MEASURES OF OBESITY

Body Mass Index

Body mass index (BMI) is the most commonly misused obesity diagnostic measure in doctors' offices. BMI was not meant to be used as a diagnostic tool because gauging a patient's obesity and health risk requires a careful look at their body composition. Nonetheless, BMI is a useful measure when studying populations or when screening patients for obesity. When weighing a patient, it is important to calibrate the scale monthly to be certain the weight is not inadvertently over- or underestimated. Patients should be weighed with as little clothing as possible, and each time the patient is seen in the office, they should be weighed in exactly the same manner. Figure 8.2 is the body mass index calculator and has been controversial due to the arbitrary nature of BMI category cutoffs. For example, it is possible that a healthy weight individual will be classified as overweight because she has a large bone and muscle mass.

Waist Circumference

Abdominal adiposity is a contributor to cardiovascular disease risk and metabolic syndrome. It is important to screen patients using a simple measure, such as waist circumference, because it directly measures how much fat is stored around the abdomen. Waist circumference is measured in the following way: locate the top of the hip bone, place the tape measure evenly around the bare abdomen at the level of this bone, read the tape measure and record the waist circumference in inches. In addition, ensure the tape is snug but does not push tightly into the skin and measure waist circumference after breathing out normally; do not "suck in" the stomach (Figure 8.3) (3). Furthermore, patients can attest to surrogate measures of body composition.

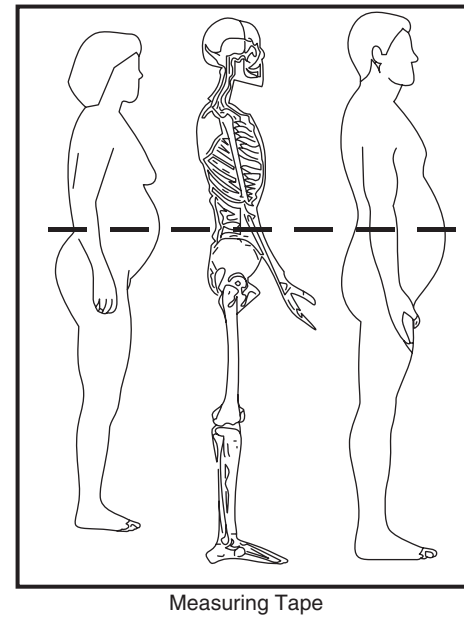

FIGURE 8.3 Measuring tape position for measuring waist circumference.
Source: Waist circumference. McKinley Health Center. University of Illinois at Urbana-Champaign. 2009. http://www.mckinley.illinois.edu/handouts/pdfs/waist_circumference.pdf

Patients losing weight will notice changes in their clothes related to waist circumference. Men will need to use more notches on their belt. Women will notice clothing feeling looser on their hips and thighs.

According to the U.S. Department of Heath and Human Services (HHS) the following individuals are at increased risk for developing chronic diseases: women with a waist circumference more than 35 inches and men with a waist circumference of more than 40 inches. However, the World Health Organization, due to recent research findings, has recommended lower thresholds for waist circumference for Asian populations. Therefore, those at increased risk for developing chronic disease include Asian women with a waist circumference of more than 31 inches and Asian men with a waist circumference of more than 35 inches.

The evaluation of body composition offers quantification of the body's major structural components. Because there are marked age and sex differences in body composition there are more or less complicated measures to obtain body density. The three most popular and indirect methods are hydrostatic weighing, prediction methods from skinfolds and circumferences, and bioelectrical impedance (BIA). Dual energy x-ray absorptiometry (DEXA) is considered very safe because the low-dose radiation requires virtually no cooperation from the patient and has been considered the highest standard today. All of them have limitations, but for research purposes a combination of all four methods would be the "gold standard" (35–36).

OBESITY AND HEART DISEASE

The Framingham risk score is used to identify high-risk individuals, defined by a 10-year risk greater than 20% (13–15). However, Framingham risk assessment does not include measures of obesity and therefore surrogate risk measures including BMI and waist circumference are analyzed. Obesity measures based on BMI are categorized in three classes: BMI of 30 to 34.9 is class I, BMI of 35 to 39.9 is class II, and BMI ≥40 is class III. Waist circumference measurements are categorized differently with cut points indicating greater risk for diabetes, hypertension, dyslipidemia, and CVD. These cut points are >102 cm in men and >88 cm in women. Both BMI and waist circumference have been associated with type 2 diabetes and obesity alone has been shown to double the risk of heart failure (16).

A study with over 130,000 participants over the course of nine years assessed the relationship between BMI and CHD incidence and found that even after adjustment for standard risk factors, a unit increase in BMI was correlated with a 14% higher risk of CHD (17). A similar analysis using the Nurses' Health Study determined a linear relationship between BMI and CHD (18). The Women's Health Initiative found that in both white and black women, overweight and obese women were associated with CHD incidence (19).

The Framingham Heart Study, which followed over 5,000 individuals for over 40 years linked CVD risk to obesity. Analysis of Framingham data showed that obesity increased an individual's risk for not only CVD, but also risk factors such as diabetes, hypertension, and hypercholesterolemia (20). Finally, a study of 17,000 nurses established that nurses who were obese at around 50 years of age were approximately 79% less likely to be healthy by 70 years of age (21).

According to the HOPE Study, men and women in the highest tertile of waist circumference have a 29% greater risk of CVD mortality compared to the lowest tertile. Abdominal obesity is independently associated with CVD (Figure 8.4). The endocrine activity of abdominal fat cells can cause dyslipidemia, hypertension, glucose intolerance, and insulin resistance, all of which contribute to cardiometabolic risk. Intra-abdominal adipocytes are more akin to endocrine organs than storage cells.

PHYSICAL ACTIVITY COUNSELING: A WEIGHTY PROBLEM

Currently, physical activity counseling by physicians is meager in the United States for many well-known reasons (Figure 8.5). Lack of effort has been a contributing factor to our national weight problem. As a physician, do you feel comfortable counseling the families of obese children or adults on what physical activity modifications are safe for them to implement in order to increase energy expenditure? The treatment theme that has been most successful is one of energy balance. Increasing energy expenditure and reducing energy intake should be the patient's goal. Increasing incidental physical activity in conjunction with recommended physical activity programs is the recommended approach. The hard work can be accomplished by reduced energy intake through moderating sedentary activity, portion size, sweetened beverages, and snacking. Reducing energy intake includes energy intake while watching TV or using the computer or mobile devices is a necessity. Decrease sedentary activity to 3 hours or less per day (excluding work). Furthermore, limiting "screen time" to 3 hours daily (excluding work) may be beneficial as research has shown that Americans now spend most of their screen time with the computer and mobile devices rather than the TV (25).

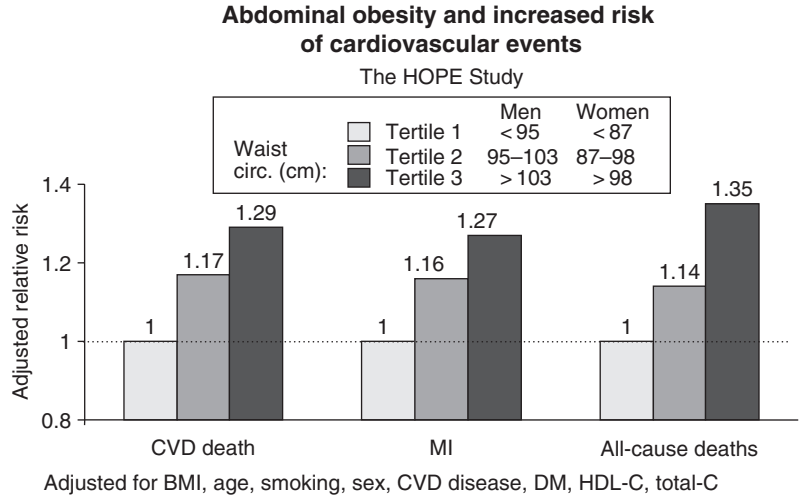

FIGURE 8.4 The HOPE Study.
Source: GR1 Dagenais, Q. Yi, J. F. Mann, J. Bosch , J. Pogue, and S. Yusuf, Prognostic impact of body weight and abdominal obesity in women and men with cardiovascular disease. *Am Heart J*. 2005;Jan;14954-60.

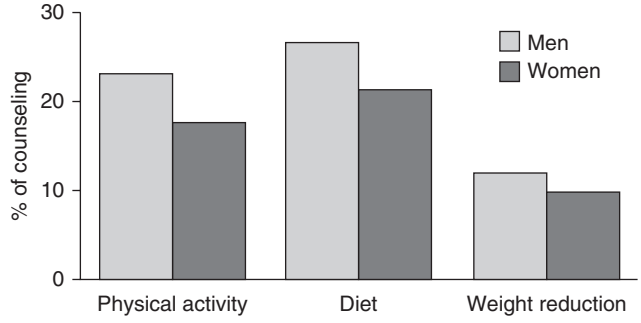

FIGURE 8.5 Percentage of physician counseling time by topic.
Source: B.M. Pinto , M.G. Goldstein , J.D. DePue , and F.B. Milan. Acceptability and feasibility of physician-based activity counseling. The PAL Project. *Am J Prev Med*. 1998;15:95–102.

MOTIVATIONAL INTERVIEWING

The goal of Motivational Interviewing (MI) is to improve healthy habits overall by focusing on a vigorous lifestyle that features healthy eating and physical activity (26). One example, treatment spirit, is defined by engaging your patient using collaboration, evocation, and autonomy. Collaboration includes acting as the patient's guide on the journey to a physically active life, as well as exploring and supporting what the patient can and is willing to accomplish. Collaborators must avoid persuasion and be open to ideas from the patient as well as be willing to negotiate with the patient in order for her to set her own goals. The clinician generally lacks lifestyle expertise, but can be the coach in improving the patient's health. Evocation involves focusing on the behavior change the patient is willing to do and providing continuous personal reinforcement. Additionally, evocation elicits the patient's ideas about change in his life and builds a time and a timetable regarding his daily incidental and recommended physical activity. Finally, autonomy deals with reinforcing ultimately any healthy behavior as a step toward the goal and accepting that the patient may not choose to change at this time. Finally, physicians should be aware of recommending physical activity just as they might prescribe a drug; patient education has to be provided by the physician to her staff and the patient (Table 8.5).

TABLE 8.5 Comparison of Exercise and Medication

Parameter	Exercise	Drugs
Type	Aerobic, anaerobic, stretch, relaxation, flexibility, coordination, toning	Antibiotics, analgesics, anti-inflammatories, sedatives, antidepressants, hormones
Frequency	1–3 times/day, 7 days a week	1–3 times/day, 7 days a week
Duration	Lifetime	Short-term or lifetime
Time of Day	Various	Various
Contraindications	Illness, pain	Allergy, rash, polypharmacy, other diseases
Side Effects	Overuse injuries to muscles, tendons, or ligaments; joint injury; fatigue	Organ damage, anemia, gastrointestinal symptoms, drowsiness, etc.
Patient Education	Required	Required
Compliance	Variable	Variable

Source: Nieman DC. Exercise Testing and Prescription A Health Related Approach. 4th ed. 1999. Mayfield. Mountain View California

PUTTING TOGETHER A PROGRAM FOR YOUR PATIENT

The following seven steps are the procedure for creating an energy expenditure program for your patient.

- Step 1: Obtain history from childhood to today of their perceived body weight including a Physical Activity Readiness Questionnaire. Additionally, consider how much time she can set aside for daily activity for energy expenditure and what activities she enjoys presently.
- Step 2: Set body weight goals first and clothes size later with the patient during your appointment/counseling and develop rapport and a sense of trust.
- Step 3: Select activities, incidental and treatment, that the patient would have accessibility to and be able to enjoy, increasing energy expenditure.
- Step 4: Set targets for each activity including focusing on increasing energy expenditure.
- Step 5: Review the goals that were established by what the patient was willing to undertake and reinforce accomplishments and achievement and think about raising the bar for the next visit by increasing duration, frequency, and intensity.
- Step 6: Begin the obesity reduction program by giving the patient a pedometer to record walking energy expenditure per day.
- Step 7: The patient will record activity, return the log, and assess the progress in the next appointment.
- Step 8: Review patient body weight and counsel patient's progress on meeting goals.

Patient recommendations include ideas for incidental activity, for example, parking far away, taking the stairs, avoiding valet service, and getting off the bus earlier and walking the remainder of the way. Dosage must be assessed carefully; take baby steps at first and increase intensity from the baseline. A good measure of intensity and perceived exertion is whether the patient can carry on a conversation or count out loud. If he cannot, he needs to decrease intensity of the activity until he can. Duration can be altered by increased physical activity time if the patient prefers, up to 60 minutes per day, 6 days per week. The patient can perform these activities in separate blocks of time as long as the total time amounts to 60 minutes per day. Furthermore, age; gender; behavior such as lifestyle, habits, and schedules (work/home); family/community barriers; risks; cardiovascular health; and musculoskeletal status must be assessed.

An assessment of baseline activity and physical condition can be done through PAR-Q, questionnaire, surveys, and the Bruce protocol stress test. The Bruce protocol stress test includes heart rate and rating of perceived exertion, which are taken every minute and blood pressure every three minutes (Table 8.6). The test has been modified for sedentary and elderly patients and can be cross-referenced with target heart rate by age (Figure 8.6). It begins at a lower workload compared to the standard test. Here, the first level is performed at 0% incline and 2.74 km/h. The second level is done at 5% incline and 2.74 km/h. The third level matches the first level of the Standard Bruce Protocol Test (10% incline).

TABLE 8.6 Bruce Protocol (Maximal) Stress Test for Treadmill

Stage	Minutes	% Grade	Km/h	MPH	METS
1	3	10	2.7	1.7	4
2	6	12	4	2.5	6.6
3	9	14	5.4	3.4	9.1
4	12	16	6.7	4.2	12.9
5	15	18	8	5	15
6	18	20	8.8	5.5	16.9
7	21	22	9.6	6	19.1

Source: Nieman DC. Exercise Testing and Prescription A Health Related Approach. 4th ed. 1999. Mayfield., Mountain View California

Assessment of appropriate physical activity can also be divided by visual and behavioral. Visual includes observation of how clothing fits, distribution of fat, and posture. Ask about body fat loss and if female clothing size has changed and for males, if belt size has changed. In addition, develop a framework for qualitative assessment. Behavioral assessment involves patients setting specific, reasonable, and attainable goals. Goals should stem from the idea of becoming more healthy as a facet of improving overall lifestyle (Figure 8.7).

Monitoring the patient involves weighing the patient at every visit. Waist circumference should be measured bimonthly and patient logs kept (Table 8.7). Some body composition changes should be expected within 3 months. If they are compliant, there should be an 8–12 lb. (about a pound a week) weight loss within 3 months, especially a reduction in abdominal obesity. The patient's clothes should feel looser at the waist area. If the patient is losing considerably more, then a thorough inquiry is suggested.

Barriers will exist and patients should reduce and perhaps eliminate contributors to a sedentary lifestyle (TV, computers, elevators). Additionally, take note that family, friends, and work associates, may not understand a patient's desire to be more physically active. Figure 8.8 includes examples of activities in which patients should partake.

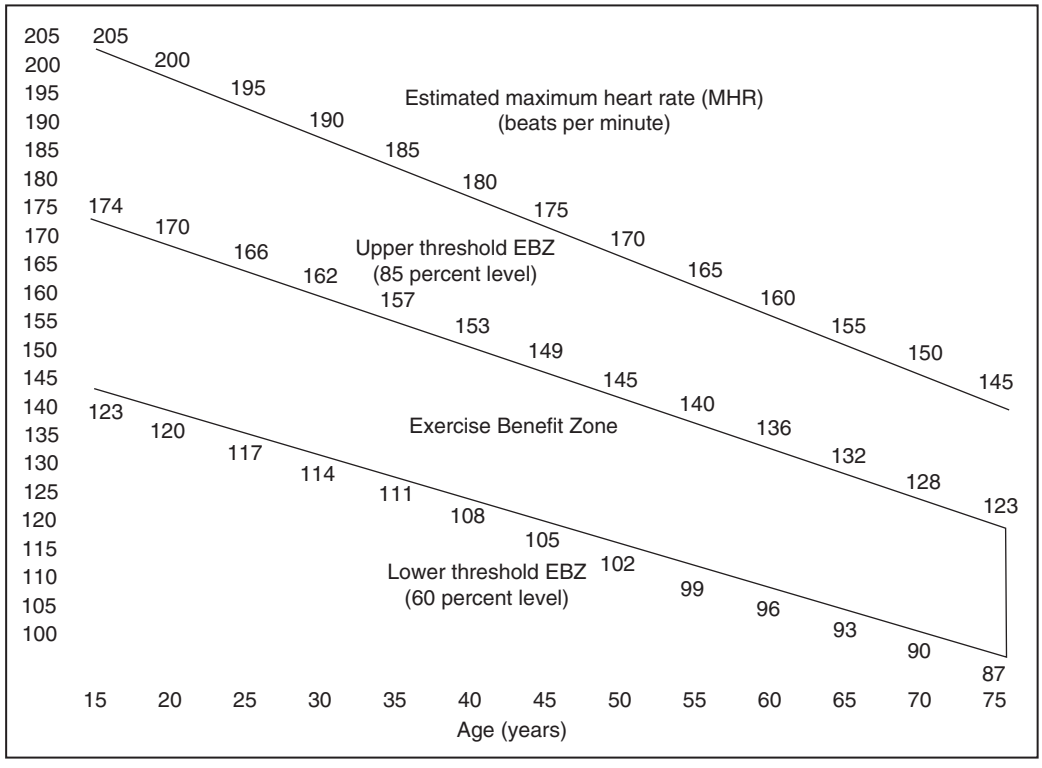

FIGURE 8.6 Longitudinal examination of age-predicted symptom-limited exercise maximum heart rate, target heart rates by age.
Source: W.R. Thompson, N.F. Gordon, and L.S. Pescatello, American College of Sports Medicine. *ACSM's Guidelines for Exercise Testing*. 8th ed. Philadelphia: Lippincott Williams & Wilkins. 2010.

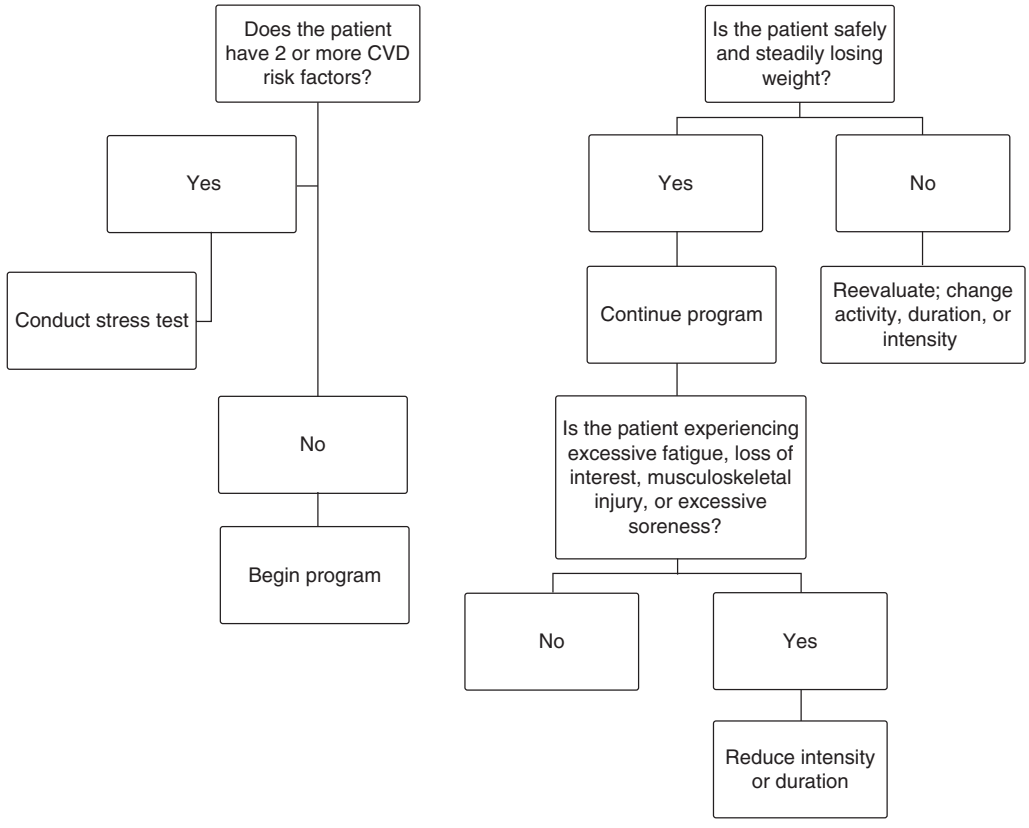

FIGURE 8.7 Assessment of appropriate physical activity.
Source: W.R. Thompson, N.F. Gordon, and L.S. Pescatello, American College of Sports Medicine. *ACSM's Guidelines for Exercise Testing*. 8th ed. Philadelphia: Lippincott Williams & Wilkins. 2010.

ADJUSTING THE PROGRAM

In children and young adults, the Young Finns Study ($n = 2{,}358$ aged 9–24) showed level of physical activity positively related to HDL-C and negatively associated with triglycerides, Apo lipoprotein B, and insulin levels in males (but only triglycerides in females) (27). The Pawtucket Heart Study showed estimated maximal oxygen consumption and self-reported physical activity related to blood pressure, BMI, and HDL-C (28). A study of 3,331 Japanese men showed frequency of physical activity related to HDL-C and number of risk factors: those who exercised 1, 2, and ≥3 days per week had 1.38, 1.19, and 0.99 risk factors (28). The PEPI study showed in 851 postmenopausal women self-reported physical activity positively associated with HDL-C and inversely related to insulin and fibrinogen (29). Figure 8.9 gives the ACSM evidence categories.

Adaptability and adjustments include something the patient enjoys that can be made progressively more or less intense. Progressively overload to increase intensity and reduce the load to reduce intensity. Intensity can be characterized using qualitative terms such as light, moderate, hard, or strenuous. Estimated energy expenditure can be calculated in metabolic equivalents (METS), a ratio of the metabolic rate during activity to resting metabolic rate: vigorous work-related activities (lifting heavy loads, heavy construction) 8.0, jogging, running, cross-country skiing 8.0, swimming, other vigorous water activities 6.0, less strenuous home maintenance, gardening 5.0, and bowling or golf 3.5. Direct monitoring requires behavioral observation or the use of mechanical or electronic devices, or physiologic measures such as calorimetry. Self-reporting techniques include diaries detailing physical activity in a given period, logs providing a record of specific activities, recalling surveys useful in large populations, retrospective quantitative history, and global self-reports. Finally, frequency of contact includes face-to-face contact at least once every 2 months to ensure progress and long-term follow up via phone with doctor or nurse including videoconferencing if possible (eg, Skype/FaceTime).

TABLE 8.7 Example Walking Schedule

Week	Workout 1	Workout 2	Workout 3
1	Slow five-minute warm-up walk. Then alternate 60 seconds of moderate and 90 seconds of fast walking for a total of 20 minutes.	Slow 10-minute warm-up walk. Then alternate ten minutes of brisk walking for a total of 30 minutes.	Slow 10-minute warm-up walk. Then 15 minutes of moderate walking, 20 minutes of brisk walking for a total of 45 minutes.
2	Slow five-minute warm-up walk. Then alternate 60 seconds of moderate and two minutes of fast walking for a total of 20 minutes.	Slow 10-minute warm-up walk. Then alternate ten minutes of brisk walking for a total of 30 minutes.	Slow 10-minute warm-up walk. Then 15 minutes of moderate walking and 25 minutes of brisk walking for a total of 50 minutes.
3	Slow five-minute warm-up walk, then do two repetitions of the following: • Moderate walk for 90 seconds • Brisk walk for 90 seconds • Brisk walk for 3 minutes • Moderate walk for three minutes Total 20 minutes	Slow 10-minute warm-up walk, 18 minutes of moderate walking, 12 minutes of brisk walking. Total 40 minutes	Slow 10-minute warm-up walk, then 20 minutes of moderate walking followed by 30 minutes of brisk walking. Total 60 minutes.
4	Repeat above schedule for the rest of the week	Repeat last schedule	Repeat last schedule for the next 4 sessions
5		Walk 1.5 miles at own pace	Walk 3 miles at own pace
6		Walk 2 miles at own pace	Walk 3.5 miles at own pace
7		Walk 2 miles at own pace	Repeat last schedule
8		Walk 2.5 miles at own pace	Walk four miles
9		Walk 2.5 miles at own pace	The final workout! Congratulations!

Note: Effective Walking Program
Source: Nieman DC. Exercise Testing and Prescription A Health Related Approach. 4th ed. 1999. Mayfield. Mountain View California

Deconditioning

Getting back on track is important because even a few weeks' break can reduce flexibility, strength, and endurance. Some patients overdo it when they resume either due to guilt or perceived strength. Patients should begin reconditioning if they have been away from their program for longer than 2 weeks (age, gender) by returning to the approximate range of 40–60% of their intensity when the program was discontinued. Add 10–15% each week until she reaches the threshold when she discontinued. Delayed onset muscle soreness is to be expected when resuming a program. For travel, the ACSM has several recommendations (1). Exercise in the vicinity of your lodging or hotel; ask staff for running routes, however, always be careful in unfamiliar areas. Additionally, pack equipment such as resistance bands and jump ropes, plan extra time for exercise, take colleagues out for a walk for business meetings, and walk and stretch on airplanes/buses and in the airport. AAOS Safety Guidelines include using proper equipment, balanced fitness, warm up, stretch, take time, drink water, cool down, and rest (2). First-aid techniques include resting the injury; icing it to lessen swelling, bleeding, and inflammation; applying a compression bandage to limit swelling; and elevating the injury above heart level to reduce swelling.

AHA AND ACC GUIDELINES FOR MANAGEMENT OF OBESITY

The 2013 AHA and ACC recommendations include that all Americans should engage in regular physical activity at a level appropriate to their capacity, needs,

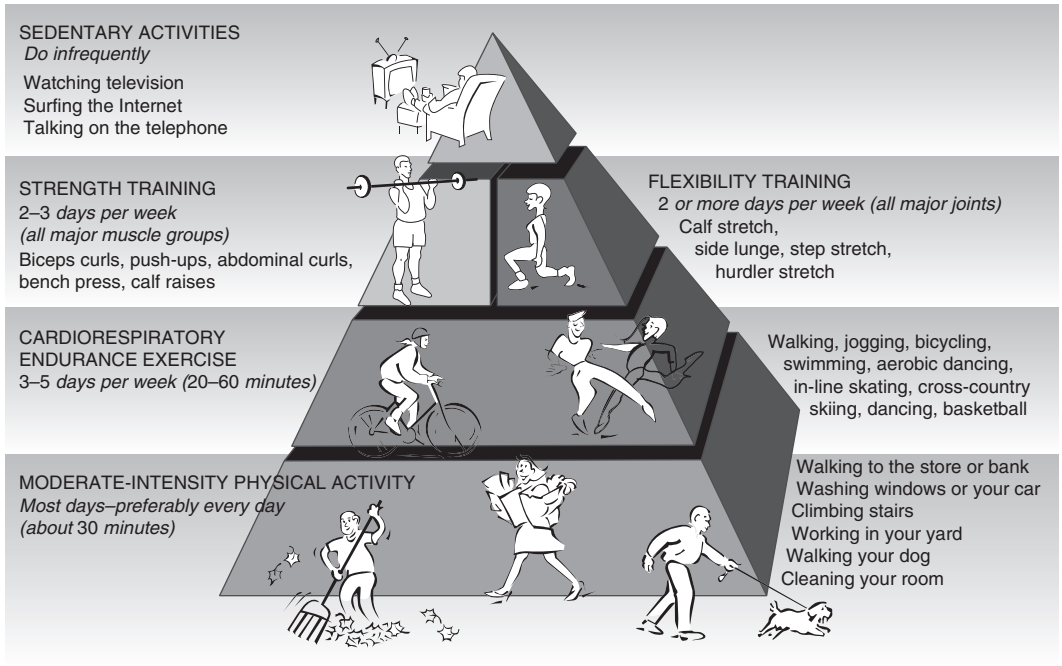

FIGURE 8.8 Exercise pyramid. Proportion of physical activity dedicated to each category.
Source: W.R. Thompson, N.F. Gordon, and L.S. Pescatello, American College of Sports Medicine. *ACSM's Guidelines for Exercise Testing.* 8th ed. Philadelphia: Lippincott Williams & Wilkins. 2010.

and interests. Regular physical activity has been shown to improve both lipid levels and blood pressure. It is recommended for individuals to engage in aerobic activity 3 to 4 times a week, with each session lasting approximately 40 minutes at moderate to vigorous level intensity (11,12). In addition, overweight and obese adults should participate in 6 months of increased physical activity until weight loss maintenance is achieved, which transitions into 200–300 minutes of physical activity each week (11,12).

Several strategies exist for weight loss including dietary changes to decrease both food and calorie intake. The first option is a 1,200 to 1,500 kcal/day diet for women and 1,500 to 1,800 kcal/day diet for

I. ACSM Evidence Categories

Evidence Category	Source of Evidence	Definition
A	Randomized, controlled trials (overwhelming data)	Provides a consistent pattern of findings with substantial studies
B	Randomized, controlled trials (limited data)	Few randomized trials exist, which are small in size and results are inconsistent
C	Nonrandomized trials, observational studies	Outcomes are from uncontrolled, nonrandomized, and/or observational studies
D	Panel consensus judgment	Panel's expert opinion when the evidence is insufficient to place it in categories A–C

II. ADA Evidence-Grading System for Clinical Practice Recommendations

Level of Evidence	Description
A	Clear evidence from well-conducted, generalizable, randomized controlled trials that are adequately powered, including the following: • Evidence from a well-conducted multicenter trial • Evidence from a meta-analysis that incorporated quality ratings in the analysis Compelling nonexperimental evidence, i.e., the "all-or-none" rule developed by the Centre for Evidence-Based Medicine at Oxford Supportive evidence from well-conducted randomized controlled trials that are adequately powered, including the following: • Evidence from a well-conducted trial at one or more institutions • Evidence from a meta-analysis that incorporated quality ratings in the analysis
B	Supportive evidence from well-conducted cohort studies, including the following: • Evidence from a well-conducted prospective cohort study or registry • Evidence from a well-conducted meta-analysis of cohort studies Supportive evidence from a well-conducted case–control study
C	Supportive evidence from poorly controlled or uncontrolled studies, including the following: • Evidence from randomized clinical trials with one or more major or three or more minor methodological flaws that could invalidate the results • Evidence from observational studies with high potential for bias (such as case series with comparison to historical controls) • Evidence from case series or case reports Conflicting evidence with the weight of evidence supporting the recommendation
E	Expert consensus or clinical experience

FIGURE 8.9 ACSM evidence categories.
Source: W.R. Thompson, N.F. Gordon, and L.S. Pescatello, American College of Sports Medicine. *ACSM's Guidelines for Exercise Testing.* 8th ed. Philadelphia: Lippincott Williams & Wilkins. 2010.

men (11,12). The second option is a general reduction in kcal/day by either 500 for women or 750 for men (11,12). The final option is to follow an evidence-based diet to reduce high-carbohydrate, low-fiber, or high-fat foods (11,12).

Furthermore, several lifestyle interventions and counseling options exist as well. Patients should be advised to participate in comprehensive lifestyle programs for greater than six months that follow low-calorie diets and increased physical activity by behavioral strategies (11,12). A second option includes high-intensity interventions for over 14 sessions in six months either individually or in a group (11,12). Third, weight loss programs by a trained interventionist can be delivered either electronically or over a phone. However, these mediums result in smaller weight loss than person-to-person sessions. Commercial-based programs can be followed as well as long as their safety and efficacy can be proven through peer-reviewed evidence. Fifth, extremely low calorie diets of less than 800 kcal/day can only be administered under limited circumstances and when the individuals will

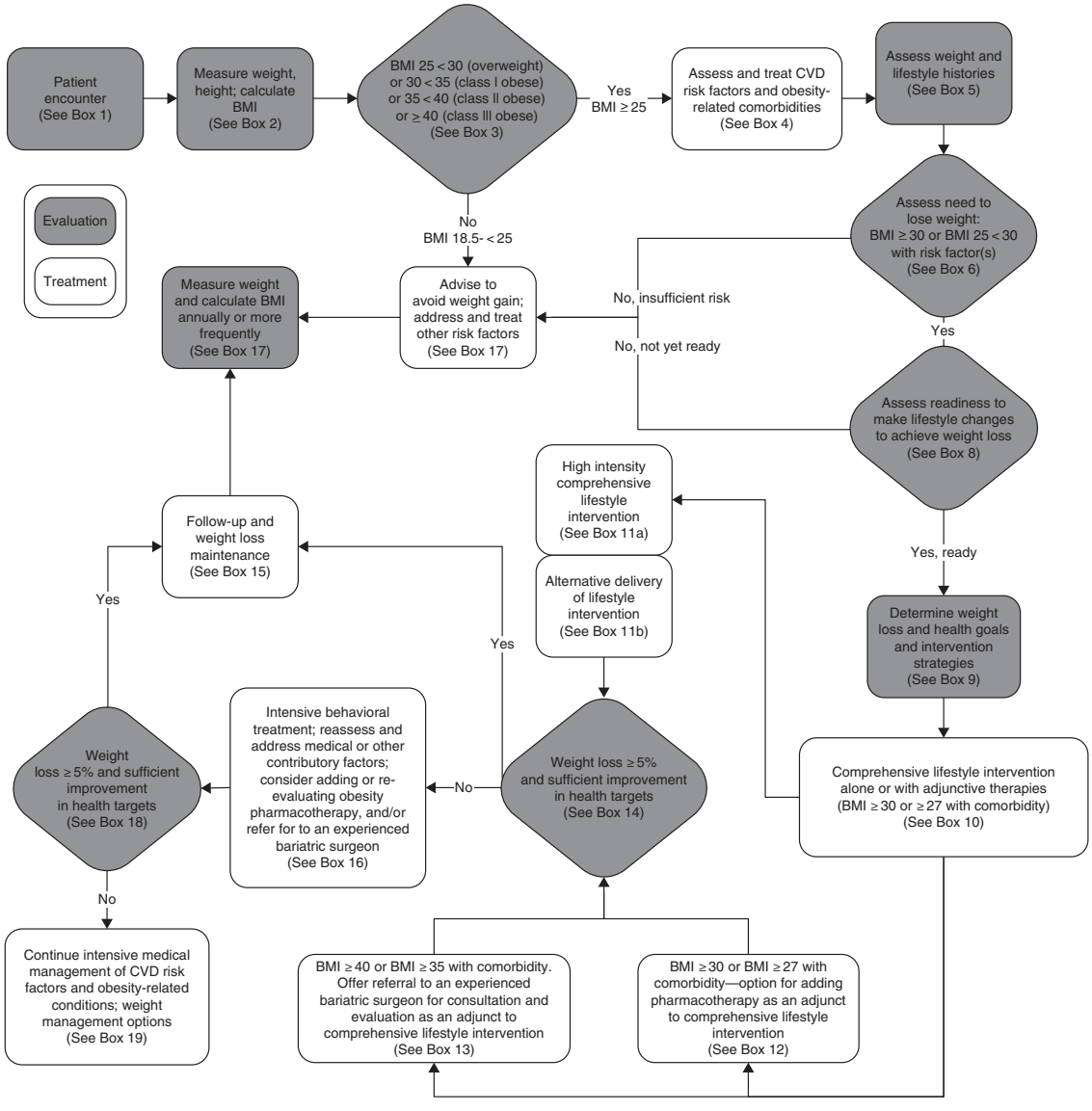

FIGURE 8.10 Treatment algorithm for overweight and obese patients.
Source: M.D. Jensen, D.H. Ryan, C.M. Apovian, C.M. Loria, J.D. Ard, B.E. Millen, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults. *J Am Coll Cardiol*. (2013), Figure 1 on page 19. doi: 10.1016/j.jacc.2013.11.004.

be in a medical monitoring center for possible complications (11,12). Sixth, patients should be encouraged to participate in weight-loss programs for over a 1 year in duration. Finally, maintenance can be achieved through monthly contact, either in person or over the phone, with a trained interventionist. The interventionist should motivate individuals to participate in 200–300 minutes of physical activity per week, monitor their weight weekly, and consume a low-calorie diet.

Finally, the last criterion is determining which patients should undergo bariatric surgery as a treatment for their obesity. Adults with a BMI ≥35 with obesity-derived comorbidities or BMI ≥40 who have not responded to behavioral treatments or pharmacological measures are advised to consult with a bariatric surgeon (11,12). Bariatric procedures for individuals with a BMI <35 have resulted in insufficient evidence (11,12). Finally, patients should understand that bariatric procedures are determined based on common risk factors, behavior, and psychosocial factors.

Figure 8.10 represents the AHA/ACC treatment algorithm for overweight or obese individuals. The following information provides details on the steps of the flowchart:

- Box 1: Patient's weight must be assessed to determine overweight or obesity by primary care physician.
- Box 2: BMI is calculated manually or electronically.
- Box 3: BMI classification into one of four categories, overweight, class I obese, class II obese, and class III obese.
- Box 4: Assess for CVD risk factors and obesity-related comorbidities through physical examination, clinical assessment, and laboratory assessment.
- Box 5: The clinicians must assess weight and lifestyle history to determine the origins, contributory factors, and potential successes and difficulties involving weight loss.
- Box 6: Weight loss is needed if BMI ≥30 or BMI 25< 30 with additional CVD risk factors.
- Box 7: Individuals are advised to avoid weight gain.
- Box 8: Physician must assess individual's readiness to make lifestyle changes in order to lose weight as well as identify potential barriers.
- Box 9: Weight-loss goals and health goals must be determined as well as intervention strategies.
- Box 10: Assess weight-loss options of lifestyle intervention alone or with adjunctive therapies.
- Box 11: Refer to high-intensity comprehensive lifestyle interventions and alternative lifestyle interventions.
- Box 12: Potential addition of pharmacotherapy.
- Box 13: Refer to bariatric surgeon.
- Box 14: Assessment of goals.
- Box 15: Weight-loss maintenance.
- Box 16: More intensive treatment if individuals unable to lose enough weight or meet goals.
- Box 17: BMI measurement annually.
- Box 18: Assessment of goals.
- Box 19: Continue management of CVD risk factors and obesity related comorbidities.

SUMMARY

Lifestyle modification is essential in reducing obesity's contribution to cardiometabolic risk. Focusing on diet, physical activity/exercise, stress, and smoking alone can delay or prevent the onset of cardiometabolic disease. Increasing physical activity will continue to be one of the easiest and most effective tools in the fight against obesity in the future. Furthermore, the AHA and ACC guidelines must be incorporated and referenced in order truly to initiate a decrease in the obesity epidemic.

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Henry G. Cheng, MD,
Seth S. Martin, MD,
and Steven R. Jones, MD

9

Novel Biomarkers and Risk Factors

Low-density lipoprotein cholesterol (LDL-C) has been the primary target of lipid-lowering strategies to reduce cardiovascular disease (CVD) risk. Significant residual CVD risk remains despite successful lowering of LDL-C levels (1). This residual risk is often seen in patients with metabolic syndrome or diabetes (2). In an effort to identify patients with residual CVD risk, the NCEP ATP III and joint ACC/AHA blood cholesterol management panels examined non–high-density lipoprotein cholesterol (non-HDL-C) as a secondary therapeutic target (3,4). Several studies have supported the inclusion of non-HDL-C as a therapeutic target by demonstrating its superiority over LDL-C as a marker of CVD risk. However, implementation of non-HDL-C measurement and treatment goals has been poor (5). Intense interest in advanced lipoprotein testing has emerged to identify biomarkers that are elevated in this residual CVD risk population who are undertreated by traditional LDL-C targeted therapies. Biomarkers such as lipoprotein (a) [Lp(a)], high-sensitivity C-reactive protein, LDL particle concentration, apolipoproteins A and B, and lipoprotein-associated phospholipase A_2 are emerging as the next-generation biomarkers to assess CVD risk. Currently, the new ACC/AHA guidelines have not introduced significant changes in biomarker recommendations (4). The ACC/AHA Risk Assessment guidelines do note it as one of the tests that can be performed if the treatment decision based on global risk assessment is uncertain, and that levels of >2 mg/L can be used to restratify patient risk (4a).

LIPOPROTEIN(a)

Lipoprotein(a) [Lp(a)] was first described by Berg in 1963 as an antigenic variant of LDL. It is composed of an apolipoprotein (a) particle covalently linked via a disulfide bond to the apolipoprotein B of a low-density lipoprotein (LDL)-like particle (6–8). Since its discovery, many epidemiological studies have examined its association with cardiovascular disease, sparking a growing interest in its pathogenesis (1,6,9–13). ATP III classified it as an emerging risk factor in 2001 (3).

Genetics of Lp(a)

Lp(a) is a dense protein (1.050–1.080 g/mL) synthesized by the liver. Plasma concentrations of Lp(a) are dependent upon the *LPA* gene, which codes for the apolipoprotein(a) particle. Apolipoprotein(a) is structurally similar to plasminogen due to the location of *LPA* near *PLA* on chromosome 6q26. Apo(a) and plasminogen both contain several repeating kringle (K) domains. Apo(a) contains K–$IV_{1\text{-}10}$ and plasminogen contains K–I to K–V. Apo(a) isoform size is determined by the number of K–IV_2 repeats (6,7,13,14). Plasma Lp(a) concentration is generally inversely related to Apo(a) isoform size (small isoform size is associated with higher plasma concentrations and increased CVD risk).

Lp(a) and CVD Risk

In the general population, there is a less than a thousandfold variability in plasma Apo(a) size and Lp(a) concentration, making it very difficult to establish CVD risk tertiles (1). Recent studies have suggested that Lp(a) cholesterol >10 mg/dL, mass >25 mg/dL, or molar concentrations >70 nmol/L—each representing approximately the 75–80th population percentile—independently predict excess CVD risk in the presence of other CVD risk factors. Several studies have examined the relationship between apo(a) isoform size, plasma concentration, and CVD risk across different ethnicities. In Caucasian populations, small apo(a) isoforms of <22 K–IV_2 repeats were associated with high plasma concentrations of Lp(a) and increased CVD risk. Compared to the black population, whites tended to have a smaller isoform size and higher CVD risk despite similar Lp(a) concentration (1,9,10,13). This suggests that apo(a) isoform size may have a stronger association with CVD than plasma Lp(a) levels. Studies have also indicated that small isoform size may be an independent risk predictor of CVD in men but not women regardless of ethnicity (15). In postmenopausal women not receiving hormone replacement therapy, elevated levels of Lp(a) >80th percentile were associated with excess risk when accompanied by LDL-C greater than median levels, >121 mg/dL. Lp(a) was not associated with excess risk in women treated with hormone replacement therapy (16).

Although Lp(a) levels are in large part heritable, nephrotic disease and diabetes mellitus have been shown to increase plasma Lp(a) concentrations markedly (1,2). This is likely caused by increased synthesis of apo(a) in these patients, and not due to impaired excretion caused by renal disease. Contrary to patients with normal renal function, patients on hemodialysis with elevated Lp(a) levels tend to have large isoform sizes. Lp(a) concentration increases with poor glycemic control (2).

There have been several proposed mechanisms by which Lp(a) causes CVD but the studies were limited by the variability in their study design, sample collection and analysis, and Lp(a) isoforms (10,13,15,17). Analysis of culprit lesions from patients with unstable angina showed Lp(a) deposition in the atherosclerotic plaques at levels proportional to circulating plasma Lp(a) (18). Lp(a) is structurally similar to LDL, which facilitates its deposition in atherosclerotic lesions where it binds the extracellular matrices composed of glycosaminoglycans, fibrin, fibrinogen, and fibronectin. Lp(a) prevents thrombolysis by directly binding tissue plasminogen activator (tPA) or upregulating plasminogen activator inhibitor-1, both of which prevent the conversion of plasminogen to plasmin (19). In addition, Lp(a) is the major transporter of oxidized phospholipids (15).

Lp(a) as a Therapeutic Target

Lp(a) concentration is generally unaffected by classic lipid-lowering strategies such as diet/lifestyle modification and statins. Niacin has been shown to lower Lp(a) levels by an unknown mechanism. Estrogen therapy can reduce Lp(a) levels in women but is also associated with an increased risk for cancer. High-dose statin therapy to lower LDL-C levels aggressively has been shown to be effective in lowering CVD risk in patients with high Lp(a) levels (9,12,15) and is generally accepted as the primary strategy for risk reduction in conjunction with control of other risk factors.

Several challenges remain before Lp(a) can be classified as a therapeutic target. These include:

1. Establishing that lowering Lp(a) reduces CVD risk, currently Class IIIc recommendation (no benefit) (21)
2. Standardizing Lp(a) measurement and establishing clinical cutoffs
3. Finding an effective and well-tolerated medication to directly target Lp(a)

C-REACTIVE PROTEIN (CRP)

CRP is an acute phase reactant produced by the liver. It was discovered in 1930 as a reactant of somatic C polysaccharide in patients with Streptococcal pneumonia. Since then, it has been associated with increased vascular events in patients with coronary artery disease. Several prospective studies have shown that elevated CRP is an independent risk factor for MI, stroke, and peripheral vascular disease (5,15).

CRP binds to lectin-like oxidized LDL receptor-1 on endothelial cells and increases intravascular inflammation by activating complement and macrophages, inhibiting nitric oxide release, and promoting thrombosis (5).

There is conflicting data on the predictive value of CRP for CVD risk. In the clinical setting, high-sensitivity CRP (hsCRP) has a Class IIa recommendation in men ≥50 years old and women ≥60 years old with LDL <130 mg/dL; not on hormone, lipid, or immunosuppressant therapy, and without CVD, diabetes, or CKD (Class IIb recommendation for men <50 and women <60 years old) (3,4,20). However, whether

the incremental predictive value is clinically meaningful beyond other risk factors and the role of CRP in therapeutic decision making remain topics of ongoing debate (4,19,21). More recent recommendations from the ACC/AHA have suggested hsCRP as one of the tests that may be performed if the treatment decision based on global risk scoring is uncertain, with a level of >2 mg/L being a criterion for upstaging of risk.

Serum high-sensitivity CRP is classified into three tertiles:

1. <1.0 mg/L (low risk)
2. 1.0–3.0 mg/L (intermediate risk)
3. >3.0 mg/L (high risk)

The main areas of controversy regarding CRP are whether it has a direct effect on atherosclerosis independent of other processes and whether a direct CRP lowering agent will be effective in reducing CVD events.

LIPOPROTEIN-ASSOCIATED PHOSPHOLIPASE A_2 (LP-PLA_2)

Most prospective studies have classified Lp-PLA_2 as an independent predictor of both CVD and stroke risk (WOSCOPS, ARIC, MONICA) (22–24). Lp-PLA_2 is secreted by macrophages, T-cells, mast cells, hepatocytes, and monocytes. It is primarily transported by LDL, but is also located on Lp(a) and HDL. LDL accumulation in the vascular intima leads to upregulation of Lp-PLA_2 activity causing progression of plaque formation. Lp-PLA_2 hydrolyzes oxidized phospholipids (OxPL) into two inflammatory molecules, lysophosphatidylcholine (lyso-PC) and oxidized fatty acids, which increases cytokine expression and macrophage transformation into foam cells (5,17).

Lp-PLA_2 and Lp(a)

Under normal conditions Lp(a) acts as a scavenger of OxPL and degrades it into a proinflammatory molecule: lyso-PC. Under inflammatory conditions, OxPL levels increase and overwhelm the ability of Lp(a)-Lp-PLA_2 to degrade OxPL. In patients with high Lp(a) levels, there is more transportation of Lp-PLA_2 to the vascular endothelium leading to higher Lp-PLA_2 activity. This leads to enhanced oxidation within the plaque (17).

Lp-PLA_2 Screening and Therapy

Lp-PLA_2 screening has not been well established. Some experts recommend its use for risk stratification of intermediate/moderate CVD risk populations (Class IIb recommendation) that meet any of the following criteria (3,4,21).

1. Smokers
2. Patients with two or more major CVD risk factors
3. Patients >65 years old with 1 CVD risk factor
4. Diabetics
5. Patients with metabolic syndrome who are at moderate CVD risk

Because LDL primarily transports Lp-PLA_2, statin therapy targeting LDL also indirectly lowers Lp-PLA_2 levels. In the PROVE-IT study, Lp-PLA_2 mass and activity decreased about 20% with therapy and was independently shown to have favorable CV outcomes (5).

Darapladib is a direct Lp-PLA_2 inhibitor currently being studied in the STABILITY trial to determine its efficacy in reducing CVD risk. This trial will also examine the efficacy of Lp-PLA_2 guided therapy. Results of this trial may help establish a clinical role for Lp-PLA_2 screening. The latest 2013 ACC/AHA guidelines for risk assessment do not address LpPla2.

LDL PARTICLES

LDL-C has been the long-standing target for statin therapy. However, it is not the best indicator of CVD risk because risk correlates better with LDL particle number rather than cholesterol concentration. An example of this is individuals who have LDL particles that contain less cholesterol than average, and thus the LDL-C level in these patients would underestimate the number of LDL particles. This is clinically important because these patients have higher risk than indicated by the LDL-C level (25). Patients with diabetes mellitus or metabolic syndrome tend to have high levels of small dense LDL, and therefore discordantly low LDL-C relative to LDL-P. The current ACC/AHA guidelines have a Class III recommendation for monitoring LDL-P (4). LDL-P can serve as a secondary marker to further risk stratify patients with normal LDL-C levels but have additional CVD risk factors (5).

APOLIPOPROTEINS A1 AND B

Apoproteins are structural proteins attached to lipoproteins to form apolipoproteins. There are two main classes of clinically relevant apolipoproteins: Apo A1 and Apo B. Apo A1 is primarily located in HDL, facilitating removal of cholesterol from macrophages to prevent the formation of foam cells. It also functions as the binding site for lecithin cholesterol acyl transferase

in the formation of cholesteryl esters found in mature, spherical HDL particles. ApoAI levels measured in serum are inversely associated with CVD risk, similar to HDL-C but usually with higher strength of statistical association for incident CVD both in epidemiologic studies (26) and in patients treated with statins (27).

Apo B is a robust marker of total atherogenic particle concentration given that one apo B molecule is present on each non-HDL particle, VLDL, IDL, and LDL and Lp(a). Prospective studies have established that Apo B levels correlate more closely with CVD risk than LDL-C. Its clinical use as a lipid biomarker has

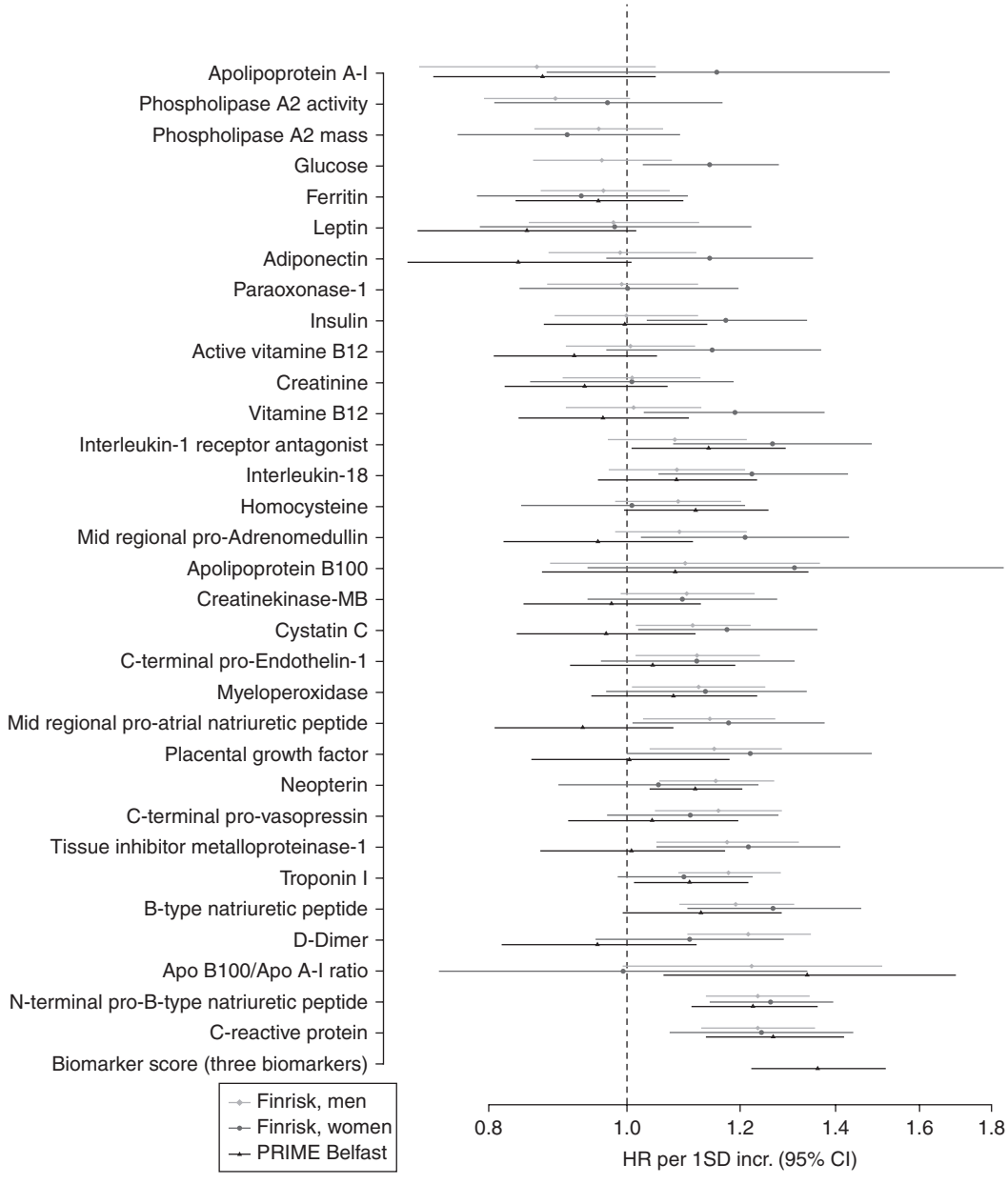

FIGURE 9.1 Fully adjusted HRs of biomarkers for incident cardiovascular events. HRs are per 1-SD increment and are adjusted for age, area, body mass index, systolic blood pressure, diabetes mellitus, smoking, non-HDL cholesterol, HDL-cholesterol, and cardiovascular medication. Shown on the bottom is the HR associated with a continuous score derived from NT-proBNP, C-reactive protein, and troponin I. Apo indicates apolipoprotein; CI, confidence interval. *Source*: Adapted with permission from *Circulation*. Contribution of 30 biomarkers to 10-year cardiovascular risk estimation in 2 population cohorts: the MONICA, risk, genetics, archiving, and monograph (MORGAM) biomarker project. Blankenberg S1, Zeller T, Saarela O, Havulinna AS, Kee F, Tunstall-Pedoe H, Kuulasmaa K, Yarnell J, Schnabel RB, Wild PS,Münzel TF, Lackner KJ, Tiret L, Evans A, Salomaa V; MORGAM Project. *Circulation*. 2010 Jun 8;121(22):2388–2397.

been well established. LDL-P is strongly correlated with apoB inasmuch as typically 90% of apoB containing non-HDL particles are LDL. Both Apo B and LDL-P are considered to be coprimary targets of lipid therapy by the Canadian Lipid Guidelines. The ACC/AHA guidelines have a Class III recommendation for monitoring apolipoproteins (3,4,21). However, the NLA Biomarkers Expert Panel recommends that Apo B measurement is reasonable for patients with intermediate or higher risk (3,5). Patients receiving statin therapy can also be monitored with Apo B measurements because it has a 1:1 relationship with the number of atherogenic particles. Apo B is regarded as a superior risk indicator to LDL-C and is equivalent or superior to non-HDL-C, particularly when the two measures are discordant (28). Additional clinical trial data are necessary to clearly establish Apo B treatment targets, although levels of <80 mg/dL are commonly accepted as goals in high risk and secondary prevention patients.

OTHER BIOMARKERS (NT-proBNP AND TROPONIN I)

NT-proBNP is the cleaved portion of proBNP, which is elevated with increased ventricular stretch (29). Mild troponin I elevations in these studies suggest cardiac micronecrosis. Elevations in N-terminal-pro-brain natriuretic peptide and troponin I have been shown to be independently associated with CVD risk. In the MONICA-MORGAM study, CRP, NT-proBNP, and troponin I were the only three biomarkers found to have consistent additive predictive value over conventional predictors and lipids (Figure 9.1). Improvement in risk reclassification was observed with the addition of all three biomarkers scores (NT-proBNP, troponin I, and CRP); each individual biomarker did not improve CVD risk prediction (30). NT-proBNP and troponin I individually received Class III recommendations from the ACC/AHA (4,21); moreover, panels of multiple biomarkers may not have been endorsed for general use in ACC/AHA or NLA guidelines.

SUMMARY

Advanced lipid biomarkers help refine CVD risk in a low-intermediate CVD risk population. The evidence for some biomarkers is stronger than others. The recommendations above, summarized in Table 9.1, are based on current NLA guidelines, which are more liberal than the NHLBI ATP IV guidelines (4). When using advanced lipid biomarkers in the clinical setting, the physician should consider the clinical context and whether additional pharmaceutical therapy will be well tolerated by the patient.

TABLE 9.1 NLA Recommendations Regarding Biomarker and Advanced Lipoprotein Testing

	Initial Clinical Assessment					
	CRP	**Lp-PLA$_2$**	**Apo B**	**LDL-P**	**Lp(a)**	**HDL or LDL Subfractions**
Low risk (<5% 10-year CHD event risk)	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended
Intermediate risk (5-20% 10-year CHD event risk)	Recommended for routine measurement	Consider for selected patients	Reasonable for many patients	Reasonable for many patients	Consider for selected patients	Not recommended
CHD or CHD Equivalent	Consider for selected patients	Consider for selected patients	Consider for selected patients	Consider for selected patients	Consider for selected patients	Not recommended
Family History	Reasonable for many patients	Consider for selected patients	Reasonable for many patients	Reasonable for many patients	Reasonable for many patients	Not recommended
Recurrent Events	Reasonable for many patients	Consider for selected patients	Reasonable for many patients	Reasonable for many patients	Reasonable for many patients	Not recommended

(*continued*)

TABLE 9.1 NLA Recommendations Regarding Biomarker and Advanced Lipoprotein Testing (*continued*)

	On-Treatment Management Decisions					
	CRP	**Lp-PLA$_2$**	**Apo B**	**LDL-P**	**Lp(a)**	**HDL or LDL Subfractions**
Low Risk (<5% 10-year CHD event risk)	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended
Intermediate Risk (5-20% 10-year CHD event risk)	Reasonable for many patients	Not recommended	Reasonable for many patients	Reasonable for many patients	Not recommended	Not recommended
CHD or CHD Equivalent	Reasonable for many patients	Not recommended	Reasonable for many patients	Reasonable for many patients	Consider for selected patients	Not recommended
Family History	Consider for selected patients	Not recommended	Consider for selected patients	Consider for selected patients	Consider for selected patients	Not recommended
Recurrent Events	Reasonable for many patients	Not recommended	Reasonable for many patients	Reasonable for many patients	Consider for selected patients	Not recommended

Apo, apolipoprotein; CHD, coronary heart disease; CRP, C-reactive protein; HDL, high-density lipoprotein; Lp-PLA2, lipoprotein-associated phospholipase A2; LDL, low-density lipoprotein; LDL-P, LDL particle number/concentration; Lp(a), lipoprotein(a).
Source: Adapted from Ref. (5) with permission from the *Journal of Clinical Lipidology*. Davidson MH, Ballantyne CM, Jacobson TA, et al., Clinical utility of inflammatory markers and advanced lipoprotein testing: Advice from an expert panel of lipid specialists, *J Clin Lipidol*, 2011;5:338–367.

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Terence Hill, MD,
Ty J. Gluckman, MD, FACC, FAHA
Jessica L. Mega, MD, MPH, FACC, FAHA
and Omair K. Yousuf, MD

Antithrombotic Therapy in the Primary and Secondary Prevention of Cardiovascular Disease

Thrombosis is central to the pathophysiology of most acute cardiovascular (CV), cerebrovascular, and peripheral vascular events. Platelet activation and blood coagulation are two dependent and complementary pathways that serve as the bedrock of hemostasis and thrombosis, both physiologically and pathologically. An understanding of platelet biology and the coagulation cascade has led to the identification of various factors that serve as targets for antithrombotic therapies (Table 10.1). Over the last decade, many novel oral anticoagulants and antiplatelet agents have been added to our armamentarium in CV medicine. This chapter reviews landmark trials and recommendations from current guidelines related to various existing and new antithrombotic therapies in the primary and secondary prevention of CV disease.

ASPIRIN

Primary Prevention

- Aspirin is recommended for men over age 45 years who are at increased risk for CV events (1–3).
- Aspirin is recommended for women over age 65 years for stroke prevention (4).
- Aspirin is recommended for men over age 50 years and women over age 60 years with diabetes mellitus (DM) (5).
- Aspirin may be used for stroke prevention in patients with atrial fibrillation (AF) as an alternative to warfarin and the novel oral anticoagulants (NOACs) in patients at intermediate risk for stroke (CHA_2DS_2-VASc score of 1) (6). Alternatively, aspirin may be used for those who refuse oral anticoagulant (OAC) therapy (7).

Given its long history, wide availability, and low cost, aspirin is the most commonly used medication in the primary prevention of CV disease. Divergent guidelines regarding its use have been published by several organizations, including the U.S. Preventive Services Task Force (USPSTF) (3), American Heart Association (AHA) (2), American Stroke Association (ASA) (4,6), American College of Chest Physicians (ACCP) (1,8), and European Society of Cardiology (ESC) (7,9). Variability in recommendations primarily involves the primary prevention population, where more limited efficacy of aspirin must be weighed against its bleeding risk.

The efficacy and safety of aspirin in primary prevention was reviewed in a landmark meta-analysis by the Antithrombotic Trialists' Collaboration (10). This study demonstrated a small absolute reduction in the risk of major coronary events in men (Relative Risk [RR]: 0.77 95% Confidence Interval [CI]: 0.67–0.89, Absolute Risk Reduction [ARR]: 0.15% per year) and a small absolute reduction in the risk of ischemic stroke in women (RR: 0.77 [0.59–0.99], ARR: 0.02%

TABLE 10.1 Antithrombotic Agents Used in the Prevention of Cardiovascular Disease

Drug	Mechanism of Action	Primary Use
Aspirin	Cyclooxygenase-1 inhibitor	Primary and secondary prevention of CV disease
Ticlopidine, clopidogrel, prasugrel, and ticagrelor	$P2Y_{12}$ receptor antagonist	Predominantly secondary prevention following an ACS or PCI
Dipyridamole	Phosphodiesterase inhibitor (only studied in combination with aspirin)	Secondary prevention following a TIA or stroke
Cilostazol	Phosphodiesterase III inhibitor	Secondary prevention in symptomatic PAD
Warfarin	Vitamin K antagonist	Primary and secondary stroke prevention in those with valvular and nonvalvular atrial fibrillation
Dabigatran	Direct thrombin inhibitor	Primary and secondary stroke prevention in those with nonvalvular atrial fibrillation
Rivaroxaban, Apixiban, Edoxaban*	Factor Xa inhibitor	Primary and secondary stroke prevention in those with nonvalvular atrial fibrillation
Vorapaxar	Protease-activated receptor-1 antagonist	Secondary prevention in those with prior MI or PAD

Abbreviations: ACS: acute coronary syndrome, CV: cardiovascular, MI: myocardial infarction, PAD: peripheral artery disease, PCI: percutaneous coronary intervention, TIA: transient ischemic attack.
*Not currently FDA approved.

per year). This came, however, with the cost of a small absolute increase in hemorrhagic stroke (RR: 1.32 [CI: 1.00–1.75], Absolute Risk Increase [ARI]: 0.01% per year) and extracranial major bleeding (RR: 1.54 [CI: 1.30–1.82], ARI: 0.03% per year), with resultant uncertain net benefit.

A subsequent meta-analysis by the USPSTF (3) suggested that for men, the benefit of aspirin increased with age and coronary heart disease (CHD) risk (as assessed by the Framingham Study), whereas the risk of bleeding largely increased with age alone. Net clinical benefit occurred in (a) men aged 45–59 years with a 10-year CHD risk of 4%, (b) men aged 60–69 years with a 10-year CHD risk of 9%, and (c) men aged 70–79 years with a 10-year CHD risk of 12%. Given the impact of age, it comes as no surprise that most men over age 60 years will have a 10-year CHD risk >9% and only men in their 40s with multiple risk factors will have a 10-year CHD risk >4%. In persons who do not meet these levels of risk, the potential side effects of aspirin outweigh the potential benefit.

Contrary to the USPSTF recommendations, the AHA/ASA guidelines recommend aspirin for all adults with a 10-year CHD risk of 6% to 10% (4) and the ACCP guidelines encourage low-dose aspirin in all adults over 50 years of age with one other risk factor and no relative contraindications to aspirin use (1). Additionally, given the high CV risk in DM, the AHA and American College of Cardiology (ACC) recommend that diabetics with one additional risk factor for CHD be treated with aspirin beginning at age 50 years for men and at age 60 years for women (5). Altogether different are the ESC guidelines, which recommend against the use of aspirin for primary prevention (9).

Aspirin's efficacy for stroke prevention in AF is less pronounced compared to other anithrombotic therapies. Current ACC/AHA guidelines (6) recommend aspirin as an option in those with a CHA_2DS_2-VASc score of 1. In contrast, the ESC (7) and ACCP guidelines (8) suggest that an anticoagulant be used in those with a CHA_2DS_2-VASc score ≥1. Under these guidelines, for those who cannot be anticoagulated, the use of aspirin in combination with clopidogrel should be considered if bleeding risk is permissive, whereas aspirin monotherapy should be limited to those who refuse oral anticoagulation altogether.

Overall, the effect size of aspirin in primary prevention is small. As such, only patients with predominantly high risk of CHD and low risk of bleeding should be considered for aspirin therapy.

Secondary Prevention

- Aspirin (at a dose of 75–162 mg/day) is recommended for all patients with coronary artery disease unless contraindicated (1,11).
- Aspirin (at a dose of 75–325 mg/day) is an option for patients following an ischemic stroke (11,12).
- Aspirin (at a dose of 75–100 mg/day) is an option recommended for patients with peripheral artery disease (PAD) (13).

In contrast to the debated benefits of aspirin in primary prevention, its role in secondary prevention is more certain and established. The previously mentioned Antithrombotic Trialists' Collaboration meta-analysis found ten-fold greater benefit in secondary as compared to primary prevention. This benefit was consistent among men and women and those with a history of stroke and CHD (10). Because patients with a history of acute coronary syndrome (ACS), stroke, CHD, or PAD face greater CV risk, it is not surprising that they derive greater benefit from aspirin therapy.

Consistent with prior observational studies, the CURRENT-OASIS 7 trial (14) demonstrated similar efficacy between higher dose (300–325 mg/day) and lower dose (75–100 mg/day) aspirin in patients with an ACS undergoing percutaneous coronary intervention (PCI), with slightly increased risk of minor bleeding at the higher dose (Hazard Ratio [HR]: 1.13 [CI: 1.00–1.27], ARI: 0.6%). Based on this, current guidelines give preference to low-dose aspirin (75–162 mg/day) in this population (1,11).

$P2Y_{12}$ RECEPTOR ANTAGONISTS

Primary Prevention

$P2Y_{12}$ receptor antagonists are not recommended in the primary prevention of CHD. Among the currently approved $P2Y_{12}$ inhibitors, only clopidogrel has been studied in this population. The CHARISMA study compared dual antiplatelet therapy (DAPT) with aspirin and clopidogrel to aspirin alone in a mixed population of primary and secondary prevention. Treatment with DAPT was associated with no greater efficacy and only increased risk of bleeding (15).

In patients with AF, DAPT with aspirin and clopidogrel was compared with aspirin monotherapy in the ACTIVE-A trial and with a vitamin K antagonist (VKA) in the ACTIVE-W trial. In ACTIVE-A, DAPT reduced the risk of stroke (RR: 0.72 [CI: 0.62–0.83], ARR: 0.9% per year) at the expense of increased major bleeding (RR: 1.57 [CI: 1.29–1.92], ARI: 0.7% per year). The ACTIVE-W trial was stopped early as patients in the DAPT arm were found to be at an increased risk of adverse CV events compared to those taking a VKA (RR: 1.44 [CI: 1.18–1.76], ARI: 1.67% per year), with no difference in major bleeding (12).

Given this, current guidelines recommend limiting the use of clopidogrel in the primary prevention of CHD to patients who are unable to take aspirin (eg, hypersensitivity reaction) (1). For AF patients at increased risk of stroke who are not candidates for a VKA, DAPT with aspirin and clopidogrel may be considered (7,8). With the availability of NOACs however, DAPT is less commonly used for this indication.

Secondary Prevention

- Clopidogrel may be used as monotherapy in patients who are intolerant to aspirin for secondary prevention of CV events (11), stroke (9, 12), or PAD (13).
- A $P2Y_{12}$ receptor antagonist should be used in combination with aspirin for at least 1 year in patients following an ACS (1,9,11).
  - If no percutaneous coronary intervention (PCI) was performed, either clopidogrel or ticagrelor should be used (1,11).
  - If PCI was performed, clopidogrel, ticagrelor, or prasugrel may be used (1,11).
- A $P2Y_{12}$ receptor antagonist should not be used in patients revascularized with coronary artery bypass graft (CABG) surgery for stable coronary artery disease (1,11).
- Clopidogrel should be used in combination with aspirin in patients receiving PCI for stable coronary artery disease and for a time period specific to the type of stent placed, followed thereafter by lifelong aspirin (16).
  - Patients receiving a bare metal stent (BMS) should be treated with clopidogrel for a minimum of 1 month and ideally 1 year (16).
  - Patients receiving a drug eluting stent (DES) should be treated with clopidogrel for at least 1 year (16).

Coronary Artery Disease

There is strong evidence supporting the addition of a $P2Y_{12}$ receptor antagonist to aspirin in the secondary prevention of CV disease following an ACS or in those undergoing PCI. Guideline recommendations by the ACC/AHA, ACCP, and ESC each provide consistent support for their use. There are also data to support the use of a $P2Y_{12}$ receptor antagonist as monotherapy in stable CV disease or after a transient ischemic attack (TIA) or stroke.

The CURE trial was one of the first studies to establish the role of DAPT in secondary prevention. In this trial, patients with a non-ST–segment elevation ACS, managed medically or with revascularization, were randomized to aspirin plus clopidogrel versus aspirin alone for a mean of 9 months. The addition of clopidogrel was associated with a 2.1% absolute reduction in major cardiac events and a 1.0% absolute increase in major bleeding. Maximal benefit was noted to occur at 3 to 6 months, with continued benefit out to 1 year (17).

Subsequent studies sought to evaluate the effects of more potent $P2Y_{12}$ receptor antagonists (eg, prasugrel, ticagrelor) following an ACS. In the TRITON-TIMI 38 study (18) prasugrel was compared to clopidogrel on a background of aspirin therapy in ACS patients undergoing PCI. Treatment with prasugrel was associated with a significant reduction in major adverse CV events (HR: 0.81 [CI: 0.73–0.90], ARR: 2.2%) at the expense of increased non-CABG TIMI major bleeding (HR: 1.32 [CI: 1.03–1.68], ARI: 0.6%). Notably, an approximate 50% relative reduction in stent thrombosis was observed with prasugrel.

Subgroup analyses demonstrated prasugrel's greatest efficacy in patients with DM or ST-segment elevation myocardial infarction (STEMI). Higher bleeding was observed with prasugrel in those (a) ≥75 years of age, (b) under 60 kg, and (c) undergoing CABG surgery, prompting recommendations to limits its use in the first two populations and withhold it at least 7 days prior to anticipated surgery for the third group. In addition, prasugrel should not be used in patients with a history of TIA or stroke (16). More recently, the TRILOGY ACS study found that the benefit of prasugrel over clopidogrel in patients undergoing PCI did not apply to medically managed ACS patients, with a similar risk of major adverse cardiac events in both groups (HR: 0.91, CI: 0.79–1.05) (19).

In the PLATO study, ticagrelor was compared to clopidogrel in ACS patients who were medically managed, underwent PCI, or had CABG surgery (20). Treatment with ticagrelor was associated with a significant reduction in major adverse CV events (HR: 0.84 [CI: 0.77-0.92], ARR: 1.9%), with no overall increased risk of major bleeding (HR: 0.99, CI: 0.89–1.10). Further review of the PLATO data demonstrated geographic heterogeneity in response, with decreased efficacy in the North American cohort. This was thought to be due to use of aspirin at higher doses in this region, prompting recommendations to use ticagrelor only with low-dose aspirin (75-100 mg/day). Furthermore, although ticagrelor was not associated with an increase in the rate of overall major bleeding, the rate of non-CABG–related TIMI major bleeding was higher among those treated with ticagrelor (HR: 1.25, CI: 1.03–1.53).

Preference among the $P2Y_{12}$ inhibitors varies among the different guidelines. The ACC/AHA guidelines (11) list ticagrelor, prasugrel, and clopidogrel as equivalent alternatives, whereas the ACCP guidelines (1) give preference to ticagrelor over clopidogrel in all patients with an ACS, and the ESC guidelines (9) give preference to ticagrelor or prasugrel over clopidogrel in patients with an ACS. Largely because of its relatively low cost, clopidogrel still remains the most widely used $P2Y_{12}$ inhibitor in the United States today.

The efficacy of DAPT with clopidogrel and aspirin in stable CAD remains uncertain. Among patients with known CV disease in the CHARISMA trial (15), DAPT was associated with a significant reduction in major CV events when compared to aspirin alone (RR: 0.88 [CI: 0.77–0.998], ARR: 1.0%). This came, however, with an increased risk of moderate bleeding (ARI: 0.8%). Investigation of long-term ticagrelor in this population is currently underway.

Outside of DAPT after an ACS, clopidogrel remains the only $P2Y_{12}$ receptor antagonist to be evaluated as monotherapy. The CAPRIE study compared clopidogrel to aspirin in patients with stable CV disease. Clopidogrel monotherapy was associated with a small but statistically significant reduction in major adverse CV events compared to aspirin (RRR: 8.7% [CI: 03–16.5%], ARR: 0.5% per year) (21). Historically, though, clopidogrel's higher cost has largely limited its use to patients who are intolerant of aspirin.

Cerebrovascular Disease

In the MATCH trial, DAPT with aspirin and clopidogrel was compared to clopidogrel alone in patients with a recent TIA or stroke. Use of DAPT provided no incremental benefit and was associated with a statistically significant 1.3% increased risk of major bleeding. These findings, along with data from the PROFESS trial, which demonstrated similar efficacy between clopidogrel and combination therapy with aspirin and extended-release dipyridamole, support the use of clopidogrel monotherapy in the secondary prevention of TIA or stroke (12).

Optimal Duration of DAPT

The optimal duration of DAPT following PCI is the subject of ongoing investigation. Current guidelines recommend DAPT ideally for 1 year, especially

when prescribed in the setting of an ACS, with lifelong aspirin thereafter (1,9,11,16). Although recent trials have evaluated treatment durations of 6 to 24 months, 12 months of DAPT still remains the standard.

Platelet Function Testing and Pharmacogenetic Testing

Clopidogrel is a prodrug that is metabolized to its active form by intestinal esterases and several hepatic cytochrome (CYP) P450 enzymes (Figure 10.1). Because environmental and genetic factors contribute to the variable antiplatelet effect of clopidogrel, there has been significant interest in identifying who is likely to be a "nonresponder." High on-treatment platelet reactivity (HPR) has emerged as a potent risk factor for recurrent ischemic events following PCI and can be measured using various platelet function tests (eg, VerifyNow assay) (22).

Among the genetic polymorphisms, CYP2C19*2 has been most associated with attenuated platelet inhibition and increased CV risk. In a meta-analysis of 9 studies, one and two loss-of-function (LoF) CYP2C19*2 alleles were present in 26.3% and 2.2% of patients treated with clopidogrel, respectively, and were associated with increased risk of CV events compared to noncarriers (HR 1.55 and 1.76, $P = .01$ and $P = .002$, respectively) (23).

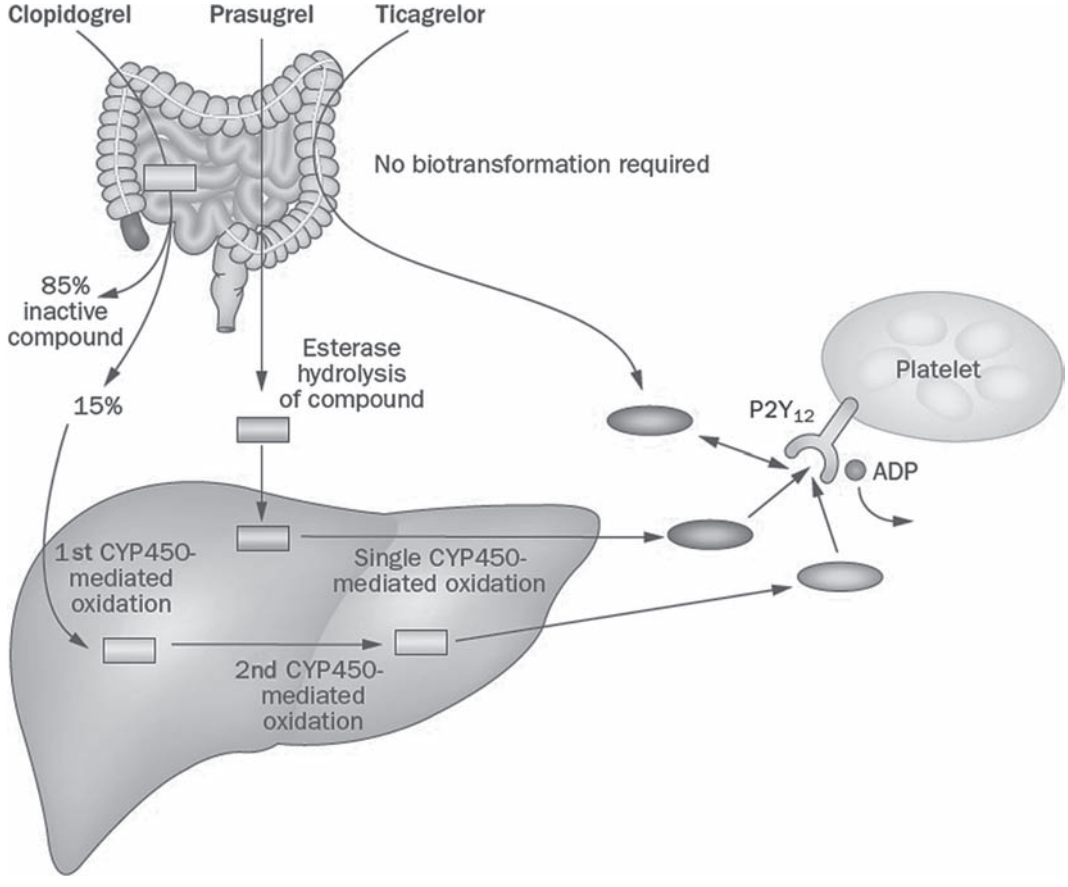

FIGURE 10.1 Metabolism of $P2Y_{12}$ Inhibitors. Clopidogrel and prasugrel are both prodrugs that require oxidation by hepatic cytochrome P450 enzymes to generate their active metabolites that inhibit the anucleate cell for its lifespan. The majority of clopidogrel is inactivated by carboxylesterases, such that only 15% of the active metabolite reaches the platelet receptor after undergoing two steps of oxidative biotransformation. Prasugel confers greater and more rapid platelet inhibition than clopidogrel through its efficient metabolism, requiring only one hepatic CYP450 oxidation step to generate its active metabolite. The cyclo-pentyl-triazolo-pyrimidine ticagrelor, unlike the thienopyridines, is rapidly absorbed as an active metabolite without requiring any hepatic or intestinal oxidative biotransformation. Its reversible affinity toward $P2Y_{12}$ receptors allows potent and consistent platelet inhibition.
Source: Reprinted, with permission, from Ref (22). Yousuf O, Bhatt DL. The evolution of antiplatelet therapy in cardiovascular disease. *Nat Rev Cardiol.* 2011;8547–8559.

Although HPR with clopidogrel can be overcome by increasing the maintenance dose of clopidogrel or switching to more potent antiplatelet therapy (eg, prasugrel or ticagrelor), improvement in clinical outcomes with this strategy has not been confirmed. In the GRAVITAS study, patients on clopidogrel with HPR were randomized to double dose versus standard dose clopidogrel one day after PCI. The 30-day and 6-month outcomes between the two strategies were unchanged (HR: 1.01 [CI: 0.58–1.76], ARR: 0%) and the reduction in HPR was not significantly predictive of outcome (24). Alternatively, the TRIGGER-PCI study randomized patients with HPR following elective PCI to continued use of clopidogrel or a switch to prasugrel. Given the extremely low event rate and small sample size, no benefit was demonstrated with the more potent antiplatelet agent despite greater platelet inhibition (25). Thus, although HPR and LoF genotypes remain risk factors for adverse CV events, it remains uncertain whether a change in pharmacotherapy can mitigate this risk.

OTHER ANTIPLATELET AGENTS

Dipyridamole

Low-dose aspirin with extended release dipyridamole is another choice for the secondary prevention of cerebrovascular events (9,12).

Dipyridamole has been studied in combination with aspirin for secondary stroke prevention in several trials and has been shown to have incremental benefit compared with aspirin alone (12). Of concern in these trials, however, has been variability in the dose of aspirin studied. Most recently in the ESPRIT study, aspirin (30–325 mg/day) was compared to aspirin plus dipyridamole (200 mg twice daily). Combination therapy reduced the risk of adverse CV events (HR: 0.80 [CI: 0.66–0.98], ARR: 1% per year) (12). Current ASA/AHA guidelines (12) consider the combination of aspirin and dipyridamole to be an equivalent alternative to aspirin monotherapy for the secondary prevention of stroke, however, the ESC guidelines (9) state that it should be used preferentially.

Cilostazol

For patients with PAD and continued symptoms of intermittent claudication despite exercise therapy, smoking cessation, and treatment with aspirin, cilostazol is recommended for symptom relief (13).

Cilostazol's benefit in symptomatic PAD comes from its ability to decrease symptoms and improve quality of life (13). It has not been shown, however, to improve CV mortality or reduce major cardiac events. As such, it is generally recommended as second-line therapy following aspirin.

More recently, there has been interest in cilostazol as an addition to DAPT where it has been shown to reduce restenosis 1 to 12 months after PCI (26). At the present time, however, there are no guideline recommendations for this indication.

Vorapaxar

Vorapaxar is a thrombin receptor (protease-activated receptor-1) antagonist that was recently approved to reduce adverse CV events in patients with a history of myocardial infarction (MI) or PAD. In the TRA 2P-TIMI 50 study, 26,449 patients with known CV disease were randomized to vorapaxar (2.5 mg daily) or placebo for a median of 30 months (27). Patients in both arms of the trial could have been on aspirin and/or a thienopyridine. Treatment with vorapaxar was associated with a significant reduction in CV death, MI, or stroke (HR: 0.87 [0.80–0.94], ARR: 1.2%). This came, however, at the expense of increased moderate to severe bleeding (HR: 1.66 [1.43–1.93] ARI: 1.7%) and intracranial hemorrhage (ARI: 0.5%). Therefore, vorapaxar should not be used in patients with a history of stroke, TIA, or intracranial hemorrhage.

The timing of vorapaxar initiation continues to be discussed. In the TRACER study (28), when vorapaxar was given in conjunction with a loading dose at the time of ACS presentation, there was no significant reduction in the primary endpoint of CV death, MI, stroke, recurrent ischemia with rehospitalization, or urgent coronary revascularization and there was an increased risk of major bleeding. Patients in the TRA 2P-TIMI 50 study, however, were eligible for enrollment as early as 2 weeks after their index event.

WARFARIN

Primary Prevention

- Patients with AF at increased risk for stroke (based on the CHA_2DS_2-VASc score) should be treated with warfarin for primary prevention (6–8).
- Patients with AF and a mechanical heart valve should be treated with warfarin for primary prevention of stroke (6, 12).

AF is a potent risk factor for stroke with an annualized risk of 3.5% for all comers (12). Current guidelines recommend the use of a stroke assessment tool to determine optimal antithrombotic therapy. The most common of these is the $CHADS_2$ score, which assigns 1 point each for congestive heart failure, hypertension, age ≥75 years, and DM, and 2 points for a prior history of TIA or stroke. In general, a score of 0 indicates a relatively low risk of stroke, a score of 1 indicates a moderate risk of stroke, and a score of 2 or greater indicates a high risk of stroke. Many have argued, however, that the $CHADS_2$ score can underestimate stroke risk, particularly in those deemed low risk.

This has prompted the development of the CHA_2DS_2-VASc score, which in addition to the $CHADS_2$ score, assigns a point each to female gender, history of vascular disease, and age between 65 and 74 years, as well as an additional point to age ≥75 years. The CHA_2DS_2-VASc score has the primary benefit of further stratifying those patients with low $CHADS_2$ scores into groups that are truly low risk where no therapy is needed and higher risk patients where an OAC is recommended (7).

Warfarin has been shown to reduce the risk of stroke in patients with AF by over 60%, at a cost of increased clinically significant bleeding. Current ACC/AHA guidelines (6) recommend the use of (a) any OAC (with no preference given) in patients at high risk of stroke (CHA_2DS_2-VASc score ≥2), (b) no antithrombotic therapy in those at low risk of stroke (CHA_2DS_2-VASc score of 0), and (c) either no antithrombotic therapy, aspirin, or an OAC in those at moderate risk of stroke (CHA_2DS_2-VASc score of 1)

Several risk scores have been developed to assess the likelihood of bleeding in those receiving anticoagulant therapy (most notably with a VKA). The HAS-BLED score, which assigns one point each for uncontrolled hypertension, abnormal renal function, abnormal liver function, stroke, bleeding history, labile international normalized ratio (INR), elderly (age >65 years) and concomitant drug use (eg, NSAID, antiplatelet agent, alcohol) is the most widely used among them. Although other bleeding risk scores (eg, ATRIA, HEMORR2HAGES) exist, the HAS-BLED score has better predictive value than the ATRIA score, is less complicated than the HEMORR2HAGES score, and is recommended by the ESC (9). A score ≥3 generally indicates an increased risk of bleeding and mandates caution when using an OAC. Patients with high HAS-BLED scores, however, also tend to be at exceptionally high risk for stroke. Because of this, an OAC should not necessarily be withheld from patients with increased bleeding risk, but instead modifiable risk factors should be mitigated and caution undertaken when starting these patients on anticoagulation.

Warfarin Genotyping

Given warfarin's narrow therapeutic window, considerable interest has been focused on tailoring warfarin dosing based on genotyping. Several genes are involved in warfarin metabolism, including CYP2C9, VKORC1, and CYP4F2. The first two have mutations that cause an increased anticoagulant effect at a given dose of warfarin, whereas mutations in CYP4F2 require increased doses to achieve a therapeutic INR. Even though commercial testing is available for mutations of all three genes, the cost may be prohibitive and knowledge of genotyping does not limit the necessity for routine INR monitoring.

NOVEL ANTICOAGULANTS

Dabigatran, rivaroxaban and apixiban are reasonable alternatives to warfarin in patients who are at moderate to high risk of stroke (CHA_2DS_2-VASc score ≥1) (6,7).

Based on warfarin's need for ongoing monitoring, along with its narrow therapeutic index, long half life, and wide variability in response, there has been significant interest in developing NOACs that overcome each of these limitations. Three new anticoagulants have received FDA approval (dabigatran, rivaroxaban, and apixaban) and one (edoxaban) has completed a phase III trial for prevention of stroke or systemic embolism in non-valvular AF. Each of these medications has the benefit of providing reliable rapid anticoagulation without the need for routine anticoagulant monitoring. They also have a shorter, more predictable half-life that makes periprocedural management easier, however, none currently has an antidote.

Dabigatran is a predominantly renally excreted twice daily direct thrombin inhibitor that was approved based on a head-to-head comparison to warfarin in patients with AF and high risk of stroke at two different doses in the RE-LY trial (29). Dabigitran reduced the primary outcome (combination of stroke and systemic embolism) compared to warfarin (RR: 0.66 [CI: 0.53–0.82], ARR: 0.59% per year), with a similar risk of major bleeding. Notably, annual rates of life threatening and intracranial bleeding with the 150-mg dose of dabigitran (1.45% and 0.30%, respectively) were lower than those observed with warfarin (1.80% and 0.74%, respectively), whereas annual rates of

GI bleeding were higher with dabigitran (1.51% vs. 1.02% for warfarin).

Rivaroxaban is a predominantly renally excreted once daily factor Xa inhibitor that was approved based on a head-to-head comparison to warfarin in the ROCKET-AF study (30). At the 20 mg dose, rivaroxaban was found to be noninferior to warfarin for the primary endpoint (composite of ischemic stroke, hemorrhagic stroke, and systemic embolism) (HR: 0.88 [0.74–1.03] in the intention-to-treat analysis). The annual rates of intracranial hemorrhage and fatal bleeding observed with rivaroxaban (0.5% and 0.2%, respectively) were lower than those observed with warfarin (0.7% and 0.5%), with a similar rate of clinically significant and major bleeding (14.9% with rivaroxaban and 14.5% with warfarin).

Apixaban is an oral, factor Xa inhibitor that was the latest of the NOACs to receive FDA approval for stroke prevention. The primary support came from the ARISTOTLE trial (31), in which 18,201 patients with AF and a mean $CHADS_2$ score of 2.1 were randomized to receive apixaban 5 mg twice daily or adjusted-dose warfarin. Apixaban was found to be superior to warfarin for the primary endpoint (stroke or systemic embolism), with an event rate of 1.27% per year with apixaban and 1.6% per year with warfarin (HR: 0.79 [0.66–0.95]) that was primarily driven by a reduction in hemorrhagic stroke. Compared to warfarin, apixaban was associated with a statistically significantly lower rate of major bleeding (2.1% vs. 3.1%) and reduced all-cause mortality (3.52% vs. 3.94%). The treatment effect appeared to be consistent across multiple subgroups including patients who were 75 years of age and older and those with renal impairment.

Although not yet approved, the once daily factor Xa inhibitor, edoxaban, was evaluated in the ENGAGE AF-TIMI 48 trial (32). This study randomized 21,105 patients with AF and a mean $CHADS_2$ score of 2.8 in a 1:1:1 design to high-dose edoxaban (60 mg daily), low-dose edoxaban (30 mg daily), or warfarin to achieve an INR goal of 2.0 to 3.0. Noninferiority for the low-dose of edoxaban (HR 1.07, 1.5% vs. 1.61% annual event rate) and superiority for the high-dose of edoxaban (HR 0.79; 1.5% vs. 1.18% annual event rate) was demonstrated for the primary endpoint of stroke or systemic embolism in the modified intention-to-treat population. The primary safety endpoint of annualized major bleeding was 3.43% with warfarin versus 2.75% with high-dose edoxaban and 1.61% with low-dose edoxaban. The corresponding annualized mortality rates were 3.17% versus 2.74% and 2.71%, respectively.

Because dabigitran and rivaroxaban are largely renally excreted, they must be dose-adjusted in patients with stage 3 to 4 chronic kidney disease and are not approved in patients with lesser degrees of renal function. Patients taking apixaban, however, require dose adjustment for a serum creatinine ≥1.5 mg/dL, if another risk factor for bleeding is present. In addition, apixaban can be used in patients with end-stage renal disease maintained on hemodialysis. Finally, use of all NOACs in AF is limited to those without significant valvular heart disease.

SUMMARY

Antithrombotic therapies remain central to the primary and secondary prevention of CV disease. In each medication class, it is important to balance the ischemic benefits against the bleeding risks to determine the relative benefit. Although the past decade has witnessed prodigious advancements with the addition of new antiplatelet therapies and novel oral anticoagulants, important questions remain unanswered and are the subject of on-going investigation.

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Alan Rozanski, MD, FACC

11

Psychosocial Risk Factors for Cardiovascular Disease

Epidemiological studies have established the importance of psychosocial risk factors for coronary heart disease (CHD) (1,2). The psychosocial risk factors that have been linked to CHD include depression, anxiety syndromes, various negative cognitive thought patterns, chronic stress, social isolation, and poor social support. In addition, clinical studies indicate that in addition to exercise, poor diet, overeating, and smoking, two other lifestyle habits are also associated with increased clinical risk: inadequate sleep and inadequate rest and relaxation. As depicted in Figure 11.1, psychosocial risk factors promote the development or progression of CHD in three ways.

Psychosocial risk factors are directly pathogenic: they promote unhealthy behaviors, such as overeating, poor nutrition, physical activity, and increased smoking, and their presence inhibits the initiation and adherence to efforts designed to change health-damaging habits. Conversely, poor health habits, such as physical inactivity and lack of sleep, can increase vulnerability to psychosocial stress.

The direct pathogenic effects of psychosocial risk factors stems from their persistent activation of the hypothalamic pituitary adrenal axis and dysregulation of the sympathetic nervous system. The resultant elevation in serum cortisol levels and enhanced sympathetic stimulation and interplay between the neuroendocrine and immune systems can produce widespread systemic effects, varying in presentation according to the type and magnitude of stress (1,2). These effects include:

- Endocrine abnormalities, including insulin resistance, metabolic syndrome, diabetes, and central obesity
- Autonomic dysfunction
- Inflammation (eg, elevation in C-reactive protein and inflammatory cytokines)
- Increase in cardiovascular reactivity (ie, exaggerated heart rate and blood pressure responses to stress, and delayed recovery)
- Hypertension
- Endothelial dysfunction
- Platelet abnormalities
- Telomere erosion (accelerated aging)
- Unfavorable alterations in brain plasticity

Unlike the treatment of conventional CHD risk factors, such as hypercholesterolemia, hypertension, and diabetes, there are no current practice guidelines for the treatment of psychosocial risk factors in cardiovascular practice. However, an increasing evidence base, adapted from various clinical studies and other aspects of the medical literature, including the rich development of medical psychology, provide a clinical basis for approaching psychosocial risk factors, as summarized below.

DEPRESSION

Depression has been extensively studied as a CHD risk factor and it occurs commonly in cardiac populations. Consistent study has shown that the frequency of major depression is ~15% in cardiac populations, which is

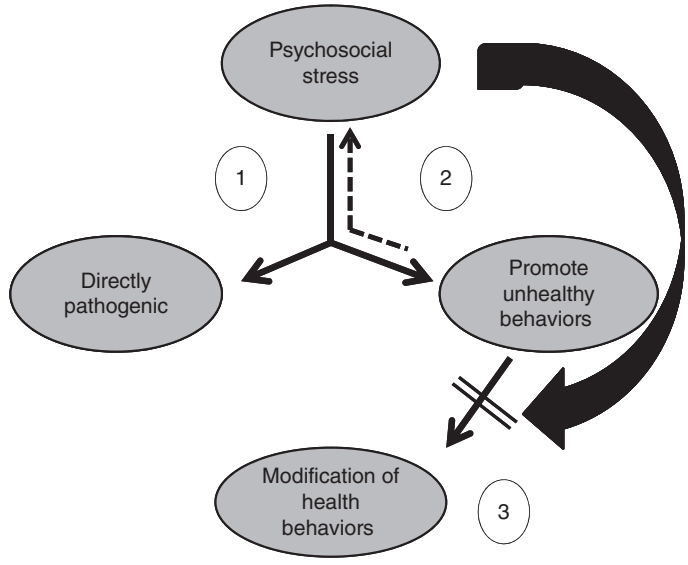

FIGURE 11.1 The three ways that psychosocial risk factors promote the development or progression of CHD.

approximately threefold higher than the point prevalence of depression in the general population. In addition, approximately another 15% of CHD patients may manifest subsyndromal levels of depression. Studies that have examined the relationship between the severity of depressive symptoms and cardiac events have generally found the presence of a graded relationship between the two, and depression, when severe, is of comparable strength to other major CHD risk factors.

In a recent meta-analysis of 52 studies, involving 146,538 subjects, depression was associated with a nearly twofold increased risk of myocardial infarction and/or cardiac death in community cohorts (3), and comparable risk for adverse clinical events has been noted among patients with known CAD who have depression (3,4). Similar risk has been noted for depression among patients with known CAD.

A variety of scales has been developed to diagnose depression and is frequently used in epidemiological research, but a multidisciplinary council from the American Heart Association (5) has recommended at least screening cardiac patients with a two-item subscale of the Patient Health Questionnaire (PHQ-2) which asks patients:

How often over the last two weeks have you been bothered by (0 = not at all; 1 = several days; 2 = more than half the days; 3 = nearly every day):

- *Little interest in or pleasure in doing things*
- *Feeling, down, depressed, or hopeless*

For those indicating a positive answer to either question (ie, scores ≥2, reflecting the occurrence on more than half of days), a 9-item version of the PHQ is recommended that further queries patients regarding other symptoms, such as sleeping difficulties, fatigue, poor appetite or overeating, and suicide risk (see Appendix 11.1). In patients with high scores (≥10), a more comprehensive clinical evaluation by a qualified professional is recommended according to the published algorithm shown in Figure 11.2 (5).

The treatment of depression includes both the use of antidepressant medications and/or use of psychotherapy. Selective serotonin reuptake inhibitors (SSRIs) are the first-line medication of choice for treating depression and randomized control trials have demonstrated their safety in the treatment of cardiac patients including after acute myocardial infarction. Following the initiation of antidepressant medications, patients should be closely monitored for at least two months to watch for the development of adverse symptoms and to monitor patient adherence.

Psychotherapy for treating depression may include either the use of cognitive behavioral therapy or interpersonal psychotherapy. Cognitive therapy, based on the concept that the quality of our thinking affects our emotions, targets helping patients to identify distortions in their thoughts and behavior patterns and assisting them to develop tools to change these distortions. Interpersonal psychotherapy attempts to reduce depressive symptoms by helping patients in their social interactions, targeting such problems as social isolation, role conflicts, and prolonged grief.

It should be noted that whether treating depression will alter CHD prognosis is currently inconclusive and awaits further study. In the interim, the treatment of depression in cardiac patients still appears warranted for reduction of depressive symptoms and improvement in lifestyle.

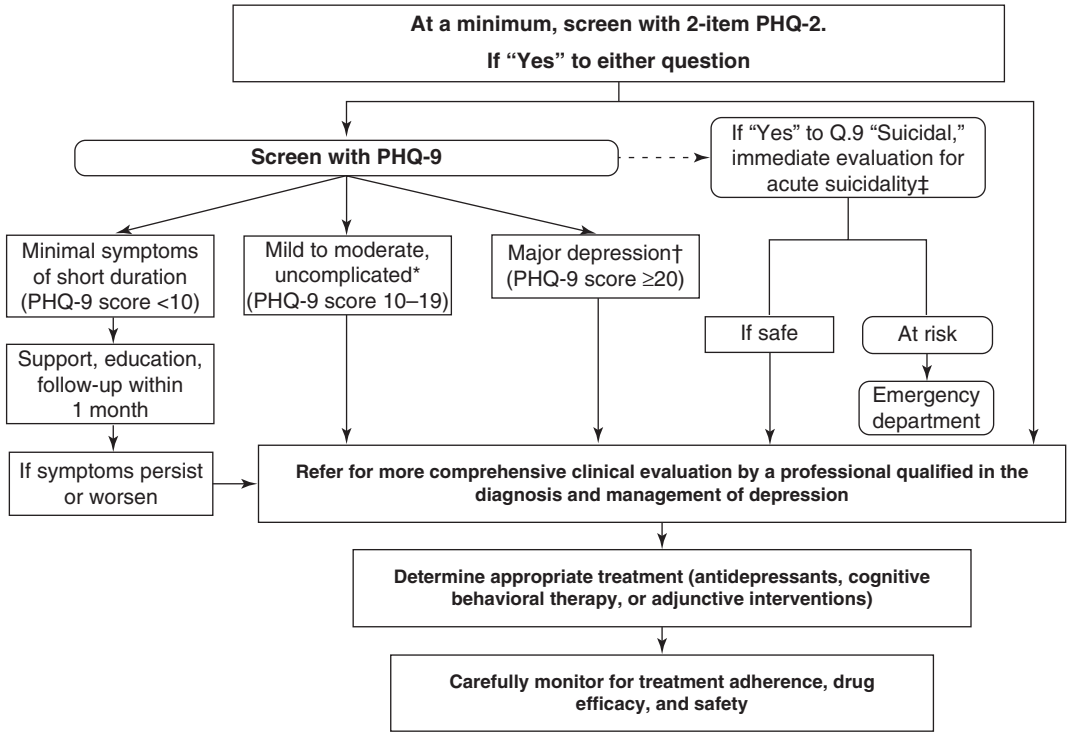

FIGURE 11.2 Screening for depression in patients with coronary heart disease.

*Meets diagnostic criteria for major depression, has a PHQ-9 score of 10–19, has had no more than 1 or 2 prior episodes of depression, and screens negative for bipolar disorder, suicidality, significant substance abuse, or other major psychiatric problems.

†Meets the diagnostic criteria for major depression and 1) has a PHQ-9 score ≥20; or 2) has had 3 or more prior depressive episodes; or 3) screens positive for bipolar disorder, suicidality, significant substance abuse, or other major psychiatric problem.

‡If "Yes" to Q.9 "suicidal," immediately evaluate for acute suicidality. If safe, refer for more comprehensive clinical evaluation; if at risk for suicide, escort the patient to the emergency department.

(*Source*: Litchman JH, Bigger JT, Blumenthal J, et al. Depression and Coronary Heart Disease: Recommendations for screening, referral, and treatment: A Science advisory from the American Heart Association Prevention committee of the Council on Cardiovascular nursing, Council on clinical cardiology, Council of Epidemiology and Prevention, and Interdisciplinary council on Quality of care and Outcomes research: Endorsed by the American Psychiatric Association. *Circulation.* 2008;118:1768–1775).

Exercise has also been recently advocated as a treatment for depression, based on cross-sectional and epidemiological studies and a series of randomized studies that found a large treatment effect for exercise compared to other treatments for depression (standard treatment, no treatment, or placebo) (6). In addition, a series of randomized control studies, including a recent study in cardiac patients, has found exercise to be comparable to antidepressant medication in alleviating depressive symptoms (7).

ANXIETY SYNDROMES

Early studies regarding anxiety revealed an unclear relationship to CHD, partly due to insufficient scales for measuring anxiety symptoms. In recent years, epidemiological studies have increasingly revealed a strong association between anxiety symptoms and CHD. For instance, in a meta-analysis of 9 community cohort studies, Roest et al. observed a nearly 1.5-fold increase in cardiac mortality for those who had anxiety symptoms at baseline (8). Four major anxiety syndromes have been linked to increased cardiac risk:

- Generalized Anxiety Disorder (GAD) consists of excessive and generally uncontrollable anxiety or worry, present for most days for at least six months, resulting in social and occupational dysfunction. In two studies, a nearly twofold increase in adverse outcomes has been noted among patients suffering from GAD (9,10).
- Phobias consist of marked and persistent fear of objects or situations, which upon exposure, commonly provoke anxiety and a fear of acting in a dysfunctional manner. In one study of 33,999 males, a graded relationship was noted between the presence of phobic anxiety symptoms and cardiovascular death (11). The group with the highest level of phobic anxiety had an odds ratio for cardiovascular death that was threefold higher than the lowest symptom group, with the attributable risk due primarily to sudden cardiac death. Similarly, in the Nurses' Health Study, the presence of

phobic anxiety was associated with an increased risk for sudden cardiac death and fatal CHD (12).

- Panic disorder consists of recurrent panic attacks, with persistent concern of more panic attacks or concern for their sequalae. Among 3,369 postmenopausal women in the Women's Health Initiative Observational Study, 10% reported full-blown panic attacks, with a fourfold increase in cardiac events and a nearly twofold increase in all-cause mortality in these patients (13).
- Posttraumatic stress syndrome consists of the occurrence of a characteristic constellation of symptoms that continue for >1 month after a traumatic event, such as flashback memories or other persistent re-experiencing, persistent avoidance of stimuli related to the original trauma, numbing of feelings, and hyperarousal, leading to significant impairment in daily life functioning. A recent meta-analysis of six studies found that PTSD is associated with a 1.55 (95% CI 1.34–1.79) adjusted hazard ratio for CHD, which remained significant after further adjustment for comorbid depression (14).

As with depression, anxiety can also be screened for by using a two-item subscale of the GAD-7 scale that is used to screen for anxiety (15):

Over the last 2 weeks, how often have you been bothered by the following problems:

- *Feeling nervous, anxious, or on edge*
- *Not being able to stop or control worrying*

The two questions are scored on a four point scale (0 = not at all, 3 = nearly every day). Those with increased scores can then be assessed using the GAD-7, as shown in Appendix 2. Elevated anxiety scores should be followed by referral of patients to a professional who can provide a more comprehensive evaluation as to the type and severity of anxiety symptoms and determine the appropriate mode of therapy.

Various treatment options are available to treat anxiety symptoms. A mainstay for treating many anxiety syndromes includes the use of cognitive behavioral therapy, with modifications, as appropriate, for specific forms of anxiety such as PTSD or phobias. Other forms of targeted psychotherapies may also be applied. Pharmacological interventions include the use of SSRIs or benzodiazepines, which may be combined with concomitant psychotherapy. For milder forms of anxiety, relaxation techniques and problem-solving counseling may be useful.

NEGATIVE COGNITIVE STATES

Various negative cognitive states have been investigated as to their relationship to CHD. The most studied of these has been hostility and anger. A meta-analysis of 25 studies by Chida et al. found that the presence of anger or hostility increased the risk for CHD by approximately 20% among community cohorts, and increased event risk by 25% among a meta-analysis of 19 studies involving patients with known CHD (16). Increasing interest has also centered on the CHD-risk posed by pessimism versus optimism.

In the first such study, Kubzansky et al. noted a relative risk for myocardial infarction or cardiovascular death of only 0.44 (95% CI 0.26–0.74) among optimistic versus pessimistic men followed for approximately 10 years in the Normative Aging Study (17) and optimism was also associated with lower risk of CHD and cardiovascular death among 97,253 women who were followed in the Women's Health Initiative (18). A report from the Normative Aging Study also found an increased event risk in association with worry (19) and indirect data suggest that rumination could also be linked to CHD, but formal epidemiological study of this cognitive state is presently lacking.

The importance of negative cognitive states is also emphasized by data indicating that such states may serve as precursor states for depression, disturb cardiovascular physiology, and promote negative health behaviors, such as poor diet and physical inactivity.

Anger can be successfully treated by referral to anger management programs (20). Patients who are noted to have excessive pessimism, worry, or rumination may benefit from referral to trained mental health professionals as a preventive strategy to ward off more serious downstream emotional sequalae.

CHRONIC STRESS

Various lines indicate a strong link between chronic stress and CHD. In controlled experimental animal studies, chronic stress is directly causative of atherosclerosis, even among animals on a low cholesterol diet (1). Investigational study has further linked chronic stress to many of the pathophysiological disturbances listed above. Various situational stressors have been linked to CHD and/or increased risk of cardiac events including "job strain" (ie, high job demand in the face of little job latitude) and other forms of job stress, including unemployment (21), marital strain (22), and exposure to adverse childhood experiences, such as sexual abuse (23).

In the multinational INTERHEART study (24), a proportional relationship was noted between the magnitude of stress and risk for myocardial infarction. The odds ratio for myocardial infarction in subjects with family or work stress was comparable to that noted for more conventional CHD risk factors in this study.

Scales have also been developed for screening for chronic stress. One such scale is a four-item

subscale of the perceived stress scale (see Appendix 3). Scales have also been developed to screen for job stress, such as the assessment for job strain. Alternatively, it has been suggested that a short open-ended review of systems can be conducted to screen for undue distress and other psychosocial risk factors as well. One that has been proposed includes the following seven open-ended questions (2):

- How would you describe your energy level?
- How have you been sleeping?
- How has your mood been recently?
- What kind of pressure have you been under at work or at home?
- What do you do to unwind after work or at the end of the day? Do you have difficulty unwinding?
- Who do you turn to for support?
- Are there any personal issues that we have not covered that you would like to share with me?

Approaches to treatment of chronic stress are quite varied and depend on many factors, including the objective nature of situational stressors, individuals' appraisals of stress, personality factors, and other life circumstances, such as social support, preferred coping mechanisms, and the like. At a minimum, physicians can make practical suggestions to patients regarding positive health practices that they can adopt to support themselves during periods of stress. This point is supported by data which indicate that patients tolerate stress better when they feel energetic (25). Thus encouraging and helping patients to exercise, obtain more sleep, and eat properly can assist some patients in handling stress.

In addition, physicians can make practical suggestions regarding rest and relaxation or stress reduction practices, such as breathing exercises and progressive relaxation techniques, and/or refer patients to structured programs, such as mindfulness-based stress reduction (MBSR) classes, yoga, or Tai Chi.

Physicians, by listening to their patients discuss symptoms they have when they are ill or experiences of increased concerns about their health, can also make appropriate lifestyle suggestions, such as the need to have more unwinding time for patients with long work hours, or the need for more vacation time. Physicians can also refer patients with more severe or specific forms of life stress to appropriate forms of psychotherapeutic intervention, such as cognitive behavioral therapy.

SOCIAL ISOLATION AND POOR SOCIAL SUPPORT

The need for positive social connection is a basic psychological need. Loneliness and poor social support have consistently been shown to increase the risk for CHD, cardiac events, and all-cause mortality, and strong social support has been found to be a buffering agent against medical illness. In a meta-analysis of 148 studies, involving 308,849 participants, both functional support and structural support were found to be predictors of increased longevity and a complex measure of social integration was found to be associated with a 1.91 (95% CI 1.63–2.23) odds of increased survival, an effect size that is comparable to many therapeutic interventions, such as smoking cessation, and cardiac rehabilitations (26).

Pathophysiological studies indicate multiple mechanisms by which poor social support is health-damaging. Poor social support is also associated with an increased prevalence of health-damaging behaviors. In addition, in another meta-analysis of 122 studies, Dimatteo et al. found that various measures of social support were significant predictors of patient adherence (27).

Various questionnaires can be used to screen for the quality of emotional and structural support among patients. Alternatively, an open-ended question or series of questions can be used to query patients with respect to the quality of their social lives. As a minimum, it behooves physicians to be aware of the community- or hospital-based programs that can provide the opportunity for social interaction or support for patients presenting with significant loneliness or lack of social support. Second, when appropriate, physicians can emphasize to patients the need to spend more time with friends or families. Third, some patients, particularly the elderly, may benefit from volunteering, which appears to enhance well-being and longevity (28). Finally, for patients experiencing a high level of social isolation, referral to social services may be indicated.

INADEQUATE SLEEP AND/OR REST AND RELAXATION

Both short and long sleep have been linked to the development of CHD (29). Short sleep is of particular interest because of a temporal trend to voluntary decreased sleep time in contemporary society. Experimental and clinical study have demonstrated that short sleep is associated with an increased risk for hypertension, diabetes, and weight gain, as well as various mediators of CHD, including abnormalities in neuroendocrine function and increased inflammation. Insomnia is also a risk factor for CHD, as indicated in a recent meta-analysis (30). Data regarding the importance of downtime and unwinding after work are more scant, but epidemiological studies have observed an

increased risk for clinical events among individuals who report difficulty in unwinding after work (31,32).

Sleep questionnaires customarily target a few domains of sleep difficulty, such as difficulty falling asleep within 30 minutes, waking up in the middle of the night with difficulty falling back to sleep, or waking up not feeling rested. Alternatively, physicians can screen for sleep and unwinding difficulty by adding such targeted questions to their general review of systems. For patients with insomnia, sleep hygiene measures can be suggested or a trial of a sleeping medication may be indicated.

If sleeping difficulties are substantial, patients can also be referred to sleep medicine programs accustomed to dealing with these issues. In vulnerable patients who are restricting their sleep voluntarily (eg, those who are highly stressed), the physician can also serve as a strong advocate for increasing sleep. Patients who have trouble unwinding may be candidates for stress management techniques, such as those discussed above.

EUROPEAN GUIDELINES

Although specific guidelines regarding management of psychosocial risk factors do not yet exist in the United States, in 2007 a Joint Task Force of the European Society of Cardiology in conjunction with other European societies on cardiovascular disease prevention issued guidelines on CHD prevention that included guidelines regarding the management of psychosocial risk factors (33). The central elements of their recommendations called for the following:

- Assess for the presence of psychosocial risk factors in all patients, with core questions concerning socioeconomic status and social isolation, work and family stress, depression, and hostility.
- Apply principles of effective behavioral counseling (eg, promotion of internal motivation in patients and promoting self-efficacy).
- Concentrate special preventive efforts and support among patients with low socioeconomic status.
- Use recommended interventions, which include individual or group counseling, cognitive behavioral therapy, referral to stress management programs, and stress management practices (eg, meditation, progressive relaxation, breathing exercises, yoga, and biofeedback).
- Refer patients with clinically significant emotional distress to behavioral specialists.

These European guidelines were recently updated, with psychosocial interventions receiving the class of recommendations for clinical management shown in Table 11.1 (34).

SUMMARY

Psychosocial risk factors are prevalent in cardiac populations and generally manifest a graded relationship between the severity of these risk factors and the likelihood of adverse clinical events. Psychosocial risk factors manifest their effects through three general mechanisms: (a) they are directly pathogenic; (b) they promote unhealthy lifestyle habits; and (c) they impede patient adherence to recommended lifestyle interventions.

Screening for depression and anxiety can be performed using a brief, four-item questionnaire (PHQ-4) and these and other psychosocial risk factors can also be assessed by using a short series of open-ended questions as part of physicians' review of systems. Formal practice guidelines for the management of psychosocial risk factors do not yet exist in the United States, however, there is a wide variety of practical steps that physicians can take to manage psychosocial risk factors in clinical practice, as reviewed in this chapter.

TABLE 11.1 Recommendations for Clinical Management

Recommendations	Class	Level*	Grade
Multimodal behavioral interventions, integrating health education, physical exercise, and psychological therapy for psychosocial risk factors and coping with illness, should be prescribed.	I	A	Strong
In the case of clinically significant symptoms of depression, anxiety, and hostility, psychotherapy, medication, or collaborative care should be considered. This approach can reduce mood symptoms and enhance health-related quality of life, although evidence for a definite beneficial effect on cardiac endpoints is inconclusive	IIa	A	Strong

*Level of evidence.

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APPENDIX 1

Patient Health Questionnaire-9 (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems?

	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself—or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed; or the opposite—being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

APPENDIX 2

Generalized Anxiety Disorder 7-Item (GAD-7) Scale

Over the last 2 weeks, how often have you been bothered by any of the following problems?

	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious, or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it's hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

APPENDIX 3

Perceived Stress Scale-4 Item

1. In the last month, how often have you felt that you were unable to control the important things in your life?
__0=Never __1=Almost never __2=Sometimes __3=Fairly often __4=Very often

2. In the last month, how often have you felt confident about your ability to handle your personal problems?
__0=Never __1=Almost never __2=Sometimes __3=Fairly often __4=Very often

3. In the last month, how often have you felt that things were going your way?
__0=Never __1=Almost never __2=Sometimes __3=Fairly often __4=Very often

4. In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?
__0=Never __1=Almost never __2=Sometimes __3=Fairly often __4=Very often

12

Amil M. Shah, MD, MPH and
Samia Mora, MD, MHS

Role of Stress Testing

Exercise stress testing is a safe procedure in asymptomatic or minimally symptomatic individuals and provides both diagnostic and prognostic information. A growing body of literature supports the utility of nonelectrocardiographic (non-ECG) parameters, including exercise capacity, heart rate recovery, chronotropic response, and exercise blood pressure in determining prognosis in asymptomatic subjects beyond traditional risk factors or global risk scores. There are no Class I indications for exercise testing in asymptomatic individuals in the American College of Cardiology/American Heart Association guidelines due to insufficient clinical trial evidence of efficacy. Exercise testing may be considered in asymptomatic subjects prior to starting vigorous exercise if they are diabetic, older, at higher risk for coronary heart disease (CHD) due to comorbid conditions, or involved in occupations potentially affecting public safety. Exercise testing with imaging should be used as an initial test in the following situations: (a) pre-excitation syndrome (Wolff-Parkinson-White), (b) electronically paced ventricular rhythm, (c) greater than 1 mm resting ST segment depression, (d) complete left bundle branch block. Although some studies suggest additional prognostic value of imaging along with stress testing in asymptomatic individuals, this is not cost effective in low-risk populations (low event rates and low specificity).

CURRENT GUIDELINES

Current guidelines allow for exercise testing in selected individuals with risk factors prior to starting a vigorous exercise program other than walking (Table 12.1), but do not recommend exercise testing for routine screening in asymptomatic subjects for detection of CHD.

USE AS A SCREENING TEST

The purpose of a screening test is either earlier diagnosis of disease or risk stratification to allow for effective interventions to prevent adverse outcomes. Guidelines recommend office-based risk stratification of asymptomatic individuals age 20 to 79 years old using a risk factor score to determine global risk, with higher risk individuals (10-year predicted risk of CVD ≥7.5%) treated more aggressively with preventive therapies (1). Non-ECG parameters, particularly exercise capacity, add prognostic information beyond risk factor scores, and are more predictive of outcomes than ECG evidence of ischemia. However, it is uncertain whether such refinements in prognostic assessment influence patient management and outcomes.

SAFETY, CONTRAINDICATIONS, AND INDICATIONS

Exercise stress testing is generally safe, with rare complications including acute MI (0.9 to 3.6 per 10,000 tests), malignant ventricular arrhythmias (0.3 to 4.8 per 10,000 tests), and sudden death (0 to 0.5 per 10,000 tests). The risk is higher post-MI and in patients with malignant ventricular arrhythmias (2). Any patient with evidence of clinical or hemodynamic instability should not undergo exercise testing. Absolute and relative contraindications for exercise testing (3) and for terminating exercise testing are listed in Table 12.2 (2).

TABLE 12.1 Guideline Recommendations for the Use of Stress Testing in Asymptomatic Individuals without Known CHD

	2002 ACC/AHA Guidelines for the Use of Exercise Testing in Asymptomatic Individuals Without Known CHD (3)	2010 ACCF/AHA Guidelines for Assessment of Cardiovascular Risk in Asymptomatic Adults (4)	2012 USPSTF Recommendation Statement: Screening for CHD With Electrocardiography (5)	2013 ACC/AHA Cardiovascular Risk Guideline (4)
Class I				
	• None	• None	• None	• None
Class IIa				
	• Evaluation of asymptomatic persons with diabetes mellitus who plan to start vigorous exercise. *(Level of Evidence: C)*	• None	• None	• None
Class IIb				
	• Evaluation of persons with multiple risk factors as a guide to risk-reduction therapy • Evaluation of asymptomatic men older than 45 years and women older than 55 years: ◦ Who plan to start vigorous exercise (especially if sedentary), or ◦ Who are involved in occupations in which impairment might affect public safety, or ◦ Who are at high risk for CHD due to other diseases (eg peripheral vascular disease and chronic renal failure)	• Cardiovascular risk assessment in intermediate-risk asymptomatic adults (including sedentary adults considering starting a vigorous exercise program), particularly when attention is paid to non-ECG markers such as exercise capacity *(Level of Evidence: B)* • ***Stress MPI:*** Cardiovascular risk assessment in asymptomatic adults with diabetes, a strong family history of CHD, or when previous risk assessment testing suggests high risk for CHD, such as CAC score of ≥400 *(Level of Evidence: C)*	• None	• None
Class III				
	• Routine screening of asymptomatic men or women	• ***Stress MPI or stress ECHO***: Cardiovascular risk assessment in low- or intermediate-risk asymptomatic adults *(Level of Evidence: C)*	• Asymptomatic adults at low risk for CHD *(Grade: D)*	• None
Insufficient Evidence/No Recommendation				
			• Asymptomatic adults at intermediate or high risk for CHD events *(Grade: I)*	• The contribution of cardiorespiratory fitness to risk assessment is uncertain. No recommendation for or against (NHLBI Grade: N)

EXERCISE STRESS TEST INTERPRETATION

The clinically relevant information in interpreting the results of any given patient's test is the likelihood that a positive result is truly indicative of disease (positive predictive value) and that a negative result truly excludes disease (negative predictive value), which depend on the prevalence of disease in the population (ie the pretest probability) (3).

$$\textbf{Positive predicted value} = \frac{\text{Sensitivity} \times \text{Pretest prob}}{[\text{Sensitivity} \times \text{Pretest prob}] + [(1 - \text{Specificity})(1 - \text{Prestest prob})]}$$

Where: *Sensitivity* = [True positive/(True positive + False negative)] × 100

Specificity = [True negative/(False positive + True negative)] × 100

Pretest prob = Pretest probability of coronary artery disease

Bayes' theorem states that the probability of disease after a diagnostic test is equal to the pretest probability of disease multiplied by the probability of a true positive result from the test (3). A corollary is that the chance of a positive result truly reflecting disease (ie, positive predictive value) will be higher in high-prevalence populations and lower in low-prevalence populations.

TABLE 12.2 Absolute and Relative Contraindications to Exercise Stress Testing and Indications for Terminating an Exercise Stress Test

	Contraindications to Exercise Stress Testing	Indications to Terminate an Exercise Stress Test
Absolute	• Acute myocardial infarction (within 2 days) • High-risk unstable angina (as defined in the ACC/AHA Guidelines for the Management of Patients With Unstable Angina/Non-ST-Segment Elevation Myocardial Infarction) • Uncontrolled cardiac arrhythmias causing symptoms or hemodynamic compromise • Symptomatic severe aortic stenosis • Uncontrolled symptomatic heart failure • Acute pulmonary embolus or pulmonary infarction • Acute myocarditis or pericarditis • Acute aortic dissection	• Drop in systolic blood pressure of >10 mmHg from baseline blood pressure despite an increase in workload, when accompanied by other evidence of ischemia • Moderate to severe angina • Increasing nervous system symptoms (eg, ataxia, dizziness, or near-syncope) • Signs of poor perfusion (cyanosis or pallor) • Technical difficulties in monitoring ECG or systolic blood pressure • Subject's desire to stop • Sustained ventricular tachycardia • ST elevation (≥1.0 mm) in leads without diagnostic Q-waves (other than V_1 or aVR)
Relative	• Left main coronary stenosis • Moderate stenotic valvular heart disease • Electrolyte abnormalities • Severe arterial hypertension (systolic blood pressure >200 mmHg and/or diastolic blood pressure >110 mmHg) • Tachyarrhythmias or bradyarrhythmias • Hypertrophic cardiomyopathy and other forms of outflow tract obstruction • Mental or physical impairment leading to inability to exercise adequately • High-degree atrioventricular block	• Drop in systolic blood pressure of >10 mmHg from baseline blood pressure despite an increase in workload, in the absence of other evidence of ischemia • ST or QRS changes such as excessive ST depression (>2 mm of horizontal or downsloping ST-segment depression) or marked axis shift • Arrhythmias other than sustained ventricular tachycardia, including multifocal PVCs, triplets of PVCs, supraventricular tachycardia, heart block, or bradyarrhythmias • Fatigue, shortness of breath, wheezing, leg cramps, or claudication • Development of bundle branch block or IVCD that cannot be distinguished from ventricular tachycardia • Increasing chest pain • Hypertensive response (systolic blood pressure >250 mmHg and/or diastolic blood pressure >115 mmHg)

Test Interpretation: Diagnosis

Determining the pretest probability of CHD: age, gender, and chest pain history are the most powerful predictors of CHD (1,6), although additional factors such as smoking and history of diabetes are also predictors (6). The pretest probability of CHD for asymptomatic men and women of all ages is considered low. The presence of chest pain symptoms (typical/definite angina > atypical/probable angina > nonanginal chest pain) and older age increase the pretest probability for men and women. Typical angina is characterized by: (1) substernal discomfort, (2) precipitated by exertion, and (3) prompt relief by rest or nitroglycerin. Atypical angina is defined as the presence of two out of three of these characteristics. Nonanginal is defined as less than two of these characteristics.

Interpretation of ECG response: ECG manifestations of exercise-induced ischemia focus on the ST segment deviation, measured relative to the P–Q junction (5). Diagnostic ST segment changes include horizontal or downsloping ST segment depression of ≥0.10 mV (1 mm) for 60 to 80 ms, with downsloping ST segment depression being more specific than horizontal or upsloping ST segment depression (5). Resting ST segment depression of < 1 mm increases the sensitivity but decreases the specificity of exercise testing and exercise ECG testing is considered a reasonable first test in these patients (3). Ischemic ST segment depression occurring only during the recovery phase of an exercise test has comparable diagnostic significance to ST segment depression occurring during exercise. A meta-analysis of 147 studies involving 24,074 patients and comparing exercise-induced ST depression with coronary angiography reported a mean sensitivity and specificity of 68% and 77%, respectively, although estimates vary widely: from 23 to 100% for sensitivity and from 17 to 100% for specificity (7). Important methodological limitations that may inflate estimates of ST segment depression sensitivity are (a) inclusion of subjects with high probability of having disease, and (b) work-up bias (3). Studies that avoided these limitations suggest a sensitivity of 50% and a specificity of 90% associated with exercise-induced 1 mm ST segment depression (3). Exercise-induced ST segment depression has been associated with higher mortality in asymptomatic men but not in asymptomatic women (16). Exercise-induced ST segment elevation in subjects without pre-existing Q waves occurs in an estimated 0.1% of patients, is associated with transmural ischemia, and reliably localizes the area of ischemia (3). The development of ST segment elevation is not infrequent in leads with pre-existing Q waves and is of unclear significance among patients with prior MI (3).

Test Interpretation: Prognosis

Duke Treadmill Score

The Duke treadmill score (DTS) is a commonly used prognostic score in exercise testing. The DTS was initially developed in 2,842 subjects referred for cardiac catheterization who had also undergone exercise testing for evaluation of symptoms of CHD (8) and incorporates three prognostic variables: the largest ST segment deviation (horizontal or downsloping ST depression, or ST elevation in leads without pathologic Q waves excluding aVR, after subtracting any resting changes), exercise time on Bruce protocol, and Duke angina index. The DTS is defined as:

$$\text{DTS} = \text{Exercise time (in minutes)} - (5 \times \text{maximal ST deviation in mm}) - (4 \times \text{angina index}).$$

where angina index 0 = no angina, 1 = typical angina, 2 = angina reason for test termination. The 5-year event-free survival (death or MI) was 93% with low risk scores (≥ +5), 86% with intermediate risk score (–10 to +4), and 63% with high risk score (≤ –11) (8). In unselected outpatients, 4-year survival among low-risk patients was 99%, whereas among high-risk patients it was 79% (9). The DTS may, however, have limited discrimination in elderly subjects.

Non-ECG Prognostic Parameters

Exercise Capacity

Exercise capacity is commonly measured by maximum oxygen consumption (VO_{2max}), defined as the maximal amount of oxygen a subject can take in from inspired air during dynamic exercise (5). When peak consumption is achieved, VO_{2max} can estimate cardiac output. Exercise capacity can also be quantified in metabolic equivalents (METs) where 1 MET is the basal oxygen uptake during quiet sitting and is equal to 3.5 mL/kg/min. Exercise protocols with progressive incremental increases in workload tend to estimate VO_{2max} more accurately, and should last for 6 to 12 minutes to reliably reflect the upper limit of the patient's cardiorespiratory function (5). Compared to the cycle ergometer, treadmill tests tend to demonstrate 10% to 15% higher VO_{2max}, 5% to 20% higher peak heart rate, and more frequent ST

segment changes (10). Exercise capacity is influenced by age and gender (11,12). Normograms have been developed to estimate age-predicted exercise capacity:

$$\text{Extimated age-predicted capacity for men} = 18.0 - [0.15 \times \text{age}] \quad [11]$$

$$\text{Extimated age-predicted capacity for women} = 14.7 - [0.13 \times \text{age}] \quad [12]$$

Exercise capacity is the most powerful prognostic parameter for future mortality from an exercise test, in both asymptomatic and symptomatic subjects, and in both men and women (13).

Exercise capacity provides prognostic information beyond traditional risk stratification using a global risk score in both men and women as discussed below (14).

Chronotropic Incompetence

Chronotropic incompetence is defined as the inability to achieve the expected increase in heart rate with exercise, possibly reflecting abnormal physiologic parasympathetic withdrawal and increased sympathetic activity with exercise (15). The chronotropic response to exercise is affected by age, resting heart rate, and physical fitness, and is commonly evaluated by the proportion of age-predicted maximal heart rate achieved during the stress test (peak HR/[220 – age]) (15). Chronotropic incompetence has been consistently associated with increased risk of all-cause and cardiovascular mortality, even after adjusting for demographics and standard risk factors, and in both referral populations and healthy asymptomatic individuals (15). In asymptomatic individuals, measures of chronotropic incompetence appear to provide additional prognostic information beyond Framingham risk score (16). The majority of studies assessing the prognostic role of chronotropic incompetence excluded patients on beta-blocker therapy at the time of the exercise test.

Heart Rate Recovery

Heart rate recovery is the rate of decrease in heart rate postexercise, and likely reflects parasympathetic reactivation. Heart rate recovery is defined as (15):

$$\text{Heart rate recovery} = \text{heart rate}_{\text{peak exercise}} - \text{heart rate}_{\text{1 or 2 minutes post exercise}}$$

Impaired heart rate recovery is commonly defined as a decrease in heart rate of ≤12 bpm within the first minute postexercise on a plain treadmill test, or ≤18 bpm after an exercise echocardiogram. Impaired heart rate recovery is associated with an increased risk of death, even after adjustment for patient demographics, standard risk factors, and perfusion abnormalities on nuclear imaging, and independent of exercise capacity and peak chronotropic response. How concurrent use of beta-blockers affects the predictive power of heart rate recovery is unclear. Subgroup analysis in >2,400 subjects referred for exercise testing, 13% of whom were on beta-blocker therapy, did not find any significant modification by concurrent beta-blocker use of the relationship between impaired heart rate recovery and risk of death (17).

Incremental Value of Exercise Capacity and Heart Rate Recovery Beyond Traditional Risk Scores

Impaired heart rate recovery, in combination with exercise capacity, provides incremental prognostic information beyond traditional global risk scores such as the Framingham Risk Score (14) and European SCORE (18). Among asymptomatic individuals with low- or intermediate-risk Framingham scores (14), low exercise capacity combined with heart rate recovery was associated with an eight- to tenfold higher risk of cardiovascular death. Both exercise capacity and heart rate recovery are at least partially modifiable and may be improved with moderate regular physical activity and exercise training by approximately 15% to 30% in a period of several months.

Blood Pressure Responses

The normal blood pressure response to exercise is characterized by a steady rise in systolic blood pressure, little change in diastolic blood pressure, and an increase in pulse pressure (systolic minus diastolic blood pressure) (5). Exercise-induced hypotension, often defined as an initial increase in blood pressure followed by a 20 mmHg decrease during exercise or by a decrease in blood pressure during exercise >10 mmHg below standing rest blood pressure (5), is associated with an increased prevalence of 3-vessel disease or left main coronary artery disease and is associated with a threefold increased risk in death at 2-year follow-up. Conversely, exaggerated systolic blood pressure response to exercise (defined as peak SBP >200–220 mmHg) is associated with an increased risk of subsequent hypertension. Based on data from the Framingham Offspring Study (19) and Lipid Research Clinics Study (20), elevated low-level exercise blood pressure (Bruce Stage 2 BP >180/90) is associated with cardiovascular disease events in asymptomatic individuals independent of traditional risk factors and rest blood pressure.

Ventricular Arrhythmias

The prognostic role of exercise-induced ventricular ectopy remains controversial (5) with conflicting data. Recent studies suggest that exercise-induced frequent ventricular ectopy, both during exercise and the recovery phase, is associated with increased long-term all-cause and cardiac mortality. Frequent ventricular ectopy is generally defined as increased frequency of premature ventricular contractions (eg, >7 per minute or >10% of beats in a 30-s period), ventricular bigeminy or trigeminy, couplets or triplets, or ventricular tachycardia.

Silent Ischemia

Silent ischemia is defined as the presence of demonstrable myocardial ischemia in the absence of angina symptoms, and has low prevalence (~2.5% in asymptomatic men). The burden of silent ischemia reflected in the number of ischemic episodes on ambulatory ECG monitoring was significantly associated with the incidence of ischemic events at 1-year follow-up in the Asymptomatic Cardiac Ischemia Pilot (ACIP) study (21). Ischemic electrocardiographic response to stress has been associated with increased risk of subsequent cardiac events but has poor predictive value due to the high false-positive rate in low-risk populations.

STRESS TESTING WITH IMAGING FOR SCREENING RISK ASSESSMENT OF ASYMPTOMATIC INDIVIDUALS?

Some studies, but not all, have found additional prognostic value to stress-induced imaging abnormalities in asymptomatic or mildly symptomatic populations. However, absolute event rates were consistently low (even in subjects with abnormal tests) and the sensitivity was too low to justify cost-effective use of these tests.

Indications for Testing With Imaging

In the diagnosis of CHD, exercise testing with imaging as an initial test is only recommended in a limited number of circumstances (22) in which baseline ECG abnormalities make interpretation of ischemic ST segment deviation unreliable: (a) pre-excitation syndrome (Wolff-Parkinson-White), (b) electrically paced ventricular rhythm, (c) greater than 1 mm resting ST segment depression, and (d) complete left bundle branch block (3). Subjects with ventricular-paced rhythms and complete left bundle branch block should generally undergo vasodilator stress perfusion studies due to the increased false-positive rate associated with exercise stress and echocardiographic imaging (22).

Myocardial Perfusion Imaging (MPI)

The Detection of Ischemia in Asymptomatic Diabetics (DIAD) study was a randomized clinical trial to test a strategy of screening pharmacologic (adenosine) MPI versus no screening in asymptomatic individuals with type 2 diabetes to reduce cardiac events, defined as fatal and nonfatal coronary events (23). The DIAD study found no clinical benefit over a 5-year period for routine screening of type 2 diabetic patients without history of CAD with adenosine-MPI, despite a higher risk associated with moderate to large perfusion abnormalities. Despite this, the 2010 ACCF/AHA Guidelines for assessment of cardiovascular risk in asymptomatic adults (1) does provide a Class IIb recommendation (Level of Evidence C) for cardiovascular risk assessment with stress MPI in asymptomatic adults with diabetes, a strong family history of CHD, or when previous risk assessment testing suggests high risk for CHD, such as CAC score of ≥400 (Table 12.1).

Exercise Echocardiograms

A recent study of 1,859 individuals (mean age 51) with no angina, heart failure symptoms, nor history of CHD who were referred for exercise testing by their healthcare providers found no additional prognostic value to exercise echocardiograms for screening these relatively asymptomatic individuals but confirmed the value of exercise capacity or DTS in predicting risk (24).

SUMMARY

Exercise stress testing is a safe procedure and provides both diagnostic and prognostic information in asymptomatic or minimally symptomatic individuals. A growing body of literature supports the utility of nonelectrocardiographic parameters—in particular exercise capacity, chronotropic response, and heart rate recovery—in determining prognosis in asymptomatic subjects beyond traditional risk factors or global risk scores. However, data are still lacking that the screening use of exercise testing results in improved patient outcomes. There are

currently no Class I indications for exercise testing in asymptomatic adults in the American College of Cardiology/American Heart Association guidelines. Guidelines suggest that testing in asymptomatic individuals may be reasonable in the following situations: prior to starting vigorous exercise in the presence of diabetes, older age (men >45 years, women >55 years), higher absolute risk for CHD due to comorbid conditions such as peripheral vascular disease and chronic kidney disease, or for individuals involved in occupations potentially affecting public safety.

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13

Eric Y. Yang, MD
and Vijay Nambi, MD, PhD

Role of Carotid Intima-Media Thickness Assessment in Preventive Cardiology

Carotid intima-media thickness (C-IMT) is a measurement of the combined thickness of the intimal and medial layers of the carotid arterial walls. Since the initial description of ultrasonic measurements of intima-media thickness by Pignoli et al., its measurement with ultrasonography has been well validated against histologic measurements in humans (1,2). Given that atherosclerosis typically occurs in the subintimal region, C-IMT is considered a surrogate measure of atherosclerosis (3–5). In this chapter, we review available evidence from epidemiologic and clinical studies and discuss the current role, recommendations, and guidelines related to the use of C-IMT measurements in preventive cardiology.

MEASURING C-IMT

Consensus statements from the American Society of Echocardiography (ASE) and from the updated 2011 Mannheim Carotid Intima-Media Thickness and Plaque Consensus provide an excellent framework for reproducible measurement of C-IMT (4,5). The authors of these statements make the recommendations shown in Table 13.1.

Patients are usually positioned supine with the neck tilted contralateral to the side to be imaged. External aids that allow for standard imaging angles, such as a Meijer's arc, should be employed to aid in standardizing the neck-probe angle, relative to the midline of the patient's head (Figure 13.1). For tortuous vessels, the patient may be asked to further extend or rotate the neck to elongate the segment. For translation artifacts from pulsatile jugular veins, the patient may be asked to perform a midinspiratory breath hold maneuver to stabilize the images (4).

Standardized image scanning protocols from a large epidemiologic study that has reported C-IMT values in percentiles by age, sex, and race/ethnicity should be used to allow for interpretation of results in the context of an appropriate population (4,5). B-mode ultrasonography is preferred for ultrasound imaging for C-IMT for capturing an entire carotid segment (4,5). The use of M-mode ultrasonography has been reported in previous studies of C-IMT. Although it provides higher temporal resolution than B-mode ultrasonography, this modality has fallen out of favor because it samples only a single scan line and may miss thicker carotid wall regions (4).

An ultrasound sweep of the carotid artery in transverse should be performed from the neck base to the jaw angle to screen for presence of atherosclerotic plaque. (See section below on plaque.) The C-IMT usually appears as a double echogenic parallel line on long-axis views of the carotid artery by B-mode ultrasound (Figure 13.2A) (4,5). Care should be taken to align the carotid vessel of interest horizontally in long-axis and to maximize the length of the double line for C-IMT measurement (4,5). If possible, images should be acquired over at least 2 long-axis imaging planes (Meijer's arc; Figure 13.1). Ideally, the "tuning fork" view, where the bifurcation of the internal and external carotid arteries are

TABLE 13.1 Comparison of Recommendations from the American Society of Echocardiography and the Mannheim Consensus

American Society of Echocardiography Consensus	Mannheim Carotid Intima-Media Thickness and Plaque Consensus
Instrumentation and Display	
• State-of-the-art ultrasound system ◦ Digital image acquisition and storage, preferably Digital Imaging and Communications in Medicine (DICOM) format ◦ Phantom scans every 6 months and after any system changes ◦ Semiannual routine preventive maintenance • Transducer ◦ Linear array ◦ Minimal signal compression (<10:1) ◦ Fundamental frequency ≥7 MHz ◦ Footprint ≥3 cm • Display ◦ Depth 4 cm ◦ Single focal zone ◦ Frame rate ≥25 Hz ◦ High dynamic range ◦ Clear 3-lead electrocardiographic signal ◦ Annotate images to describe segments, angles, and other findings • Carefully adhere to predefined scanning protocols	• High-resolution B-mode system operating in the black and white mode, preferentially with linear ultrasound transducers at frequencies >7 MHz • Appropriate depth of focus (ie, 30–40 mm), and optimal frame rate 25 Hz (15 Hz) provide optimal image quality and facilitate edge detection • Log gain compensation of approximately 60 dB • Gain settings adjusted to obtain a symmetrical brightness on the near and far walls, or in the mid part of the field to eliminate intraluminal artifacts • Each vascular laboratory must perform quality control of their equipment periodically by phantom scans and reliability studies of scans and measurements for ultrasonographers and readers. Reporting requirements include the intra-class correlation coefficients to be evaluated for intra- and interobserver variability, both for IMT and plaque measurements.
Scanning Protocol	
• Transverse B-mode scan (3–5 beat cine-loop in each segment) ◦ From proximal common carotid through the middle of the internal carotid artery ◦ Notch of tranducer oriented to right of patient ◦ Slowly advance probe while keeping vessel in center of screen and showing double lines on near and far walls • Internal and external carotid artery Doppler recordings (one frame of each) ◦ Pulsed wave Doppler of proximal 1 cm of each branch ◦ Sample volume parallel to flow by beam steering and angle correction ≤60° ◦ If narrowing seen, obtain pre- and post-velocities to document severity • Longitudinal plaque screen scan (3–5 beat cine-loop from at least 3 different angles in each segment) ◦ Near and far walls of common carotid, bulb, and internal carotid artery segments ◦ Rotate 90° from transverse plane with notch of transducer oriented toward head of patient ◦ Circumferential plaque screen scan from anterior, lateral, and posterior imaging angles • C-IMT imaging (3–5 beat cine-loop and optimized R-wave gated still frames at each angle) ◦ Distal 1 cm of each common carotid ◦ Longitudinal images from 3 imaging planes: optimal angle of incidence and two complementary angles (anterior, lateral, and posterior) ◦ Use cursor to mark location of bifurcation ◦ Display clear images of distal common carotid perfectly horizontal with double lines on near and far walls, indicating true perpendicular scanning plane ◦ Optimize transducer depth (usually 4 cm) to avoid slice thickness artifacts • Arterial wall segments should be assessed in a longitudinal view, strictly perpendicular to the ultrasound beam • Both walls should be clearly visualized in order to achieve diameter measurements. The optimal diameter should be obtained during diastole by automatic cine-loop detection or by looking for the minimal diameter during the cardiac cycle. • Measurements obtained from radiofrequency signals are equivalent to those obtained with conventional video signals • Lateral probe position is recommended as it offers the best resolution in the midfield. • Acquisition of multi-insonation angles increases procedure time consumption without benefit for measurements; however, in clinical trials they result in better reproducibility and facilitate statistical analysis. • Horizontal arterial image display optimizes the interface between blood and vessel wall structures. • Imaging of the carotid bifurcation provides a landmark essential in serial imaging. • Longitudinal and cross-sectional views are required to visualize focal atherosclerosis.	

Source: Adapted from Refs. (4,5): Stein JH, Korcarz CE, Hurst RT, Lonn E, Kendall CB, Mohler ER, et al. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Endorsed by the Society for Vascular Medicine. *J Am Soc Echocardiogr.* Feb 2008;21:93–111; quiz 89–90. Touboul PJ, Hennerici MG, Meairs S, Adams H, Amarenco P, Bornstein N, et al. Mannheim carotid intima-media thickness and plaque consensus (2004–2006–2011). An update on behalf of the advisory board of the 3rd, 4th and 5th watching the risk symposia, at the *13th, 15th and 20th European Stroke Conferences*, Mannheim, Germany, 2004, Brussels, Belgium, 2006, and Hamburg, Germany, 2011. *Cerebrovasc Dis.* 2012;34:290–296.

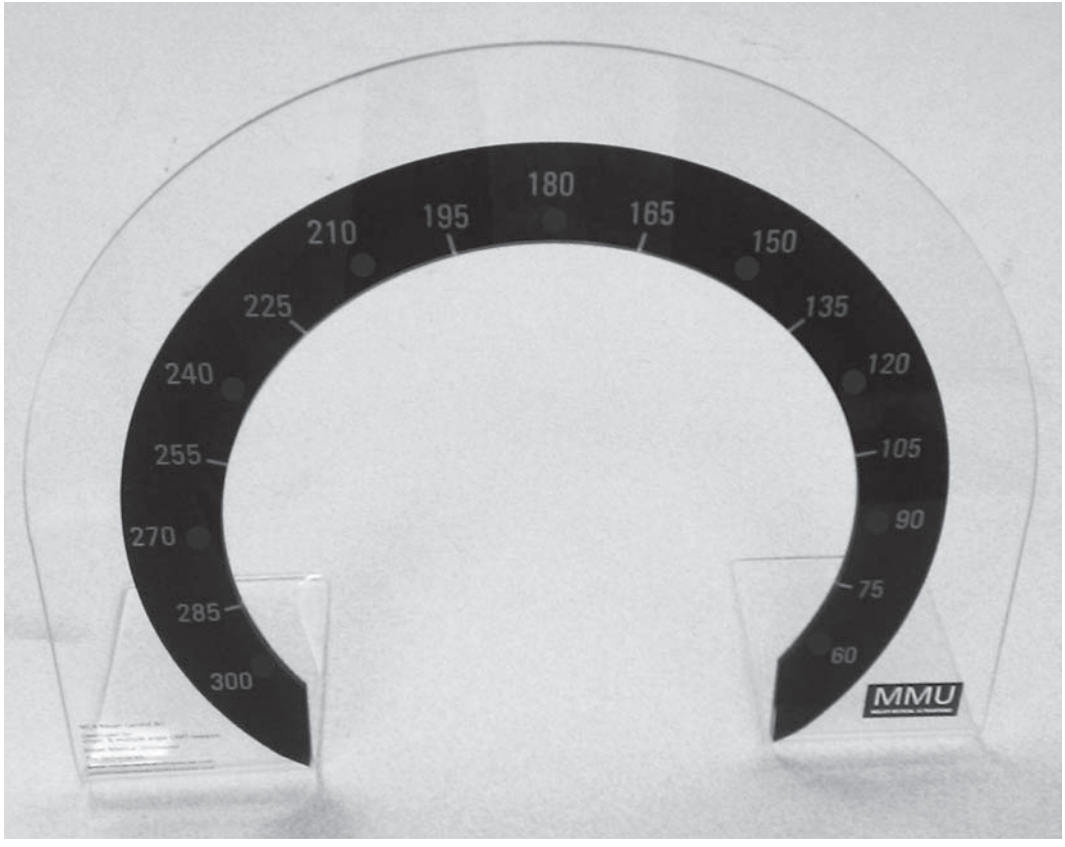

FIGURE 13.1 Meijer's arc used to standardize neck-probe angles.

visualized simultaneously at the flow divider, should be obtained to provide internally reproducible landmarks. Images should be ECG-gated as variations in C-IMT have been observed over the cardiac cycle (6,7). For measurement, the use of semiautomated border detection programs with validated accuracy has been recommended to improve reproducibility (Figure 13.2B) (4,5).

Possible C-IMT Measures (Carotid Segments)

Different carotid segments have been evaluated for their reproducibility in various studies. These comparisons have included near versus far carotid wall and individual carotid segments (ie, common carotid, carotid bulb, internal carotid arterial segments) (8). Additionally, published epidemiologic studies have used different protocols, reporting maximum thickness or mean thickness over the length of a carotid arterial segment or multiple segments (8). These protocols have also differed in measuring C-IMT either at peak systole or at end diastole (6,7).

The current ASE consensus and 2011 Mannheim Consensus have suggested that the mean C-IMT measurement of the distal 1 cm of the far wall of each common carotid artery and averaging for both sides (ie, mean of means) be reported (4,5). However, use of means has been controversial as other epidemiologic and clinical studies suggest use of the maximum C-IMT measurement. The measurement of C-IMT at end diastole versus peak systole has also been controversial (6). Although the authors of both consensuses have recommended measuring C-IMT at end diastole (4,5), the Atherosclerosis Risk in Communities investigators used C-IMT measures acquired at peak systole (9). A study from the Framingham Offspring was reported to show up to 42% of individuals being risk-classified differently depending on the timing in the cardiac cycle used (6). Investigators for the Multi-Ethnic Study on Atherosclerosis (MESA) have also noted similar variations across cardiac cycles with up to 31% of individuals being classified differently (7). In our vascular labs, we have preferred to use measurements obtained at peak systole. Lastly, the use of validated semiautomated or automated edge detection

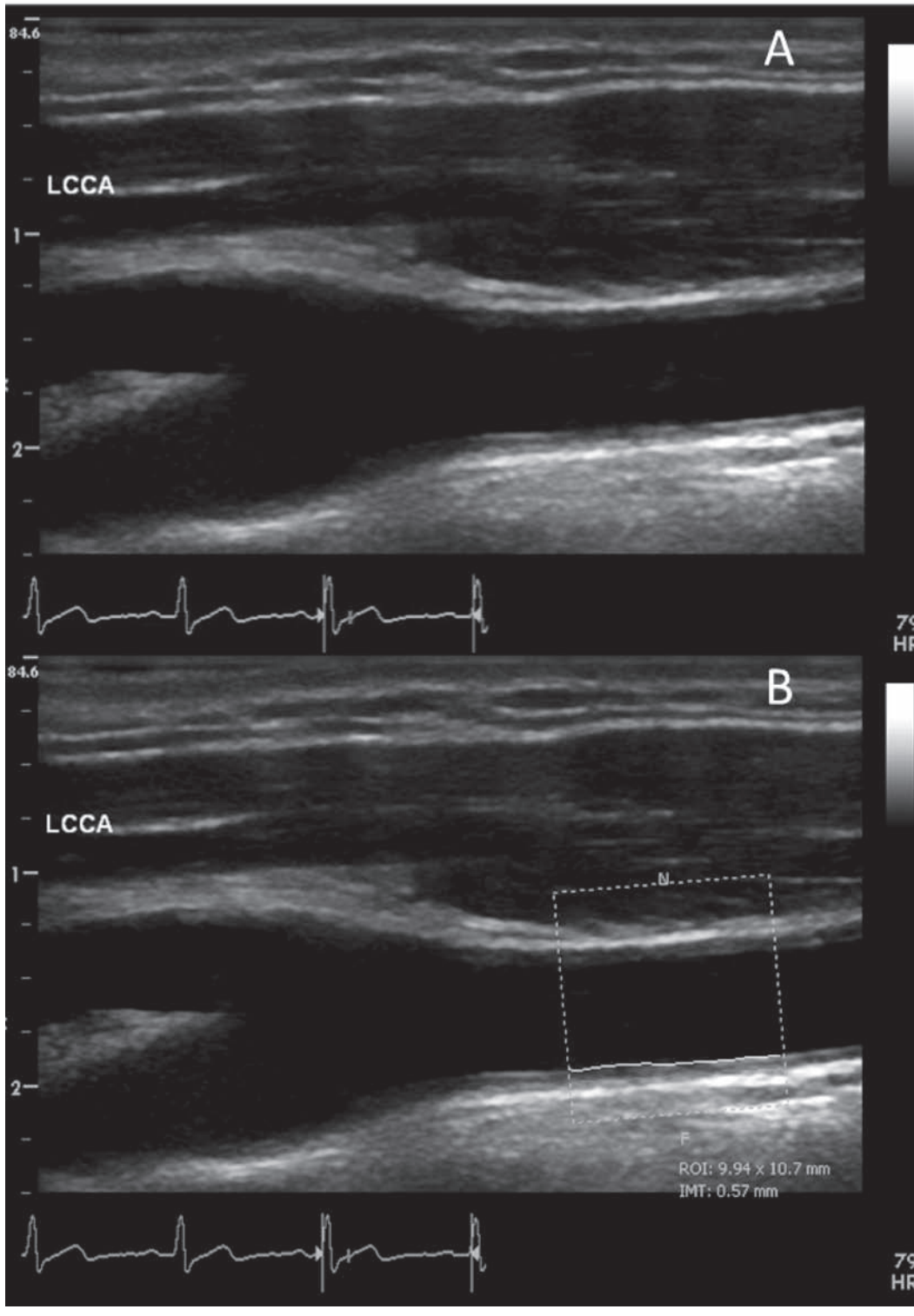

FIGURE 13.2 Electrocardiography-gated images of the left common carotid artery (LCCA) in long-axis A) without and B) with an intima-media layer (IMT) measurement by a validated semiautomated edge detection program.

systems for measuring C-IMT has been recommended to reduce intra- and interreader variability (4,5).

Overall, protocols used for measuring C-IMT should preferentially come from large epidemiologic studies that report C-IMT reference values by age, gender, and race/ethnicity. Ultimately, C-IMT measures should be reported within the context of a normative dataset from an epidemiologic study with a population appropriately matched for a given patient's demographics (4).

REASONS FOR INCREASES IN C-IMT

Atherosclerosis has been considered a process involving the intimal and subintimal layers (2,3) whereas C-IMT measures the combined thickness of both the intima and media. Therefore, although C-IMT is typically thought to represent atherosclerosis, it can increase due to other disease processes as well (ie, other causes that can increase the thickness of the intima or media). Some of these other causes include:

- Medial hypertrophy associated with age-related hypertension (10)
- Vasculitides (Takayasu arteritis, giant cell arteritis)
- Radiation induced arteriosclerosis

In general, when one considers the relative contribution of the intima and media to the C-IMT measurement, the medial contribution is higher irrespective of health or disease (ie, even in atherosclerosis the relative contribution of the media is more). However, in individuals with CVD the relative contribution of the intima increases (11). Therefore, given atherosclerosis is a subintimal process, the C-IMT measure is not an exclusive measure of atherosclerosis alone. Hence, plaque, which may be a better representative of the process of atherosclerosis, has been evaluated as well.

DEFINITION OF CAROTID PLAQUES

Based on the 2011 Mannheim Consensus, carotid plaques have been defined as (a) a ≥0.5 mm or ≥50% focal wall thickening compared with the surrounding vessel wall or (b) a focal region with C-IMT >1.5 mm protruding into the lumen and distinct from the adjacent boundary on carotid ultrasound (5). The presence of significant plaque should be reported because of its prognostic implications for development of coronary heart disease and ischemic strokes (see Use of C-IMT in Epidemiological Studies), a recommendation supported both by the ASE consensus and the 2011 Mannheim Consensus (4,5).

Plaque characteristics could also have value and should be noted. Authors of a National Heart, Lung, and Blood Institute 2012 report have noted that heterogeneous plaques on carotid ultrasounds were more likely to be at risk for embolization or thrombosis than homogeneous ones (12). In contrast, calcified plaques, which have high echogenicity and acoustic shadowing, were considered generally stable (12). However, the very presence of carotid calcifications may be suggestive of atherosclerotic disease presence in other vascular beds, still carries prognostic significance for cardiovascular outcomes, and should also be reported (13,14). Lastly, the advent of 3-dimensional ultrasonography (3D US) will likely change the utility of atherosclerotic plaque assessment (discussed later) in cardiovascular disease assessment and management (15–17).

USE OF C-IMT IN EPIDEMIOLOGICAL STUDIES

C-IMT and Incident Cardiovascular Disease

Many epidemiologic studies have explored the association of carotid intima-media thickness alone with incident cardiovascular disease and have reported significant associations with incident cardiovascular events in general populations.

The published results of several large epidemiologic studies (>5,000 participants) with at least a mean or median follow-up of 5 years have been included in Table 13.2. With the exception of the Malmö Diet and Cancer Study, these epidemiologic studies have found a significant association between C-IMT and incident cardiovascular events (Table 13.2). More recent data from the Atherosclerosis Risk in Communities Study have supported that the addition of mean C-IMT of all segments to traditional cardiovascular risk factors may improve reclassification of individuals, with net reclassification index (NRI) of 7.1 (95% confidence interval [CI] 2.2%, 10.6%) (24).

Other studies in general populations (less than 5,000 participants) with at least mean or median follow-up of 5 years event data have come from the Carotid Atherosclerosis Progression Study (CAPS) and the Framingham Offspring Study (25,26). In CAPS, 4,904 participants (51.8% women, mean age 49.7 years) had the mean of means of the far wall common and internal C-IMT measured and had follow-up over 10 years for CHD events, including myocardial infarction and CHD death (25). For every 0.1 mm common C-IMT increase, the cohort was found to have an adjusted hazard ratio (HR) of 1.089

TABLE 13.2 Association Between Carotid Intima-Media Thickness and Incident Cardiovascular Events

Study	N; Women (%)	Age (years)	Follow-Up (y)	C-IMT Method	Event	Absolute Change in C-IMT (mm); Adjusted HR (95% CI)	C-IMT Cut Point; Adjusted HR (95% CI)
ARIC (18)	12,481; 58	45–64	Median 5.2	Mean of mean CCA/ bulb/ICA	MI, CHD death	0.19; W: 1.38 (1.28, 1.58), M: 1.17 (1.04, 1.31)	Highest tertile; W: 3.76 (1.68, 8.43), M: 2.02 (1.32, 3.09)
ARIC (19)	14,214; 55	45–64	Median 7.2	Mean of mean CCA/ bulb/ICA	Strokes	0.18; W: 1.36 (1.16, 1.59), M: 1.21 (1.05, 1.39)	Highest tertile; W: 2.32 (1.09, 4.94), M: 2.24 (1.26, 4.00)
MDCS (20)	5,163; 59	46–68	Median 7	Mean of right far wall CCA	MI, CHD death	0.15; 1.23 (1.07, 1.41)	Highest tertile; 1.50 (0.81, 2.59)
Rotterdam (21)	6,389; 62	≥55	Range 7–10	Mean of max CCA	MI, CHD death	0.21; 1.28 (1.14, 1.44)	Highest quartile; 1.95 (1.19, 3.19)
CHS (22)	5,020; 60	≥65	Median 11	Mean of max CCA/ ICA	Stroke, MI, CHD death	–	Highest tertile; 1.84 (1.54, 1.79)
MESA (23)	6,562	45–84	Mean 7.8	Mean of max ICA	Stroke, MI, CHD death	Not reported; 1.33 (1.18, 1.49)	–
				Mean of max CCA	MI, CHD death	Not reported; 2.10 (1.30, 3.40)	–

Abbreviations: CI = confidence interval; CCA = common carotid artery; ICA = internal carotid artery; MI = myocardial infarction; CHD = coronary heart disease; ARIC = Atherosclerosis Risk in Communities; MDCS = Malmö Diet and Cancer Study; CHS = Cardiovascular Health Study.

($P = 0.011$) when adjusted for Framingham CHD risk factors, and a HR of 1.063 ($P = 0.041$) when adjusted for Systematic Coronary Risk Evaluation (SCORE) risk factors (25). In the Framingham study, 2,965 participants (55.3% women, mean age 58 years) had the mean of the common C-IMT and the max of the internal C-IMT measured and were followed over an average of 7.2 years for incident cardiovascular disease, including myocardial infarction, CHD death, strokes, peripheral arterial disease, and heart failure (26). This cohort was found to have a HR 2.46 (95% confidence interval [CI] 1.18, 5.13) for every 1-mm common C-IMT increase and HR 1.26 (95% CI 1.16, 1.36) for every 1-mm internal C-IMT increase (26). When internal C-IMT measures were used to reclassify individuals, the investigators found a significant net reclassification index of 7.6% ($P < 0.001$).

Thus, available epidemiologic studies have supported an incremental benefit of using C-IMT over traditional cardiovascular risk factors for risk assessment.

Meta-Analyses

Two recent meta-analyses reported on the association of C-IMT with CVD. Lorenz et al. identified 8 observational studies in 12 publications through January 31, 2006, pooling a total of 37,197 subjects with age range 19 to 75 years over a mean follow-up of 5.5 years (27). They found a hazard ratio (HR) of 1.26 (95% confidence interval [CI] 1.21 to 1.30)

for myocardial infarction and a HR 1.32 (95% CI 1.27 to 1.38) for stroke, for every 1 standard deviation (SD) difference in C-IMT (27). For every absolute C-IMT difference of 0.1 mm, they found a HR 1.15 (95% CI 1.12 to 1.17) for myocardial infarction and a HR 1.18 (1.16 to 1.21) for stroke (27). They observed a nonlinear relationship between C-IMT and cardiovascular events.

On the other hand, Den Ruijter et al. identified 14 observational studies through June 2012, pooling a total of 45,828 individuals with mean age 58 (range 35 to 75 years) (28). They reported that over a median follow-up of 11 years, every absolute C-IMT difference of 0.1 mm was associated with a HR 1.09 (95% CI 1.07 to 1.12) for any first-time myocardial infarction or stroke (28). For the same C-IMT difference, the authors reported a HR 1.08 (95% CI 1.05 to 1.10) for myocardial infarction alone and a HR 1.12 (95% CI 1.10 to 1.15) for stroke alone (28).

Neither meta-analysis pursued a strategy of restratifying intermediate risk individuals using the highest (≥75th percentile) and lowest (<25th percentile) quartiles for appropriately age- and gender-matched groups, as recommended by the ASE consensus (4). Nor did these studies include the contribution of plaque to risk or the combined effect of both C-IMT and plaque.

Progression of C-IMT

Limited data exist to support the use of serial measurement of C-IMT. One investigation of the Multi-Ethnic Study on Atheosclerosis (MESA) cohort found an association between C-IMT progression and incident stroke, showing an hazard risk ratio of 1.23 per 0.05 mm/year (95% confidence interval 1.02 to 1.48) increase in the common C-IMT (29). A recent study from a European longitudinal cohort study (the IMPROVE study) following 3,711 individuals aged 54 to 79 years showed that although all IMT measures increased over time, only one IMT measure (the fastest IMT max change or the segment with the most change in maximum IMT) was associated with increased risk of subsequent vascular events (30). On the other hand, a meta-analysis of 22 population-based studies that pooled 36,984 participants with 257,067 person-years of follow-up reported that the mean common C-IMT progressed by 0.001 to 0.030 mm and the maximal common C-IMT by 0.001 to 0.065 (31) but was associated with an adjusted hazard ratio for incident cardiovascular events of 0.98 (95% CI 0.95, 1.01) (31) for every one standard deviation in mean common C-IMT progression suggesting that the change in C-IMT was not associated with incident CVD. However, one of the many limitations for this meta-analysis was the possibility of measurement errors, which newer technologies such as 3-dimensional ultrasound tracking and coregistration mapping may help to reduce (32). Currently, more contemporary studies are needed before serial C-IMT measurements can be considered for use in clinical practice.

C-IMT Versus Coronary Artery Calcium Score

Overall, there have been limited data that have reported on the relative value of C-IMT when compared to coronary calcium score (CACS) in CVD prediction. The MESA investigators compared C-IMT and coronary calcium score in (33) 6,698 adults aged 45 to 84 years who were followed over a median 3.9 years (maximum, 5.3 years). The authors reported that for every 1-SD increment in C-IMT, the adjusted HR (95% CI) were 1.3 (1.1 to 1.4) for all cardiovascular disease events, 1.2 (1.0 to 1.4, $P = 0.01$) for CHD events, and 1.4 (1.2 to 1.8) for stroke events (33). On the other hand, for every 1-SD increment in CACS, the adjusted HR (95% CI) were 2.1 (1.8 to 2.5) for all cardiovascular disease events, 2.5 (2.1 to 3.1) for CHD events, and 1.1 (0.8 to 1.5) for stroke events (33) suggesting that CACS had a stronger association with CHD events and C-IMT had a stronger association with ischemic strokes. However, the authors reported notifying primary care providers for 17% of participants for high CACS and 1% for high C-IMT (33). Whether this led to any bias related to the management of subjects and how this affected the association between CACS and C-IMT with incident CVD is not clear.

In a more elderly cohort, Newman et al. have previously reported a comparison between CACS and C-IMT measures for incident cardiovascular disease (34). In this study, 559 subjects ranging in age from 70 to 99 years underwent CT scans and carotid ultrasonography between 1998–2000 and were followed for 5 years (34). In comparing highest with lowest quartiles of CACS and C-IMT for incident cardiovascular disease, CACS was associated with an adjusted HR of 2.3 [95% CI 1.20, 3.9] whereas the common C-IMT was associated with an adjusted HR 2.3 [95% CI 1.3, 4.1] (34). When individual events were evaluated CACS had a stronger association with MI and common C-IMT with stroke. Neither of these studies evaluated the use of plaque along with C-IMT in their comparisons. Therefore, currently, only inadequate and suboptimal data exist to evaluate the comparison

of C-IMT/plaque with CACS; however, in general, CACS has been better associated with MI and C-IMT with stroke.

Importance of Plaque

A number of epidemiologic studies have examined the association of carotid plaques seen on ultrasound with incident cardiovascular events, and a summary of a few have been included for reference (Table 13.3).

Of the studies in Table 13.3, two large population-based studies have included analyses on carotid plaque presence in reclassifying cardiovascular risk categories for individuals: the ARIC and the MESA studies. In the ARIC study, the net reclassification index (NRI) when C-IMT alone was added to traditional cardiovascular risk factors was previously discussed, suggesting significant improvement in cardiovascular risk prediction models. When the presence of carotid plaque was added on top of risk factors and C-IMT, the NRI increased to 9.9% (95% CI 3.8%, 13.5%) (14). In the MESA study, plaques were defined as either any presence of causing >25% diameter narrowing at the bulb (23). When combined with a model with traditional risk factors and mean of maximum common C-IMT, the NRI for incident cardiovascular events were 5.7% ($P = 0.010$) and 4.7% ($P = 0.014$), respectively (23).

Additional analyses from the ARIC study have found similar improvements in cardiovascular risk prediction models with plaque presence and C-IMT measurements, regardless if the C-IMT measurements come from only the common carotid or from an average of all carotid artery segments (ie, common, bulb, and internal carotid arteries) (35). With an ARIC risk score model, the addition of plaque presence and only common C-IMT resulted in an NRI of 7.6% (95% CI 2.9%, 13.0%), whereas the addition of plaque presence and averaged C-IMT resulted in an NRI of 8.9% (95% CI, 4.1, 14.4) (35). With a Framingham risk score model, the NRI was 16.2 (95% CI 11.2%, 21.9%) for only common C-IMT and 16.5 (95% CI 11.6%, 23.6%) for averaged C-IMT (35).

A meta-analysis of 11 population-based studies has also been conducted to examine the association of carotid plaque and of C-IMT with future myocardial infarction (36). In this analysis, 54,336 individuals with mean follow-up of 8 years were pooled (36). Although a higher area under the curve (AUC) for carotid plaque (0.64 [95% CI 0.61, 0.67]) than for C-IMT (0.61 [95% 0.59, 0.64]), there was no significant difference in AUC between the two (36). Significant differences in sensitivities and specificities for each imaging marker were noted, but very high heterogeneity in the analyses was also found (36). When the diagnostic odds ratio of future myocardial infarction given carotid plaque presence was compared with that of given C-IMT, there were increased odds for future MI with carotid plaque (odds ratio 1.35 [95% CI 1.03, 1.82]) (36).

TABLE 13.3 Association Between Carotid Plaque Presence and Incident Cardiovascular Events

Study	N; Women (%)	Age (years)	Follow-Up (y)	Event	Plaque Presence Adjusted HR (95% CI)
ARIC (14)	12,375; 57	45–64	Mean 7.0	MI, CHD death	Without AS: 1.47 (1.10, 1.97) With AS: 2.96 (2.19, 3.99)
ARIC (24)	13,145; 57	45–64	Mean 15.1	MI, revascularization, CHD death	–
MDCS (20)	5,163; 59	46–68	Median 7	MI, CHD death	1.81 (1.14, 2.87)
Rotterdam (21)	6,389; 62	≥55	Range 7–10	MI, CHD death	Severe; 1.83 (1.27, 2.62)
CHS (22)	5,020; 60	≥65	Median 11	Stroke, MI, CHD death	High risk; 1.38 (1.14, 1.67)
MESA (23)	6,562	45–84	Mean 7.8	Stroke, MI, CHD death	1.49 (1.22, 1.82)

Abbreviations: NRI = net reclassification index; CI = confidence interval; AS = acoustic shadowing; MI = myocardial infarction; CHD = coronary heart disease; ARIC = Atherosclerosis Risk in Communities; MDCS = Malmö Diet and Cancer Study; CHS = Cardiovascular Health Study.

USE OF C-IMT AND CAROTID PLAQUE FOR CHD RISK ASSESSMENT

A 10-year CHD risk prediction tool that incorporates C-IMT and presence of plaque is available for use at http://www.aricnews.net/

WHEN TO MEASURE C-IMT

The use of C-IMT measurements in the clinical setting has been controversial. As early as 2002, the National Cholesterol Education Program recognized the potential of C-IMT measurements in restratifying persons with multiple risk factors to a higher risk category but expressed reservations because of the lack of standard consensus on examination technique (37). In 2009, the United States Preventative Services Task Force (USPSTF) conducted a systematic review of the available evidence regarding C-IMT measurement. The USPSTF concluded that C-IMT measurement may be useful in certain settings but could not recommend incorporating its use in risk assessment for primary prevention (38,39). However, the task force also made similar recommendations for a number of emerging risk markers, including coronary artery calcium scores, high-sensitivity C-reactive protein levels, and ankle-brachial index scores (38,39). Since the USPSTF recommendations, several studies supporting the value of C-IMT and plaque presence in cardiovascular disease risk prediction have been published (24,35,36). The USPSTF again pointed out the need for consensus in examination techniques and the need for further studies (a) to validate its use in prospective, population-based cohorts with appropriate assessment of other cardiovascular risk factors and (b) to establish its incremental benefit in persons classified as intermediate-risk by the Framingham risk score (38, 39).

The American Heart Association (AHA) and American College of Cardiology (ACC) have gone on to issue joint recommendations on assessing cardiovascular risk in asymptomatic adults in 2010 (40). For C-IMT, the guideline task force has endorsed the following class IIA recommendation (reasonable, level of evidence B from nonrandomized studies):

> Measurement of carotid artery IMT is reasonable for cardiovascular risk assessment in asymptomatic adults at intermediate risk. Published recommendations on required equipment, technical approach, and operator training and experience for performance of the test must be carefully followed to achieve high-quality results.

Since then, the European Society of Hypertension and European Society of Cardiology have also endorsed the use of C-IMT measurements, but for the screening of asymptomatic organ damage, cardiovascular disease, and chronic kidney disease. In their joint 2013 guidelines, the ESH/ESC give the following class IIA recommendation (should be considered, level of evidence B from large nonrandomized studies) (41):

> Ultrasound scanning of carotid arteries should be considered to detect vascular hypertrophy or asymptomatic atherosclerosis, particularly in the elderly.

However, more recently, the ACC/AHA Guideline for Cardiovascular Risk Assessment does not recommend routine measurement of C-IMT in clinical practice for assessing risk of a first CVD event (Class IIIb) (45).

In conclusion, current guidelines suggest that C-IMT may be useful for refining cardiovascular risk in individuals classified as intermediate-risk or for screening for vascular diseases, especially in the elderly.

LONG-TERM OUTLOOK ON C-IMT

The utility of C-IMT in other populations is being investigated. An international consortium on cardiovascular health in childhood has assembled data on 5,785 young adults, one of the largest pools of epidemiologic studies in the young with C-IMT measurements (42). The consortium has included the Minneapolis Childhood Cohort Studies, the Princeton Follow-up Study, the Bogalusa Heart study, the Cardiovascular Risks in Young Finns Study, and the Childhood Determinants of Adult Health Study (42). As these cohorts age, we will learn the associations between C-IMT measured in the young and cardiovascular risk factors in middle age, and may find indications for measuring C-IMT expanded to this population.

New ultrasound technologies have been in development to improve the assessment of C-IMT and plaque. Our group has conducted early clinical work using coregistration for fusing ultrasound with other imaging modalities and for improving upon serial assessment of C-IMT (32). Three-dimensional ultrasound holds promise in quantifying carotid intima-media volumes and plaque burden, and groups have already begun validation studies of such technologies (15–17). Landry et al. have reported work with early forms of 3D US suggesting reasonable intraobserver and interobserver reproducibility and the ability to detect 10% to 30% increases in plaque volume, depending on absolute plaque volume size (15).

Johri et al. have described a similar analysis system used in a series of 70 subjects (16). The more recent High Risk Plaque BioImage study has begun following 6,101 asymptomatic subjects in whom a number of vascular assessments were measured, including C-IMT and carotid plaque volume or burden (17). The study has already found a stronger correlation at baseline for coronary artery calcium scoring with carotid plaque volume than with other indices (C-IMT, ankle-brachial index, and abdominal aortic diameter) and will complete a 12-month follow-up for each participant over a 3-year period (17).

Other groups have also been working on software algorithms for processing tissue echogenicity and on the use of ultrasound contrast agents for detecting neovascularization to achieve ultrasound-based tissue characterization and plaque detection (43,44). Lastly, the lack of any officially endorsed lab standards has limited C-IMT measurements from clinical use.

CONCLUSIONS

Measurement of carotid intima-media thickness (C-IMT) has been recognized as a potential risk marker for subclinical atherosclerotic disease. It has been well validated in large epidemiologic studies and may provide incremental benefit in cardiovascular risk assessment over traditional cardiovascular risk factors. The presence and characteristics of carotid atherosclerotic plaques should also be noted because of their prognostic significance for cardiovascular risk. Consensus statements support the use of standardized protocols for measuring C-IMT, and recent guidelines endorse its use in asymptomatic intermediate risk individuals or in the elderly.

SUMMARY

The measurement of carotid intima-media thickness (C-IMT) is a noninvasive surrogate of subclinical atherosclerotic disease. Data from large population-based studies have demonstrated the prognostic value of C-IMT measures. The use of standardized protocols from a large population-based study has been recommended in consensus statements from the American Society of Echocardiography and the Mannheim Consensus Group. Per consensus recommendations, we have used ultrasound systems with a linear array transducer with at least a 3-cm footprint and set to a 10 to 14 MHz fundamental frequency with minimal signal compression (<10:1), single focal depth, and frame rates of at least 25 Hz. We recommend the use of electrocardiographic (ECG) gating, measures to standardize neck-probe angle for imaging, and the use of validated semiautomated edge detection software (to reduce inter- and intraobserver variability) for C-IMT performance and measurements. We routinely measure C-IMT averaged over a 1-cm length of the far carotid wall of the distal common carotid artery but it is reasonable to include other segments such as bulb and internal carotid arteries as well. In addition to C-IMT, the presence and characteristics of atherosclerotic plaques should also be noted in reports. The future will likely see the use of 3-D based plaque volume measurements replacing the measurement of C-IMT.

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Salman Waheed, MD, MPH, MHS
and Khurram Nasir, MD, MPH

Role of Noncontrast Coronary CT for Detection of Coronary Heart Disease and Cardiovascular Disease Risk Stratification

Cardiovascular disease (CVD) carries a major morbidity and mortality. It is the leading cause of mortality worldwide for both men and women, with coronary heart disease accounting for almost half of all CVD deaths (1–3). In the United States, it is estimated that 600,000 people die of heart disease every year (4). Data suggest that the overall mortality rate from CVD has declined in the last two decades, implying improved secondary prevention strategies. However, the incidence of CVD remains relatively steady, suggesting that more robust primary prevention efforts are needed (5–7). Moreover, almost one-half of those with coronary heart disease present with either myocardial infarction or sudden death (1). To effectively identify individuals at risk, several different risk prediction tools have been developed and validated combining different sets of variables (8–10). Unfortunately, traditional risk factors only predict 65% to 85% of future cardiovascular events (1). Although they identify a large proportion of those at risk, they misclassify many individuals into low-risk categories who actually are at increased risk for a major cardiovascular event (11).

Over the past decade, there has been increasing interest in using noncontrast coronary computerized tomography (CT) to screen individuals for coronary artery calcium (CAC), which is considered a comparable measure of coronary atherosclerotic burden in adults. There is an association between the total atherosclerotic plaque burden and the future risk of an acute cardiovascular event (12). Although it has been debated whether calcific or noncalcific plaques cause acute rupture leading to an acute event, presence of extensive calcification specifies the presence of both plaque morphologies (13,14). A growing body of evidence suggests that there is an important role of noncontrast coronary CT for the identification of CAC in both asymptomatic as well as symptomatic individuals, which can not only provide important prognostic information but also refined risk stratification.

In this chapter, we address the role of noncontrast coronary CT in asymptomatic and symptomatic individuals.

CORONARY ARTERY CALCIUM: HOW IS IT MEASURED AND SCORED?

Multidetector CT (MDCT) is the most frequently used modality to assess coronary artery calcification (15). With newer techniques, radiation dose has significantly been reduced to approximately 1.0 mSv (16). Without the use of any contrast agent, usually 40 consecutive 2.5 to 3.0 mm thick images are acquired using prospective ECG triggering in axial mode at a predetermined offset from the R wave. CAC is defined as a hyperattenuated lesion above a threshold of 130 Hounsfield units (HU) with an area ≥3 adjacent pixels (at least 1 mm^2). CAC is scored using either the Agatston method (15) or the volume score

method (17). Both methods provide a total CAC score that is the sum of the individual scores calculated from the lesions visualized in one of the four coronary vessels: that is, the left main, left anterior descending, left circumflex, and the right coronary arteries. Zero score means no CAC whereas scores of 1–99, 100–399, and ≥400 (or >75th percentile for age, gender, and race) suggest mild, moderate, and significant CAC, respectively. For a particular age, gender, and race, a Web tool provides the estimated probability of nonzero CAC and the 25th, 50th, 75th, and 90th percentiles of CAC score distribution. By entering an individual's age, race, and gender information and the observed CAC score, this tool will also provide the estimated percentile for the individual's thereby comparing an individual CAC score to others with the same age, race, and gender (18,19).

ROLE OF NONCONTRAST CORONARY CT IN ASYMPTOMATIC INDIVIDUALS

Independent Association of CAC With Risk of Future Cardiovascular Events

Several studies have assessed the role of CAC among asymptomatic individuals and its association with future risk of cardiovascular events as well as all-cause mortality (20–36; Table 14.1). Overall, there is consensus among studies that CAC is a strong independent predictor for future coronary heart disease events as well as all-cause mortality even after adjusting for conventional cardiovascular risk factors.

Data from the Multi-Ethnic Study of Atherosclerosis (MESA), on 6,722 men and women free of cardiovascular disease at baseline who were followed for a median of 3.8 years, showed that among those with CAC of 1–100, 101–300, and >300, the adjusted hazard ratios (95% confidence interval) for a major coronary event (myocardial infarction or death from coronary heart disease) were 3.89 (1.72–8.79), 7.08 (3.05–16.47), and 6.84 (2.93–15.99), respectively, compared to those with a CAC score of zero. Risk ratios from this prospective population-based cohort were similar to findings reported by prior studies (21,26–28,31,34–38).

A recent study from MESA on 6,698 individuals also examined the joint association of CAC score and cardiovascular risk factors with future risk of coronary heart disease events. They categorized the cohort into several groups according to the number of risk factors (0, 1, 2, or ≥3) and CAC score (0, 1–100, 101–300, and >300). Risk factors that they considered included current cigarette smoking, hypertension, diabetes, family history of coronary heart disease, high LDL-C ≥130 mg/dL, and low HDL cholesterol (<38 mg/dL in men or <50 mg/dL in women). They found that 35% of those with ≥3 risk factors had a CAC score of zero whereas 19% of those with zero risk factor had a CAC score of >300 (Figure 14.1 shows distribution of CAC by risk factors). After a mean follow-up of more than 7 years, event rates were 3.5-fold lower in the former group (3.1/1,000 person-years) compared to the latter group (10.9/1,000 person-years) (33).

Another recent study from MESA examined the combined association of CAC score and lipid abnormalities with future risk of cardiovascular disease. They divided the cohort into several categories according to the number of lipid abnormalities ([no lipid abnormality when LDL-C< 130 mg/dL, HDL-C <40 mg/dL for men and <50 mg/dL for women, and triglyceride ≥150 mg/dL], 1, 2, or 3 lipid abnormalities) and CAC score (0, 1–99, ≥100). Results showed that those with CAC score of zero and 3 lipid abnormalities had event rate of 5.9/1,000 person-years compared to 22.7/1,000 person-years in those with zero lipid abnormality and CAC score ≥100 (29).

All these results from MESA further strengthen the existing evidence that there is a strong independent association between CAC score and future risk of cardiovascular events as well as mortality; the higher the CAC score, the higher is the risk of future events. More important, CAC score is predictive of future risk independent of other risk factors.

Studies have also assessed the role of CAC score across different ethnic groups and have shown that a higher CAC score is associated with higher risk of future cardiovascular events across different ethnic groups, and therefore, provides useful predictive information for all ethnic groups (24,38).

Added Value of CAC to Traditional Risk Factors for Cardiovascular Risk Prediction

Framingham risk score (FRS), an inexpensive and easily accessible tool, has long been widely accepted as the standard risk assessment method to predict future risk of cardiovascular events. It incorporates age, gender, smoking history, hypertension, total cholesterol, and HDL-C to derive estimated risk of developing a future cardiovascular event within 10 years, defined as angina, myocardial infarction, or coronary death (39). However, data suggest that FRSs misclassify a large number of individuals into lower risk categories when their risk for future events is actually high (11). Studies have compared newer markers such as high-sensitivity C-reactive protein (hsCRP) with FRS to

TABLE 14.1 Summary of Studies Examining the Association of Coronary Artery Calcium with Risk in Asymptomatic Individuals

Author (Year)	Sample Size	Duration of Follow-Up	Study Design	Exposure	Outcome	Results
Arad et al. (37) (2000)	1,172	3.6 years	Observational	CAC	Death, non-fatal MI and revascularization procedures	Compared to those with CAC score < 160, odds ratio of 20 among those with CAC score ≥ 160.
Wong et al. (36) (2000)	926	3.3 years	Observational	CAC	MI, stroke, and revascularization	Compared to CAC = 0, relative risk was 4.5 and 8.8 among those with CAC 81–270 and ≥ 271, respectively.
Raggi et al. (31) (2001)	676	2.7 years	Observational	CAC	Fatal and nonfatal MI	Compared to those with CAC = 0, odds ratio of 21.6 among those with CAC score at 90th percentile.
Kondos et al. (27) (2003)	5,635	3.1 years	Observational	CAC	Death, MI, revascularization	Compared to those with CAC = 0, relative risk of 7.2 in the highest quartile of CAC score (170–7,000) for hard events (death & MI).
Shaw et al. (32) (2003)	10,377	5.0 years	Observational	CAC	All-cause mortality	Compared to CAC score of 10 or less, relative risk of 4.0 among those with CAC score of > 1000.
Greenland et al. (26) (2004)	1,312	7.0 years	Prospective population based	CAC, FRS	Nonfatal MI, CHD death	CAC score significantly improved risk prediction in all categories of FRS when FRS is higher than 10%.
Arad et al. (21) (2005)	4,613	4.3 years	Prospective population based	CAC, CRP, FRS	ASCVD, CAD, nonfatal MI, and death	Compared to CAC score of < 100, relative risk of 11.1 for CAD among those with CAC ≥ 100.
Vliegenthart et al. (35) (2005)	1,795	3.3 years	Prospective population based	CAC, FRS	CHD, hard CHD (MI and CHD mortality), CVD, and total mortality.	Compared to CAC score of 0–100, relative risk of coronary events was 8.3 for CAC score > 1000.
Taylor et al. (34) (2005)	1,983	3.0 years	Prospective cohort	CAC, FRS, FH of CHD	CHD events	11.8-fold increased risk for CHD among those with the presence of CAC after controlling for FRS.
Lamonte et al. (28) (2005)	10,746	3.5 years	Retrospective	CAC	Hard events (CHD death & nonfatal MI) All events (hard events plus revascularization)	Four CAC categories as: zero CAC and sex-specific CAC thirds (men: 1–38, 39–249, ≥ 250; women: 1–16, 17–112, ≥ 113). Rates/1000 person-years for hard events were 0.4, 1.5, 4.8, and 8.7 in men and 0.7, 2.3, 3.1, and 6.3 in women.

(*continued*)

TABLE 14.1 Summary of Studies Examining the Association of Coronary Artery Calcium with Risk in Asymptomatic Individuals (*continued*)

Author (Year)	Sample Size	Duration of Follow-Up	Study Design	Exposure	Outcome	Results
Anand et al. (20) (2006)	510	2.2 years	Prospective	CAC, myocardial perfusion imaging	CHD death, nonfatal MI, ACS, stroke, late revascularization	Compared to CAC score 0–100, relative risk of 10.1, 40.7, and 58.1 for CAC 101–400, 401–1000, and >1000, respectively.
Nasir et al. (30) (2007)	14,812	6.8 years	Observational	CAC, Race	All-cause mortality	Compared to non-Hispanic white, relative risk was 16.1 for African-Americans with CAC>400, 7.9 to 9.0 for Hispanics with CAC≥400, 6.6 for Asians with CAC≥1000.
Budoff et al. (23) (2007)	25,253	6.8 years	Observational	CAC, CHD risk factors	All-cause mortality	Compared to CAC=0, scores of 11–100, 101–299, 300–399, 400–699, 700–999, and >1000 were associated with 2.2, 4.5, 6.4, 9.2, 10.4, and 12.5-fold increased risk, respectively.
Detrano et al. (24) (2008)	25,253	3.4 years	Prospective population based	CAC, CHD risk factors	MI, CHD death	Compared to CAC=0, scores of 101–300 and >300 were associated with 7.7 and 9.7-fold increased risk, respectively.
Becker et al. (22) (2008)	25,253	3.3 years	Prospective population based	CAC	MI, CHD death	Compared to CAC<75th percentile, CAC score>75th percentile was associated with higher event rate (MI: 3.6% vs. 1.6%, $P<0.05$ and CHD death: 2.2% vs. 0.9%).
Erbel et al. (25) (2010)	4,129	5.0 years	Prospective population based	CAC, FRS, NCEP ATP III	Nonfatal MI, CHD death	Compared to CAC=0, higher CAC was associated with a significantly higher risk (1.4–16.4-fold). Adding CAC to FRS and NCEP ATP III categories significantly improved risk prediction.
Silverman et al. (33) (2013)	6,698	7.1 years	Prospective population based	CAC, CHD risk factors	CHD events	Event rates were 3.5-fold lower in those with ≥3 risk factors and CAC=0 (3.1/1,000 person-years) compared to those with 0 risk factor and CAC≥300 (10.9/1,000 person-years).
Martin et al. (29) (2014)	6,698	7.0 years	Prospective population based	CAC, lipid abnormalities	CVD	Those with CAC score of zero and 3 lipid abnormalities had event rate of 5.9/1,000 person-years compared to 22.7/1,000 person-years in those with zero lipid abnormality and CAC score ≥100.

Abbreviations: CAC = coronary artery calcium, MI = myocardial infarction, FRS = Framingham risk score, CRP = C-reactive protein, CAD = coronary artery disease, ASCVD = atherosclerotic cardiovascular disease, CHD = coronary heart disease, FH = family history, NCEP = National Cholesterol Education Program, ATP = Adult Treatment Panel, CVD = cardiovascular disease.

see if there is an improvement in risk prediction above and beyond the FRS. However, the improvement has been modest, which makes their clinical utility limited for this purpose.

On the other hand, studies that have examined the predictive ability of CAC score for future risk of cardiovascular events and mortality have shown that there is marked improvement in risk prediction above and beyond the FRS when the CAC score is combined with FRS. In one study, it was shown that within each risk category of FRS, an increasing level of CAC score is associated with a higher risk of nonfatal myocardial infarction or coronary heart disease death (26). They also demonstrated that the event rates among those in the high FRS risk group with a lower CAC score were lower than those in the intermediate FRS risk group with a high CAC score. This is particularly interesting because the intermediate risk group is actually the group where misclassification is the highest and improved risk stratification is the most needed.

Similar findings have been noted in other population-based cohort studies (21,24). In MESA, the C-statistic for major coronary events was 0.79 with traditional risk factors as compared to 0.83 ($P = 0.006$) when CAC score was added to the model with traditional risk factors (24). A summary of these studies is shown in Table 14.2.

Studies have also shown that although a high CAC score identifies those at significantly increased risk for a future cardiovascular event and/or mortality, absence of CAC appears to be one of the strongest factors to provide reassurance that risk for future events is significantly lower (40,41). This was reported in a meta-analysis of 64,873 asymptomatic individuals where they found that among those with zero CAC, only 0.47% (154/29,312) had a cardiovascular event during mean follow-up of 4.2 years compared to 4.14% (1,749/42,283) among those with some degree of CAC (total relative risk ratio of 0.15, $P < 0.001$), Figure 14.3a (42). This finding is particularly important because a large proportion of those with several risk factors actually have zero CAC (33).

This was shown in a recent study from the MESA cohort that examined the distribution of CAC by risk factor burden and reported that a large number of individuals with ≥3 risk factors have a CAC score of zero (35%) (Figure 14.1). The rate of hard coronary heart disease events in this group (1.4/1,000 person-years) was more or less similar to those with fewer risk factors: that is, 1.1/1,000 person-years among those with only 1 risk factor and CAC = 0. On the other hand, it was observed that risk is severalfold higher among those with a FRS <6% who have a CAC >300 compared to those with FRS >20% but no CAC (Figure 14.2). When they ignored the CAC score, risk was about twofold higher among those with ≥3 risk factors compared to those with only 1 risk factor (1.6 vs. 2.9 compared to those with no risk factors) (33).

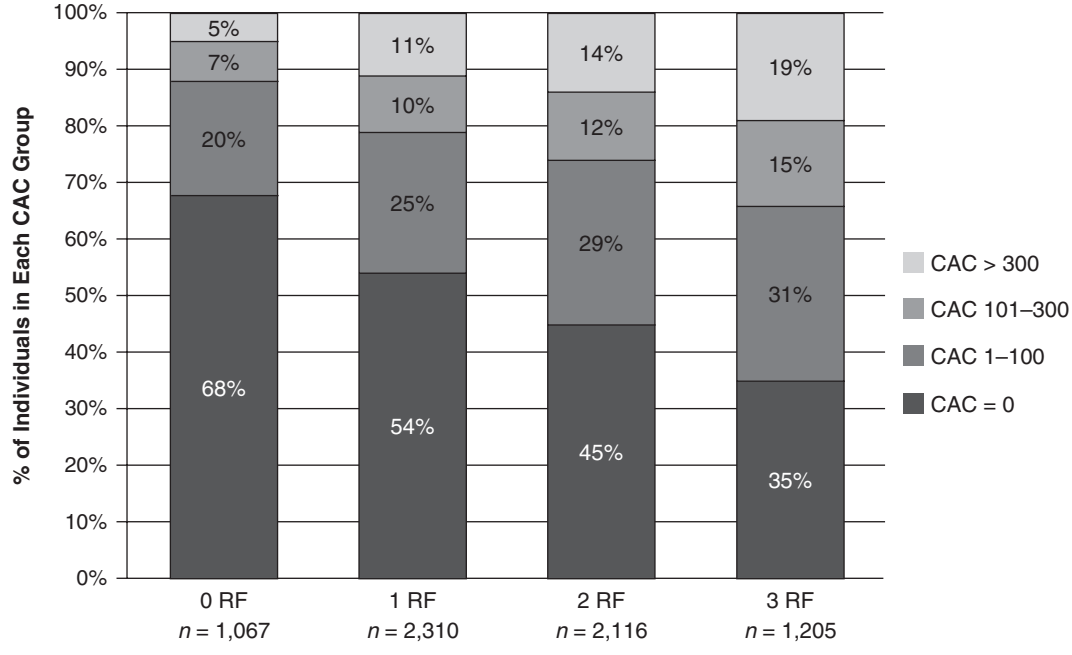

FIGURE 14.1 Distribution of coronary artery calcium by risk factor burdern

Source: Ref. (33). Silverman MG, Blaha MJ, Krumholz HM, et al. Impact of coronary artery calcium on coronary heart disease events in individuals at the extremes of traditional risk factor burden: the Multi-Ethnic Study of Atherosclerosis. *Eur Heart J*. Dec 23 2013.

TABLE 14.2 Comparison of Predictive Ability of Coronary Artery Calcium, Traditional Risk Factors, and Combined for Different Cardiovascular Outcomes

Author (Year)	Study Design	Outcomes[#]	Framingham Risk Score (AUC)	CAC (AUC)	Framingham Risk Score + CAC (AUC)	Traditional CV Risk Factors (AUC)	Traditional CV Risk Factors + CAC (AUC)	*P* Value*
Arad et al. (37) (2000)	Observational	Nonfatal MI or CHD death		0.86				NA
Raggi et al. (31) (2001)	Observational	MI or CHD death				0.71	0.84	<0.001
Shaw et al. (32) (2003)	Observational	All-cause mortality	0.72		0.78			<0.001
Greenland et al. (26) (2004)	Prospective population based	MI or CHD death	0.63		0.68			<0.001
Arad et al. (21) (2005)	Prospective population based	CAD events	0.69		0.79			0.0006
Vliegenthart et al. (35) (2005)	Prospective population based	CHD	0.749		0.774			0.02
Anand et al. (20) (2006)	Prospective	CV events	0.6	0.92				<0.0001
Budoff et al. (23) (2007)	Observational	All-cause mortality				0.61	0.81	<0.0001
Detrano et al. (24) (2008)	Prospective population based	MI or CHD death				0.79	0.83	0.006
Erbel et al. (25) (2010)	Prospective population based	Nonfatal MI or CHD death	0.681		0.749			<0.003

Abbreviations: AUC = area under the curve, CAC = coronary artery calcium, CV = cardiovascular, CHD = coronary heart disease, MI = myocardial infarction, NA = not applicable, CAD = coronary artery disease.

[#]Outcomes for which area under the curve are given in Figure 14.2.

**P* value comparing area under the curve from the two models given in the table.

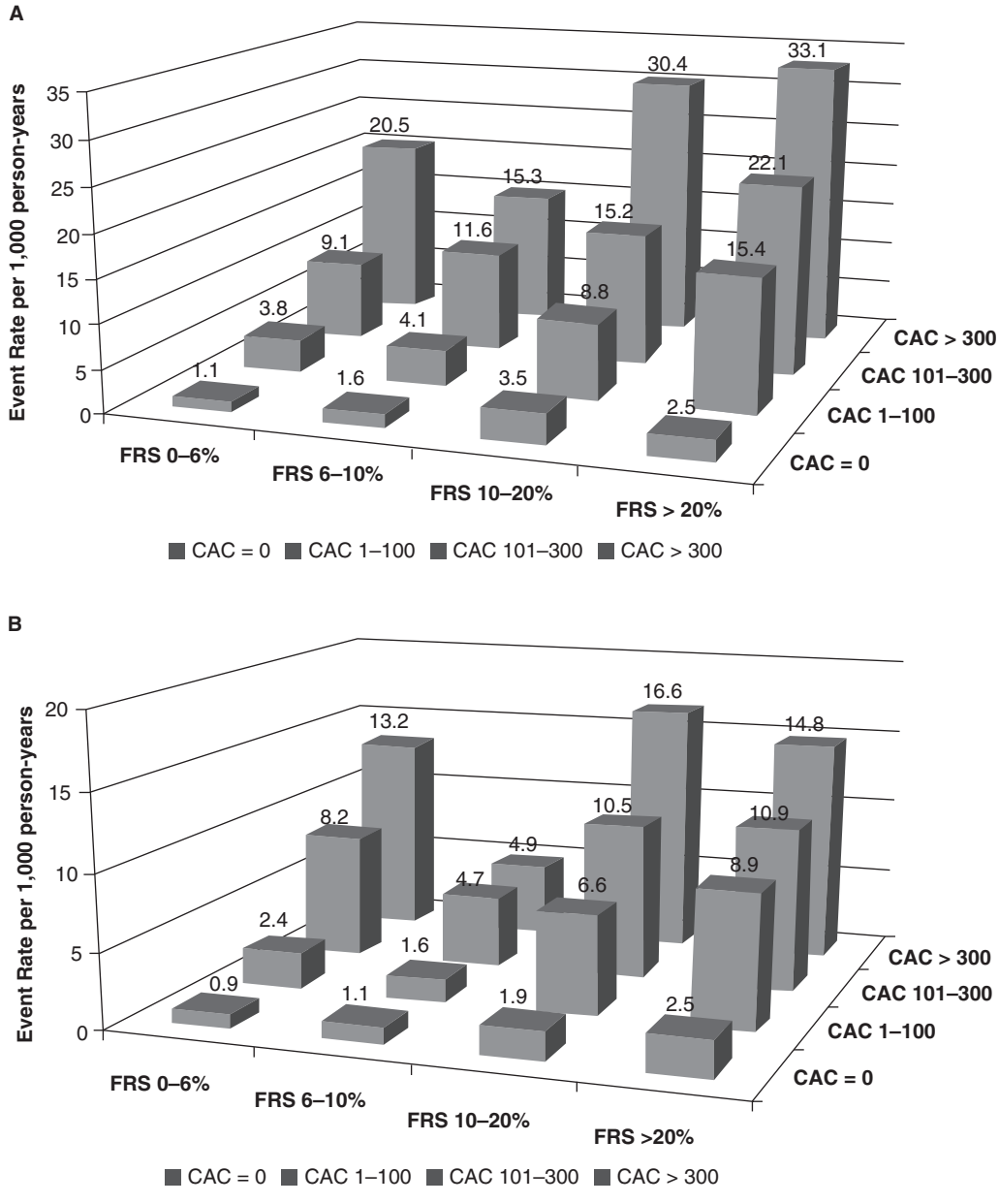

FIGURE 14.2 Total (A) and hard (B) coronary heart disease event rates (per 1,000 person-years) with increasing coronary artery calcium scores according to Framingham risk score category.

Source: Ref. (33). Silverman MG, Blaha MJ, Krumholz HM, et al. Impact of coronary artery calcium on coronary heart disease events in individuals at the extremes of traditional risk factor burden: the Multi-Ethnic Study of Atherosclerosis. *Eur Heart J*. Dec 23 2013.

This suggests that incorporation of CAC score into the current risk prediction models significantly improves risk stratification. Due to a very small risk of a future cardiovascular event among those with zero CAC, some researchers are actually advocating that lifestyle modification alone may be reasonable in this group as compared to starting pharmacotherapy if the LDL-C is not markedly elevated.

Who Should Be Screened With a Noncontrast Coronary CT Among Asymptomatic Individuals?

According to the 2010 expert consensus document by the American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA), "Measurement of CAC is reasonable for

TABLE 14.3 Summary of Recommendations for Coronary Artery Calcium Screening in Adults

Measurement of CAC is reasonable for cardiovascular risk assessment in asymptomatic adults at intermediate risk (10% to 20% 10-year risk).
Measurement of CAC may be reasonable for cardiovascular risk assessment in persons at low to intermediate risk (6% to 10% 10-year risk).
Among those with LDL-C < 190 mg/dL where treatment decisions are uncertain, CAC screening could be used to determine risk. If CAC score > 300, treatment with a statin should be considered.
In asymptomatic adults with diabetes, 40 years of age and older, measurement of CAC is reasonable for cardiovascular risk assessment.

cardiovascular risk assessment in asymptomatic adults at intermediate risk (10% to 20% 10-year risk)" (43).

According to the 2013 American College of Cardiology/American Heart Association guidelines on treatment of blood cholesterol in adults, CAC screening could be used to determine risk among those with LDL-C < 190 mg/dL where treatment decisions are uncertain and who do not fall into one of the four statin benefit groups. If CAC score > 300, treatment with a statin may be considered (44). A brief summary of recommendations for CAC screening in adults is given in Table 14.3.

Although those at high risk are candidates for aggressive preventive approaches and may not need screening by a noncontrast coronary CT for CAC determination, we believe that a subgroup among those at low risk may benefit from CAC screening, where screening might hypothetically be cost-effective. Results from some studies have shown that a large proportion of those considered being at low risk by FRS and having a positive family history of premature coronary heart disease have significant CAC (30,45,46).

A recent large study from the MESA cohort examined the association of premature family history of coronary heart disease with incident and progressive CAC. They followed over 5,000 participants for a mean of 3.1 years and found that family history of premature coronary heart disease is associated with a 55% higher odds of future development of CAC, and that those with family history have 14.4 units greater CAC than those without a family history of premature coronary heart disease (47). Because family history is not considered in the FRS, traditional risk estimators such as the FRS or the ASCVD risk score tend to misclassify a proportion of individuals into the lower risk category, when they might actually have increased risk for future events. We believe this may be the subset of individuals from the low-risk group that may benefit from CAC screening.

Studies have also demonstrated that serial CAC measurement to track CAC progression may provide useful prognostic information (48,49). However, evidence on the role of therapeutic intervention such as statins on affecting the rate of progression is controversial (50). With that said, exposing a large proportion of individuals to radiation may not be justifiable until we have more good quality evidence that it would lead to significant changes in patient management.

In addition to providing important prognostic information as well as improving risk stratification, emerging evidence also suggests that knowing one's atherosclerotic burden as measured by a noncontrast coronary CT may stimulate healthy changes in one's lifestyle as well as may improve compliance with protective pharmacotherapy (51–53). Whether this can reduce future events still needs to be known, and well-designed future studies will, it is hoped, be able to address this important question.

In summary, there is an important role of CAC score in asymptomatic individuals for both prognostic reasons as well as risk stratification. Although it identifies individuals at high risk for a future cardiovascular event when it is high, it provides reassurance to a large group of individuals when it is zero, thereby focusing primary preventive efforts on the truly high-risk individuals. It may also lead to avoidance of medications and unnecessary diagnostic testing in those with zero coronary artery calcium.

ROLE OF NONCONTRAST CORONARY CT IN SYMPTOMATIC INDIVIDUALS

Similar to its role in asymptomatic individuals, the prognostic value of the CAC score has been studied in those presenting with chest pain. In a pooled meta-analysis of 3,924 symptomatic individuals, it was observed that symptomatic individuals have a lower likelihood of having a zero CAC score compared to those who are asymptomatic (23% vs. 40%). The proportion of those with zero CAC is lower among symptomatic individuals, however, they observed that only 1.8% of those with a zero CAC score had a future cardiovascular event compared to 8.9% of those with some degree of CAC (overall risk ratio of 0.09, 95% CI: .04–.20), Figure 14.3b (42).

In this large meta-analysis, they also compared the diagnostic accuracy of CAC to the presence of myocardial ischemia on stress myocardial perfusion imaging and observed that only 7% of those with a zero CAC score had evidence of myocardial ischemia compared to 13% of those with the presence of CAC on

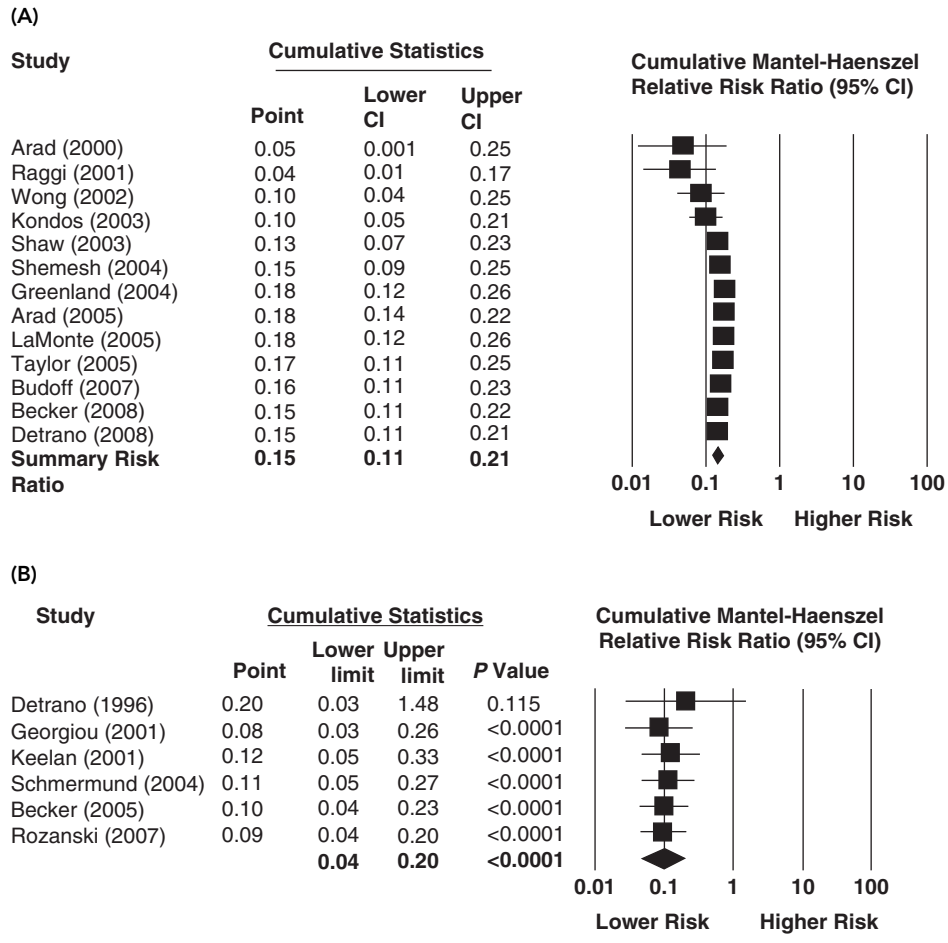

FIGURE 14.3 Diagnostic and Prognostic Value of Absence of Coronary Artery Calcification.

(*Source*: Ref. (42). Sarwar A, Shaw LJ, Shapiro MD, et al. Diagnostic and prognostic value of absence of coronary artery calcification. *JACC. Cardiovasc Imag.* Jun 2009;2(6):675–688.) (A) Asymptomatic individuals: Forest plot of the cumulative relative risk ratio for events in no CAC versus CAC asymptomatic patients. The relative risk ratio is calculated using a Mantel-Haenszel relative risk ratio (95% confidence interval [CI]). The individual study relative risks are reported, but the Forest plot details a cumulative risk ratio. All $P < 0.0001$. CAC = coronary artery calcium. (B) Symptomatic individuals: Forest plot of the cumulative relative risk ratio for events in the no CAC versus CAC symptomatic patients. The relative risk ratio is calculated using a Mantel-Haenszel relative risk ratio (95% confidence interval [CI]). CAC = coronary artery calcium.

a noncontrast coronary CT. When they compared the diagnostic accuracy of CAC to invasive angiography, they found that only 2% of those with CAC = 0 had significant coronary stenosis defined as greater than 50%. This means that in this group of patients with a zero CAC score, the likelihood of having significant coronary stenosis is significantly low, and therefore the risk for a future cardiovascular event is likewise smaller compared to someone with the presence of CAC.

The role of noncontrast coronary CT in symptomatic individuals can be discussed by dividing this group into two subgroups:

a. In low-risk patients presenting with chest pain, CAC could provide useful prognostic information. In a large meta-analysis, it was observed that absence of CAC had a negative predictive value of 99% for the identification of ACS, 93% for significant CAD on invasive imaging, and 93% for the identification of myocardial perfusion defects. On the other hand, when CAC was present, sensitivity for identifying these conditions was 99%, 98%, and 88%, respectively (42). In the Rule Out Myocardial Infarction Using Computer-Assisted Tomography (ROMICAT) study, only 0.27% (1/368) low-risk individuals presenting to the emergency department had acute coronary syndrome when CAC was zero (54). Similar findings were noted in other studies (42,55,56).

Results from the Coronary CT Angiography Evaluation for Clinical Outcomes International Multicenter (CONFIRM) registry with over 10,000 participants

showed that among those who are low–intermediate risk and have zero CAC, the negative predictive value for ruling out ≥70% coronary stenosis as noted on invasive coronary angiography was 99% (57). These results suggest that noncontrast coronary CT could provide useful prognostic information in the low to low–intermediate risk individuals presenting with symptoms. This is also endorsed by the 2010 expert consensus document by the ACCF/AHA that "Measurement of CAC may be reasonable for cardiovascular risk assessment in persons at low to intermediate risk (6% to 10% 10-year risk)" (43).

b. Although CAC scoring may be useful in low to low–intermediate risk individuals presenting with symptoms, the role of noncontrast coronary CT in those presenting with symptoms and having high pretest probability is less clear. Studies have shown that in these high-risk patients, absence of CAC does not rule out significant coronary heart disease (58,59). In fact, in this group of symptomatic individuals, it would be hard for any of the current noninvasive tests to rule out significant coronary stenosis with great degree of certainty.

In summary, there is an important role of CAC in low to low–intermediate risk patients presenting with symptoms where a zero CAC provides a great degree of confidence that prognosis is favorable. In this group, further testing can potentially be avoided especially when the presentation is atypical and EKG and cardiac enzymes do not suggest ischemia. Note that a large proportion of patients presenting to the emergency department with cardiac symptoms fall into this category. Thus CAC testing can play an important role as a gatekeeper for further testing in a considerable proportion of those presenting with symptoms, and therefore, could reduce costs substantially (60).

SUMMARY AND CONCLUSION

Coronary artery calcium is independently associated with future risk of coronary heart disease and all-cause mortality; the higher the CAC score, the higher is the risk. It improves risk prediction for a future cardiovascular event and mortality above and beyond the current global risk assessment methods such as the Framingham risk score. Current guidelines recommend its use in intermediate-risk asymptomatic individuals where it appears to be the most predictive of future risk. It may also be useful in low-risk asymptomatic individuals with family history of premature coronary heart disease, although current recommendations do not support its use. It is not recommended in high-risk asymptomatic individuals who are candidates for aggressive preventive strategies. Among those with symptoms, it may be a useful tool in the low to low–intermediate risk group, where a zero CAC score has a very high negative predictive value for ruling out significant coronary stenosis. It is not recommended in the high-risk symptomatic individuals, as it is not shown to rule out significant disease with confidence.

A zero CAC score is associated with a significantly lower risk for future disease compared to those with the presence of CAC even among those with many cardiovascular risk factors. Although high CAC provides useful prognostic information and helps risk-stratify individuals into the higher risk categories so that aggressive preventive strategies could be applied, a zero CAC score is considered as one of the strongest negative risk factors, and can help minimize the need for unnecessary pharmacotherapy as well as additional testing in the selected group of individuals.

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15

Geeta Sikand, MA, RDN, FAND, CDE, CLS, FNLA

CardioProtective Dietary Patterns and Preventions of Atherosclerotic Cardiovascular Disease

Cardiovascular disease remains the leading cause of death in both men and women and among all major ethnic groups in the United States and other developed as well as developing countries. According to the recently released (November 2013) joint report on "Lifestyle Management for Atherosclerotic Cardiovascular Disease (ASCVD) Prevention" by the American Heart Association (AHA) and the American College of Cardiology (ACC) (1) and the International Atherosclerosis Society (IAS) paper (October 2013) on "Global Recommendations for the Management of Dyslipidemia" (2), there is a shift toward recommending cardioprotective dietary patterns rather than individual nutrients or food groups or supplements. This is because dietary components are consumed in combination and work in synergism.

RECENT DIETARY GUIDELINES AND RECOMMENDATIONS

Recent guidelines have been published jointly by the AHA, ACC, and The Obesity Society (TOS) that address management of overweight and obesity in adults (3). These recommendations have evolved from a large evidence base demonstrating the importance of lifestyle risk factors including dietary habits, physical inactivity, smoking, and adiposity that are the targets for the prevention of cardiovascular disease. In addition, it is well recognized that a healthy diet and other lifestyle practices also affect novel risk pathways for CVD that include inflammation/oxidative stress, endothelial function, thrombosis/coagulation, and arrhythmia (1,2).

Collectively, this evidence base was the impetus for dietary recommendations for heart health that were issued by numerous organizations prior to the recent release of the guidelines issued by the AHA/ACC and IAS. These include the following recommendations: the American Heart Association 2020 Impact Goals Committee (4); the AHA Nutrition Committees (5–7); the 2010 U.S. Dietary Guidelines Advisory Committee (8); the World Health Organization Expert Consultation on Fats and Fatty Acids in Human Nutrition (9); the World Health Organization Global Burden of Diseases, Risk Factors, and Injuries Nutrition and Chronic Diseases Expert Group (10); and the Institute of Medicine Report on Strategies to Reduce Sodium Intake (11). Thus, there is overwhelming support for current dietary recommendations for CVD risk reduction.

Figure 15.1 shows the risk factors that affect the long-term risk for atherosclerotic cardiovascular disease defined by the 2013 International Atherosclerosis Society (IAS) Global Recommendations for the Prevention of Atherosclerotic Cardiovascular Disease (2).

Figure 15.2 shows the role that lifestyle can play in modifying established and novel risk factors for cardiovascular (CV) risk. Implementing the lifestyle behaviors significantly reduces CVD risk and markedly reduces CVD morbidity and mortality. Dyslipidemia and hypertension, two key CVD risk factors, along with other risk factors must be aggressively

Atherogenic lipoproteins (LDL and VLDL) initiate and promote atherogenesis

- Alone can cause premature ASCVD

Other risk factors accelerate atherogenesis

- Cigarette smoking
- Hypertension
- Diabetes
- Low HDL
- Genetics (family history)

FIGURE 15.1 Screening for risk factors affecting long-term risk for atherosclerotic cardiovascular disease 2013 International Atherosclerosis Society (IAS) www.athero.org.

Source: Adapted from Ref. 2. The International Atherosclerosis Society Position Paper: Global Recommendations for the Management of Dyslipidemia. Accessed February 20, 2013, www.athero.org

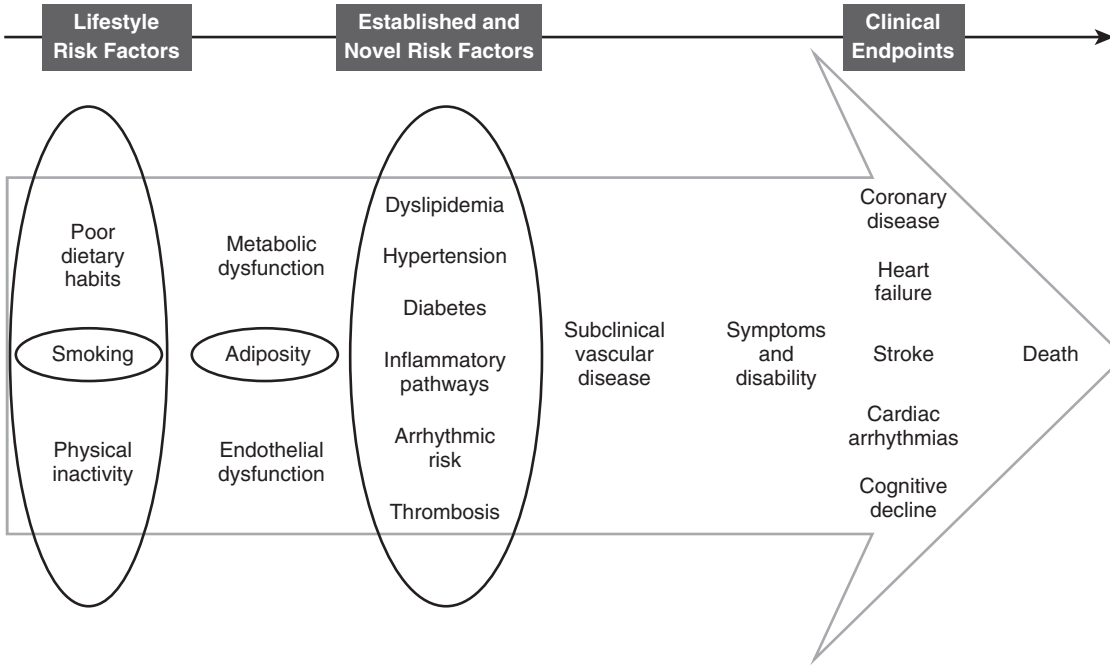

FIGURE 15.2 Established and lifestyle risk factors that need to be improved to lower cardiovascular disease risk. *Source*: Adapted from Mozaffarian D, Wilson PW, Kannel WB. Beyond Established and Novel Risk Factors Lifestyle Risk Factors for Cardiovascular Disease. *Circulation.* 2008;117:3031–3038.

treated with recommended lifestyle behaviors and drug therapy to prevent coronary heart disease (12).

The AHA 2020 goals are to improve the CV health of all Americans to reduce CVD morbidity and mortality by 20%. To attain this goal, the AHA released a tool, "Life's Simple 7™" Heart Health Factors (4):

1. Get active
2. Control cholesterol
3. Eat better
4. Manage blood pressure
5. Lose weight
6. Reduce blood sugar
7. Stop smoking

Lifestyle recommendations by the AHA/ACC and the IAS are listed in Tables 15.1 and 15.2, respectively (1,2). The AHA, ACC, and the IAS agree on the following recommendations (1,2).

■ Strong evidence supports that adults should consume a dietary pattern that emphasizes vegetables, fruits, and whole grains; includes low-fat dairy products, poultry, fish, legumes, nontropical vegetable oils and nuts; and limits intake of sodium, sweets,

TABLE 15.1 American Heart Association & American College of Cardiology Joint Dietary Lifestyle Recommendations for Lipid Disorders and Blood Pressure Reduction

Lipid Disorders
• Consume a cardioprotective dietary pattern such as the DASH Dietary Pattern (Dietary Approaches to Stop Hypertension), the USDA Food Pattern, or the American Heart Association Dietary Pattern. A cardioprotective dietary pattern emphasizes the intake of vegetables, fruits, and whole grains, low-fat dairy products, poultry, fish, legumes, nontropical oils, and nuts while limiting the intake of sweets, sugar-sweetened beverages, and red meats.
• Caloric intake should be appropriate for achieving and maintaining optimal weight. Integrate the patients' caloric requirements to achieve and maintain optimal weight, personal and cultural food preferences, and nutrition therapy for other medical conditions (e.g., diabetes mellitus, dyslipidemia, metabolic syndrome).
• Reduce intake of saturated fat to 5% to 6% of calories. Strong evidence shows that reduction in LDL-C was achieved when saturated fat intake was reduced from 14% or 15% to 5% or 6%. A high saturated fat intake is not consistent with consuming a cardioprotective dietary pattern.
• Decrease in intake of *trans*-fatty acids lowers LDL-C with little or no effect on HDL-C or triglycerides. The reduction in LDL-C is consistent regardless of whether the *trans*-fatty acids are replaced by carbohydrates or monounsaturated or polyunsaturated fatty acids. The FDA has ordered the removal of *trans*-fatty acids from the U.S. food supply. However, it is still present in meat and dairy products in small amounts in the U.S. diet.
• Dietary planning and nutrition counseling is often facilitated by referral to a nutrition professional such as a registered dietitian nutritionist (RDN).
Blood Pressure Reduction
• Blood pressure reduction can be achieved by following dietary meal patterns such as the DASH Dietary Pattern, the USDA Food Pattern, or the AHA Dietary Pattern. The DASH and DASH-sodium Dietary Patterns provide highest quality evidence for improvements in lipid profiles and blood pressure. This evidence was supplemented by studies of low quality in which various adaptations of the Mediterranean dietary pattern were tested and also found to reduce blood pressure. Evidence suggests that the effects of the recommended dietary patterns persist as long as the dietary pattern is consumed by adults with hypertension and prehypertension. Studies in men, women, African Americans, non-African Americans, in older and younger adults replicated these findings. This dietary pattern's effect on BP is independent of changes in weight and sodium intake. The magnitude of effect is sufficient to prevent progression from pre-HTN to HTN, promote nonpharmacological BP control in those with HTN, and supplement pharmacological blood pressure lowering.
• Reduction of sodium intake lowers blood pressure in adults 25 to 80 years of age with BP 120–159/80–95 mmHg. Consume no more than 2,400 mg/d of sodium. Further reduction to 1,500 mg/d is desirable because it is associated with an even greater reduction in blood pressure. Reducing sodium intake by at least 1,000 mg/day will lower blood pressure even if the limit of 2,400 mg/day is not reached.
• Combine the DASH dietary pattern with lower sodium intake. Both a healthy dietary pattern and reduced sodium intake independently reduce BP. However, when these two dietary changes are combined, the BP lowering effect is even greater.
• Dietary planning and nutrition counseling is often facilitated by referral to a nutrition professional such as a registered dietitian nutritionist (RDN).

Source: Adapted from Ref. (1). 2013 AHA/ACC Guidelines on Lifestyle Management to Reduce Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Eckel RH, Jakicic JM, Ard JD, et al. *Circulation*. November 12, 2013.

sugar-sweetened beverages, and red meats. Adapt this dietary pattern to appropriate calorie requirements, personal and cultural food preferences, and nutrition therapy for other medical conditions (including diabetes mellitus). Achieve this pattern by following plans such as the DASH dietary pattern, the USDA Food Pattern, or the American Heart Association Diet.

■ Cardioprotective dietary patterns including the Dietary Approaches to Stop Hypertension (DASH), the USDA dietary pattern, AHA dietary pattern, and Mediterranean dietary pattern are recommended based on high quality of evidence (DASH, USDA, AHA) and low strength of evidence (Mediterranean), respectively (1,2).

TABLE 15.2 Diet Recommendations from International Atherosclerosis Society for LDL Cholesterol Lowering

1. Reduce the intake of saturated fatty acids to < 7% of total calories, and at least to < 10%; decrease intake of *trans*-fatty acids to < 1% of total calories and reduce intake of dietary cholesterol to < 200 mg/day. Recently the FDA ordered a complete removal of *trans*-fatty acids from the U.S. food supply. However, *trans*-fatty acids are still present in meat and dairy products. If fat is consumed above the recommended amounts for saturated and *trans*-fatty acids, it should be in the form of unsaturated fatty acids. Flexibility in total fat intake could be based on cultural preferences. For example, in Pacific Rim countries, the usual total fat intake could be lower (20–25% of calories). In Mediterranean countries, usual total fat intake could be higher (30–35% of calories).
2. Nutrient needs must be met and energy intake should be appropriate to achieve and maintain a healthy body weight. Measure body mass index (BMI) in all patients. National standards for BMI should be used when using BMI to classify weight status.
3. Alcohol intake should not exceed 2 servings daily for men and 1 serving daily for women.
4. Obesity and physical inactivity contribute importantly to development of the metabolic syndrome. For patients with this syndrome, weight reduction and increased physical activity can reduce metabolic risk factors.
5. Consume foods low in sodium and high in potassium. Sodium intake should be < 2 g per day and < 1,500 mg for individuals at risk.
6. Consume high intakes of fruits, vegetables, and fiber. Replace excessive saturated fat intake with either complex, fiber-rich carbohydrates (whole grains) or monounsaturated/polyunsaturated fatty acids. Consume some fish rich in n-3 fatty acids. Include cardioprotective foods such as nuts, seeds, and vegetable oils.
7. Include plant sterols/stanols (2 g/day) and soluble/viscous fiber (10 to 25 g/day) as a dietary adjunct to further lower LDL-C levels.

Source: Adapted from Ref. (2). Grundy SM, Arai H, Barter P, Bersot TP et al. An International Atherosclerosis Society Position Paper: Global Recommendations for the Management of Dyslipidemia www.athero.org (accessed Nov 20, 2013).

■ Reduce percent of calories from saturated fat and *trans* fat (1,2). Strong evidence suggests that reducing saturated fat intake to no more than 5% to 6% of energy intake and reducing *trans*-fat intake lower LDL-C (1).

■ Limit sodium intake to no more than 2,400 mg/day; for greater blood pressure reduction a further reduction in sodium to 1,500 mg/day is desirable. There is strong evidence that a reduction in sodium intake lowers blood pressure. Moderate evidence further supports that reduction of sodium intake along with a DASH-style dietary pattern lowers blood pressure more than reducing sodium intake alone. Strong evidence supports that reducing sodium intake by 1,150 mg/day lowers blood pressure by 3–4/1–2 mmHg (1).

■ Dietary planning and nutrition counseling is often facilitated by referral to a nutrition professional such as a registered dietitian nutritionist (RDN) (1).

■ Engage in 2 hours and 30 minutes a week of moderate-intensity or 1 hour and 15 minutes (75 minutes) a week of vigorous-intensity aerobic physical activity, or an equivalent combination of moderate- and vigorous-intensity aerobic physical activity. Aerobic activity should be performed in episodes of at least 10 minutes, preferably spread throughout the week (1).

■ Achieve and maintain a healthy weight. Refer to the 2013 Obesity Expert Panel Report (3) for recommendations on weight loss and maintenance (1).

Overall, the 2013 IAS and the 2013 AHA/ACC recommendations include consumption of a relatively high intake of fruits, vegetables, replacement of excess saturated fatty acids with either complex, fiber-rich carbohydrates (emphasis on whole grains) or monounsaturated/polyunsaturated fatty acids, some fish rich in omega-3 fatty acids, and inclusion of nuts, seeds, and vegetable oils. A reduction in intake of *trans*-fatty acids is also recommended. In addition, the IAS also recommends plant sterols/stanols (2 g/day) and soluble/viscous fiber (10 to 25 g/day) as a dietary adjunct to further lower LDL-C levels (2). Similar to the recommendations of the 2010 Dietary Guidelines for Americans Committee (8) by the Departments of Health & Human Services (DHHS) and the United States Department of Agriculture (USDA), there is an emphasis on whole food dietary patterns rather than a focus on individual nutrients. For lowering LDL-C and blood pressure, the guidelines recommend three to four sessions per week of 40 minutes of moderate-intensity physical activity for lowering blood pressure and LDL-C (1,2).

The guidelines also call for additional research to investigate which exercise patterns might be optimal and how primary-care providers, health systems, public-health agencies, local and federal government, community organizations, and other stakeholders can "effectively" and "cost-effectively" help patients adopt these recommendations. They also acknowledge that more research is needed about the effect of racial, ethnic, and socioeconomic factors on the adoption of these recommendations (2).

OBESITY MANAGEMENT GUIDELINES BY AMERICAN HEART ASSOCIATION (AHA) & THE OBESITY SOCIETY (TOS)

There are 155 million U.S. adults who are overweight, as defined by a body mass index (BMI) of 25 to 29, or obese with a BMI of 30 or higher. Obesity is associated with an increased risk of stroke and heart attack, as well as increased risk of all-cause mortality. A sustained weight loss of 5% to 10% in the first six months is recommended. The AHA/TOS guidelines recommend calculating BMI of each patient at least annually and measuring waist circumference (3). Table 15.3 shows the definitions of overweight and obesity by the AHA/TOS guidelines. A waist circumference of >35 inches for women and >40 inches for men increases risk of chronic diseases. Table 15.4 shows the evaluation and treatment guidelines issued by the AHA/TOS.

Treatment approach for weight management by AHA/TOS (3):

- Include the explanation of reduced-calorie diets, increased physical activity, and behavioral programs that encourage adherence.
- Direct patients to work through their primary-care provider to access a registered dietician, behavioral psychologist, or trained weight-loss counselor. Specific mention is made that in 2014 under the Affordable Care Act, these services should be supported by third-party payers, including private insurance. At least "two to three in-person meetings per month" are optimal. A minimum of 14 visits over 6 months is recommended.

TABLE 15.3 Definition of Overweight and Obesity (3)

Classification	BMI (kg/m²)
Underweight	<18.5
Normal	18.5–24.9
Overweight	25.0–29.9
Obesity	
Class I	30.0–34.9
Class II	35.0–39.9
Class III (extreme obesity)	≥40

Source: Adapted from 2013 AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults. *Circulation*. 2013: Published online before print November 12, 2013, 10.1161/01.cir.0000437739.71477.ee.

TABLE 15.4 Evaluation of Overweight and Obesity

- Body mass index calculated annually or more frequently.
- A baseline score of 25–29 continues to define overweight and 30 and over defines obesity.
- Waist circumference measured during annual visits, and more frequently in overweight or obese individuals. Levels over 40 inches in men and over 35 inches in women define abdominal obesity (although different cutpoints have been proposed by the International Diabetes Federation for European Caucasians, Asians and other groups).
- Patients should be counseled on modest weight loss (3–5% of body weight) as this can result in meaningful benefits in reducing diabetes and cardiovascular disease risk factors.
- Reduced calorie intake and increased physical activity for overweight and obese individuals.
- Counseling with a weight management interventionist should be done at a high-intensity in an individual or group program lasting at least six months with a minimum of 14 sessions.

Source: Adapted from 2013 AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults. *Circulation*. 2013: published online before print November 12, 2013, 10.1161/01.cir.0000437739.71477.ee. (3)

The guidelines also note that obesity is an economic liability. Obese patients incur an increase of 46% of in-patient costs, 27% more physician visits and out-patient costs, and a staggering 90% increase in prescription-drug spending. It has been estimated that obesity cost the U.S. economy $147 billion in increased health care costs in 2008.

Morbidly obese individuals with BMIs of >40 or BMIs >35 with comorbidities who have not succeeded with conventional weight loss methods should be advised that bariatric surgery may be an appropriate option to improve health. Referral to an experienced bariatric surgeon is advised and surgery can result in a weight loss of 16% that is sustained for 10 years. Fasting glucose and insulin levels are reduced, but BP can increase after 10 years following surgery; hence, ongoing patient monitoring is necessary. Postoperative complications are infrequent with laparoscopic adjustable gastric banding, at 1% to 3%, including DVT, reoperations, and wound infection. The panel "did not review comprehensive evidence of pharmacotherapy for weight loss." It stated that the addition of orlistat was associated with a reduction in fasting blood glucose levels (3).

According to the AHA/ACC/TOS overweight and obesity management guidelines, the strength of the evidence was high for the following (3):

- A 5% to 10% reduction in weight is considered "successful." Weight losses of 2.5 to 5.5 kg over two years or more achieved with lifestyle intervention reduced the risk of developing diabetes by 30% to 60%.
- Individuals with diabetes who lost 9 kg to 13 kg had a 25% decrease in mortality compared with weight stable patients. Failing to lose weight is associated with a higher risk of ischemic and hemorrhagic stroke.
- A 3-kg weight loss was associated with a weighted mean reduction in triglycerides of at least 15 mg/dL.
- A 5- to 8-kg weight loss was associated with low-density lipoprotein cholesterol (LDL-C) reductions of approximately 5 mg/dL and increases in high-density lipoprotein cholesterol (HDL-C) 2 to 3 mg/dL.
- With <3-kg weight loss, more modest and more variable improvements in triglycerides, HDL-C, and LDL-C are observed.

The guidelines recommend "high-intensity" lifestyle interventions including recommendations for a diet that provides 1,200 to 1,500 calories per day for women and 1,500 to 1,800 calories per day for men. Although 150 minutes per week of exercise is a typical recommendation, 200 to 300 minutes per week can be recommended to maintain weight loss or to minimize weight regain. Self-monitoring of food intake, physical activity, and weight monitoring are recommended to maintain weight loss. Face-to-face meetings are recommended as well as electronically delivered information by trained interventionists. There was no difference in weight loss irrespective of whether these were individual or group support meetings. If phone contact is maintained for periods of up to 2.5 years, weight regain is reduced (3).

REFERRAL TO A NUTRITION PROFESSIONAL

Medical nutrition therapy by a registered dietitian nutritionist (RDN) is an integral part of CVD prevention. It includes nutrition education, nutrition counseling, and coordination of care. Patients often do not present with only one medical condition or illness. Frequently they have multiple comorbidities including dyslipidemia, hypertension, diabetes, weight management, and metabolic syndrome (1). In the primary care setting, a RDN can counsel patients concurrently with the primary care physician. This counseling approach in an outpatient physician office in the primary care setting is effective in achieving and maintaining weight loss and to optimize blood pressure and lipids. In addition, it is reimbursable in the primary care setting (3).

After screening for risk factors, a referral for medical nutrition therapy (MNT) to a RDN could be made to personalize a cardioprotective dietary pattern for treating dyslipidemia, overweight, metabolic syndrome (MetS), diabetes (DM), and/or hypertension (HTN). Strong evidence supports the importance of multiple visits with a RDN to reduce LDL-C, TG, HTN, dysglycemia, and BMI (13–22).

DIETARY PLANNING AND NUTRITION COUNSELING

- Facilitated by referral to a nutrition professional such as a RDN (1) includes three components: (i) nutrition assessment, (ii) nutrition diagnosis, and (iii) nutrition intervention (23–25).

1. Nutrition Assessment

Nutrition assessment is an ongoing process that involves data collection at initial and follow-up sessions, and ongoing evaluation of patient/client data as well as patient/client needs. At the beginning of each session it is important to assess the reasons why the patient has scheduled the appointment. For example, a patient's response to a question such as, "What is your most important reason for being here today?" can help determine his or her readiness to change. Questions such as, "What are your goals for our session today?" could help to personalize each nutrition counseling session and address patient/client needs. Information for nutrition assessment when seeing patients with lipid disorders, hypertension, diabetes, metabolic syndrome, and weight management includes:

- **Biochemical Data:** laboratory data for lipids, glucose, kidney function, and other nutrition-related tests, for example, lipid/lipoprotein profile, comprehensive metabolic panel, A1c, vitamin D, complete blood count, hs-CRP, LP(a).
- **Nutrition-Focused Physical Findings**: body weight, blood pressure, body fat assessment.
- **Anthropometrics:** height, weight, BMI, waist circumference, and weight change over time.
- **Client History**:
  - Age, gender, race/ethnicity, language, literacy, occupation, and education
  - Medical/health history: medical treatment, goals of nutrition intervention and prescribed medications related to the medical condition for which nutrition intervention is being implemented
  - Socioeconomic history: social and family support, cultural and religious beliefs, and socioeconomic status

- Patient/client food and nutrition-related medical/health history
- Other medical or surgical treatments, and current use of alternative medicine

■ **Food/Nutrition-Related History:** food and beverage intake; energy and macronutrient intake; meal-snack pattern; bioactive compounds (e.g., use of nutrient and fish oil supplements, herbal products, etc.); food availability; physical activity; and readiness to change nutrition-related behaviors. Table 15.5 shows a list of questions that should be asked of patients when taking a diet history (25).

■ **Energy and Macronutrient Needs:** Compared to current intake based on a 24-hour food recall or a diet diary. This information could assist with nutrition diagnoses and nutrition interventions (23,24).

2. Nutrition Diagnosis

The second component of personalized nutrition intervention is to make a nutrition diagnosis for which an intervention is designed. For patients with lipid disorders, hypertension, diabetes, metabolic

TABLE 15.5 Questions to Be Asked Of Patients When Taking a Diet History for Lipid Disorders, Hypertension, Weight Management, and Diabetes

Sample Questions for All Patients
• What are your goals for today's session?
• What is the most important reason you are here?
• How do you feel about your weight?
• What is the most you have ever weighed?
• What is your usual body weight?
• What is your goal weight?
• Do you eat differently when you are alone?
• Do you indulge in binge eating?
• Do you use food to cope with stress in your life?
• Do you feel you eat a healthy balanced diet? Why or why not?
• How many meal and snacks do you eat every day?
• How often do you eat out? What kind of restaurants?
• What beverages do you drink daily including alcohol? How many glasses?
• How often do you eat fruits and vegetables?
• How often do you eat dairy products including milk, cheese, yogurt? Low fat or regular?
Sample Questions for Patients With Lipid Disorders
• How often do you eat fatty meats? (hot dogs, bacon, sausage, salami, pastrami, corned beef)
• How often do you eat fish? How is it prepared?
• What type of fats do you use in cooking or baking? Canola oil, olive oil, soybean oil, safflower oil, and so on?
• What do you spread on your bread? (butter, vegetable oil spread, peanut butter)
• How many daily servings of dairy, fruits, vegetables and whole grains do you eat?
• What type of snacks and desserts do you usually eat?
Sample Questions for Patients With Hypertension
• Do you cook your food with salt?
• Do use a salt shaker at the table?
• Do you use canned or prepared foods?
• Do you read food labels for sodium content?
Sample Questions for Patients With Diabetes
• What time do you eat your meals?
• What time do you take your medications including insulin?
• Do you skip meals?
• How many servings of starchy foods do you eat on a typical day, for example, bread, cereal, rice, pasta, corn, peas, and potatoes?
• How often do you eat sweets and desserts?
• How often do you drink sugar sweetened beverages and/or fruit juices?

Source: Adapted from Ref. (25). Hark L, Deen D, Pruzansky A. Overview of Nutrition Assessment in Clinical Care in Hark L & Morrison G. Medical Nutrition & Disease: A Case Based Approach Wiley Blackwell; 3–57, 2009.

syndrome, and weight management, important information needs to be collected. Table 15.6 shows some examples of how a RDN makes a nutrition diagnosis for patients with lipid disorders, diabetes, hypertension, and weight management (23,24).

3. Nutrition Intervention

Dietary patterns are personalized by the RDN to include specific food components that provide cardiometabolic benefits and are good sources of dietary fiber, nontropical oils, vitamins and minerals, antioxidants, and phytonutrients (23–25). These dietary patterns contain fewer foods that contribute refined carbohydrates, sugar, salt, and saturated and *trans*-fatty acids as well as dietary cholesterol (1,2,26).

TABLE 15.6 Examples of Nutrition Diagnosis Statements for Lipid disorders, Diabetes, Hypertension, Weight management

Nutrition Diagnosis: Less than optimal intake of types of fats
• Excessive saturated fat intake (P) related to lack of knowledge of saturated fat content of foods (E) as evidenced by self-report of high saturated fat intake and elevated laboratory values: TC = 300 mg/dL, LDL-C = 165 mg/dL

Nutrition Diagnosis: Excessive energy intake
• Excessive energy intake related to knowledge deficit as evidenced by self-reported food intake and limited physical activity level as well as changing anthropometrics: 10-pound weight gain in past 3 months, BMI = 27

Nutrition Diagnosis: Excessive sodium intake
• Excessive sodium intake related to overconsumption of fast-food meals and prepackaged foods, more than 4-grams sodium consumed daily as well as recent increase in blood pressure to 140/90 mmHg

Nutrition Diagnosis: High intake of refined carbohydrate foods
• Excessive intake of sugar related to frequent self-reported intake of regular soft drinks, recent dx of impaired glucose tolerance fasting blood glucose 120 mg/dL and high BMI status

Source: Adapted from Ref. (23). ADA Pocket Guide to Lipid Disorders, Hypertension, Diabetes and Weight Management. Franz MJ, Boucher JL,Pereira RF. Academy of Nutrition and Dietetics 2012. www.eatright.org. (23)

DIET RECOMMENDATIONS FOR LDL-C LOWERING

Dietary recommendations according to the ACC/AHA Guidelines for Lifestyle Management (1) advise adults who would benefit from LDL-C lowering to:

■ **Consume a dietary pattern that achieves 5% to 6% calories from saturated fat. (NHLBI Grade: A strong evidence):** Strong evidence shows that LDL-C was reduced when following a dietary pattern where saturated fat was reduced from 14% or 15% of calories to 5% or 6% of calories. Current estimated intake of saturated fat in the United States is 11% of energy. In addition, consumption of recommended foods such as vegetables, fruits, low-fat dairy products, whole grains, poultry, fish, legumes, nuts, and vegetable oils is far lower than advised. Moreover, consumption is high of foods that should be limited, that is, sweets, sugar-sweetened beverages, and red meat (1,2).

■ **Reduce percent of calories from *trans* fat. (NHLBI Grade: A strong evidence):** By reducing consumption of partially hydrogenated oils, LDL-C will be lowered with little or no effect on HDL-C or triglyceride levels. Look for partially hydrogenated vegetable oils mostly found in baked goods, fried foods, and processed foods. *Trans* fats are also found in food sources of saturated fat (meat and dairy fat). Therefore reduction of dietary saturated fat will also help reduce *trans*-fat intake (1,2).

■ For reducing LDL-C levels the guidelines recommend the use of nontropical vegetable oils within an isocaloric diet and avoidance of coconut and palm oil. Nuts such as walnuts, almonds, pistachios, and hazelnuts, fruits and vegetables, poultry, fish, and low-fat dairy products are recommended. There is an emphasis on limiting red meat, butter, tropical oils, and sweets. Also recommended are spreads blended with rapeseed or flaxseed oils in lieu of butter. Avoidance of sugar-sweetened beverages is also recommended (1,2).

DIET RECOMMENDATIONS FOR TRIGLYCERIDE (TG) REDUCTION

Epidemiological and controlled clinical trials have shown that triglycerides are markedly affected by body weight status and body fat distribution. Table 15.7 shows the American Heart Association 2011 classification of serum triglyceride levels (27).

Dietary treatment recommended by the American Heart Association is as follows (27):

TABLE 15.7 American Heart Association Classification of Triglycerides

Optimal	< 100 mg/dL
Desirable	< 150 mg/dL
Borderline	< 150–199 mg/dL
High	200–499 mg/dL
Very High	> 500 mg/dL

Source: Adapted from Ref. (27) Miller M, Stone NJ, Ballantyne C, Bittner V, et al. Triglycerides and Cardiovascular Disease: A Scientific Statement From the American Heart Association. *Circulation*. 2011;123:2292–2333.

- Weight loss has the most profound TG effect. Weight loss of approximately 5% to 10% of body weight can lower TG 20% as well as reduce the risk of developing MetS and diabetes. Weight reduction with a Mediterranean diet is recommended.
- Avoid excessive intake of carbohydrates, especially refined carbohydrates such as sugar and sweets. When 60% to 65% of energy is consumed as carbohydrate it leads to upregulation of VLDL secretion.
- Choose vegetable oils and lower the intake of fat to <35% of caloric intake.
- Include whole grains, vegetables, fruits, low-fat or nonfat dairy products, fatty fish, poultry, tofu, soybeans, lentils, and legumes.
- Abstain or limit alcohol intake as alcohol can raise triglyceride levels.
- Regular physical activity such as walking for a minimum of 30 minutes on most days of the week.
- If TGs are ≥500 mg/dL, a very low fat diet (≤15% of calories from fat) is recommended to prevent pancreatitis.
- Addition of an omega-3 supplement that provides 2 to 4 gm/d (of EPA + DHA) may confer an additional TG reduction of 5% to 10%.

DIET RECOMMENDATIONS FOR BP LOWERING IN HTN AND PRE-HTN

Advise adults who would benefit from BP lowering to (1):

- Consume a dietary pattern that emphasizes intake of vegetables, fruits, and whole grains including low-fat dairy products, poultry, fish, legumes, nontropical vegetable oils, and nuts, and to limit intake of sweets, sugar-sweetened beverages, and red meats. (Level of evidence NHLBI Grade: A strong.)

This recommendation is based on the studies of the DASH dietary pattern which provided the highest quality of evidence. In addition, the Mediterranean dietary pattern also reduced BP. Caloric intake should be appropriate for those attempting weight loss. The U.S. Dietary Guidelines have also endorsed the DASH eating plan and the USDA food pattern. Overall, the recommended dietary patterns are consistent with the AHA diet and the USDA food pattern.

- Lower sodium intake to less than 2,400 mg/day. A further reduction to 1,500 mg/day in sodium intake is recommended for those at higher risk or for those who seek further BP lowering. Furthermore, reduction of sodium intake by 1,000 mg/day at any intake level will further reduce BP (NHLBI Grade B moderate). The primary source of sodium in the diet comes from that added in preparation, preservation, and/or at the time of consumption. Reducing sodium intake is challenging because of the inclusion of sodium in many foods in the American diet. Thus, behavior modification and changes in food manufacturing and processing are needed to achieve this goal. A reduction in sodium intake of approximately 200 mg/day reduces CVD events by around 30%.
- Combine DASH dietary pattern with lower sodium intake. Both a healthy dietary pattern and a reduced sodium intake lower BP independently. The blood pressure lowering effect of a DASH dietary pattern is similar among all subgroups regardless of gender, age, or race. The current recommendation for sodium reduction applies to two-thirds of the U.S. population, who have either prehypertension or hypertension.

DIETARY PATTERNS

An expanding body of evidence demonstrates that a healthy dietary pattern confers cardioprotective benefits (1,2,8). Several healthful dietary patterns have been identified that have many common characteristics, including an emphasis on fruits, vegetables, other plant foods such as beans and nuts, and (in many patterns) whole grains and fish; with limited or occasional dairy products; and often with limited red meats or processed meats and fewer refined carbohydrates and other processed foods. Consumption of these dietary patterns substantially improves multiple cardiovascular risk factors (1,8,26).

Figure 15.3 shows the impact of dietary patterns on cardiovascular risk factors in randomized controlled trials (26). This summary compares the effects of the DASH (Dietary Approaches to Stop Hypertension) low-fat, high-protein, and high-monounsaturated-fat (MUFA) diets among 162 participants in a 6-week feeding trial; and of the Mediterranean diet compared with a low-fat diet among 180 participants in a 2-year dietary advice trial (28–30). All differences were

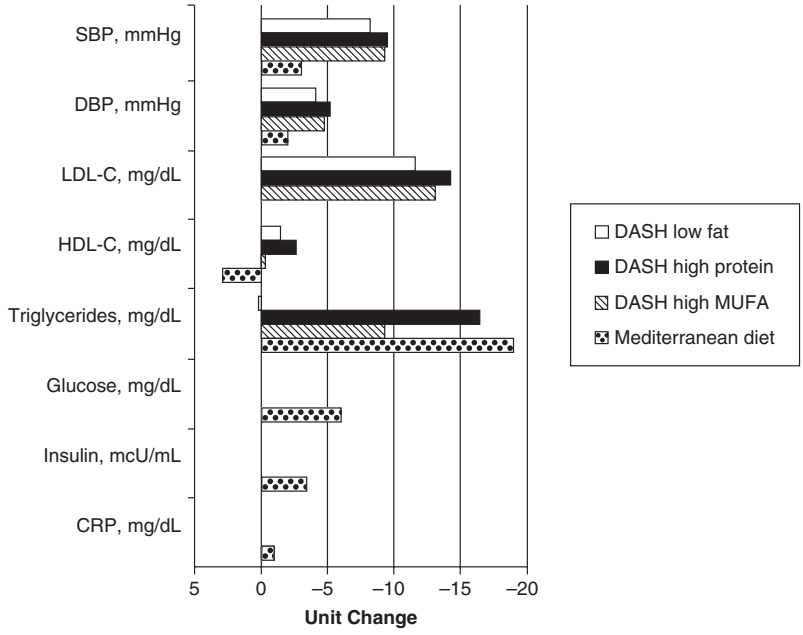

FIGURE 15.3 Examples of dietary patterns with evidence for cardiovascular health benefits.

SBP = systolic blood pressure; DBP = diastolic blood pressure; CRP = C-reactive protein

Source: Adapted from Ref. (26). Mozaffarian D, Appel L, Vanhorn L. Components of a cardio protective diet *Circulation*. 2011;123:2870–2891.

statistically significant at $P < .05$, except for changes in high-density lipoprotein cholesterol (HDL-C) with the DASH high-MUFA diet and in triglycerides with the DASH low-fat diet. Blood pressure and LDL-C were reduced to a greater extent with DASH dietary patterns, whereas atherogenic dyslipidemia and glucose–insulin measures improved to a greater extent with Mediterranean dietary patterns. Overall risk factor changes with any of these dietary patterns would predict substantial reductions in cardiovascular risk (1,8,26).

Dietary Approaches to Stop Hypertension (DASH) Dietary Patterns

In multiple observational studies, greater adherence to a DASH dietary pattern was associated with lower risk of CVD (8). Currently, very few U.S. adults including those with high blood pressure consume a diet that is consistent with the DASH dietary pattern (23). The original DASH diet was low in total fat (27% energy) and higher in carbohydrate (55% energy); additional DASH diet patterns have been evaluated that exchange ~10% energy of carbohydrate for vegetable sources of monounsaturated fat or protein. In controlled feeding trials, each of these DASH diets significantly lowered BP and improved blood lipids compared with a typical Western diet (28). BP reduction was greatest when DASH diets were combined with reduced sodium intake. The reduction of sodium intake to levels below the current recommendation of 100 mmol per day in combination with the DASH diet lowers blood pressure substantially more than can be achieved individually (32).

Mediterranean Dietary Pattern

Although there is no consistent definition of a Mediterranean dietary pattern, in general it is rich in fruits, vegetables, whole grains, legumes, nuts, fish, and low-fat dairy products along with moderate consumption of wine and olive oil (primary source of fat in the diet) (1). This pattern is naturally lower in saturated fat, dietary cholesterol, and red meat. When used in healthy, obese, and high CVD risk patients, this dietary pattern can reduce inflammation. This dietary pattern is associated with lower blood concentrations of inflammatory markers such as plasma levels of CRP and cytokines in healthy persons. Observational and prospective cohort studies consistently demonstrate inverse associations between consumption of traditional Mediterranean diets and risk of CHD, stroke, and total mortality (29,33–36).

Vegetarian Dietary Pattern

Several types of vegetarian diets are consumed around the world, including those consumed by

pesco-vegetarians (who consume fish); lacto-ovo-vegetarians (who consume milk and eggs); and strict vegans (who consume no animal products) (26). Observational studies with vegetarian cohorts show improved health outcomes compared with nonvegetarians (10). The Adventist Health Study – 2 conducted in 96,000 people found lower risk of chronic diseases including lower BMI (especially vegans), less hypertension (vegans lowest), less type 2 diabetes, lower LDL-C, less cancer, and decreased mortality (37,38). The EPIC Oxford study (500,000 participants) in 10 countries reported that vegetarians experienced a moderately lower rate of ischemic heart disease (39).

Vegetarians have other lifestyle behaviors that are beneficial for reducing CVD risk. These include: watching less television, sleeping more hours per night, consuming more fruits, vegetables, legumes, nuts, and vegetable oils, and consuming less saturated fat (30). Overall, fewer studies have been conducted with vegetarian diets than for DASH or Mediterranean dietary patterns (26).

Alcohol

A large number of observational studies have consistently demonstrated a reduction in coronary heart disease with moderate alcohol consumption (8). A meta-analysis of experimental studies has demonstrated a reduction in CHD with moderate alcohol consumption (40). Drinking in excess can lead to alcoholism, high blood pressure, obesity, stroke, breast cancer, suicide, and accidents. A drink is one 12-ounce beer, 4 ounces of wine, 1.5 ounces of 80-proof spirits, or 1 ounce of 100-proof spirits. Recommendations for alcohol consumption should be tailored to each patient's CVD risk profile taking into account potential benefits of moderate alcohol consumption (41).

Dietary Supplements

There is little convincing evidence that many dietary supplements confer health benefits. Several supplements have been evaluated in observational studies and RCTs as potential therapies to prevent CVD or other conditions. Substantial evidence exists that supplements have few CVD benefits and that certain supplements, including beta carotene, calcium, and vitamin E, could do harm (26). However, marine-derived omega-3 PUFA can be recommended as a supplement for CVD prevention especially for TG reduction and prevention of sudden cardiac death. However, optimal doses and target populations require further study (42).

Current evidence does not support vitamin supplements, including food fortification, as a strategy for achieving a nutrient profile that replicates a whole food dietary pattern for CVD risk reduction (1,2).

Plant Stanols/Sterols

The International Atherosclerosis Society guidelines for ASCVD prevention recommend consumption of 2 to 3 g plant stanols/ sterols per day to facilitate LDL-C reduction (10–15%) (2). Plant stanols/sterol esters lower LDL-C by reducing cholesterol absorption. Because they are present in minute amounts, the typical American diet is low in plant stanols/sterols. However, stanol/sterol fortified foods such as margarine (spreads), yogurt, and orange juice are considered a good source. Plant stanols/sterols are also available as supplements including tablets, chews, and powders (43,44).

SUMMARY

In summary, implementing current lifestyle guidelines for cardiovascular health can have a marked impact on CVD risk reduction. These include (1,2):

1) Adopt a heart healthy dietary pattern to optimize weight with appropriate caloric requirements and personal and cultural food preferences, and integrate medical nutrition therapy for other comorbidities including diabetes, hypertension, metabolic syndrome, and disorders of lipid metabolism. A dietary pattern that emphasizes vegetables, fruits, and whole grains; includes low-fat dairy products, poultry, fish, legumes, nuts, and nontropical vegetable oils; and limits intake of red meats, sugar-sweetened beverages, and sweets is recommended. The DASH dietary pattern, the USDA dietary pattern, and the AHA dietary pattern can be integrated into a cardioprotective meal plan. Evidence for these dietary patterns is strong. For hypertension, the DASH dietary pattern or the Mediterranean dietary pattern is recommended. The benefits of these patterns are independent of sodium intake and body weight.
2) Limit saturated fat intake to 5% or 6% of caloric intake. In a 2,000-kcal dietary pattern, this would translate to 120 kcal per day and 12 gm of saturated fat. In a 1,600-kcal diet pattern this would translate to 7 or 8 gm per day. By limiting meat and dairy products these goals are attainable.
3) Avoid *trans* fat as much as possible by reading labels. Any food that contains >0.5 g must be labeled per FDA requirements (45).

4) Lower sodium intake to 2,400 mg/day for the general population and 1,500 mg/day for those at high risk. Evidence is strong that lowering sodium intake lowers blood pressure and may prevent progression of prehypertension to hypertension.
5) Combine the DASH dietary pattern with lower sodium intake. Evidence is strong that combining these leads to better blood pressure reduction than implementing each individually.
6) Perform moderate to intense aerobic physical activity three to four times per week for an average of 40 minutes per session.
7) The AHA/ACC/TOS recommend that consideration be given to refer patients to nutrition professionals such as a registered dietitian or a registered dietitian nutritionist (1,3). Nutritional professionals can help patients personalize their dietary patterns and improve adherence. Patients at risk for ASCVD need help to identify the most relevant whole food dietary patterns for their nutritional goals and their lifestyles. Multidisciplinary clinic-based strategies that include onsite RDNs also can facilitate individual/group education; sustained in-person, telephone, or electronic feedback. The resources listed in the next section provide useful implementation strategies.

Health care providers must emphasize the importance of ASCVD risk reduction including the role that cardioprotective dietary patterns play in optimizing lipids, blood pressure, weight management, and reversing or preventing metabolic syndrome and type 2 diabetes mellitus (1,2). Also, health care providers should advocate for reimbursement of registered dietitians' services to provide recommended interventions that target patient behavior-change for CVD risk reduction (1,3,13,14).

RESOURCES

- Let's Eat for the Health of It. Choose MyPlate.gov. www.cnpp.usda.gov/Publications/Myplate/DG2010-Brochure.pdf
- Heart healthy sample menus including weight reduction meal plans and interactive tools https://www.supertracker.usda.gov/default.aspx
- Heart and Vascular Diseases, Detailed Information on Cholesterol, Heart Attack, High Blood pressure, Obesity, Other Heart and Vascular Diseases. www.nhlbi.nih.gov.health/prof/heart/index.htm
- AHA Diet and Lifestyle Recommendations Revision 2006. www.circ.ahajournals.org/contect/114/1/82.full
- Dietary Guidelines for Americans, 2010 www.cnpp.usda.gov.DGA's2010-PolicyDocument.htm
- Dietary Guidelines for Americans, 2010, Appendices 7 USDA Food Patterns with Various Calorie Levels, 8 Lacto-Ovo Vegetarian Adaptation of the USDA Food Patterns, 9 Vegan Adaptation of the USDA Food Patterns, 10 The DASH Eating Plan at Various Calorie Levels www.cnpp.usda.gov./Publications/DietaryGuidelines/2010/PolicyDoc/Appendices.pdf
- Calorie Results and Food Tracking Worksheets. www.choosemyplate.gov/professionals/food_tracking_wksht.html
- AHA Diet and Lifestyle Recommendations. http://www.heart.org/HEARTORG/GettingHealthy/Diet-and-Lifestyle-Recommendations_UCM_305855_Article.jsp#
- Your Guide to Lowering Blood Pressure With DASH. www.nhlbi.nih.gov/helath/public/heart/hbp/dash/new_dash.pdf
- *http://www.fda.gov/forconsumers/consumerupdates/ucm372915.htm*

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16

Arthur L. Klatsky, MD

Alcohol and Cardiovascular Diseases

Although major social and medical risks from drinking alcoholic beverages have been evident for millennia, it was also observed that light drinking was less hazardous or that there might be a safe limit of intake. Because no amount is safe for all persons, the term "sensible" may be more appropriate. Cardiovascular (CV) benefit from light to moderate alcohol intake, the lifestyle habit of a majority of American adults, is a more recent concept. The disparity between effects of lighter and heavier drinking mandates discussion both of prevention of harmful effects and optimization of possible benefit. This balancing act requires objective consideration of available data followed by exploration of public health and individual advice.

Another set of disparities in the relations of alcohol drinking to various CV conditions makes it wise to consider preventive aspects for several disorders separately (1). This chapter briefly discusses alcoholic cardiomyopathy, systemic hypertension (HTN), arrhythmias, stroke, and atherothrombotic disease, with emphasis on coronary artery disease (CAD) and the heart failure syndrome.

DEFINITIONS OF DRINKING

The operational definition of "moderate" and "heavy" drinking used here is based on the level of drinking in several epidemiologic studies above which net harm is usually seen and corresponds to the widely accepted U.S. Agriculture Department definition. The imprecise term "drink" is used, inasmuch as most persons think in terms of "drinks," not grams of alcohol. For men less than 3 drinks per day is called "light" or "moderate" drinking, and 3 or more drinks per day is called "heavy" drinking. For women the definition of heavy drinking is an average of 2 drinks per day. The lower amount for women is related to the facts that women have lower average size, greater average body fat proportion, and less metabolism of alcohol in the gastric mucosa. The amount of alcohol is approximately the same in the usual "standard" drink of wine, liquor, or beer. Thus, a 4-ounce glass of table wine at 13% alcohol, 1-¼ ounces of distilled spirits at 40% alcohol, and 12 ounces of U.S. beer at 5% alcohol all contain about 12.5 to 15 ml of pure ethyl alcohol.

ALCOHOLIC CARDIOMYOPATHY: A CONSEQUENCE OF HEAVY DRINKING

"Cardiomyopathy" is variously defined, but here means heart muscle disease not due to disorders of the valves, coronary arteries, lungs, or pericardium. Sustained heavy alcohol drinking is among the causes of "dilated cardiomyopathy," characterized by an enlarged heart with lowered ejection fraction. The condition has been recognized for more than 100 years (2), but with understanding clouded by the lack of specific diagnostic criteria and confusion with cardiovascular beriberi from thiamine deficiency. Solid circumstantial evidence establishes the existence of direct toxicity of alcohol upon myocardial cells (2–4).

Most convincing are human and animal data showing nonspecific functional and structural abnormalities in some heavy drinkers. These subclinical abnormalities may precede evident illness for years. The proportion of heavy drinkers with cardiomyopathy is less than the 15% to 20% that develop liver cirrhosis. Some improve with abstinence or reduced intake. Although a mechanism for alcoholic cardiomyopathy remains unclear, one possibility is suggested by a nonoxidative metabolic pathway for alcohol related to fatty acid metabolism in the heart, muscle, pancreas, and brain (3). Accumulated fatty acid ethyl esters are toxic to myocardial cells, and these compounds are used as markers of chronic alcohol abuse.

An important issue is whether moderate drinking impairs myocardial function. A landmark study (4) in alcoholics showed a clear relation of lifetime alcohol consumption to structural and functional myocardial and skeletal muscle abnormalities. The threshold for heart and skeletal muscle damage was high: equivalent to 120 grams alcohol/day for 20 years. It seems clear that this condition is unlikely to result from light or moderate drinking. See related discussion of heart failure below.

HYPERTENSION: A THRESHOLD ISSUE

Numerous cross-sectional and prospective analyses in diverse populations establish an empiric alcohol–HTN link, with confirmation by clinical experiments. The relationship seems independent of adiposity, salt intake, education, cigarette smoking, and several other potential indirect explanations (5,6). Alcoholic beverage type (wine, liquor, or beer) is not a major factor (5). Risk of cardiovascular sequelae of HTN is similar in nondrinkers, light drinkers, and heavy drinkers (7). With respect to light to moderate drinking, study results differ about whether blood pressure is increased, unaffected, or decreased. Both HTN and light to moderate drinking are common, therefore clarification of the risk threshold is very important.

A 1977 Kaiser Permanente study demonstrated the relationship of alcohol to higher blood pressure in men and women of 3 racial groups; later work suggested that ex-drinkers had blood pressures similar to nondrinkers and that elevated pressures regressed within a week upon abstinence (5). In these studies, HTN prevalence was approximately doubled among the heaviest (≥6 drinks daily) drinkers, compared to abstainers or light drinkers. In the later report blood pressures were slightly increased in men reporting 1 to 2 drinks per day.

Several experiments in hospitalized and nonhospitalized hypertensives and normotensives have shown that 3 to 4 days of taking several drinks and of abstinence raised and lowered BPs (5). Heavier alcohol intake can interfere with drug treatment of HTN. Moderation of heavy intake supplements other nonpharmacologic interventions for blood pressure lowering, such as weight reduction, exercise, or sodium restriction (5). The evidence is sufficient to state that heavy alcohol drinking is a probable HTN risk factor.

The alcohol–HTN relation is subacute, developing in days to weeks. Ambulatory monitoring has shown a depressor effect of a substantial dinner-time alcohol dose, lasting up to 8 hours, with a pressor effect the next morning (5). Much work has failed to establish biological mechanisms. One hypothesis is existence of a heightened responsiveness of the sympathetic nervous system (5), as exists during the alcohol withdrawal state. However, a withdrawal rise in BP has not been observed at the drinking levels in the clinical studies. Without long-term randomized controlled trials, the many traits related to alcohol drinking or HTN make it difficult to rule out all indirect explanations, especially psychosocial stress. The short-term intervention studies do provide good evidence against many confounders (5).

Relevant to the threshold issue is a report (8) suggesting that underreporting of heavier alcohol intake is a factor, thus possibly making spurious the apparent increased risk of lighter drinkers. Underreporting of alcohol intake places some heavier drinkers in light to moderate categories, a misclassification that lowers the threshold of apparent harm.

It is the author's opinion that the relation of heavier drinking to HTN is causal and that alcohol-related HTN is a common reversible form of HTN, especially in middle-aged men (5). Estimates of the proportion of HTN due to heavy drinking depend substantially upon the drinking habits of the group under study (5). Even the lowest estimates of attributable risk of 5% to 7% (5) translate into millions of persons with alcohol-associated HTN in Europe or the United States. The preponderance of evidence does not favor an adverse effect from light to moderate drinking.

SUPRAVENTRICULAR ARRHYTHMIAS: MORE DATA NEEDED

An association of alcohol consumption with atrial arrhythmias, typically occurring after a large meal with much alcohol, became popularly known as the "holiday heart phenomenon" (9). Atrial fibrillation is the most common diagnosis, and the arrhythmia typically resolves with abstinence. A prospective analysis (10) showed that atrial fibrillation risk was increased

among heavy drinkers but not in light to moderate drinkers. Pending more definitive studies, it seems sensible that persons at special risk of these rhythm problems should not exceed 1 or 2 standard-sized drinks per drinking occasion.

ATHEROSCLEROTIC CORONARY DISEASE: PROTECTION BY ALCOHOL

Epidemiology: A Nonlinear Relationship

CV mortality and morbidity statistics are dominated by the most common condition, atherosclerotic coronary artery disease. Well-known, probably causal risk factors discussed elsewhere in this handbook include cigarette smoking, HTN, diabetes mellitus, elevated low-density lipoprotein (LDL) cholesterol, and diminished high-density lipoprotein (HDL) cholesterol. Heberden's classic description of angina in 1776 included mention of relief by alcohol (2), leading to an incorrect assumption that alcohol is a coronary vasodilator. More likely, alcohol's effect on angina is anesthetic. In any case the subjective CAD symptom angina pectoris is difficult to quantify and study.

Observational prospective epidemiologic studies have consistently shown reduced risk of acute myocardial infarction and CAD death in moderate drinkers compared to abstainers (11–13). Evidence supporting benefit by alcohol also includes international comparisons, case-control studies, prospective population studies, and analyses of coronary arteriograms. In most reports the alcohol–CAD relation is nonlinear with increased risk of heavier versus lighter drinkers. Hypothetical explanations for the nonlinearity include more bingeing by heavier drinkers, the alcohol–HTN association, and misdiagnosis of cardiomyopathy as CAD.

Some question the alcohol–CAD observational data because several analyses lumped lifelong abstainers and ex-drinkers, or inadequately controlled for baseline CAD. If the nondrinking referent group includes "sick quitters" with increased CAD risk, a spurious impression of benefit from light to moderate drinking might ensue. Prospective studies that separate ex-drinkers from lifelong abstainers and/or control for baseline CAD (11–13) refute this hypothesis.

Mechanisms for CAD Protection by Alcohol: Multiple and Plausible

Good reviews are available (14–17) and Table 16.1 presents plausible mechanisms for protection against CAD by alcohol. Best established is a link via blood lipid factors. Except in persons with severe liver impairment, alcohol ingestion raises high-density

TABLE 16.1 Possible Mechanisms for CAD Protection by Alcohol

Mechanism of Alcohol Effect	Action and Comment	Strength of Evidence*
Raises high-density-lipoprotein (HDL) cholesterol	"Reverse" LDL cholesterol transport from blood vessel wall; a long-term effect; also a possible antioxidant	Excellent for ~50% of alcohol effect
Lowers fibrinogen, thromboxane A, and platelet stickiness; increases prostacyclin and endogenous tissue plasminogen activator	Decreased clot formation in atherosclerotic blood vessels (a key factor in CAD events); a short-term action	Good
Lowers risk of type 2 diabetes mellitus	Possibly by reducing insulin resistance; diabetes a major CAD risk trait	Good
Less LDL oxidation in blood vessel walls	Presumably mostly a nonalcohol effect; antioxidants plentiful in red wine, moderate in dark beer	Weak to moderate
Increased preconditioning of heart myocytes	Resistance to damage with oxygen deprivation	Fair
Decreased psychosocial stress	Stress a possible CAD risk factor	Weak

* Author's judgment.
Abbreviations: CAD = coronary artery disease; LDL = low-density-lipoprotein cholesterol. HDL = high density lipoprotein cholesterol.

lipoprotein cholesterol levels by incompletely understood pathways. Empiric inverse relations of HDL to CAD risk are well established and probably operate via removal of lipid deposits in large blood vessels plus abetting prevention of tissue oxidation of LDL cholesterol. Studies examining the hypothesis that higher HDL cholesterol in drinkers mediates CAD protection suggest that higher HDL levels mediated about half of the lower CAD risk and that both major HDL subfractions, HDL_2 and HDL_3, are involved. Although HDL_3 may be more strongly related to alcohol intake than HDL_2, both are related to lower CAD risk. Triglycerides may play an independent role in risk for CAD. A subset of heavier drinkers has a substantial increase in triglyceride levels, but this is infrequently seen with light to moderate drinking.

Antithrombotic actions of alcohol include inhibition of platelet stickiness and lower fibrinogen levels. Inasmuch as thrombosis in atherosclerotic vessels plays a key role in major CAD events, these effects may be important factors in alcohol's protection. Heavy alcohol drinking has been associated with higher blood glucose levels and poor compliance with diabetes management. However, data indicate a lower risk of developing diabetes among light to moderate drinkers (18) with beneficial changes in insulin and glucose metabolism. Because diabetes is a powerful predictor of atherosclerosis, this association represents a potentially important intermediary in protection by alcohol against CAD and ischemic stroke.

Drinking Pattern: A Crucial Factor

Binge drinking is clearly harmful. Other drinking pattern aspects of interest are frequency of drinking (number of days per week), variability over time, and whether the alcohol is taken with food. Reports suggest that drinking at mealtimes is more favorable for CAD and HTN and that frequency of intake may be a strong factor.

Beverage Choice: Wine, Liquor, or Beer?

The "French paradox" concept refers to the fact that France is an outlier on graphs of mean dietary fat intake versus CAD mortality, unless adjusted for wine intake (19). The idea that CAD benefit is limited to red wine was initiated by such international comparisons suggesting less CAD in wine-drinking countries than in beer- or liquor-drinking countries. The hypothesis that red wine has protective benefit additional to that of alcohol is indirectly supported by the presence of nonalcoholic antioxidant phenolic compounds with antioxidant and antithrombotic properties in wine, especially red wine (14–17). There are several classes of these compounds in grapes and other fruits and vegetables with hypothetical effects that might promote endothelial health, including catechins, quercetin, and resveratrol. These are observed in vitro and in animal studies to produce beneficial effects on established biological markers of vascular disease. Effects in humans in vivo are less established, and there are issues related to bioavailability because of limited absorption from the gastrointestinal tract. Resveratrol, in particular, is poorly absorbed, so huge doses would be required for human effects comparable to those reported in other species, quite incompatible with those obtainable from moderate drinking.

Epidemiological data in prospective studies suggest that white wine, red wine, and beer may all be effective in reducing CAD risk (1,20–21). The beverage choice issue is complicated by indicating that wine drinkers have the most favorable CAD risk profile (22). Drinking pattern differences could also play a role, as wine is more often sipped slowly with meals than beer or liquor.

It is the author's opinion that antioxidation is unlikely to be the primary mechanism involved in protection against CAD by alcoholic beverages. The "French paradox" has caught the public fancy, however, the wine/liquor/beer issue is unresolved at this time. It seems likely that ethyl alcohol is the major factor with respect to lower CAD risk.

ALCOHOL AND CAD: IS IT CAUSAL?

Potential confounding cannot be completely ruled out in the absence of a randomized controlled trial with CAD outcome data. Thus, uncertainty remains about the causal nature of the inverse alcohol–CAD association. Skeptics about alcohol's benefit have emphasized possible flaws in methodology that might spuriously produce apparent benefit of moderate drinking. As already mentioned, some studies failed to separate lifelong abstainers from ex-drinkers, thus increasing risk of the nondrinker referent group by inclusion of "sick quitters." Possible confounding by healthy lifestyle habits of moderate drinkers has also been postulated. Although less attention has been given to sources of bias that might reduce apparent benefit, confounding probably acts both ways. For example, residual confounding by smoking, a correlate of alcohol drinking in many populations, would reduce apparent benefit by lighter alcohol drinking. Underreporting by heavy drinkers is another likely

source of bias against apparent benefit by moderate intake. By placing some heavy drinkers in lighter categories, underreporting probably distorts alcohol–health curves by spuriously increasing risk or lessening the apparent benefit of light drinking.

Evidence that persons with an alcohol dehydrogenase polymorphism resulting in "slow metabolism" of alcohol (23) may have more CAD benefit supports a causal relationship for the protective effect of light to moderate drinking on CAD. This might be considered a form of natural randomized controlled trial. Other aspects favoring a causal hypothesis are consistency in studies, plausible biological explanations, relative specificity of benefit for atherothrombotic vascular disease, and the temporal sequence in prospective studies. The lack of a linear relation is not a major issue, because many alcohol–health associations are nonlinear. Although other factors may play a role, a causal protective effect of moderate alcohol intake is the simplest and probably correct explanation.

CEREBROVASCULAR DISEASE: THE EPIDEMIOLOGIC LABYRINTH

There are complex interrelationships of stroke, alcohol, and other cardiovascular conditions. Systemic HTN is an important risk factor for all types of stroke and a probable intermediary between heavy drinking and increased stroke risk. Antithrombotic effects of alcohol might increase hemorrhagic stroke while lowering ischemic stroke risk. Blood lipid effects of alcohol (see CHD discussion) might favorably affect ischemic stroke risk. The preponderance of evidence at present suggests that drinking has these effects but the relations of alcohol drinking to various types of stroke remain unresolved (1,13,24).

HEART FAILURE (HF): IT DEPENDS ON THE CAUSE

Because of a growing number of older persons in the population and increasing survival of heart disease patients to the stage of advanced disease, there is increasing incidence of this nonspecific syndrome. Multiple risk factors are the rule, with CAD a factor in a majority. Other common underlying factors include HTN, valvular disease, cardiomyopathies (including alcoholic), rhythm disturbances, and systemic problems such as anemia or infection. Alcoholic cardiomyopathy has dominated past thinking about alcohol and HF, however, it is now evident that the alcohol–HF relationship is dependent on the causes of the syndrome (25). Heavy, but not light–moderate drinkers, have increased risk of non-CAD–associated HF, but alcohol drinking is inversely related to risk of HF associated with CAD.

SUMMARY

Table 16.2 summarizes the disparate alcohol–CV relations, emphasizing the basic differences between

TABLE 16.2 Alcohol in Preventive Cardiology

Condition	Probable Relationship of Alcohol		Comments
	Lighter Drinking*	Heavier Drinking*	
Dilated cardiomyopathy	Unrelated	One (of several) causes	Unrelated to moderate drinking
Systemic HTN	Little or none	Probably causal in some	Mechanism unknown
CAD	Protective	? Less protective or increased risk	Drinking pattern important; additional benefit from wine phenolics
Supraventricular arrhythmia	? None	Probably a causal factor, especially binges	Mechanism unclear
Hemorrhagic stroke	? Unrelated or slightly increased risk	Increased risk	Via higher BP, antithrombotic actions
Ischemic stroke	Protective	Unclear; varies with subtype	Complex interactions with other conditions

* See text for definitions. HTN = hypertension, CAD = coronary artery disease.

favorable relations of light to moderate drinking and unfavorable relations of heavier drinking. But this is not the complete picture with respect to advice about health effects of alcohol drinking. Such advice needs to be individualized according to the specific medical history and risks of any concerned person (26). For example, the increased risk of breast cancer outweighs any cardiovascular benefit from moderate drinking in most women <50 years of age but in postmenopausal women the cardiovascular benefit for total mortality outweighs the breast cancer risk. Generally, men above the age of 40 who are established light–moderate drinkers should not be advised to abstain. Most nondrinkers have good reasons for abstinence, including religious/moral concerns, personal or family history of alcohol problems, or specific medical concerns and continued abstinence is wise for these persons.

A few common-sense rules are suggested. (i) The overall health risk of a heavy drinker will be reduced by reduction or abstinence. (ii) Because of the unknown risk of progression to heavier drinking and alcohol dependence, abstainers should not indiscriminately be advised to drink for CV health benefit. (iii) Middle-aged and older established light–moderate drinkers (the majority in the United States and Western Europe) need no change in drinking habits.

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Haitham M. Ahmed, MD, MPH
and Chiadi E. Ndumele, MD, MHS

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Physical Activity

Over the past several decades, there has been a considerable increase in sedentary behavior, due in large part to technological advances in transportation, entertainment, and workplace structures (1,2). Research has shown strong associations between sedentary lifestyles and cardiovascular risk factors including obesity, diabetes, and hypertension, as well as associations of physical inactivity with cardiovascular disease (CVD) and all-cause mortality (1,3–9). In this chapter we review the effects of physical activity on cardiovascular risk factors, prevention of CVD, and overall survival.

EXERCISE AND TRADITIONAL CARDIOVASCULAR DISEASE RISK FACTORS

Exercise has beneficial effects on several traditional CVD risk factors, often in a dose-related fashion. These favorable effects of exercise are reviewed below.

Effects of Exercise on Lipids

In adults, aerobic physical activity reduces low-density lipoprotein cholesterol (LDL-C) by an average of 3 to 6 mg/dL, and reduces non-high-density lipoprotein cholesterol (non-HDL-C) by an average of 6 mg/dL (10).

The association between high levels of atherogenic lipoproteins and CVD is well-documented in the medical literature (11). Accordingly, reductions in atherogenic lipoproteins reduce atherosclerotic progression and subsequent CVD risk.

Several studies have demonstrated favorable effects of exercise on lipoproteins, with higher amounts of exercise associated with greater improvements in lipoprotein profiles (12–16). Based on evidence from numerous meta-analyses and systematic reviews evaluating lipid outcomes, the 2013 American Heart Association (AHA)/American College of Cardiology (ACC) Lifestyle Work Group concluded that aerobic physical activity alone reduces LDL-C by 3 to 6 mg/dL and reduces non-HDL-C by 6 mg/dL (10).

Physical activity may have a greater impact on LDL particle size than on total LDL concentration per se (17–22). In subjects studied longitudinally, daily aerobic activity was shown to increase mean LDL particle size independent of weight loss (15). Given the potentially greater atherogenicity of small, dense LDL particles, the effects of exercise training on LDL particle size may be an important mechanism through which exercise reduces cardiovascular risk.

Effects of physical activity on apolipoprotein B (ApoB), HDL, and triglycerides (TG) are also promising. Longitudinal studies have shown regular exercise reduces ApoB by up to 20% (15,18–21, 23–31). Moderate-intensity exercise training increases HDL and lowers TG even in the absence of weight loss (32). With 30 to 60 minutes of moderate intensity

aerobic exercise 3 to 5 times per week, HDL levels were noted to increase by 1.9 mg/dL and TG levels to decrease by 18.6 mg/dL (31,32). Similarly, HDL has been shown to increase by 0.3 mg/dL per mile of running per week (16).

Effects of Exercise on Blood Pressure

■ Among adults, aerobic physical activity reduces systolic blood pressure (BP) by an average of 2 to 5 mmHg, and diastolic BP by 1 to 4 mmHg (10).

Regular exercise training lowers blood pressure. Although the mechanisms are not completely understood, improved myocardial contractility, increased peripheral oxygen uptake, enhanced endothelial function, and decreased sympathetic tone may all contribute to lower systemic vascular resistance over the long term (33–35).

The 2013 AHA/ACC Lifestyle Work Group reviewed evidence from multiple meta-analyses and systematic reviews of physical activity to find that aerobic physical activity reduces systolic BP on average by 2 to 5 mmHg and diastolic BP by 1 to 4 mmHg (10). It is estimated that reductions in BP may explain up to 27% of the reduction in CVD rates associated with regular physical activity (36).

In 2008, the U.S. Department of Health and Human Services published physical activity guidelines for overall health, with a statement that for most health outcomes including blood pressure, additional benefits are gained as exercise intensity, frequency, and duration increase (37). Accordingly, the AHA/ACC Lifestyle Work Group found that physical activity interventions showing the greatest effect on BP were those that included moderate-to-vigorous aerobic exercise comprised of 3 to 4 sessions per week, lasting on average 40 minutes/session, and continued for at least 12 weeks, duration (10).

Effects of Exercise on Diabetes

■ Aerobic training increases glucose uptake and insulin sensitivity.
■ Regular exercise reduces the incidence of new diabetes and helps improve blood glucose control among those already diagnosed with diabetes.

Exercise and the Prevention of Diabetes

In states of insulin resistance, there is an initial reduction in insulin-stimulated glucose uptake followed by a compensatory increase in insulin secretion by the pancreatic *B*-cells. Eventually, *B*-cells fail to compensate for ever-increasing blood glucose levels and overt diabetes develops. On a molecular level, several studies have shown that glucose clearance is slower, insulin resistance greater, and insulin rise higher with sedentary behaviors (38–40).

Multiple prospective studies have shown that physical activity can prevent or delay the onset of type 2 diabetes. The Da Qing study in China showed that 20 minutes of mild–moderate exercise, 10 minutes of strenuous exercise, or 5 minutes of very strenuous exercise reduced diabetes risk by 46% (41). Two large diabetes prevention clinical trials in the United States and Finland showed that moderate exercise for 30 minutes per day reduced the risk of diabetes by up to 58% (42,43).

Exercise and Control of Existing Diabetes

Physical activity has also been shown to lower blood glucose and improve insulin sensitivity among individuals already diagnosed with diabetes (44). Individuals with type 2 diabetes who engaged in supervised training programs exhibited better blood glucose control and compliance compared to controls (45–47).

Effects of Exercise on Weight and Body Composition

■ Physical activity is recommended as an important part of weight management by the AHA and American College of Sports Medicine (ACSM) (48).
■ A dose–response relationship exists with regard to physical activity and weight loss.

According to the World Health Organization, the prevalence of obesity has nearly doubled over the past three decades (49). Multiple large population-based studies have shown strong correlations between physical inactivity and obesity (3,50–57).

Routine physical activity has been associated with the prevention of weight gain with aging (58). Exercise training has also been associated with reductions in body fat (in particular, abdominal adiposity), preservation of lean muscle mass, overall weight loss, and weight maintenance after prior weight loss (59,60).

With regard to weight loss, the ACSM evidence statements based on multiple studies note that a dose–response relationship exists concerning physical activity and weight loss: <150 minutes exercise per week promotes minimal weight loss, 150–225 minutes per week promotes 2 to 3 kg weight loss, and >225 minutes per week promotes 5 to 7.5 kg weight loss (61).

EXERCISE AND NOVEL CARDIOVASCULAR DISEASE RISK FACTORS AND SUBCLINICAL ATHEROSCLEROSIS

Effects of Exercise on Inflammation

■ Evidence suggests that regular exercise is associated with a reduction in systemic inflammation.

Inflammation is associated with all stages of atherosclerosis, including atherogenesis, plaque progression, and atherothrombosis (62). Exercise and skeletal muscle contraction are thought to increase circulating cytokines acutely, but regular exercise is associated with decreased levels of proinflammatory cytokines and increases in anti-inflammatory markers (63,64).

In prospective studies, inverse relationships have been demonstrated between physical activity and circulating inflammatory markers including interleukin-6 (IL-6), fibrinogen, and leukocytes (65–68). As for C-reactive protein (CRP), the inflammatory marker perhaps most consistently associated with future CVD events, studies have noted the greatest reduction in CRP with higher intensity training, and particularly among individuals with high baseline levels of inflammation (69,70). However, randomized trials testing the effects of exercise on CRP reduction have yielded conflicting results (71–83).

In total, the balance of evidence from prospective studies points toward a reduction in systemic inflammation with regular exercise, but further research is needed. The effects of exercise on systemic inflammation have been less established in randomized trials, with results frequently conflicting in both healthy and coronary artery disease (CAD) patient populations.

Effects of Exercise on Thrombosis

■ Transient prothrombotic effects occur with acute exercise, but then reverse with chronic training due to increased tissue plasminogen activator (TPA) activity and decreased platelet aggregation over the long term.

Acutely, physical activity has been shown to increase coagulation and platelet aggregation simultaneously, creating a transiently prothrombotic state (84–86). However, over the long term there are clear antithrombotic effects with regular training. Large cross-sectional and prospective studies have observed antithrombotic effects with regular exercise, particularly due to high circulating levels of TPA and lower plasminogen activator inhibitor-1 with chronic training (87–91). Furthermore, platelet aggregation and adhesiveness have been shown to be significantly reduced after chronic, moderate aerobic exercise in male and female subjects (92,93).

Effects of Exercise on Subclinical Atherosclerosis

■ An abundance of data points toward associations between physical activity and markers of subclinical atherosclerosis including coronary artery calcium (CAC) and arterial intima-media thickness (IMT).

CAC and carotid IMT are early atherosclerotic markers that are strongly linked to risk of future CVD events in adult men and women (94,95). Numerous trials to date have identified associations between CAC or IMT and physical activity.

Cross-sectional and prospective studies have shown CAC to be independently associated with self-reported physical activity, number of pedometer steps per day, and walking pace in both men and women (96–100). Results from the Multi-Ethnic Study of Atherosclerosis (MESA) showed that healthy participants who exercised more than 150 minutes per week had lower CAC incidence as well as slower CAC progression over a median of eight years (9).

Prior observational data has also shown an independent correlation between cardiorespiratory fitness and carotid IMT in men and women (101–104). In the Los Angeles Atherosclerosis Study, carotid IMT progression was found to be 14.3 microns/year in sedentary participants, 10.2 microns/year in moderately active participants, and 5.5 microns/year in vigorously active participants (105). In interventional studies, authors have noted slowed progression of IMT with exercise in obese children, diabetic adults, and postmenopausal women (106–108). Wildman and colleagues noted that 1,000 to 1,500 kilocalorie (kcal) expenditure per week decreased IMT progression from 0.008 mm/year to 0.004 mm/year (108).

In summary, a wealth of data point toward associations between physical activity and markers of subclinical atherosclerosis.

PHYSICAL ACTIVITY AND CARDIOVASCULAR DISEASE

■ Exercise and fitness are strongly associated with lower CVD rates and lower all-cause mortality in both primary and secondary prevention.

■ There is a dose–response relationship between physical activity intensity and duration, and long-term outcomes.

Primary Prevention

Numerous studies have shown that physical activity and fitness are strongly associated with lower CVD- and all-cause mortality in large population-based cohorts (9,109–115). In several of these epidemiological studies, energy expenditures of approximately 1,000 kcal/week—which approximates minimal adherence to exercise guidelines—was correlated with a 20% to 30% reduction in risk of death (109–112).

Even more promising were findings from a large 35-year cohort of Swedish men, which showed that increasing physical activity in middle-aged men reduced risk of all-cause death by a level comparable to that of smoking cessation (114). Generally, the benefits of exercise in these epidemiological studies were observed irrespective of whether physical activity or fitness was studied, whether participants were men or women, and whether the outcome was CVD- or all-cause death. A dose–response relationship has been demonstrated with regard to exercise intensity where those who exercise more vigorously attain greater long-term benefits (Figure 17.1) (114).

Secondary Prevention

In addition to benefits in primary prevention, regular exercise has clear benefits both after myocardial infarction (MI) and after a diagnosis of CAD. A large meta-analysis of 63 randomized trials of physical activity including 21,295 patients with CAD (most of whom were post-MI), showed a reduction in recurrent MI by 17% at one year and 47% at two years with regular exercise (116). Among patients with stable CAD, exercise has also been shown to have substantial benefits. Hambrecht and colleagues randomized men age ≤70 with class I to III angina and angiographic evidence of CAD to an aerobic exercise training program (20 min per day) versus percutaneous coronary intervention with stenting. At one year of follow-up, event-free survival was significantly higher in the exercise training group (88% versus 70%, $P < 0.001$) (35).

Exercise via cardiac rehabilitation after coronary revascularization also has clear benefits. A 2004 systematic review and meta-analysis of patient postmyocardial revascularization showed that exercise-based rehabilitation was associated with lower cardiac and all-cause mortality (117). Patients who have undergone coronary artery bypass graft (CABG) surgery and who have participated in cardiac rehabilitation have also been shown to have a lower incidence of adjusted all-cause mortality at 10 years (23% vs. 36%, adjusted hazard ratio 0.54 with 95% confidence interval 0.40–0.74) (118). Moreover, there appears to be a dose–response relationship between number of cardiac rehabilitation sessions and long-term outcomes, where participants with higher attendance at cardiac rehabilitation programs displayed lower risk of death and MI at four years (119).

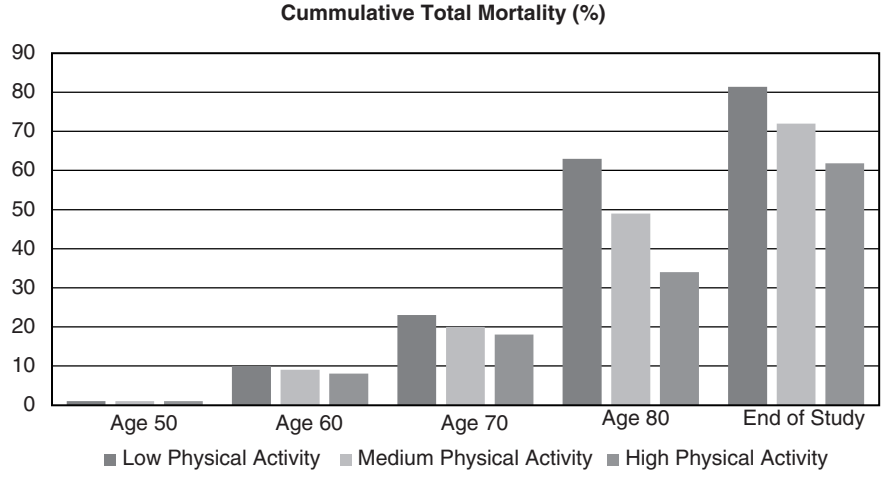

FIGURE 17.1 Cumulative Mortality From Age 50 by Leisure Time Physical Activity Level

Source: Adapted from Ref. (114) Byberg L et al. Total mortality after changes in leisure time physical activity in 50 year old men: 35 year follow-up of population based cohort. *BMJ*, 2009: 338.

In summary, exercise appears to have significant benefits with regard to reduction of recurrent MI risk and mortality in patients with stable CAD, patients who are post-MI, and patients who are post-coronary revascularization including CABG.

PHYSICAL ACTIVITY ASSESSMENT AND PRESCRIPTION

- A description of light, moderate, and vigorous physical activities is provided in Table 17.1.
- Specific guidelines for exercise regimen prescriptions are outlined in Table 17.2.

Depending on the intensity of the activity, physical activity can be described as vigorous, moderate, or light (Table 17.1). A well-validated and internationally used instrument that providers can employ to assess patients' physical activity level is the International Physical Activity Questionnaire (IPAQ) (120). The IPAQ quantifies the amount of time spent in vigorous, moderate, and sedentary activity to categorize an individual's overall activity level as high, moderate, or low (Table 17.2). Assessments of physical activity as a continuous variable (MET·min·week), calculated by multiplying METs (intensity level) × duration of activity × frequency of activity per week, are also used in scoring.

Weekly physical activity regimen can be prescribed based on patients' medical history and desired goals, as per various public health and professional guidelines (Table 17.3). Recommended physical activity prescriptions for different risk factors and conditions are detailed below.

Cholesterol: The 2013 AHA/ACC guidelines recommend aerobic physical activity lasting an average of 40 minutes per session, for 3–4 sessions per week, in order to reduce LDL-C and non-HDL-C in adults (class of recommendation IIa, level of evidence A) (10).

TABLE 17.1 MET Equivalents of Common Physical Activities by Intensity

Light <3 METs	Moderate 3–6 METs	Vigorous >6 METs
Walking slowly at home	Walking briskly	Jogging, running
Desk work, using computer	Carpentry, mowing lawn	Mining, shoveling
Light household chores (ironing, washing dishes)	Heavy cleaning – car or household	Farming, digging ditches
Playing cards or darts	Ballroom dancing, table tennis	Basketball, soccer, swimming

Source: Adapted from Ainsworth BE, Sternfeld B, Richardson MT, Jackson J. Evaluation of the Kaiser Physical Activity Survey in Women. *Med Sci Sports Exerc.* 2000;32(7):1327–1338.

TABLE 17.2 IPAQ Categories of Physical Activity

Physical Activity Level	Criteria
High	Any of the following 2 criteria: • Vigorous-intensity activity on at least 3 days and accumulating at least 1500 MET-minutes/week OR • 7 or more days of any combination of walking, moderate-intensity, or vigorous intensity activities achieving a minimum of at least 3000 MET-minutes/week
Moderate	Any of the following 3 criteria: • 3 or more days of vigorous activity of at least 20 minutes per day OR • 5 or more days of moderate-intensity activity or walking of at least 30 minutes per day OR • 5 or more days of any combination of walking, moderate-intensity, or vigorous intensity activities achieving a minimum of at least 600 MET-min/week.
Low	Not meeting criteria for moderate or high activity above

Source: Bauman A, Bull F, Chey T, Craig CL, Ainsworth BE, Sallis JF, Bowles HR, Hagstromer M, Sjostrom M, Pratt M, IPS Group. The International Prevalence Study on Physical Activity: Results from 20 Countries. *Int J Behav Nutr Phys Act.* 2009;6:21.

TABLE 17.3 Exercise Regimen Prescriptions from Various Professional Associations

Association	Regimen	Intensity	Duration	Frequency	Goals/Benefits
AHA/ACC	Aerobic Exercise	Moderate-to-Vigorous	40 min/session	3-4 sessions/week	Reduce LDL-C and non-HDL-C (10)
AHA/ACC	Aerobic Exercise	Moderate-to-Vigorous	40 min/session	3-4 sessions/week	Reduce BP (10)
ACSM/ADA	Aerobic Exercise	Moderate	150 total min per week		Prevent diabetes in high-risk adults (121)
ACSM/ADA	Aerobic Exercise	Moderate-to-Vigorous	150 total min per week		Improve blood glucose control in diabetics (121)
ACSM	Aerobic Exercise	Energy equivalent of 1,200–2,000 kcal/week	150–250 total min per week		To prevent weight gain (61)
			150–225 total min per week		To promote 2–3 kg weight loss (61)
			>225 total min per week		To promote 5–7.5 kg weight loss (61)

Blood Pressure: The 2013 AHA/ACC guidelines also recommend aerobic physical activity lasting an average of 40 minutes per session, for 3 to 4 sessions per week, for at least 12 weeks, duration in order to reduce blood pressure (class of recommendation IIa, level of evidence A) (10).

Glycemic Control: The ACSM/American Diabetes Association (ADA) joint position statement recommends 150 minutes of moderate-to-vigorous physical activity per week to prevent diabetes in high-risk adults (ADA level of evidence A) (121). They also recommend that individuals with diabetes partake in 150 minutes per week of moderate to vigorous physical activity with no more than two consecutive days without exercise (ADA level of evidence B) (121). Similarly, the AHA recommends 150 minutes of moderate-intensity and/or 90 minutes per week of vigorous-intensity exercise among individuals with type 2 diabetes (122).

Weight Management: The ACSM recommends 150 to 250 minutes of physical activity per week with an energy equivalent of 1,200 to 2,000 kcal per week to prevent weight gain in adults (61). For those wishing to lose weight, 150 to 225 minutes per week promotes 2 to 3 kg weight loss, and >225 minutes per week promotes 5 to 7.5 kg weight loss (61).

Secondary Prevention: ACC/AHA guidelines recommend referral to a multicomponent cardiovascular rehabilitation program that includes exercise training for patients with a recent MI or acute coronary syndrome, chronic stable angina, heart failure, following revascularization via percutaneous coronary intervention or coronary artery bypass surgery, or following cardiac valve surgery or heart transplantation (Class I recommendation) (123).

SUMMARY

Over the past several decades, there has been a considerable transformation toward sedentary lifestyles, due in part to advances in transportation, technology, entertainment, and the workplace. In contrast, physical activity has been thoroughly shown to have multiple favorable biological and physiological effects that reduce risk of CVD- and all-cause death in large population-based studies.

Regular exercise favorably affects lipoprotein profiles, blood pressure, and body composition, and improves insulin sensitivity and blood glucose levels. Therefore, it helps to prevent the onset of and improves control of type 2 diabetes. Exercise also reduces inflammation, thrombosis, and platelet aggregation. Regular exercise has been associated with decreased rates of subclinical CVD and CVD events, and with improved overall survival.

Most public health and scientific communities recommend approximately 150 minutes of moderate physical activity over most days of the week for reduction of LDL, non-HDL, diabetes risk, blood glucose, weight, MI risk, and all-cause mortality. In an era of increasingly sedentary lifestyles, the importance of fitness and regular exercise are of utmost importance and should not be overlooked by attention to diet and weight alone.

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18

Erin D. Michos, MD, MHS

The Prevention of Cardiovascular Disease Among Women

Much progress has been made in the past decade in the reduction of fatal cardiovascular disease (CVD) in women. Between 1979–1999, the CVD death rate among women remained essentially unchanged, hovering around 500,000 deaths annually. However, after the year 2000, the CVD mortality rate dramatically declined in women (Figure 18.1)(1) likely due to intensified secondary preventive efforts, improved treatment of risk factors, and education. Despite this progress, CVD remains the leading cause of death for American women. The 2008 death rate attributable to CVD is 200.5 per 100,000 and 277.4 per 100,000 for white and black females, respectively (1).

EPIDEMIOLOGY

Although the overall CVD mortality rates have been going down, statistics from the National Health and Nutrition Examination Survey (NHANES) found that CVD mortality rates have actually increased for younger women age 35 to 44 on average by 1.3% (95% CI 0.2 to 2.5) per year since 1997, a worrisome trend, likely due to the increased prevalence of obesity, diabetes mellitus, and metabolic syndrome among women (2).

Before age 75, a higher proportion of CVD events attributable to coronary heart disease (CHD) occur in men compared to women, but a higher proportion of CVD events from stroke is found among women. Thus, a focus on prevention of total global atherosclerotic CVD, rather than just CHD, is paramount for women and is the recommended focus of the 2011 Effectiveness-Based Guidelines for the Prevention of Cardiovascular Disease in Women (3) as well as the 2013 American Heart Association (AHA)/American College of Cardiology (ACC) Risk Assessment Guidelines (4).

Lifetime risk of CVD is very high in women. For women free of clinical CVD at 50 years of age, ~40% of women will later develop CVD compared to the lifetime risk of breast cancer (13%), lung cancer (6%), and colorectal cancer (6%). Preventive efforts need to begin early because even the presence of a single major risk factor by middle age is associated with increased lifetime risk for CVD and markedly shorter survival. Using data from 18 cohorts, women with an optimal risk-factor profile (total cholesterol level <180 mg/dl, systolic and diastolic blood pressures <120 and <80 mmHg, nonsmoking, and nondiabetic) had substantially lower risks of CVD death through the age of 80 years compared with women with two or more major risk factors (6.4% vs. 20.5%), as well as lower lifetime risks of CHD (<1% vs. 18.%) and stroke (5% vs. 11%) (5).

AHA Surveys have indicated that women's awareness of heart disease has been increasing over time, with 57% of women surveyed in 2006 (compared to 30% in 1997, $P < 0.001$) being aware that heart disease is the leading cause of death for

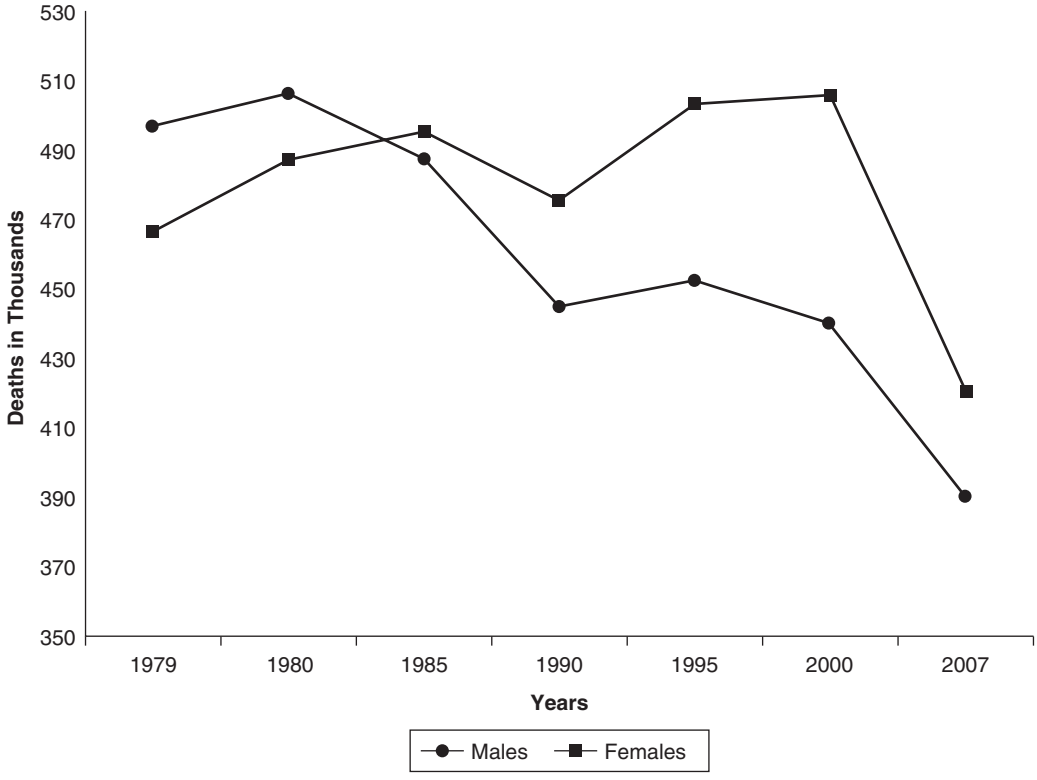

FIGURE 18.1 Cardiovascular disease mortality trends for males and females (United States: 1979–2007). *Source*: Roger VL, Go AS, Lloyd-Jones DM, et al. American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2012 update: a report from the American Heart Association. *Circulation*. 2012;12:e2-e220.

Impact of CVD in Women

- Single largest killer of American women
- More women than men die each year from CVD in absolute numbers
- In women, CVD-related deaths exceed the next 7 causes of death combined
- One woman dies of CVD ~every minute
- 2/3 of women who die had no prior symptoms

women (6). Awareness is significantly lower among black and Hispanic women. Unfortunately, the majority of women surveyed still reported taking therapies to prevent CVD that are not evidenced-based. Furthermore, only 53% of women said they would call 911 if they thought they were having a heart attack and only 23% said they would take an aspirin (6). Therefore, there is room for improvement with our educational efforts, particularly among minority race/ethnic groups.

CVD RISK FACTORS AND LIFESTYLE MANAGEMENT IN WOMEN

Reproductive Factors

Although many of the traditional CVD risk factors are the same for both men and women, several reproductive factors unique to women may identify women at elevated risk for a subsequent CVD event (Figure 18.2). Pregnancy, for example, offers a unique stress that may unmask underlying endothelial dysfunction, metabolic risk, and/or vascular disease (7).

Women with hypertension in pregnancy, preeclampsia, or gestational diabetes have a higher predicted risk of CVD later in life. Studies suggest that 35% to 60% of women with a history of gestational diabetes will develop type 2 diabetes within 10 years (7). Thus, for women diagnosed with gestational diabetes, it is recommended that after the initial postpartum testing a glucose screen should be done within a year and at a minimal interval of 3 years after that. Women

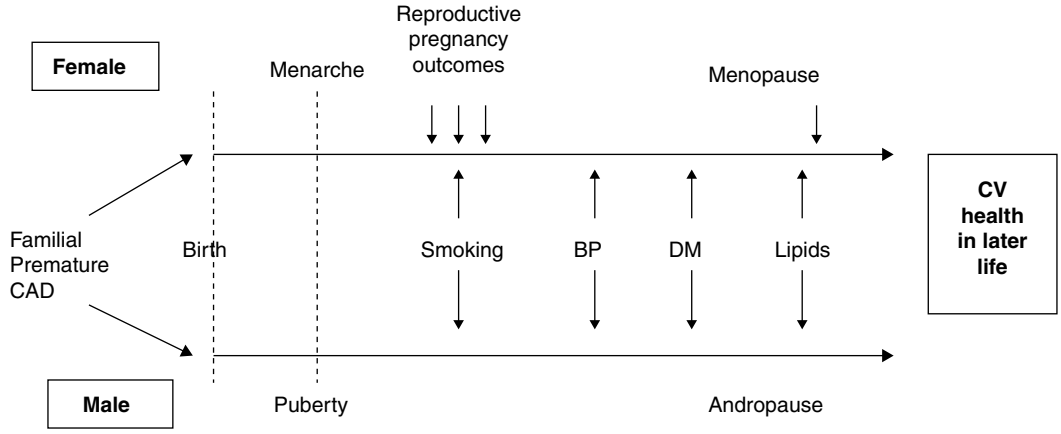

FIGURE 18.2 Reproductive factors unique to women may identify women at elevated risk for a subsequent CVD event. Adapted from Ouyang P, Johns Hopkins, personal communication.

Reproductive Factors and CVD Risk
• Ask about a reproductive and pregnancy history as part of CVD screening. • Pay particular attention to a history of gestational diabetes, hypertension in pregnancy, pre-eclampsia, preterm delivery, delivery of a low-birth-weight infant, early menarche, early menopause, surgical oopherectomy, polycystic ovarian disease. • May help identify women at increased CVD risk so that risk factor screening and treatment, particularly intensified lifestyle measures, can be implemented.

Smoking Cessation Management
• Ask about current and past smoking as well as secondary tobacco smoke exposures. • Assess readiness to quit. • At each visit, strongly encourage patient and/or family members to stop smoking and provide counseling, offer nicotine replacement or other pharmacotherapy in conjunction with a behavioral program or formal smoking cessation program. • Be prepared to give advice on weight control strategies as weight gain may be a concern for some women regarding quitting.

with a history of pre-eclampsia have nearly double the risk of CHD and stroke approximately 10 to 12 years later, and a 49% increased risk of all-cause mortality at an average 15 years follow-up (8).

On average, women experience CHD events 10 years later in life than men attributed to a "premenopausal" advantage. Data from the Framingham cohort suggest postmenopausal women are at greater risk for CHD than premenopausal women at any age. But on a logarithmic scale, the risk of CHD by age in women is more linear, without evidence for a rapid acceleration in mid-life (9).

Smoking

In 2010, 18% of adult women still continue to smoke (1). Smoking is even a stronger risk factor for CVD in women than it is for men. Female smokers die an average of 14 years earlier than female nonsmokers. For women < 50 years of age, the majority of CHD is attributable to smoking. Smoking triples a middle-aged women's risk of dying from CHD.

Hypertension

The risk of vascular and all-cause mortality risk increases linearly with increasing blood pressure, and the risk of CHD mortality associated with an elevated blood pressure may be even greater for women compared to men (10).

In 2010, the overall prevalence of hypertension was 28.5% among women, but increased with age, such that the prevalence of hypertension was 70% to 80% for women ≥70 years old. Awareness and control rates were 81% and 56%, respectively, for women, with no improvement since 2007 (11).

The AHA CVD prevention guidelines for women (3) support aiming for an optimal blood

Hypertension in Women

- Hypertension predicts CVD risk in both pre- and postmenopausal women.
- Hypertension occurs earlier and more frequently in African American women compared to white females.
- Older women are more likely to have isolated systolic hypertension.
- Women benefit as much as men in risk reduction from stroke and CVD events from HTN treatment.

pressure of <120/80 mmHg through lifestyle such as weight control, increased physical activity, keeping alcohol in moderation, sodium restriction, and increased consumption of fruits/vegetables. Women identified with prehypertension (120–139 mmHg systolic and/or 80–89 mmHg diastolic) are recommended for intensified lifestyle modifications to delay or prevent progression to hypertension.

Pharmacotherapy is indicated when blood pressure is ≥140/90 mmHg (≥140/80 mmHg for diabetes mellitus). Antihypertensive treatment recommendations do not vary by gender, although there are a few special considerations for women. Angiotensive-converting enzyme inhibitors (ACE-I) are contraindicated in pregnancy and ought to be used with caution in women who may become pregnant. For women who develop hypertension while taking oral contraceptives, the first treatment is to stop the oral contraceptives and switch to another form of birth control. ACE-I induced cough and peripheral edema associated with calcium channel blockers are more common in women than in men (10).

Diabetes

Diabetes is also an even greater CVD risk factor in women compared to men, associated with a three- to sevenfold increase in CHD event risk in women compared to a two- to threefold increased risk in men. The presence of diabetes appears to negate the "female advantage" that premenopausal women experience relative to men in regard to CVD risk. The 2011 AHA CVD prevention guidelines for women (3) recommend using lifestyle and pharmacologic therapy to target a hemoglobin A1c < 7% if this can be done safely without significant hypoglycemia. More lenient goals such as A1c < 8% may be appropriate for those with long-standing, difficult to control diabetes or who also have macrovascular disease. Women with other metabolic risk factors (i.e., hypertension, dyslipidemia, obesity) should be screened for glucose intolerance and diabetes.

Physical Activity and Exercise Capacity

Exercise capacity, as demonstrated on a treadmill stress test, can predict all-cause mortality independent of traditional risk factors. Gulati et al. developed a nonogram for predicted exercise capacity in women as follows: [predicted METS = 14.7 – (0.13 × age)]. The risk of death among asymptomatic women whose exercise capacity was <85% of their age-predicted value was double that compared to those ≥85% ($P < 0.001$) (12).

Per 2010 AHA statistics (1), only 16% of adult women met the recommended physical activity levels. Data from the Nurses' Health study show that sedentary behaviors, especially TV watching, were associated with significantly elevated risk of obesity and type 2 diabetes, whereas even light to moderate activity was associated with substantially lower risk (13).

Physical Activity Recommendations for Women from the 2011 AHA Women's Guidelines

- Aim for 150 min/wk of moderate exercise, 75 min/wk of vigorous exercise, or an equivalent combination of moderate- and vigorous-intensity aerobic physical activity.
- Muscle strengthening exercises recommended at least twice a week.
- There may be additional cardiovascular benefits by increasing moderate physical activity to 5 hrs/wk or vigorous physical activity to 2.5 hrs/wk.
- Cardiac rehab referral for women with a recent MI or revascularization, angina, CHF, or PAD.

Source: Adapted from Ref. (3). Mosca L, Benjamin EJ, Berra K, et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women--2011 update: a guideline from the American Heart Association. *Circulation*. 2011;123:1243–1262.

Obesity

Unfortunately in 2011, the AHA statistics report that among American women >20 years old, 59% of whites, 71% of blacks, and 75% of Mexican Americans were overweight/obese (1). Obesity, particularly abdominal obesity, increases the risk of metabolic

Weight Management in Women

- Calculate BMI and measure waist circumference as part of evaluation and monitor response of BMI and waist circumference to therapy.
- A desirable BMI is between 18.5 and 24.0 kg/m^2 and a waist circumference <88 cm (<35 inches).
- If BMI and/or waist circumference is above goal, initiate caloric restriction, measures to increase caloric expenditure, and treatment strategies for the metabolic syndrome.

syndrome, diabetes, and CVD in women. Intensified lifestyle modification should be aimed both at reducing caloric intake as well as increasing physical activity.

Lipids

Women experience an increase in lipid levels after menopause. SWAN (Study of Women's Health Across the Nation) demonstrated there were substantial increases in total cholesterol, LDL-C, and apolipoprotein B within the 1-year interval before and after the final menstrual period, consistent with menopause-induced changes. On the other hand, other nonlipid CVD risk factors (such as glucose, insulin, blood pressure, fibrinogen, and C-reactive protein) showed a more linear rise over time indicative of chronological aging (14).

Non-HDL was found to be a better predictor of CVD mortality in women compared to LDL-C (15). In the Women's Health Study (WHS), HDL-C was inversely associated with coronary events across a range of LDL-C values, including among women with low LDL-C levels (16). Previous guidelines from the Adult Treatment Panel III (ATP-III) (17) endorse LDL-C as the primary lipid target for screening and intervention, with non-HDL-C being a secondary goal. However, the 2013 ACC/AHA Cholesterol Guidelines (18) have moved away from lipid targets but rather endorse the use of moderate- to high-dose statins for secondary prevention and higher risk primary prevention patients. These changes broaden risk assessment, lower treatment thresholds, and now explicitly identify statins as the first-line treatment. Lipid targets and treatment recommendations do not differ by gender.

Lipids in Women

- Lipid levels rise after final menstrual period.
- Low HDL independently predicts risk in women.
- Triglycerides are a stronger predictor of risk in women compared to men.
- Nonfasting triglycerides may predict risk better than fasting triglycerides.
- Non-HDL predicts risk in women better than LDL-C.

Coronary artery calcium (CAC)

Vascular age is not always concordant with chronologic age, yet CVD risk prediction models, such as the Framingham Risk Score (FRS) and the 2013 ACC/AHA Risk Estimator, are heavily weighted on age. CAC measured by noncontrast CT is a useful surrogate measure of total coronary atherosclerotic burden. Compared to men, CAC is less prevalent in women at a given age. However, detectable CAC is highly predictive of subsequent cardiovascular events in women, independent of traditional CVD risk factors. Among women the relative risk ratios for MI or fatal CHD increased from 4.9-fold, 5.5-fold, and 8.7-fold for mild-, moderate-, and high-risk CAC scores, respectively, compared to the absence of CAC (19). Furthermore the ability of CAC to risk stratify was similar between men and women.

Even among women in the Multi-Ethnic Study of Atherosclerosis (MESA) at low predicted 10-year risk by FRS, the presence of CAC was independently associated with increased risk for CHD (HR 6.5; 95% CI 2.6–16.4) compared to women with no detectable CAC (20). Advanced CAC identifies a group of women with a higher absolute event rate than their predicted risk. Many would argue for treating this group with intensified primary prevention such as statin therapy.

Limitations of CAC scoring include the modest amount of radiation exposure (about the amount of a bilateral mammogram), the detection of incidental findings that may need follow-up, and the lack of clinical trial evidence currently available that demonstrates making treatment decisions using a CAC-based adjustment improves outcomes compared to a model based on global risk score.

Inflammation

High-sensitivity C-reactive protein (hsCRP) is a marker of inflammation and strongly associated with the metabolic syndrome. In a cohort of >27,000 apparently healthy women, hsCRP was a better predictor of risk for CVD events than LDL-C and added prognostic information to FRS (21). Women, on average, have higher hsCRP levels than men. Results from the JUPITER clinical trial would support the selective use of statins in older women >60 years of age with elevated hsCRP > 2 mg/L (22). Inflammatory systemic

2013 ACC/AHA Optional Groups for Revising Risk-Group Upward When Treatment Decisions are Uncertain

- FH of premature CVD
- CAC Score ≥300 or ≥75th age/gender/ethnicity percentile
- hsCRP ≥2 mg/L
- ABI <0.9

* Carotid IMT not recommended as screening tool.
Source: Adapted from Ref. (4). Goff DC Jr., Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*; published online November 12, 2013.

autoimmune collagen-vascular diseases, such as lupus erythematosus and rheumatoid arthritis, are more also prevalent in women, and have been shown to increase one's relative risk for atherosclerotic CVD (23).

CARDIOVASCULAR RISK ASSESSMENT TOOLS FOR WOMEN

A universal recommendation of prevention guidelines is that all women should undergo a global risk assessment (4,17). The prior ATP-III guidelines set thresholds for lipid treatment based on one's predicted 10-year risk for a CHD event using a modified FRS (17). However, there were limitations with using the ATP-III model for CVD prediction in women. The large majority of women out to age 70 are considered "low-risk" by FRS despite a high lifetime risk of CVD (24).

2013 ACC/AHA Risk Equations

- Predicts total CVD events (MI or and stroke)
- Specific equations for gender and white/black race, but may perform suboptimally for certain race/ethnic groups with overestimation of risk in Chinese/East-Asian Americans and underestimation in American-Indians and Americans of South-Asian descent
- Still does not take into account family history, exercise capacity, or subclinical atherosclerosis
- Primary focus still on short-term (10-year) risk, although there is an option to calculate "lifetime" risk
- May still over- or underestimate risk in certain groups

Previous studies had suggested the ATP-III version may underestimate risk in some women. In a study of women <65 years old who presented with their first MI, none had a prior 10-year ATP-III high predicted risk; only 5% were intermediate risk, with 95% being calculated at low-risk and only 18% meeting NCEP criteria for lipid-lowering therapy (25). We previously evaluated ATP-III predicted risk across a continuum of CAC scores in three studies of middle-aged asymptomatic nondiabetic women and found the majority (>90%) of women were classified as low-risk (<10%) by ATP-III, yet a substantial number had a significant burden of subclinical atherosclerosis measured by CAC (26). These studies suggest missed opportunities to initiate aggressive preventive lifestyle and pharmacologic strategies for at-risk women.

Other risk models have emerged including variations of FRS developed for total CVD, for 30-year risk, and a nonlaboratory model (substituting BMI for lipid variables), as well as the Reynolds Risk Score (RRS) for CVD. The RRS was developed in a population exclusively of women and incorporates three new variables to the ATP-III version (family history [FH] of premature CHD, hsCRP, and hemoglobin A1c if diabetic). In an external validation study applied to the Women's Health Initiative Observational Study (WHI-OS), the RRS performed better in predicting risk, whereas FRS-based models overestimated predicted risk (26).

Even more recently, the 2013 AHA/ACC Risk Assessment Guidelines developed new race- and sex-specific risk model equations to estimate the 10-year risk for hard atherosclerotic CVD which includes CHD and stroke, but not congestive heart failure (4). This is certainly an improvement from the ATP-III version of FRS; yet concerns arise from the exclusions of FH of premature CVD and assessment of subclinical atherosclerosis from the risk models. Also there is no guidance about how to handle younger individuals with unique risk factors such as systemic autoimmune collagen-vascular diseases or history of pre-eclampsia. When the 2013 risk models were applied to two large-scale primary prevention cohorts of women (WHS and WHI-OS), there was also systematic overestimation of risk (27).

Discrepancies in perceived risk between men and women may drive underutilization of preventive therapies in women. In a survey of physicians, primary care doctors were more likely to assign women at intermediate-risk by FRS to a lower risk category compared to men with a similar risk profile (28). Patients with a lower FRS were significantly less likely to receive counseling regarding physical activity and diet than patients at intermediate or high FRS.

PREVENTIVE TREATMENT IN WOMEN

Statin Therapy in Women

Secondary Prevention

In a meta-analysis of 11 randomized clinical trials representing 43,193 patients, statin therapy was associated with an overall reduced risk of CVD events for both women (RR 0.81 [95% CI 0.74–0.89]) and men (RR 0.82 [0.78–0.85]). However, there was not a statistically significant reduction in all-cause mortality in women (RR 0.92 [0.76–1.13]) compared to men (RR 0.79 [0.72–0.87]) (29). This may be because these clinical trials were not powered to detect a mortality benefit and were generally short term in duration.

Statin Therapy in Women

- Benefit of statin therapy with respect to the primary event is more pronounced in secondary prevention trials than in primary prevention trials for women.
- However, statin therapy is associated with significant decreases in CVD events and in all-cause mortality in both women and men.

A larger meta-analysis of 18 randomized clinical trials of statins of both primary and secondary prevention (N = 141,235 including 40,275 women) examined sex-specific outcomes (30). The effect on mortality in women was not seen for secondary prevention (OR 1.03 [0.84–1.25]). However, when primary and secondary prevention trials were combined, a mortality benefit was seen (OR 0.90 [0.82–0.99]).

Primary Prevention

The use of statins in primary prevention had been somewhat controversial, especially for women, but the numbers are now in. In a 2010 meta-analysis of exclusively primary prevention trials, statins were shown to reduce CVD in women significantly (RR 0.63 [0.49–0.82]; no heterogeneity compared with men) with a trend toward reduced mortality (RR 0.78 [0.53–1.15] (22).

Furthermore, a more recent meta-analysis (year 2012) by Kostis et al. (30) did find a benefit for all-cause mortality with statins in women when predominantly primary prevention trials were analyzed separately (OR 0.87 [0.78–0.97]). A statistically significant decrease in total CVD events was observed in women (OR: 0.81 [0.75–0.89]) as well as men, with similar lowering in both sexes. Kostis estimated that the number needed to treat a woman over a 4-year period to prevent one CVD event was 148 for primary prevention and 36 for secondary prevention (the corresponding numbers in men are 43 and 29, respectively).

Aspirin Therapy in Women

In secondary prevention, the role of aspirin is well established. Among patients with known CVD, aspirin reduces subsequent CVD events and mortality, with similar benefit among men and women (31). Among women with stable CVD enrolled in the WHI-OS, aspirin therapy reduced all-cause and cardiovascular-specific mortality, although the use of aspirin was surprisingly low, with less than 50% of women with established CVD taking aspirin, highlighting the underutilization of proven secondary prevention therapies in women (31).

In primary prevention, the use of aspirin for prevention is more controversial. In a clinical trial of nearly 40,000 initially healthy women >45 years old randomized to 100 mg of aspirin or placebo, low-dose aspirin reduced the risk of stroke over 10-year follow-up without reducing the risk of MI. Subgroup analyses showed that aspirin significantly reduced the risk of major cardiovascular events, ischemic stroke, and MI among women 65 years of age or older (32). Women assigned to aspirin therapy had higher bleeding risk, which cautioned the use of aspirin for primary prevention, particularly in women <65 years of age. In general, aspirin may be considered in higher-risk individuals without known CVD (above 1% CVD event rate per year) if the benefits are felt to outweigh the risks for that individual and taking into account patient's preference.

Aspirin Therapy in Women (3)

- *Secondary prevention*: Should use unless contraindicated (Class I).
- *Primary prevention:*
  - For women <65 years, routine use not recommended for prevention of MI (class III).
  - For women ≥65 years, low-dose aspirin may be reasonable for prevention of ischemic stroke and MI if blood pressure is controlled, and if benefits are likely to outweigh bleeding risks (Class IIa).
  - For women <65 years, low-dose aspirin may be considered for ischemic stroke prevention if blood pressure is controlled, and if benefits are likely to outweigh bleeding risks (Class IIb).

Class I (intervention is useful and effective), Class IIa (evidence favors usefulness), IIb (usefulness less well established), III (not useful, may be harmful).

Supplements

Nearly 50% of Americans report taking vitamins or supplements for health benefits. Yet, at this time, there is no convincing evidence that antioxidant and/or multivitamin use reduce CVD in women. Although low serum levels of 25-hydroxyvitamin D have been associated with adverse CVD outcomes in observational studies, it is currently unknown whether treating low-vitamin D status with supplements can reduce CVD (33). Randomized clinical trials are underway to evaluate this.

Hormone Therapy

Animal and observational studies have suggested beneficial effects of hormone therapy in reducing the risk of CVD when it is initiated early in the perimenopausal period or before the development of significant atherosclerosis. However, randomized, placebo-controlled trials in older women have not shown any benefit in either primary prevention or secondary prevention of CVD, with a concerning trend toward harm (34).

Other Therapies Not Recommended for CVD prevention (Class III – Not Useful or may be Harmful)

- Antioxidants, multivitamins, folic acid
- Hormone therapy or selective estrogen-receptor modulators

Source: Adapted from Ref. (3). Mosca L, Benjamin EJ, Berra K, et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women--2011 update: a guideline from the American Heart Association. *Circulation.* 2011;123:1243–1262.

GENDER DISPARITIES IN TREATMENT OF ACUTE CORONARY SYNDROMES

Lessons from the CRUSADE and Get with the Guidelines Registries

- Women are typically older and with more associated comorbidities (ie diabetes, hypertension) when they present with ACS.
- Women less likely to present with STEMI.
- Even adjusting for comorbidities, there are gender disparities in the utilization of both acute and discharge medications.
- Underutilization of evidence-based therapies can translate to poorer outcomes in women.

Despite advances in therapies to treat ischemic heart disease, these therapies continue to be underutilized in women compared to men. The CRUSADE National Quality Improvement Initiative collected data on 40,912 patients at 391 U.S. hospitals who presented with a high-risk non-ST elevation acute coronary syndrome (ACS) between the years of 2000–2002 (41% women). CRUSADE found that women had higher risk clinical characteristics on presentation, but even after multivariate adjustment factoring in these differences, women were less likely to receive acute heparin, ACE-I, and glycoprotein IIb-IIIA inhibitors, and were less likely to receive aspirin, ACE-I, and statins at discharge (35).

The "Get With the Guidelines" hospital registry collected data for >78,000 patients (39% women) who presented with acute MI in 420 U.S. hospitals from 2001–2006 (36). Even after multivariate analyses adjusting for age and comorbid conditions, women were less likely to receive early medical therapy such as aspirin and beta-blockers within 24 hours of presentation, were less likely to undergo cardiac catheterization and revascularization procedures, and were less likely to meet quality assurance measures such as a "door to balloon time" in under 90 minutes.

GENDER DIFFERENCES IN CVD PRESENTATION

Lessons from Wise Study: Symptomatic Angina in the Absence of Obstructive CHD is not Benign

- May be associated with ischemia on cardiac perfusion MRI.
- Associated with a higher prevalence of atherosclerosis which correlated with increased risk factors.
- Associated with higher CVD event rates.
- Associated with higher lifetime costs.
- Possible mechanisms for ischemia include impaired coronary reactivity, endothelial dysfunction, vasospasm, and plaque erosion with distal embolization.

Source: Adapted from Ref. (37). Gulati M, Shaw LJ, BaireyMerz CN. Myocardial ischemia in women: lessons from the NHLBI WISE study. *Clin Cardiol.* 2012;35:141–148.

Chronic stable angina is slightly more prevalent in women compared to men, although women with angina are less likely to have obstructive CHD. Women with angina report greater functional disability. Women are also more likely to have nonchest pain presentations of their myocardial ischemia (i.e., atypical symptoms) (38). In ACS, women compared to men are more likely to have pain in the back, neck, or jaw, or dyspnea, nausea, indigestion, or fatigue.

Diastolic heart failure is prevalent among older women and can contribute to coronary ischemia through imbalances in myocardial demand/supply. Syndrome X (characterized by angina, abnormal exercise stress test, but angiographically normal coronary arteries) is more common in women compared to men, and associated with adverse outcomes.

SUMMARY

There are sex-specific differences in CVD risk factors, in the presentation and mechanisms of ischemia, and disparities in the utilization of prevention therapies which can all contribute to poorer outcomes in women. There needs to be a continued emphasis of adequate

enrollment of women in primary and secondary clinical trials of interventions and treatment for CVD, with reporting of gender-stratified results, so that providers can make the best evidence-based treatment decisions. There need to be continued educational efforts to promote CVD risk awareness for women and their health providers and a continued emphasis on striving for ideal cardiovascular health, particularly through intensified lifestyle measures, throughout the lifespan. There is an urgent need to reverse the worrisome epidemic trend of obesity, diabetes, and metabolic syndrome which threatens to halt or even reverse the progress gained in reducing CVD mortality. Women are often the gatekeepers of their family's health; thus when women are making healthier lifestyle choices, their whole family benefits as well.

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Benjamin Oldfield, MD,
Satish Misra, MD, and
Peter Kwiterovich, MD[†]

Prevention of Cardiovascular Disease in Pediatric Populations

Many risk factors and behaviors relevant to cardiovascular disease (CVD) develop during childhood and adolescence. The strongest predictors of CVD among pediatric populations are dyslipidemia, obesity in males, hypertension, tobacco use, and diabetes mellitus. All children should undergo regular screening for CVD that includes measurement of body mass index (BMI), blood pressure, and lipid levels; at-risk children should undergo diabetes screening. Medical therapy for children with dyslipidemia should begin with a statin. Treatment of children with hypertension should focus on dietary modifications and pharmacotherapy; many classes of antihypertensive medications may be considered safe and appropriate choices. Children and adolescents with diabetes mellitus should be treated with dietary modification and insulin or metformin, depending on the type of diabetes.

BACKGROUND

Atherosclerotic cardiovascular disease (CVD) is the leading cause of death in industrialized societies. Although children and adolescents uncommonly manifest CVD, many risk factors and relevant behaviors develop during childhood and adolescence. These include dyslipidemia, obesity, elevated blood pressure, cigarette smoking, and glucose intolerance (1,2). Pediatric prevention of atherosclerotic disease must focus, then, on both (1) prevention of risk factor development (primordial prevention), as well as (2) prevention of future CVD by effective management of those risk factors already identified (primary prevention).

The most recent and comprehensive guidelines for CVD prevention in pediatric practice are found in the report by the National Heart, Lung, and Blood Institute, *Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents* (full report published in 11/2012, summary report in the December 2011 issue of the *Pediatrics*) (1,2). Here, we summarize those guidelines with a special emphasis on screening for and prevention of dyslipidemia, obesity, hypertension, cigarette smoking, and diabetes mellitus in pediatric populations.

Prospective pathologic studies, starting in youth, have clearly demonstrated that the extent of atherosclerotic lesions over the second through fourth decades of life is related to baseline CVD risk factors, and in a dose-dependent fashion (3,4). More recently, a significant link has been demonstrated between childhood CVD risk factors starting at 9 years of age and the development of more extensive lesions of carotid intima-medial thickness (IMT) in young adults from three large, diverse populations (5). Another noninvasive assessment of coronary atherosclerosis, coronary artery calcium, is significantly associated with higher LDL and blood pressure levels at 13 years of age (6).

[†]Deceased.

However, systematic evaluation of prevention strategies in pediatrics utilizing clinical end points is challenging given that the end points of interest develop decades later. For example, some have expressed concern that there are no placebo-controlled clinical trials of statins in adolescents with CVD risk factors that demonstrate that the intervention arm significantly decreased CVD events in adolescents compared with the placebo arm. There are however other strategies that can be used to inform prevention strategies.

One approach to decrease the sample size required and the time needed for follow-up is to select a higher risk baseline group for randomization. Extensively studied genetic models of dyslipidemia such as heterozygous familial hypercholesterolemia (FH) also provide a potential study population to show that 50% reduction of LDL-C starting in adolescence may decrease CVD events in young adulthood. Heterozygous familial hypercholesterolemia is the most common (1/300–1/500) Mendelian trait in humans causing premature CVD. Individuals with FH usually develop CVD in their 30s, 40s, and 50s unless treated. By one year of age the average total and LDL-C levels of a child are 300 and 240 mg/dL, respectively (1,2). Studies in these populations can and do help inform prevention strategies in pediatric populations.

RISK FACTORS IN CHILDREN

Atherosclerosis is a progressive process that can be quantified and trended using a variety of pathological, imaging, and biochemical means. The strongest and most quantifiable pediatric and adolescent risk factors for CVD include:

- Dyslipidemia
- Obesity in males
- Hypertension
- Tobacco use
- Diabetes mellitus

These risk factors are discussed individually later in the chapter. Of note, although obesity in females is not itself a strong risk factor for CVD, it does confer risk for the development of hypertension and diabetes, which are well-documented risk factors for CVD.

Less easily quantifiable risk factors bear discussion as well. Family history of premature CVD, defined as the presence of disease before age 55 years in a male parent or sibling or before age 65 years in a female parent or sibling, is significantly correlated with autopsy findings and vascular function abnormalities in children and adolescents (7). The NHLBI expert panel does recommend clinicians take a detailed family history of CVD at initial encounters with pediatric patients as well as at 3 years, 9 to 11 years, and 18 years. When a positive family history is identified, clinicians are recommended to evaluate patients for other CVD risk factors including dyslipidemia, hypertension, diabetes, obesity, history of smoking, and sedentary lifestyle (1,2).

In regard to nutritional risk factors, long-term follow-up studies consistently demonstrate that infants who were breastfed have sustained cardiovascular health benefits, including reduced prevalence of diabetes, lower measures of subclinical CVD, and lower BMI in adulthood (8–10). Reduced intake of sugar-sweetened beverages is associated with decreased obesity measures, and dietary fiber intake is inversely associated with energy density and with increased levels of body fat and is positively associated with nutrient density (1).

Physical activity is related to CVD risk factors in children and adolescents, and increases in moderate-to-vigorous physical activity are associated with:

- Lower systolic and diastolic blood pressures
- Decreased measures of body fat
- Decreased BMI
- Improved fitness measurements
- Lower total cholesterol
- Lower LDL-C
- Lower triglycerides
- Higher HDL-C
- Decreased insulin resistance

Although there is strong evidence that physical activity should be promoted in schools and well-child visits, there is less specific information on the type and amount of physical exercise required for optimal cardiovascular health. The NHLBI expert panel recommends at least one hour of moderate-to-vigorous physical activity every day of the week, with vigorous, intense physical activity on at least three of these days.

Cigarette use among high school students declined from 1997 to 2003 but rates have been stable through 2007, and reducing tobacco exposure remains an important objective for pediatric providers (11). The NHLBI expert panel recommends that, during all nonurgent encounters for individuals ages 11 to 21, clinicians obtain personal smoking histories, explicitly recommend against smoking, and provide specific smoking cessation guidance (1).

ROUTINE MONITORING

Preventive screening practices in pediatric populations is a controversial topic in large part due to limited data from randomized controlled trials. That the evaluation

TABLE 19.1 Preventive Screening Practice Recommendations

Parameter	Recommendation	Timing/Frequency
BMI	Calculate BMI in all children	Measure beginning at 2 years old annually
Cholesterol	Obtain fasting or nonfasting lipid profile in all children	Measure one time between 9 and 11 years old as well as 17 and 21 years old
Blood Pressure	Measure in all children	Measure beginning at 3 years old annually
Diabetes	Measure fasting glucose in overweight children with at least two additional risk factors	Once between 9–11 years old and once between 12–17 years old

Source: Adapted from Ref. (1). *Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents,* National Heart, Lung, and Blood Institute, NIH Publication No. 12-7486, October 2012., NHLBI guidelines (1).

of a particular screening practice's impact on hard cardiovascular end points would require a large population followed for decades renders such evaluation impractical, a challenge noted by the guideline committee. As such, the screening recommendations (Table 19.1) were in large part determined by both feasibility and availability of effective therapy. These are in addition to routine counselling regarding age-appropriate diet, exercise, and avoidance of exposure to smoking described above.

LIPIDS AND LIPOPROTEINS

Early atherosclerotic lesions in children are significantly related to dyslipidemia, particularly:

- Elevations in total cholesterol (TC)
- Elevations in LDL-C
- Elevations in non-HDL-C
- Lower levels of HDL-C

Of these, non-HDL-C has been shown to be the major correlate of coronary atherosclerosis in adolescents and young adults 15 to 34 years of age, with a 30-mg/dL increase in non-HDL-C equivalent to two years of vascular aging (5,12).

Multiple prospective screening cohort studies have demonstrated significant tracking of elevated lipid levels from childhood to adulthood. Furthermore, significant evidence suggests that using family history of premature CVD or of cholesterol disorders as the primary factor in determining lipid screening for children misses approximately 30% to 60% of children with dyslipidemias. Therefore, the expert panel recommends universal lipid assessment once for children and adolescents between the age of 9 and 11 years and repeated universal screening between the age of 17 and 21 years. Further screening is recommended for patients with a first-degree relative with cardiovascular disease prior to the age of 55 years in men and 65 years in women, a parent with total cholesterol ≥240 mg/dL or known dyslipidemia, or personal history of certain medical conditions (diabetes, hypertension, BMI ≥ 85th percentile, smoking) (1).

Serum lipid levels in children are characterized into acceptable, borderline high, and high ranges (HDL, however, may be acceptable, borderline low, or low) (Table 19.2).

TABLE 19.2 Serum Lipid Levels in Children

Category	Acceptable	Borderline	Abnormal
Total Cholesterol	<170 mg/dL	170–199 mg/dL	≥200 mg/dL
LDL-C	<110 mg/dL	110–129 mg/dL	≥130 mg/dL
Non-HDL-C	<120 mg/dL	120–144 mg/dL	≥145 mg/dL
Triglycerides (0–9 years old)	<75 mg/dL	75–99 mg/dL	≥100 mg/dL
Triglycerides (10–19 years old)	<90 mg/dL	90–129 mg/dL	≥130 mg/dL
HDL-C	<45 mg/dL	40–45 mg/dL	<40 mg/dL

Source: Adapted from Ref. (1). *Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents,* National Heart, Lung, and Blood Institute, NIH Publication No. 12-7486, October 2012., NHLBI guidelines (1).

The American Academy of Pediatrics (AAP) recommends that pharmacotherapy be considered for children 10 years of age and older who meet criteria for dyslipidemia (1,2). The following special populations should also be considered strong candidates for drug therapy:

- Children with familial hypercholesterolemia ages eight years and older
- Children younger than eight years with extreme elevation of LDL-C, above 500 mg/dL
- Children with diabetes and LDL-C ≥130 mg/dL

Once dyslipidemia is detected in a patient, the child should be referred to a dietician for family medical nutrition therapy, with a focus on minimizing calories from fat, decreasing sugar intake, and increasing dietary fish intake (1). Both LDL-C and TG guided treatment strategies may be considered. If LDL-C>250 mg/dL or TG>500 mg/dL, immediate referral to a lipid specialist is recommended. If LDL-C is between 130 mg/dL and 250 mg/dL, an LDL-C guided strategy is recommended (see Figure 19.1). If TG is between 130 mg/dL and 500 mg/dL in children between 10 and 19 years of age (100 mg/dL and 500 mg/dL in children younger than 10 years of age), then a TG guided strategy is recommended.

Figure 19.1 shows the NHLBI's suggested algorithmic approach to pediatric patients with elevated LDL-C or triglycerides on their screening lipid panels (1).

Medical therapy should begin with a statin. Atorvastatin, rosuvatatin, lovastatin, fluvastatin, and simvastatin have been approved for use in adolescent boys and postmenarchals girls older than 10 years with familial hyperlipidemia and LDL-C ≥ 190 mg/dL or 160 mg/dL with FH of premature CVD and at least two other CVD risk factors. Of note, pravastatin has been approved for children greater than 8 years of age. Clinicians should start with the lowest dose of the selected statin with incremental titrations (Table 19.3).

The most common side effects of statins in adults, elevation in liver enzymes and myopathy, do not appear to be as common in children. A recent systematic review and meta-analysis of statin therapy in children with FH found no statistically significant differences between statin-treated and placebo-treated children for adverse events related to sexual development, muscle toxicity, or liver toxicity (13).

If goals are not met after the initiation of a statin and a single dose increase, clinicians should consider referral to a lipid specialist for the addition of a second agent. Other approved agents approved in similar pediatric populations include colesevalam.

If the TG directed algorithm is utilized, management focuses on lifestyle modifications initially. If TG levels do not achieve goal with this intervention, initiation of therapy may be considered in consultation with a lipid specialist. Possible agents include fish oil supplementation, fibrate, niacin, and statin.

OVERWEIGHT AND OBESITY

There have been dramatic increases in the prevalence of childhood obesity since the 1980s, with significant implications for cardiovascular health. Because obesity is strongly associated with elevated blood pressure, dyslipidemia, and insulin resistance, obesity is thought to be particularly powerfully correlated with atherosclerosis.

Juonala and colleagues (11) pooled data from four large studies of CVD risk factors (the Bogalusa Heart Study, the Muscatine Study, the Childhood Determinants of Adult Health Study, and the CV Risk in Young Finns Study) in order to examine the effects of youth adiposity on adult CVD. Adiposity groups were parsed into the following categories: (I) those with a normal BMI in childhood and who were nonobese as adults; (II) those who were obese in childhood but nonobese as adults; (III) those who were overweight or obese in both childhood and adulthood; and (IV) those with a normal BMI in childhood but obese as adults. For each of the outcomes examined (type 2 diabetes, hypertension, high LDL-C, low HDL-C, elevated triglycerides, and high-risk carotid IMT) there was no significant difference between groups I and II, indicating that if an obese child became a nonobese adult, they would not have increased CVD risk outcomes. In distinct contrast, both Groups III and IV had highly significant relative risk for these outcomes, indicating that if a nonobese child becomes obese he or she will be in a high risk category as an adult.

Overweight and obesity are defined according to body mass index percentiles by age (Table 19.4).

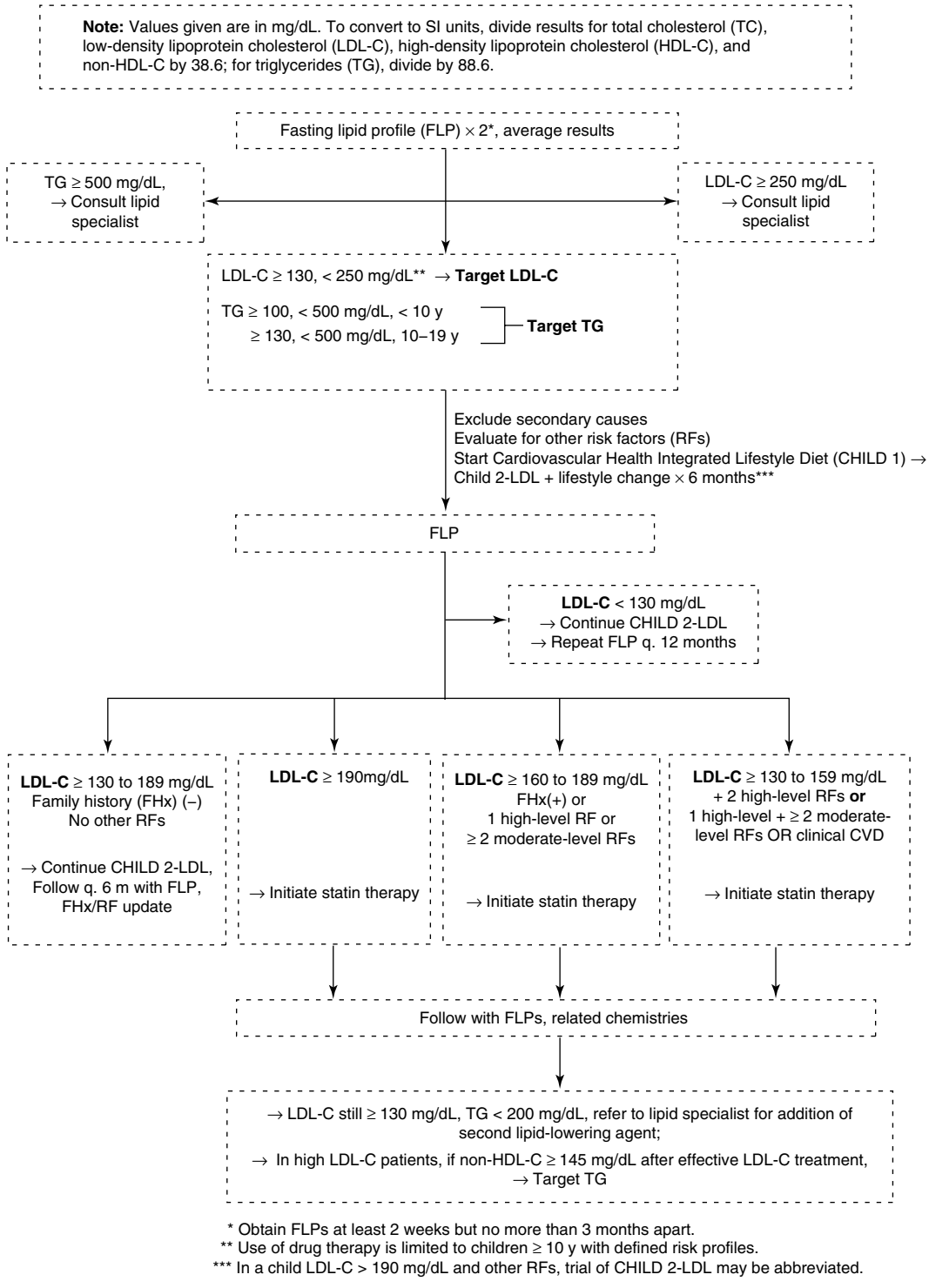
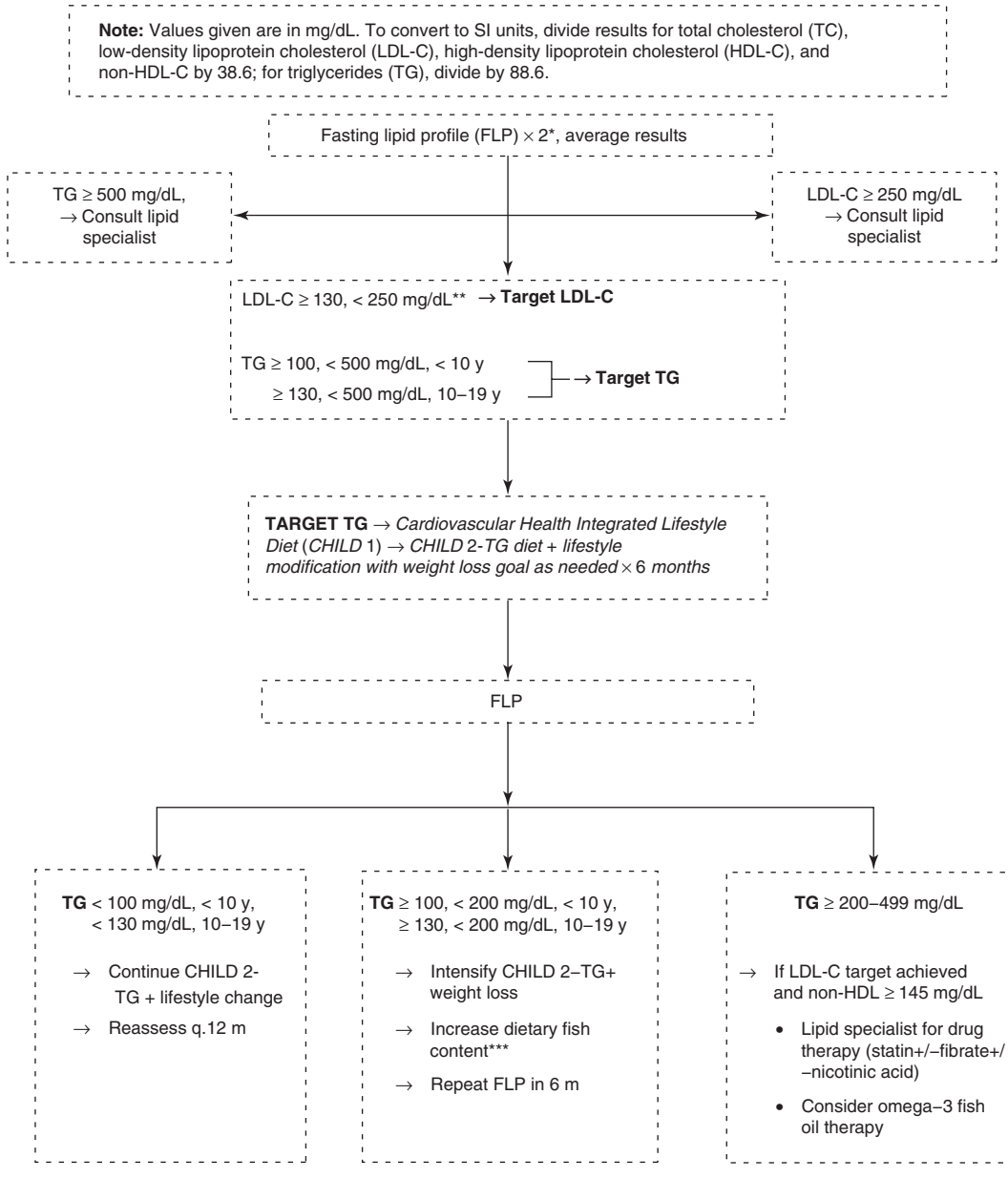


FIGURE 19.1 NHLBI algorithm for pediatric patients with elevated LDL-C or triglycerides.



* Obtain FLPs at least 2 weeks but no more than 3 months apart.

** Use of drug therapy is limited to children ≥ 10 y with defined risk profiles.

*** The Food and Drug Administration (FDA) and the Environmental Protection Agency are advising women of childbearing age who may become pregnant, pregnant women, nursing mothers, and young children to avoid some types of fish and shellfish and eat fish and shellfish that are lower in mercury. For more information, call the FDA's food information line toll free at 1-888-SAFEFOOD or visit http://www.fda.gov/food/foodborneillnesscontaminants/metals/ucm115644.htm

FIGURE 19.1 (*continued*)

For both categories, initial interventions should focus on the recommendations from the Cardiovascular Health Integrated Lifestyle Diet (CHILD 1), summarized according to age range (Table 19.5) (1).

Interventions that increase physical activity and decrease sedentary time in children and adolescents, when accompanied by dietary counseling, have been shown to be more effective at lowering BMI in overweight and obese children than dietary counseling alone.

Recommendations for increasing physical activity and decreasing sedentary time are based on age (Table 19.6).

Other strategies may be considered as well although they are not included in guidelines. Orlistat, when combined with a comprehensive weight-loss program, has been shown to improve weight loss and BMI but has a high rate of gastrointestinal side effects and is not included in guidelines for the management of overweight and obesity. For adolescents with BMI far above 35 kg/m^2, bariatric surgery on a research protocol in conjunction with a comprehensive lifestyle weight-loss program improved weight, BMI, and other outcomes (insulin resistance, glucose tolerance, and CV measures) in a small case series, but is also not included on guidelines for the management of overweight and obesity (1).

BLOOD PRESSURE

Hypertension is a well-recognized risk factor for coronary heart disease, cerebrovascular disease, renal disease, and other chronic health problems that often manifest in adulthood. In 2004, the NHLBI Task Force published *The Fourth Report on Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents* to provide guidelines for pediatric providers (13). The NHLBI then performed a review of the evidence published between 2003 and 2007 and integrated this with the previous *Fourth Report* in their 2013 Expert Panel (1).

Routine measurement of blood pressure is not recommended for children from birth to two years. For children and young adults ages 3 to 21 years, routine measurements of blood pressure during all health care visits via auscultation is recommended. Clinicians should familiarize themselves with, or have easy access to, blood pressure percentiles from the *Fourth Report* based on age, gender, and height percentiles. These are used to categorize blood pressures into prehypertension, stage 1, or stage 2 hypertension (Table 19.7).

For individuals over the age of 18, the adult definitions hold, indicating prehypertension as blood pressure ≥ 120/80 to 139/89 mmHg, stage 1 hypertension as blood pressure ≥ 140/90 to 159/99 mmHg, and stage 2 hypertension as blood pressure ≥160/100 mmHg.

For children of all ages, management of elevated blood pressure follows a similar scheme (Table 19.8).

TABLE 19.4 Overweight and Obese Definitions

	Overweight	Obese
Definition	BMI ≥ 85th percentile and < 95th percentile	BMI ≥ 95th percentile

Source: Adapted from NHLBI guidelines (1).

TABLE 19.3 Statin Recommendations

Initial medication and dose selection	Select statin based on medication interaction, patient preferences, and provider familiarity. Start at lowest dose.
Baseline evaluation	Check AST, ALT, and CK prior to therapy
Clinical monitoring for adverse effects	Muscle cramps, weakness, asthenia, and other myopathy symptoms
Medication titration	Recheck fasting lipid panel at 4 weeks, consider increase by one dose increment if goal not achieved and repeat FLP in 4 weeks. If goal still not achieved, consider referral to lipid specialist.
Biochemical monitoring for adverse effects	Recheck FLP, AST/ALT at 4 weeks, 8 weeks, 3 months, 6 months, 9 months, one year; every six months after first year. Restart this algorithm with any dose titration or therapy change. Worrisome change is ≥ to 3× upper limit of normal. Recheck CK if symptoms of myopathy.
Pregnancy	Counsel adolescent females regarding contraception and risks of statin therapy.

TABLE 19.5 Recommendations from the Cardiovascular Health Integrated Lifestyle Diet (Child 1)

Age Range	Dietary Recommendations
Birth–6 months	• Exclusive breastfeeding.
6–12 months	• Continue breastfeeding until at least 12 months. • Do not restrict fat intake. • Limit other drinks to 100% fruit juice < 4 oz. daily.
12–24 months	• Transition to reduced-fat unflavored cow's milk (2% to fat-free). • Transition to table food with ◦ Total fat 30% of daily kcal ◦ Saturated fat 8%–10% of daily kcal ◦ Monounsaturated and polyunsaturated fat up to 20% daily kcal ◦ As little *trans* fat as possible ◦ Cholesterol < 300 mg daily.
2–10 years	• Primary beverage: fat-free unflavored milk. • Limit or avoid sugar-sweetened beverages; encourage water. • Fat content: ◦ Total fat 25%–30% of daily kcal ◦ Saturated fat 8%–10% of daily kcal ◦ Monounsaturated and polyunsaturated fat up to 20% of daily kcal ◦ As little *trans* fat as possible ◦ Cholesterol < 300 mg daily.
11–21 years	• Identical to above; additionally, encourage high dietary fiber intake from foods (fruits, vegetables, whole grains).

TABLE 19.6 Recommendations for Increasing Physical Activity

Age Range	Recommendations
Birth–12 months	• Encourage an environment promoting and modeling physical activity. • Discourage TV viewing altogether.
1–4 years	• For children <2 years, discourage TV viewing altogether. • For children ≥2 years, limit total media time to no more than 1–2 hours of quality programming daily. • Discourage the presence of a TV in the child's bedroom. • Encourage family activity at least once weekly.
5–10 years	• Prescribe moderate to vigorous physical activity 1 hour daily. • Prescribe vigorous activity 3 days weekly. • Limit total media time to no more than 1–2 hours of quality programming daily. • Discourage the presence of a TV in the child's bedroom. • Support recommendations for daily physical activity in schools. • Encourage family activity at least once weekly.
11–17 years	• Prescribe moderate to vigorous physical activity 1 hour daily. • Prescribe vigorous activity 3 days weekly. • Limit total media time to no more than 1–2 hours of quality programming daily. • Encourage involvement in year-round or lifelong physical activities. • Encourage family activity at least once weekly.
18–21 years	• Prescribe moderate to vigorous physical activity 1 hour daily. • Prescribe vigorous activity 3 days weekly. • Recommend that combined leisure screen time not exceed 2 hours daily. • Encourage involvement in year-round or lifelong physical activities.

TABLE 19.7 Percentile Definitions of Hypertension

	Prehypertension	Stage 1 Hypertension	Stage 2 Hypertension
Definition	Blood pressure ≥ 90th percentile or 120/80 mmHg to <95th percentile.	Blood pressure ≥ 95th percentile to <99th percentile + 5 mmHg.	Blood pressure ≥ 99th percentile + 5 mmHg.
Temporality of diagnosis	Repeat in 6 months to confirm diagnosis.	Repeat in 1–2 weeks to confirm diagnosis.	Repeat in the office; no further measurements are needed prior to treatment initiation.

Source: Adapted from NHLBI guidelines (1).

For all categories, goal blood pressure is <95th percentile for age/sex/height, or <90th percentile if chronic kidney disease, diabetes, or target organ damage is present.

There are no guidelines to suggest which antihypertensive agent to begin after a diagnosis of hypertension is made. Angiotensin-converting enzyme inhibitors (ACE-inhibitors), angiotensin-receptor blockers (ARBs), alpha and beta agonists, calcium channel blockers, diuretics, and vasodilators have all been shown to be safe if used in short durations, but long term efficacy and safety data are unavailable (1).

DIABETES MELLITUS

Diabetes is a well-recognized risk factor for cardiovascular disease. With increasing rates of obesity in children and adolescents, both type 1 and type 2 diabetes mellitus are now both contributors to long-term cardiovascular disease in pediatric populations.

Although there are no specific recommendations for screening for type 1 diabetes mellitus, the guidelines endorse the recommendations of the American Diabetes Association (ADA) related to type 2 diabetes mellitus (15). The ADA guidelines recommend screening using fasting blood glucose of overweight children and adolescents with two of the following three risk factors:

- Family history of type 2 diabetes mellitus in a first- or second-degree relative
- High-risk race/ethnicity (Native American, African American, Latino, Asian American, Pacific Islander)
- Signs of or conditions associated with insulin resistance

With regard to therapy, insulin regimens consisting of a total of three to four daily doses of subcutaneous basal and prandial insulin is appropriate for most patients with type 1 diabetes mellitus (15). The ADA does not include specific recommendations for pediatric type 2 diabetes mellitus, however, the American Academy of Pediatrics recommends

TABLE 19.8 Pediatric Blood Pressure Management

	Prehypertension	Stage 1 Hypertension	Stage 2 Hypertension
Workup	Assess for other CV risk factors (obesity, tobacco use, diabetes, family history, dyslipidemia)	Assess for other CV risk factors; complete medical, family, and sleep history; physical exam; CBC, renal panel, lipid panel, serum glucose, urinalysis, and both renal and cardiac ultrasounds.	Initial work-up identical to that for stage 1 hypertension, and/or referral to pediatric hypertension specialist
Treatment	Counseling centered on CHILD 1 guidelines for nutrition and physical activity	CHILD 1 counseling; initiate antihypertensive agent if secondary cause of hypertension is evident or if LVH is detected on echocardiography.	CHILD 1 counseling; initiate antihypertensive agent
Monitoring	Every 6 months	Every 3–6 months until control is achieved.	Every 1–2 weeks until control is achieved

lifestyle modification and metformin as first-line therapy. Insulin is recommended in lieu of metformin in patients with a history of diabetic ketoacidosis, have blood glucose levels greater than 250 mg/dL, HbA1c greater than 9%, or in whom the type of diabetes mellitus is unclear (16).

The guidelines additionally acknowledge limited data on the use of specific interventions directed to intermediate processes related to cardiovascular disease. These include studies in type 1 diabetes with the use of melatonin to prevent the development of hypertension as well as B6 and folate to improve signs of endothelial dysfunction. However, they note that given the limited data available and lack of replicated findings, there were inadequate data to recommend specific interventions to reduce cardiovascular disease risk in diabetic patients (1).

As such, the panel modified previous recommendations of the American Heart Association which are based on a two-tier risk stratification in which the higher risk group is associated with increased risk of clinical coronary disease prior to the age of 30 and the moderate risk group is associated with increased risk of subclinical accelerated atherosclerosis. The principal modification made in these guidelines was the inclusion of pediatric patients with diabetes in the high-risk category (1).

As such, children and adolescents with diabetes mellitus are recommended to achieve the following treatment goals (1):

- BMI ≤ 85th percentile for age/sex
- BP ≤ 90th percentile for age/sex/height
- LDL-C ≤ 100 mg/dL, TG < 90 mg/dL, non-HDL-C < 120 mg/dL
- HbA1c < 7%, FG < 100 mg/dL

The initial approach for a pediatric patient who does not meet these targets centers on intensive lifestyle modifications including the Cardiovascular Health Integrated Lifestyle Diet as well as activity and weight-loss recommendations. If these goals are not met within 6 months, condition-specific treatment is recommended based on individualized risk/benefit assessment including (1):

- Consultation with an endocrinologist
- Consideration of statin therapy if age ≥ 10 years with goals as above
- Consideration of ACEI with goal BP less than 90th percentile for sex/age/height or less than 120/80 (whichever is lower)

SUMMARY

Cardiovascular disease is a significant worldwide cause of morbidity and mortality. It is well recognized that many factors that contribute to the development of cardiovascular disease begin in childhood, both pathogenic processes and contributing behaviors. An important limitation in the development and evaluation of a prevention strategy in pediatric populations is the impractically long follow-up that would be required to define effect on hard outcomes such as myocardial infarction or stroke. As such, many recommendations are based on evidence from special populations such as familial dyslipidemia and impact on intermediary outcomes such as medication effect on blood pressure control. That being said, important components of prevention of cardiovascular disease in pediatric patients include regular assessment of risk factors, instilling appropriate dietary and exercise practices at an early age, initiating lifestyle modification as soon as risk factors are identified, and use of screening practices to monitor for development conditions such as hypertension or dyslipidemia.

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Danny J. Eapen, MD, Nima Ghasemzadeh, MD, Neal Kumar Bhatia, MD, Ahsan Achtchi, DO, Aalok Patel, MD, Edward Claude Clermont, MD, Dimitri Cassimatis, MD, Ijeoma Isiadinso, MD, and Laurence Sperling, MD, FACC, FACP, FAHA

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Primary Prevention of Cardiovascular Disease Guidelines

Despite significant advances in medical therapy, cardiovascular disease (CVD) remains the leading cause of death in the United States and in most developed countries. Although genetics certainly plays a role in deciding who will suffer with CVD and its associated adverse outcomes, the importance of potentially modifiable risk factors cannot be understated. The landmark INTERHEART study revealed that approximately 90% of the population attributable risk for incident acute myocardial infarction (AMI) is attributable to nine easily measured (and potentially reversible) risk factors: smoking, lipids, hypertension, diabetes, obesity, diet, physical activity, alcohol consumption, and psychosocial factors (1). This chapter focuses on our present guidelines for the prevention of cardiovascular disease in individuals without a previously known history of CVD and addresses risk factors such as these. The targeted framework of risk factors addressed here is based on the components of ideal cardiovascular health detailed by the American Heart Association in 2010 (2).

DIET AND SUPPLEMENTS IN THE PREVENTION OF CARDIOVASCULAR DISEASE

Multivitamins, Antioxidants, and B Vitamins

Currently, there is insufficient evidence to support the use of multivitamins, antioxidants, or B-vitamins in the prevention of CVD. Despite being the most commonly used dietary supplements in the United States, there are conflicting data regarding the use of multivitamin supplementation for cardiovascular risk reduction. Some observational studies demonstrated risk reduction with multivitamin supplementation, whereas others showed no benefit or even trend toward harmful effects (3,4).

Vitamin D

It remains unclear whether low vitamin D levels are pathogenic or a marker of lifestyle factors (nutrition, activity, etc.) that may otherwise adversely affect cardiovascular risk. In the Framingham Offspring Study, subjects with low vitamin D levels had an associated hazard ratio of 1.62 ($P = .01$) for CVD events (5). A meta-analysis, however, did not demonstrate benefit with vitamin D supplementation in such patients (6). Future recommendations may be influenced by the ongoing VITAL (Vitamin D and Omega-3) trial, a large randomized, double-blind, placebo-controlled trial of cholecalciferol, 2000 IU/day, and marine omega-3 fatty acid supplements in the primary prevention of cancer and CVD (7).

Dietary Approaches to CVD Prevention

The American Heart Association (AHA) recommends maintenance of body mass index between

18.5 and 24.9 kg/m^2 through balance of caloric intake and expenditure. Particular attention is given to meals eaten outside the home due to relatively large portions and calorie counts (8).

There is little consensus regarding optimal dietary composition of macronutrients, whether carbohydrate, protein, or unsaturated fat. The Optimal Macronutrient Intake Trial to Prevent Heart Disease (OmniHeart) demonstrated that 3 separate diets—a carbohydrate-rich diet similar to the DASH (Dietary Approaches to Stop Hypertension) diet, a diet rich in protein (almost half from plant sources), and a diet rich in unsaturated, mostly monounsaturated fat—all improved blood pressure and lipid profiles. A diet low in saturated fat is generally well accepted as a means to reduce CVD risk (9). In individuals with elevated LDL-C, the 2013 AHA/ACC Lifestyle Management Guidelines recommend a dietary pattern that achieves 5% to 6% of calories from saturated fat. Dietary plans that can achieve this are the DASH, USDA Food Pattern, or the AHA Diet (69).

Effect of Diet on Hypertension

The DASH diet outlines recommendations for patients with hypertension or prehypertension, with emphasis on fresh fruits, vegetables, and low-fat dairy. Recommendations include 4 to 5 servings each of fruits and vegetables per day, 2 to 3 servings of low-fat dairy per day, and $<25\%$ of total caloric intake from fat. This diet can lead to modest reductions in blood pressure, generally the equivalent of one medical antihypertensive agent in as little as two weeks (10).

Reduced sodium intake is recommended by the AHA in nonhypertensive and hypertensive individuals as it can prevent hypertension and facilitate blood pressure control, respectively. In view of the available high-sodium food supply and the currently high levels of sodium consumption, an achievable daily sodium intake goal of no more than 2.4 grams/day is recommended. Ideally, even further reduction in blood pressure can be achieved with a 1.5 gram/day dietary limit of sodium. (69).

Other dietary measures shown to have beneficial effect on blood pressure control include moderation of alcohol intake, vegetarian diet, and potassium supplementation (11).

Mediterranean Diet

In a meta-analysis of 50 clinical trials including nearly 535,000 subjects, the Mediterranean diet demonstrated a protective role by ameliorating risk-associated components of metabolic syndrome, including waist circumference, low HDL-C, high triglyceride levels, high blood pressure, and elevated blood glucose (12). Greater improvements in lipid and inflammatory markers were also seen in the Mediterranean diet when compared to a low-fat diet (per AHA recommendations) (13). A role for the Mediterranean diet in primary prevention of CV disease was demonstrated in the more recent PREDIMED clinical trial of 7,447 patients. Patients were assigned to a Mediterranean diet supplemented with extra-virgin olive oil, a Mediterranean diet supplemented with mixed nuts, or a control diet (advised to reduce dietary fat). The Mediterranean diet groups showed significant reductions in risk of AMI, stroke, or death from cardiovascular causes (primary endpoint) as well as a nonsignificant trend toward reduction in all-cause mortality with hazard ratios for the primary endpoint of 0.70 ($P = .009$) for the group assigned to a Mediterranean diet with extra-virgin olive oil and 0.72 ($P = .02$) for the group assigned to a Mediterranean diet with nuts versus the control group (14). The U.S Department of Health and Human Services and the U.S. Department of Agriculture Dietary Guidelines for Americans 2010 have recommended a Mediterranean style diet (15). Table 20.1 displays the 2006 Diet and Lifestyle recommendations by the AHA.

Popular/Fad Diets

The most significant limitation in popular diets, which often promote low carbohydrate and/or high protein meal plans, is long-term dietary adherence. Commonly cited reasons include difficulty maintaining the required macronutrient restrictions and insufficient overall weight loss. Although such diets (Weight Watchers, Atkins Diet, Zone Diet, and Ornish Diet) have been shown to confer modest improvement in body weight, waist circumference, blood pressure, lipids, and blood glucose, in a randomized controlled trial of 160 patients where each patient was randomized into one of the 4 dietary patterns, overall adherence to each diet was low. The highest discontinuation rates were seen with the Ornish and Atkins diets. The AHA and the U.S. Department of Health have not recommended the use of such diets (16).

TOBACCO CESSATION TO REDUCE CVD RISK

Cigarette smoking remains the leading preventable cause of death in the United States. Although

TABLE 20.1 2006 American Heart Association Recommendations for a Healthy Diet

Dietary Modification	AHA Recommendation	Comments
Fruits and vegetables (rich in nutrients, low in calories, and high in fiber)	Choose fruits and vegetables that are deeply colored (e.g., spinach, carrots, peaches, berries). Prepare fruits and vegetables in a way to preserve the natural nutrient content without adding unnecessary calories, saturated/*trans*-fat, sugar, or salt.	Shown to decrease BP and improve CVD risk factors.
Whole grain and high fiber foods	At least half of grain intake should come from whole grains.	Modest reduction in LDL-C and CVD risk, slows progression of CVD in high-risk individuals. Soluble fiber increases short-chain fatty acid synthesis, thereby reducing endogenous cholesterol production.
Fish (long-chain omega-3 PUFAs: ecosapentaenoic acid [EPA] and docosahexaenoic acid [DHA])	Consume fish, especially oily fish, at least twice a week.	2 servings (8 oz) per week associated with decreased risk of sudden death and death from CHD. Note: children and pregnant women should avoid fish with high mercury content.
Saturated and *trans* fatty acids	Limit intake of saturated fat to $<7\%$ of daily energy, *trans*-fat to $<1\%$ of daily energy, and cholesterol to <300 mg/day by choosing lean meats and vegetable alternatives (beans and fish), fat-free or low-fat dairy products. Also minimize intake of partially hydrogenated fats.	This decreases CVD largely through effects on LDL-C cholesterol.
"Added sugar" (e.g., sucrose, corn syrup, and high-fructose corn syrup)	Minimize beverages and foods with added sugar.	Important for decreasing total caloric intake and weight gain.
Salt	Up to 2.3 g/day.	Salt sensitivity is more important in blacks, middle-aged, elderly, and those with HTN, DM, or CKD. Decrease in salt intake leads to an age-adjusted decline in blood pressures; this effect is found to be dose-responsive (lower is better).
Alcohol	$\leq$2 drinks a day for men and $\leq$1 drink per day for women, ideally with meals. "drink equivalent" = 12-ounce bottle of beer, 4-ounce glass of wine, 1.5 ounce shot of 80-proof spirits all contain the same amount of alcohol (one half ounce).	Note that alcohol can increase caloric intake and has the potential for addiction.

Source: From Ref. (11). Lichtenstein AH, et al. Diet and lifestyle recommendations revision 2006: a scientific statement from the American Heart Association Nutrition Committee. *Circulation* 2006;114:82–96.

contributing to a multitude of diseases, smoking contributes significantly to cardiovascular morbidity and mortality. Currently, an estimated 69.9 million American adults continue to use tobacco products, with 21.3% of men and 16.7% of women still smoking according to 2010 estimates (5). The economic

cost of smoking is predicted to be greater than $301 billion per year, with $116 billion from direct medical expenditures (17). Cigarette smoking is a well-established risk factor for cardiovascular disease, including coronary heart disease (CHD), stroke, and peripheral artery disease (18,19). Certain subgroups have been shown to be at increased risk: a recent meta-analysis shows female smokers have a 25% increased risk of developing CHD when compared to male smokers (20). Although precise mechanisms are unclear, smoking has been shown to promote vasomotor dysfunction, atherogenesis, and thrombosis (21). Secondhand smoke, or passive smoking, carries a 30% increased risk of developing coronary heart disease and increased rates of myocardial infarction (22,23).

AHA primary prevention guidelines (24) recommend complete cessation of smoking and no environmental exposure. Smoking cessation is well studied and has been shown to decrease cardiac events from 7% to 47% in those without known CHD as well as a decreased risk of developing CVD over time (18,23,25). No evidence suggests that reducing the amount of cigarettes reduces cardiovascular risk (19). Guidelines recommend clinicians ask about tobacco use at every visit and advise every user to quit. This is especially important as clinicians often fail to address smoking cessation. Patient motivation to quit, however, is the most important predictor for cessation (26) and can improve with professional assistance. There are several ways clinicians can assist patients in quitting. Counseling on quitting strategies and aids, such as nicotine replacement therapy and medications, can significantly improve quit rates.

DYSLIPIDEMIA: SCREENING AND TREATMENT GUIDELINES

Lipid goals for the primary prevention of cardiovascular events have evolved over the last four decades. Initially, total cholesterol was a targeted endpoint. However, subsequent randomized controlled trials have demonstrated a clear benefit in lowering low-density lipoprotein cholesterol (LDL-C). Although elevated triglycerides (TG) have been associated with CVD, a causal relationship has not been established. On the other hand, although clinical trials with high-density lipoprotein cholesterol (HDL-C) have been inversely correlated to adverse cardiovascular outcomes, clinical trials with raising HDL-C levels as the endpoint have had mixed results (27).

In November 2013, the American College of Cardiology–American Heart Association (ACC-AHA) Task Force released revised guidelines (28) for the treatment of high blood cholesterol levels. These new guidelines represented a significant departure from the previous and widely adopted Adult Treatment Panel III guidelines that focused on specific lipid targets based on a patient's level of cardiovascular risk.

The new guidelines recommend screening adults ≥ 21 years of age and identifying four subgroups for which the benefit of adding statins outweighs any associated risks. These patients include those with (a) clinically evident atherosclerotic CVD; (b) primary LDL-C levels of ≥ 190 mg/dL; (c) type 1 or 2 diabetes mellitus with an LDL-C of ≥ 70 mg/dL; or (d) a 10-year risk of atherosclerotic cardiovascular disease of at least 7.5% according to publicly available, pooled cohort equations, and an LDL-C level of at least 70 m/dL. In these four subgroups, high-intensity statin therapy (designed to reduce LDL-C levels by $\geq 50\%$) is recommended. Moderate-intensity statin therapy (aiming for a reduction of 30 to $< 50\%$ in LDL-C levels) is recommended for patients who cannot tolerate high-intensity treatment or patients with diabetes and a 10-year risk of atherosclerotic cardiovascular disease of less than 7.5%.

The ACC-AHA 2013 guidelines also identify groups of patients for whom available data do not support statin therapy and for whom no recommendations are made. These include (a) an age ≥ 75 years unless CVD is present, (b) those on hemodialysis, and (c) New York Heart Association class II–IV heart failure. The guidelines also noted no evidence to support the use of nonstatin cholesterol-lowering drugs, either combined with statin drugs or in statin-intolerant patients (29).

Therapeutic lifestyle changes should be initiated in all patients with coronary disease regardless of concomitant use of pharmacotherapy. These include dietary changes such as: saturated fat $< 7\%$ of daily calories or less than 200 mg/day, soluble fiber 10 to 25 g/day, and plant sterols/stanols of at least 2 g/day. Additionally, patients should be encouraged to increase physical activity and smoking cessation.

HMG-CoA reductase inhibitors (statins) vary in their potency and are first-line therapy for lowering LDL-C. The overall reduction ranges from 18% to 55%. On the other hand, they have a very modest HDL-C raising capacity of only 5% to 15%, and TG lowering of 7% to 30%. Bile acid sequestrants are often used by those who are intolerant to statins. They lower LDL-C 5% to 15%, raise HDL-C 3% to

5%, and have no effect on lowering TG. Nicotinic acids are employed for their ability to raise HDL 15% to 35%. They have modest impact on LDL-C of 5% to 25% and TG of 20% to 50%. Fibric acids (fibrates) lower LDL-C (5–15%), raise HDL-C (10–20%), and lower TG (20–50%).

Targeting other non-LDL cholesterol endpoints such TG, total cholesterol, and HDL-C is an ongoing area of research; however, there has not been an established mortality benefit as has been seen with lowering LDL-C (3).

HYPERTENSION: SCREENING AND TREATMENT GOALS

High blood pressure affects approximately 76.4 million adults in the United States, comprising the number one primary diagnosis for ambulatory office visits and drug prescriptions. Moreover, as a major risk factor for CHD and strokes, the first and third leading causes of mortality in the United States, respectively, high blood pressure is also considered the number one attributable risk factor for death both nationally and worldwide (30–32). With evidence that 90% of normotensive adults aged 55 will go on to develop high blood pressure, the aging of our population highlights the importance of primary prevention (33).

By definition, hypertension represents systolic or diastolic blood pressure measurements ≥ 140 or ≥ 90 mmHg, respectively, on two separate office visits or the administration of antihypertensive medications. Further classification designates severity by stage (1–2) with the added distinction of prehypertension (systolic blood pressure 120–139 or diastolic blood pressure 80–89) that identifies patients who are twice as likely to develop hypertension as compared to their normotensive counterparts (34,35). Screening is strongly recommended for patients aged ≥ 18 by the U.S. Preventative Services Task Force (Grade A). Furthermore, the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) endorses screening every 2 years for normotensive patients and annually for those classified as prehypertensive. Blood pressure control is defined as systolic and diastolic blood pressures < 140 and < 90 mmHg, respectively, although goals may vary in the context of several comorbidities. The recently released JNC-8 guidelines departed from tighter blood pressure limits set in JNC-7 in the general population and in the subsets of diabetics and elderly (age $>= 60$). A general target blood pressure of $<= 140/90$ mmHg has now been applied to (a) those < 60 years of age without diabetes or chronic kidney disease and (b) individuals with diabetes or chronic kidney disease, regardless of age. Individuals > 60 years of age without diabetes or chronic kidney disease have a target blood pressure <150 systolic and <90 diastolic blood pressure (70).

TABLE 20.2 Classification of Body Weight According to BMI in Adults

Weight Category	BMI (kg/m^2)
Underweight	<18.5
Normal	18.5–24.9
Overweight	25.0–29.9
Obese	≥ 30
Class I	30.0–34.9
Class II	35.0–39.9
Class III	≥ 40
Class IV	≥ 50
Class V	≥ 60

CURRENT GUIDELINES ON WEIGHT MANAGEMENT AND PRIMARY PREVENTION

Recent data from the Centers for Disease Control and Prevention reveal that close to 68% of Americans are either overweight or obese, and 34% are obese (36). Table 20.2 demonstrates the classification of body mass index (BMI) based on the latest classification system (37). Improving the obesity epidemic would require involvement of multiple stakeholders, including patients, employers, governments, industries, and health care providers (38). There has been convincing evidence from well-conducted randomized controlled trials that 5% to 10% weight reduction in overweight subjects with metabolic risk is effective in decreasing the development of type 2 diabetes and reducing multiple other CVD risk factors (39). Studies have shown that a diet that is high in fruits and vegetables can reduce the risk of several major causes of death and contribute to weight management (40,41). Similarly, intensive lifestyle interventions focusing on diet and physical activity have been shown to be beneficial in achieving weight loss in severely obese adults (42,43) and to reduce all of the components of the metabolic syndrome simultaneously (44–46). Table 20.3 summarizes current guidelines on weight management. According to the National Heart, Lung, and Blood Institute Expert Panel guidelines on obesity (47), weight loss drugs approved by the FDA may be used as part of a comprehensive weight loss program, including dietary therapy and physical activity for patients with a BMI of ≥ 30 with no concomitant obesity-related risk

TABLE 20.3 American Heart Association Recommendations for Weight Management

Weight Management	Initiate Weight-Management Program Through
• Goal: Achieve and maintain desirable weight (body mass index 18.5–24.9 kg/m^2). If BMI is $\geq$ 25 kg/m, waist circumference at iliac crest level should be $\leq$ 40 inches in men, $\leq$ 35 inches in women	• Caloric restriction and increased caloric expenditure as appropriate. For overweight/obese persons, reduce body weight by 10% in first year of therapy (Evidence Category A). Weight loss should be about 1–2 lb/week for a period of 6 months (Evidence Category B). • A diet that is individually planned to help create a deficit of 500 to 1,000 kcal/day should be an integral part of any program aimed at achieving a weight loss of 1–2 lb/week (Evidence Category A) • Physical activity is recommended as part of a comprehensive weight loss therapy as it modestly contributes to weight loss in overweight and obese adults (Evidence Category A) and it may help with maintenance of weight loss (Evidence Category C). All adults should set a long-term goal to accumulate at least 30 minutes or more of moderate intensity physical activity on most and preferably all days of the week (Evidence Category B).
Dietary modification: • Goal: An overall healthy eating pattern.	Advocate consumption of a variety of fruits, vegetables, grains, low-fat or nonfat dairy products, fish, legumes, poultry, and lean meats. Match energy intake with energy needs and make appropriate changes to achieve weight loss when indicated. Modify food choices to reduce saturated fats (10% of calories), cholesterol (300 mg/d), and *trans*-fatty acids by substituting grains and unsaturated fatty acids from fish, vegetables, legumes, and nuts. Limit salt intake to $<$ 6 g/d. Limit alcohol intake (2 drinks/d in men, 1 drink/d in women) among those who drink.

factors or disease, and for patients with a BMI of $\geq$ 27 with concomitant obesity-related risk factors or disease (47). Weight loss drugs should never be used without concomitant lifestyle modifications (Evidence Category B) (47). Guidelines recommend bariatric surgery for carefully selected patients with clinically severe obesity (BMI $\geq$ 40 or $\geq$ 35 with comorbid conditions) when less invasive methods of weight loss have failed and the patient is at high risk for obesity-related morbidity or mortality (Evidence Category B) (37,47).

PHYSICAL ACTIVITY IN THE PREVENTION OF CVD

Physical inactivity has become an increasingly recognized epidemic in the United States. According to recent data, 32% of the adult population does not engage in adequate physical activity (48). Metabolic syndrome, diabetes, and obesity are associated with increased physical inactivity. The 2013 ACC/AHA Lifestyle Management Guidelines recommend that adults engage in 3 to 4 sessions of aerobic physical activity per week, averaging 30 to 40 minutes per session, and involving moderate-to-vigorous intensity physical activity. These recommendations target LDL-C, non HDL-C, and blood pressure lowering (69).

Decreased physical activity is associated with a 30% to 40% increased risk of developing CVD. The INTERHEART study, which included patients from 52 countries, demonstrated a decreased odds ratio of AMI (OR 0.86) in those engaged in moderate physical activity. The Health Professional Follow Up Study (49) illustrated that increasing levels of physical activity had an dose-dependent relationship with reducing CHD risk. The AHA recommendations suggest vigorous-intensity activity ($>$60% of maximum capacity) and resistance training in addition to moderate-intensity exercises. Examples of moderate intensity exercise include hiking, running, swimming, as well as walking briskly, climbing stairs, and housework. Physical activity has been shown to have a positive effect on other cardiovascular risk factors: reducing blood pressure, controlling body weight, lowering the risk of developing diabetes, and increasing HDL-C (50).

Furthermore, aerobic exercise has been shown to induce ischemic preconditioning, improving tolerance of ischemic stress (51,52). Alterations of coronary anatomy, increases in diameter of coronary arteries, and improvement in microcirculation and endothelial function have been observed in previous studies (53).

DIABETES SCREENING AND CARDIOVASCULAR DISEASE

Diabetics have two- to fourfold higher risk of CVD mortality compared to people without diabetes mellitus. The estimated cost of diabetes mellitus in the United States in 2007 was $174 billion, with 28% of expenditures attributed to cardiovascular complications of diabetes mellitus (54). A critical component of CVD prevention is screening for diabetes mellitus, along with early interventions to treat and prevent its complications. The American Diabetes Association (2013) recommends screening for type 2 diabetes in every adult at 45 years of age. Asymptomatic adults who are overweight or obese (BMI ≥ 25 kg/m^2) and who have one or more additional risk factors for diabetes are also recommended to be screened for diabetes (Evidence Category B). Detailed screening recommendations are listed in Table 20.4 (55). The Finnish Diabetes Prevention Study demonstrated that lifestyle modification could prevent or delay the development of type 2 diabetes (56). Similarly, the U.S. diabetes prevention program (2002) demonstrated that both metformin and lifestyle modification could prevent or delay the development of type 2 diabetes with 58% reduction in its incidence with lifestyle changes versus

TABLE 20.4 Criteria for Diabetes Screening in Asymptomatic Adults from the American Diabetes Association

1. Screening should start at 45 years of age in the absence of other risk factors. Testing should be repeated at least at 3-year intervals.
2. Testing should be considered in all overweight or obese adults who have at least one of the following risk factors:
   - Physical inactivity
   - First-degree relative with diabetes
   - High risk race or ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
   - Women who delivered a baby weighing >9 lbs. or were diagnosed with gestational diabetes during pregnancy
   - Hypertension
   - HDL cholesterol level <35 mg/dL and/or triglyceride level >250 mg/dL
   - Women with polycystic ovary syndrome
   - Presence of conditions associated with insulin resistance such as severe obesity or acanthosis nigricans
   - History of CVD

TABLE 20.5 Recommendations for Primary Prevention of CVD in People with Diabetes

Lifestyle Management:
- Weight: Structured programs to promote changes such as reduced fat intake (<30% of daily energy) and increased regular physical activity to achieve 5%–7% weight loss.
- Medical Nutrition Therapy (MNT) Goals:
  - Saturated fats <7% of energy intake
  - Dietary cholesterol intake <200 mg/dL
  - *trans*-Unsaturated fatty acids <1% of total calorie intake
  - Total dietary fat intake: 25%–35% of total calorie intake mainly from mono- or polyunsaturated fat
  - Ample dietary fiber intake
  - Alcohol intake limitation to 1 drink/day for women and 2 drinks/day for men
  - Sodium intake limitation to 1,200–2,300 mg/day

Physical Activity:
- At least 150 minutes of moderate-intensity physical activity or at least 90 minutes of vigorous aerobic exercise per week is recommended. The physical activity should be distributed over at least 3 days per week, with no more than 2 consecutive days without physical activity.

Blood Pressure:
- Blood pressure should be measured at every visit with goals ≤130 mmHg systolic and ≤80 mmHg diastolic.
- Pharmacologic therapy is only indicated after a failed 3-month trial of lifestyle modification for those with systolic blood pressure 130 mmHg or diastolic ≥80 mmHg.
- All patients with diabetes and hypertension should be treated with a regimen that includes either an ACE inhibitor or an ARB. Other drug classes are only indicated as add-on regimens to achieve the blood pressure target.

(*continued*)

TABLE 20.5 Recommendations for Primary Prevention of CVD in People with Diabetes (continued)

Lipids:
• In adults ages 40 to 75 years old with diabetes and with LDL-C levels 70–189 mg/dL, the 10-year atherosclerotic CVD risk score should be calculated. If risk is <7.5%, moderate-intensity statin therapy should be instituted. If risk is ≥7.5%, high-intensity statin therapy should be prescribed.

Aspirin Therapy:
• Aspirin (75–162 mg/d) should be recommended as a primary prevention strategy to all diabetics at increased cardiovascular risk

Glycemic Control:
• The A1C goal for patients in general is <7%.
• A1C for the individual patient can be lowered as close to normal (<6%) as possible, without causing significant hypoglycemia.

Tobacco Cessation:
• Assessment of tobacco use and interventions to help patient quit should be implemented at every visit.

a 31% reduction with metformin use (57). Based on current American Diabetes Association (ADA) guidelines, in those with impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or hemoglobin A1C of 5.7% to 6.4%, an ongoing support program to target 7% weight loss and to increase physical activity to at least 150 minutes/week is recommended (55). Metformin therapy for prevention of type 2 diabetes may be considered in those with IFG (Evidence Category E*)*, IGT (Evidence Category A*)*, or an A1C 5.7–6.4% (Evidence Category E), especially those with BMI >35 kg/m^2, aged <60 years, and women with prior gestational diabetes based on current ADA guidelines (55). Once a patient develops type 2 diabetes, there is strong evidence that it is cost-saving to implement multicomponent interventions including standard antidiabetic care, education, screening for complications, and angiotensin-converting enzyme inhibitors (Table 20.5) (58).

THE USE OF ASPIRIN IN PRIMARY PREVENTION OF CVD

A number of guidelines have been published with regard to aspirin use for the primary prevention of cardiovascular events. There is, however, no overall consensus among these guidelines and clinician judgment with

TABLE 20.6 Selected Major Guidelines Regarding use of Aspirin in Primary Prevention

Guideline	Recommendation for Aspirin Use
USPSTF (2009) (59)	Men, 45–79 years old, MI prevention benefit > bleeding risk Women, 55–79 years old, stroke prevention benefit > bleeding risk
ACCF/AHA (2009) (62)	Men, 10-year CHD risk ≥ 10% Women, 10-year CHD risk ≥ 20%
ACCP (2012) (66)	Men and women > 50 years old
CCS (2011) (67)	In special circumstances in men and women without evidence of manifest vascular disease in whom vascular risk is considered high and bleeding risk low, aspirin 75 to 162 mg daily may be considered
AHA Guidelines for Prevention of CVD in Women (2011) (68)	In women ≥ 65 years old, if blood pressure is controlled and benefit of ischemic stroke and MI prevention > bleeding risk. Use of aspirin is reasonable in women < 65 years old for ischemic stroke prevention

Abbreviations: USPSTF = United States Preventive Services Task Force. ACCF = American College of Cardiology Foundation. AHA = American Heart Association. ACCP = American College of Chest Physicians. CCS = Canadian Cardiovascular Society. MI = myocardial infarction. CHD = coronary heart disease.

respect to the benefits of aspirin must be weighed against the potential bleeding harms associated with its use. The two most readily used recommendations in the United States, the 2009 USPSTF guidelines and the 2009 ACC/AHA guidelines, are presented here. A summary of other selected guidelines can be found in Table 20.6.

USPSTF

The United States Preventive Service Task Force (USPSTF) 2009 guidelines (59) have made separate recommendations for men and women, acknowledging the differential effect that gender has with regard to aspirin and individual CVD outcomes. For men, aspirin use is recommended in those age 45 to 79 years when the potential benefits from a reduction in rate of MI outweighs the potential harm of an increase in gastrointestinal hemorrhage (A recommendation). For women, aspirin use is recommended in those aged 55 to 79 years when the potential benefit of a reduction in ischemic stroke outweighs the potential harm of an increase in gastrointestinal hemorrhage (A recommendation). There is insufficient evidence to balance the benefits versus harm of aspirin use in men and women older than age 80 years (I statement). The USPSTF assigned a D recommendation for the use of aspirin for MI reduction in men less than 45 years and for stroke reduction in women less than 55 years.

Ten-year CHD risk in men is typically calculated using the Framingham Risk Score (60) and the 10-year stroke risk for women is assessed using tools such as the Western Stroke Calculator (61). The USPSTF provided a table that displays the age-defined levels where the benefit of aspirin with regard to CVD events (MI in men, stroke in women) outweighs the harm of significant bleeding events (Table 20.7) associated with its use.

TABLE 20.7 USPSTF estimated CUT POINTS where benefit of low-dose Aspirin exceeds bleeding risk (59)

Men		Women	
Age (Years)	10-Year CHD Risk (%)	Age (Years)	10-Year Stroke Risk (%)
45–59	≥4	55–59	≥3
60–69	≥9	60–69	≥8
70–79	≥12	70–79	≥11

Abbreviations: USPSTF= United States Preventive Services Task Force; CHD= coronary heart disease.

ACCF/AHA

The focused ACC/AHA 2009 Performance Measures for Primary Prevention of Cardiovascular Disease in Adults (62) provides a more broad-based, though gender-specific guideline with regard to the use of aspirin for primary prevention. They recommend administration of aspirin as preventive therapy for men with a 10-year coronary heart disease risk of 10% or more and for women with 10-year CHD risk of 20% or more. The decision of the committee to leave out age cut points was based on clinical trial data demonstrating fewer CVD events reported in younger individuals rather than an effect modification by age.

Diabetes

The ADA/AHA/ACCF 2010 Scientific Statement for Aspirin Use for Primary Prevention of Cardiovascular Events in People With Diabetes recommend low-dose aspirin (75–162 mg/day) for primary prevention of CVD in diabetic patients who have a 10-year CVD risk of 10% (63). Those at risk include most men over the age of 50 years and women over the age of 60 years who have one or more of the following additional major risk factors: smoking, hypertension, dyslipidemia, family history of premature CVD, and albuminuria (ACCF/AHA Class IIa, Level of Evidence: B) (ADA Level of Evidence: C). Low-dose aspirin might be considered for patients with intermediate CVD risk (younger patients with one or more risk factors, or older patients with no risk factors, or patients with 10-year CVD risk of 5%–10%) (ACCF/AHA Class IIb, Level of Evidence: C) (ADA Level of Evidence: E). Low-dose aspirin is not recommended for CVD prevention in diabetic patients at low CVD risk (men under age 50 years and women under 60 years with no major additional CVD risk factors; 10-year CVD risk under 5%) as the potential adverse effects from bleeding offset the potential benefits (ACCF/AHA Class III, Level of Evidence: C) (ADA Level of Evidence: C).

10-year CVD risk for diabetics can be assessed using calculators such as the United Kingdom Prospective Diabetes Study Risk Engine or the Atherosclerosis Risk in Communities Study CHD Risk Calculator (63).

Optimal Aspirin Dose

Primary prevention trials have used various aspirin-dosing regimens from 75 mg/day to 325 mg/every other day in individuals without a history of GI

bleeding and concomitant NSAID use. Low-dose aspirin (75 to 81 mg/day) is adequate to inhibit platelet aggregation fully and has been demonstrated to be effective (64). However, evidence also links higher doses of aspirin to increased bleeding events. Nearly all guidelines recommend patient evaluation with regard to risk and benefits on a case-by-case basis.

MILD TO MODERATE ALCOHOL INTAKE IN THE PREVENTION OF CVD

There are no large randomized control trials examining the effects of alcohol use with regard to CVD development and related outcome measures. Guidelines are primarily based on observational data but for the most part convey a similar message: if alcohol is being consumed, mild to moderate alcohol intake has been associated with beneficial cardiovascular effects in both men and women.

2006 AHA Diet and Lifestyle Recommendations

The AHA recommends that if alcoholic beverages are consumed, they should be limited to no more than 2 drinks per day for men and 1 drink per day for women, and ideally should be consumed with meals. A drink is defined as one half ounce of alcohol. Examples of drink equivalents include items such as a 12-ounce bottle of beer, a 4-ounce glass of wine, and a 1.5-ounce shot of an 80-proof spirit. Given the known associated risk of alcohol with breast cancer, vehicular and work accidents, hypertension, liver damage, hypertriglyceridemia, and addiction, the AHA does not recommend the consumption of alcohol solely for CVD risk reduction (11).

Similar recommendations with regard to amount of alcohol intake in men and women who choose to drink are stated in the 2005 Dietary Guidelines for Health published by the U.S. Departments of Health and Human Services and Agriculture and in the 2008 American Diabetes Association for diabetics (15,65).

SUMMARY

There is a Chinese proverb that states: "The superior doctor prevents sickness, the mediocre doctor attends to an impending sickness, and the inferior doctor treats the sickness already there." Without a doubt, one of the greatest goals in medicine is to prevent disease before it occurs. We are fortunate in cardiology to have elucidated a variety of modifiable risk factors. Addressing these can substantively alter an individual's chances of developing cardiovascular disease. Taken on a broader societal level, gradual but major swings in exercise, smoking, and dietary patterns can redefine a population's cardiovascular risk, for better and for worse. By focusing attention on the modifiable risk factors highlighted in this chapter, and by educating both individual patients and the public, we in health care have the opportunity to prevent illness and suffering while simultaneously decreasing health care costs: a win–win, if there ever was one.

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Monika Sanghavi, MD and
Amit Khera, MD, MSc, FACC

21

Secondary Prevention Guidelines

Coronary artery disease (CAD) continues to be the leading cause of death in the United States. Once an individual suffers a myocardial infarction (MI), he or she has a roughly 20% chance of having a heart attack or dying from coronary heart disease in the next 5 years (1). The goal of secondary prevention is to slow the progression of disease once it is established and reduce the risk of future cardiovascular (CV) events. In 2011, the American Heart Association and American College of Cardiology (AHA/ACC) updated their secondary prevention guidelines, previously published in 2006, and expanded the title to *Secondary Prevention and Risk Reduction Therapy for Patients With Coronary and Other Atherosclerotic Vascular Disease*. The addition of the phrase "Risk Reduction" comes from the expanding body of literature confirming that risk factor management in patients with coronary disease improves survival, reduces recurrent events and the need for revascularization, and improves quality of life (2). Thus, increasing awareness and promoting implementation of these guidelines, in concert with improving primary prevention at the individual and policy level, is of utmost importance for the reduction of future CV events. This chapter highlights the most important aspects of the AHA/ACC Secondary Prevention Guidelines, expands on those parts that are controversial, and contrasts these guidelines with those of other professional societies.

COMPONENTS OF SECONDARY PREVENTION RECOMMENDATIONS

I. Lifestyle and Risk Factor Modification
II. Medication Recommendations
III. Other Treatments and Alternative Therapies

I. LIFESTYLE AND RISK FACTOR MODIFICATION

Risk factors are those characteristics that have been highly associated with the development of CV disease, and can be divided into two groups: modifiable and nonmodifiable. This chapter reviews only those risk factors that are modifiable.

Nonmodifiable Risk Factors: Age, Gender, Family History

Modifiable Risk Factors: Smoking, Blood Pressure, Hyerlipidemia, Physical Activity, Weight, Diabetes Mellitus (DM)

Smoking Cessation

Key Points
Follow the 5 As at every visit.

Discussion
■ There is a very strong, clearly established causal relationship between smoking and the entire spectrum

of CV disease (cerebrovascular disease, CAD, and peripheral arterial disease [PAD]).

■ Smoking cessation has significant CV reduction and mortality benefit. Those who quit smoking can cut their CV risk by half (3). It is potentially the single most important intervention for secondary prevention of CV disease. Smoking reduction does not have the same benefits and does not increase the likelihood of eventual smoking cessation; therefore encouraging smoking cessation is preferred.

■ The guidelines for smoking cessation parallel the 5 As (ask, advise, assess, assist, and arrange) that should be routinely used by physicians and health care practitioners to counsel patients to quit smoking. In addition, the avoidance of passive environmental tobacco exposure should be emphasized (Table 21.1).

Blood Pressure Control

Key Points

Goal blood pressure $< 140/90$ mmHg.

Discussion

■ The blood pressure treatment goal for those with elevated blood pressure in the 2006 AHA/ACC Secondary Prevention guidelines were stratified based on those with DM and/or chronic kidney disease (CKD), and those without; a goal of $< 140/90$ mmHg for most, and a more stringent goal of $< 130/80$ mmHg for those with DM or CKD. However, this more stringent recommendation did not carry over to the more recent 2011 guidelines (Table 21.2).

■ The 2003 JNC 7 guidelines and the 2003 NKF-K/DOQI recommend a target blood pressure goal of $< 130/80$ mmHg in "high risk patients." The American Diabetes Association (ADA) previously had the same recommendation. However, in their 2013 Position Statement (4), the ADA modified their recommendation based on the results of the ACCORD trial to a goal of $< 140/80$ mmHg for everyone with diabetes and stated that lower targets of $< 130/80$ mmHg may be appropriate in certain individuals in whom the goal can be achieved without "undue treatment burden."

■ The New 2014 JNC8 Panel Guidelines also support a blood pressure goal <140/90mmHg in those with diabetes or chronic kidney disease (30).

■ The current AHA/ACC secondary prevention guidelines recommend using beta-blockers or ACE-I as the first-line therapy for BP control. However, in the absence of an absolute indication for beta blockade (eg left ventricular dysfunction, angina, acute coronary syndrome [ACS] event in the past 3 years, arrhythmias, etc.), the recommendation of initial treatment with beta-blockers is controversial and has recently come under scrutiny (5). In addition, many of the recommendations for beta-blocker use in stable CAD are based on data extrapolated from post-ACS data (6) rather than randomized controlled trials.

Lipid Management

Key Points

■ Treatment recommendations for the management of cholesterol in the secondary prevention guidelines were based on the Adult Treatment Panel (ATP) III. However, new cholesterol guidelines published in November 2013 suggest a slightly different treatment strategy (7).

■ All patients with clinical atherosclerotic cardiovascular disease (ASCVD), defined as history of MI,

TABLE 21.1 Smoking

Class I	1. Every tobacco user should be ADVISED at every visit to quit.
	2. The tobacco user's willingness to quit should be ASSESSED at every visit.
	3. Patients should be ASSISTED by counseling and by development of a plan for quitting that may include pharmacotherapy and/or referral to a smoking cessation program.
	4. ARRANGEMENT for follow-up is recommended.
	5. All patients should be advised at every office visit to avoid exposure to environmental tobacco smoke at work, home, and public places.

TABLE 21.2 Blood Pressure Control

Class I	1. All patients should be counseled regarding the need for lifestyle modification: weight control; increased physical activity; alcohol moderation; sodium reduction; and emphasis on increased consumption of fresh fruits, vegetables, and low-fat dairy products.
	2. Patients with blood pressure $\geq 140/90$ mmHg ($\geq 140/80$ in those with diabetes) should be treated, as tolerated, with blood pressure medication, treating initially with beta-blockers and/or ACE inhibitors, with addition of other drugs as needed to achieve goal blood pressure.

stable or unstable angina, coronary revascularization, stroke or TIA presumed to be of atherosclerotic origin, and peripheral arterial disease or revascularization, should be initiated on a statin for secondary prevention.

- Previously, guidelines suggested treating with statins to the target cholesterol levels listed below; however, specific targets have been eliminated in the new guidelines (Table 21.3):
  - Low-density lipoprotein cholesterol (LDL-C) <100 mg/dL (or <70 mg/dL for very high risk individuals) and a 30% reduction in LDL-C.
  - Non-high-density lipoprotein cholesterol (non-HDL-C) should be lowered to <130 mg/dL (or <100 mg/dL for very high risk individuals) using statin agents, particularly in those with high triglycerides (>200 mg/dL).
- The new recommendations suggest treatment with high-intensity statin (ie, atorvastatin 80 mg, rosuvastatin at least 20 mg) in everyone with ASCVD with no specific cholesterol targets. The exception to this recommendation is for those older than 75 and those who are not candidates for high-intensity statins, where moderate-intensity statins are recommended.

TABLE 21.3 Lipid Management

Class I	1. A lipid profile in all patients should be established, and for hospitalized patients, lipid-lowering therapy as recommended below should be initiated before discharge.
	2. Lifestyle modifications including daily physical activity and weight management are strongly recommended for all patients.
	3. Dietary therapy for all patients should include reduced intake of saturated fats (to $<7\%$ of total calories), *trans* fatty acids (to $<1\%$ of total calories), and cholesterol (to <200 mg/d).
	4. In addition to therapeutic lifestyle changes, high potency statin therapy (ie., atorvastatin 80 mg or rosuvastatin at least 20 mg) should be prescribed to all patients with clinical ASCVD in the absence of contraindications or documented adverse effects.
	5. Treating to specific LDL-C targets of <70 mg/dL and non-HDL-C <100 mg/dL are no longer advocated in the recent 2013 AHA/ACC Cholesterol Guidelines.
	6. Patients who have triglycerides >500 mg/dL should be started on fibrate therapy (or omega 3 fatty acids) in addition to statin therapy to prevent acute pancreatitis.

Discussion

- There is a strong and clearly established causal relationship between LDL-C level and CV risk. In addition, the reduction of LDL-C correlates with reduced CV risk. However, as randomized controlled trials have not evaluated strategies of achieving specific LDL-C targets, they were eliminated in the new cholesterol guidelines.
- Non-HDL-C is calculated as total cholesterol minus HDL-C, and includes atherogenic triglyceride rich lipoproteins such as VLDL in addition to LDL; it is a better predictor of CV risk than LDL-C. The goal for non-HDL-C was 30 mg/dL higher than the LDL-C goal in ATP III.
- Because specific non-HDL-C targets have not been evaluated in clinical trials, and adjunctive agents beyond high potency statins have not proven beneficial for CV risk reduction in recent studies, treating to specific non-HDL-C levels is not recommended in the new guidelines.
- Low HDL-C has consistently correlated with increased CV risk at the epidemiologic level, however, the pharmacologic modification of HDL using niacin and other agents has not translated clinically to improvement in CV outcomes in recent randomized studies and is not currently recommended (8).
- Although the new cholesterol guidelines suggest considering a reduction in statin dose in patients who have two consecutive LDL-C values less than 40 mg/dL (IIb recommendation) there is little evidence to support modifying statin dose for an arbitrary low LDL-C level.
- Since the elimination of specific cholesterol targets, the frequency and utility of routine lipid level evaluation on treatment has not been addressed in the new guidelines and is based on physician discretion. Possible uses include verification of patient compliance with medications and recommended lifestyle behaviors.

Physical Activity

Key Points

- The goal is at least 30 minutes of moderate intensity aerobic physical activity 5 days a week, and preferably 7 days a week (Table 21.4).
- Resistance training at least two days a week should complement aerobic activity.

TABLE 21.4 Physical Activity

Class I	1. For all patients the clinician should encourage 30–60 minutes of moderate-intensity aerobic activity, such as brisk walking, at least 5 days and preferably 7 days a week, supplemented by an increase in daily lifestyle activities to improve cardiorespiratory fitness and move patients out of the least fit, least active high-risk cohort (bottom 20%).
	2. The new AHA/ACC Lifestyle Management guidelines have expanded the recommendations to include 150 minutes of moderate intensity physical activity as before or 75 minutes a week of vigorous-intensity aerobic physical activity, or an equivalent combination of moderate- and vigorous-intensity aerobic physical activity.
	3. For all patients, risk assessment with a physical activity history and/or an exercise test is recommended to guide prognosis and prescription.
	4. The clinician should counsel patients to report and be evaluated for symptoms related to exercise.

TABLE 21.5 Weight Management

Class I	1. Body mass index (BMI) and/or waist circumference should be assessed at every visit, and the clinician should consistently encourage weight maintenance/reduction through an appropriate balance of lifestyle, physical activity, structured exercise, caloric intake, and formal behavior programs when indicated to maintain/achieve a body mass index between 18.5 and 24.9 kg/m^2.
	2. If waist circumference (measured horizontally at the iliac crest) is $\geq$35 in. ($\geq$89 cm) in women and $\geq$40 inches ($\geq$102 cm in men), therapeutic lifestyle interventions should be intensified and focused on weight management. The cut points for waist circumference are lower for certain ethnicities.
	3. The initial goal of weight loss therapy should be to reduce body weight by approximately 5% to 10% from baseline. With success, further weight loss can be attempted if indicated.

Discussion

- A careful physical activity and angina history, and in some cases exercise stress testing, are required to formulate an individualized exercise prescription.
- There are emerging data to suggest that shorter bursts of high-intensity exercise (ie, interval training) may be more beneficial for improved cardiorespiratory fitness than the current recommendation, with reasonable safety. The new AHA/ACC Lifestyle Management guidelines suggest either moderate intensity physical activity as mentioned above or 75 minutes a week of vigorous-intensity aerobic physical activity, or an equivalent combination of moderate- and vigorous-intensity aerobic physical activity (9).
- The 30 minutes of daily activity can be cumulative and do not have to occur in one stretch.
- Pedometer use can be a good motivational tool that has been shown in randomized trials to increase physical activity, and improve body weight and blood pressure.

Weight Management

Key Points

- Goal body mass index (BMI) 18.5 to 24.9 kg/m^2 (Table 21.5)
- Goal waist circumference $<$35 inches for women, $<$40 inches for men, with lower cut points for those of Southeast or East Asian descent.

Discussion

- A standardized measurement of waist circumference is required (at the level of the iliac crest) in order to minimize intra- and interobserver variability for serial measurements, and waist circumference should be ascertained at every visit.
- Central obesity, measured by waist circumference, adds prognostic information beyond BMI and may be a better predictor of adverse outcomes than BMI in patients with CAD (11).
- The International Diabetes Foundation (IDF) has published country/ethnic specific waist circumference measurements that are consistent with the metabolic syndrome: $\geq$90 cm (35.4 in.) in men and $\geq$80 cm (31.5 in.) in women for South Asians, Chinese, and Japanese. (10). Goal waist circumference for these ethnicities would be lower than the stated values.
- In patients with CAD, there is an "obesity paradox" such that being overweight or obese may be associated with better outcomes than normal weight.

Type 2 Diabetes Management

Key Points

- A comprehensive approach to risk reduction including physical activity, weight management, BP control, and lipid management is required in patients with diabetes and CAD.
- Glycemic control is associated with improved microvascular outcomes, but only a modest reduction in CV events.
- Target HbA1c in the 2011 AHA secondary prevention guidelines was ≤7% with the caveat to avoid hypoglycemia and liberalize targets as needed (Table 21.6); however, the ADA 2013 Position Statement now recommends a less stringent goal (<8%) in those with advanced macrovascular complications (ie, secondary prevention) (12).
- BP targets are discussed in the BP section.
- Metformin is an effective first-line agent and should be used if not contraindicated.

Discussion

- Glycemic control alone is only one component of a comprehensive strategy to reduce CV events in patients with diabetes and CAD.
- Recent studies targeting more stringent HbA1C targets (<6.5%) in patients with diabetes demonstrated no overall CV benefit and possible harm compared with more liberal targets (eg, <8%), particularly in those with established vascular disease (13).
- Metformin is one of the only oral agents demonstrated to reduce macrovascular events in a randomized clinical trial (UKPDS), and its use should be emphasized in the treatment of diabetes (4), even after initiation of insulin if not contraindicated (14).

TABLE 21.6 Type 2 Diabetes Mellitus Management

Class I	1. Care for diabetes should be coordinated with the patient's primary care physician and/or endocrinologist.
	2. Lifestyle modifications including daily physical activity, weight management, blood pressure control, and lipid management are recommended for all patients with diabetes.
Class IIa	1. Metformin is an effective first-line pharmacotherapy and can be useful if not contraindicated.

II. MEDICATIONS

There are several medications that have proven efficacy in those with established CAD to help decrease the risk of subsequent events and mortality.

Antiplatelet Agents/Anticoagulants

Key Points

- Aspirin 75 to 162 mg daily is recommended in all patients with CAD unless contraindicated.
- Clopidogrel 75 mg daily is an alternative for those intolerant or allergic to aspirin.
- The specific antiplatelet agent, dose, and duration for various manifestations of atherosclerotic disease are outlined in Table 21.7.
- The addition of a P2Y12 receptor antagonist (eg, clopidogrel, prasugrel, or ticagrelor) to aspirin is recommended postpercutaneous coronary intervention (at least 1 month for bare-metal stent and 12 months for drug-eluting stent) or after an acute coronary syndrome (at least 12 months post-ACS).

Discussion

- Several studies demonstrate that low-dose aspirin (81 mg) is as efficacious as higher dose aspirin in CV disease prevention with less bleeding risk, thus the lower dose is now generally preferred.
- In patients requiring warfarin or other vitamin K antagonists, the addition of aspirin and a P2Y12 inhibitor (ie, "Triple Therapy") significantly increases bleeding risk. In such circumstances, it is imperative to use low-dose aspirin and continue the P2Y12 inhibitor (clopidogrel) for as brief a period as possible.
- One recent small study suggested in patients with recent stenting who required warfarin, the combination of clopidogrel and warfarin was as effective as aspirin, clopidogrel, and warfarin with more than a 50% lower bleeding risk (15).

Renin-Angiotensin-Aldosterone Blockers

Key Points

- Angiotensin Converting Enzyme Inhibitors (ACE-I) should be started and continued indefinitely in all patients with left ventricular ejection fraction (LVEF) ≤40% and in those with hypertension, diabetes, or CKD, unless contraindicated. Angiotensin Receptor Blockers (ARBs) can be substituted in those who are ACE-I intolerant (Table 21.8).

TABLE 21.7 Antiplatelet Agents/Anticoagulants

Class I	1. Aspirin 75–162 mg daily is recommended in all patients with coronary artery disease unless contraindicated. – Clopidogrel 75 mg daily is recommended as an alternative for patients who are intolerant of or allergic to aspirin. 2. A P2Y12 receptor antagonist in combination with aspirin is indicated in patients after ACS or PCI with stent placement. – For patients receiving bare-metal stent or drug eluting stent during PCI for ACS, clopidogrel 75 mg daily, prasugrel 10 mg daily, or ticagrelor 90 mg twice daily should be given for at least 12 months. 3. For patients undergoing coronary artery bypass grafting (CABG), aspirin should be started within 6 hours after surgery to reduced saphenous venous graft closure. Dosing regimens ranging from 100 to 325 mg daily for 1 year appear to be efficacious. 4. In patients with extracranial carotid or vertebral atherosclerosis who have had an ischemic stroke or TIA, treatment with aspirin alone (75–325 mg daily), clopidogrel alone (75 mg daily), or the combination of aspirin plus extended release dipyridamole (25 mg and 200 mg twice daily, respectively) should be started and continued. 5. For patients with symptomatic atherosclerotic peripheral artery disease of the lower extremity, antiplatelet therapy with aspirin (75–325 mg daily) or clopidogrel (75 mg daily) should be started and continued. 6. Antiplatelet therapy is recommended in preference to anticoagulant therapy with warfarin or other vitamin K antagonists to treat patients with atherosclerosis. – If there is a compelling indication for anticoagulant therapy, such as atrial fibrillation, prosthetic heart valve, left ventricular thrombus, or concomitant venous thromboembolic disease, warfarin should be administered in addition to the low-dose aspirin (75–81mg daily). – For patients requiring warfarin, therapy should be administered to achieve the recommended INR for the specific condition. – Use of warfarin in conjunction with aspirin and/or clopidogrel is associated with increased risk of bleeding and should be monitored closely.

TABLE 21.8 Renin-Angiotensin-Aldosterone System Blockers

Class I	1. ACE Inhibitors should be started and continued indefinitely in all patients with left ventricular ejection fraction ≤40% and in those with hypertension, diabetes, or chronic kidney disease unless contraindicated. 2. The use of ARBs is recommended in patients who have heart failure or who have had a myocardial infarction with left ventricular ejection fraction ≤40% and who are ACE-inhibitor intolerant. 3. Use of aldosterone blockade in postmyocardial infarction patients without significant renal dysfunction or hyperkalemia is recommended in patients who are already receiving therapeutic doses of an ACE inhibitor and beta-blocker who have left ventricular ejection fraction ≤40% and who have either diabetes or heart failure.
Class IIa	1. It is reasonable to use ACE inhibitors in all other patients.

■ Use of aldosterone blockade is recommended for postmyocardial infarction patients who have LVEF ≤40%, and who have either diabetes or clinical heart failure, but without significant renal dysfunction or hyperkalemia.

Discussion

■ ACE-I/ARBs/Aldosterone blockers have clear benefit in patients with depressed left ventricular systolic function.

■ The routine use of ACE-I in all other patients with CAD or CAD risk factors for vasculoprotective effects without another specific indication is debated. Older trials such as HOPE (16) and EUROPA (17) demonstrated an approximate 20% risk reduction in CV events that was not solely dependent on blood pressure lowering effects. However, more recent data (18) are equivocal in terms of CV risk reduction with ACE-I.

Beta-Blockers

Key Points

■ Beta-blockers should be used in all patients with LV systolic dysfunction (Table 21.9).

■ Beta-blockers should be initiated and continued in patients with normal LV function post MI or ACS for 3 years. Extending treatment beyond 3 years is a reasonable consideration.

■ Using beta-blockers as chronic therapy in patients with stable coronary or other vascular disease can be considered. Although, this recommendation is based on consensus opinion of experts rather than randomized controlled trials.

Discussion

■ As discussed above in the BP control section, the use of beta-blockers in those without LV systolic dysfunction, angina, and a recent ACS event is controversial. They are excellent agents for improving anginal symptoms, but in stable patients without one of these concomitant factors, their value for improving clinical CV events is unclear.

TABLE 21.9 *Beta-Blockers*

Class I	1. beta-Blocker therapy should be used in all patients with left ventricular systolic dysfunction (ejection fraction ≤40%) with heart failure or prior myocardial infarction, unless contraindicated. (Use should be limited to carvedilol, metoprolol succinate, or bisoprolol, which have been shown to reduce mortality.)
	2. beta-Blocker therapy should be started and continued for 3 years in all patients with normal left ventricular function who have had myocardial infarction or ACS.
Class IIa	1. It is reasonable to continue beta-blocker beyond 3 years as chronic therapy in all patients with normal left ventricular function who have had myocardial infarction or ACS.

■ In the 2006 ACC/AHA secondary prevention guidelines, the use of beta-blockers was recommended indefinitely in post-ACS patients as a Class I recommendation. However, the updated guidelines in 2011 reduced the Class I recommendation to 3 years post ACS, inasmuch as this was the time interval studied in clinical trials. Extending treatment beyond 3 years is now considered a Class IIa recommendation.

III. OTHER/ALTERNATIVE THERAPIES

Influenza Vaccination

Key Points

Patients with CV disease should have an annual influenza vaccination (Table 21.10).

Discussion

■ Randomized controlled trials FLUVACS (19) and FLUCAD (20) evaluated the benefit of influenza vaccination post-acute-MI and in stable secondary prevention patients. The studies demonstrated significant benefit in 1-year mortality and MACE events in those receiving the vaccine.

■ Based on these and other data, a science advisory from the ACC/AHA was released in 2006 emphasizing the importance of annual influenza vaccination in the secondary prevention of CAD (21). The advisory commented that "Influenza vaccination is now recommended with the same enthusiasm as control of cholesterol, blood pressure, and other modifiable risk factors."

■ Immunization with live attenuated vaccine (administered intranasally) is not recommended for persons with CV conditions as it has not yet been approved for these patients (21).

Depression

Key Points

■ There are no class I recommendations in this section (Table 21.11).

■ Although treatment of depression has not been shown to improve CV disease outcomes, it is reasonable to screen patients with recent CABG or MI for depression for its other clinical benefits.

TABLE 21.10 Influenza Vaccination

Class I	1. Patients with CV disease should have an annual influenza vaccination.

TABLE 21.11 Depression

Class IIa	1. For patients with recent coronary artery bypass grafting surgery or myocardial infarction, it is reasonable to screen for depression if patients have access to case management, in collaboration with their primary care physician and a mental health specialist.

Discussion

■ In 2008, the AHA published a science advisory regarding depression and coronary heart disease (22). This report recommended that patients with coronary disease be routinely screened in a variety of settings, and when depression is identified, they should be evaluated by a professional qualified in the diagnosis and management of depression. In addition, these patients should be carefully monitored for adherence.

■ There is some controversy about depression management in secondary prevention as there are no clinical trials demonstrating benefit of depression screening and treatment in clinical CV disease outcomes (23).

■ However, randomized trials such as SADHEART (24) and CREATE (25) suggest that selective serotonin reuptake inhibitors (SSRIs) seem to be safe in patients with CAD and can improve depressive symptoms.

Cardiac Rehabilitation

Key Points

■ Cardiac rehabilitation is recommended for all of the following patients with atherosclerotic disease (Table 21.12):

- Post-ACS
- Post-PCI
- Post-CABG
- Chronic angina within the past year
- Peripheral artery disease

Discussion

■ There is compelling evidence supporting the use of cardiac rehabilitation for secondary prevention such that the AHA elevated the referral and appropriate delivery of cardiac rehabilitation services to the level of performance measure in 2007 (26).

■ A recent meta-analysis confirms previously reported 20% to 25% lower total and cardiac mortality rates in those undergoing exercise-based cardiac rehabilitation compared to usual medical care (27).

TABLE 21.12 Cardiac Rehabilitation

Class I	1. All eligible patients with ACS or whose status is immediately post coronary artery bypass surgery or post-PCI should be referred to a comprehensive outpatient CV rehabilitation program either prior to hospital discharge or during first follow-up office visit. 2. All eligible outpatients with diagnosis of ACS, coronary artery bypass surgery, or PCI, chronic angina, and/or peripheral artery disease within the past year should be referred for a comprehensive outpatient CV rehabilitation program. 3. A home-based cardiac rehabilitation program can be substituted for a supervised, center-based program for low-risk patients.

Hormone Replacement Therapy (HRT)

Key Points

■ HRT is currently not recommended for the secondary prevention of coronary artery disease in women (28).

■ Short-term HRT use may be considered for the treatment of refractory postmenopausal symptoms after discussion of the risks and benefits with the patient.

Discussion

■ Initial data from observational studies were compelling for the use of HRT for primary and secondary prevention of CAD which resulted in widespread use of HRT for these purposes. However, subsequent randomized, placebo-controlled trials swung the pendulum the other direction. Specifically the Heart Disease and Estrogen Replacement Study (HERS) reported no benefit of HRT on CV disease events in secondary prevention, with a signal for harm (29).

SUMMARY

The 2011 ACC/AHA Secondary Prevention Guidelines and newer guideline documents outline several components that can effectively reduce recurrent CV risk in those with ASCVD. Smoking cessation is essential, and the 5 As (ask, advise, assess, assist, and arrange) should be followed at every visit. Goal blood pressure is $<140/90$ mmHg with beta blockers and ACE inhibitors as first-line therapy. Virtually all patients with clinical ASCVD should be prescribed high-potency statin therapy regardless of LDL-C level.

A combination of at least 150 minutes of moderately intense physical activity and 75 minutes of vigorous activity weekly is also recommended. In addition to targeting a normal BMI (18.5–25kg/m^2), waist circumference should also be evaluated at each visit.

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Jenna Kay, MD and
Javed Butler, MD, MPH

22

Preventing Heart Failure

Unlike coronary heart disease, the vast majority of heart failure research efforts to date have focused on treatment rather than prevention. Considering the increasing elderly proportion in the population and the projected epidemiology of heart failure in the intermediate-term future, a more focused effort on prevention is needed.

HEART FAILURE EPIDEMIOLOGY

Over 5.5 million Americans have heart failure and more than 650,000 are diagnosed each year (1). Patients with impaired versus preserved left ventricular ejection fraction each comprise about half of the overall heart failure population (2). Heart failure is related to 12 to 15 million office visits and 6.5 million hospital days annually. Patients are prone to rehospitalizations, with readmission rates near 50% within six months of discharge. The total direct and indirect cost of heart failure in the United States exceeds $30 billion (3). Outcomes remain suboptimal, with only approximately 50% of patients surviving five or more years after diagnosis (4). There have been no major advances in therapy for patients with heart failure and preserved ejection fraction or those hospitalized for acute heart failure. The prevalence of heart failure is expected to increase, owing to an aging population and the increasing prevalence of cardiovascular risk factors, for example, diabetes. Heart failure is more common in the elderly, and 80% of patients hospitalized with heart failure are over 65 years old.

RISK FACTORS

There are many known risk factors for heart failure. Age, gender, and socieoeconomic status are associated with risk, as are lifestyle factors such as physical inactivity, coffee consumption, increased salt intake, and excessive alcohol intake (5). Hypertension and coronary artery disease are the most common and strongest risk factors, conferring a two- to threefold increased risk (1). Laboratory abnormalities such as dyslipidemia, anemia, and renal dysfunction all predispose individuals to heart failure (6). Multiple medications, including chemotherapeutic agents, are associated with heart failure. Cyclooxygenase-2 inhibitors may increase risk of myocardial infarction, and thiazolinediones are associated with precipitation of heart failure (4). There is also growing interest in the genomic predictors of heart failure.

RISK PREDICTION

Although many individual risk factors for heart failure (eg., hypertension) are well described, how to quantify individual risk in patients with various combinations of risk factors is unclear. Multiple risk factor prediction schemes such as the Framingham Risk Score have been developed for coronary events. Recently, the Health ABC Heart Failure Risk Model was developed using the data from 2,935 individuals participating in the Health ABC Study. Using individual predictors

of heart failure, a simple point score was created to predict incident heart failure risk into 4 risk groups. The model predicted risk equally well in both men and women, and in white and black races.

CHALLENGES IN RISK PREDICTION

Assessing an individual's risk for developing heart failure is challenging. It is a clinical diagnosis that is prone to diagnostic uncertainty. The most common clinical criteria used to diagnose heart failure are the Framingham criteria that require the presence of at least two major criteria, or one major and two minor criteria (7) (major criteria: paroxysmal nocturnal dyspnea, neck vein distension, rales, radiographic cardiomegaly, pulmonary edema, S3 gallop, central venous pressure >16 cm H_2O, circulation time ≥ 25 seconds, hepato-jugular reflux, or congestion or cardiomegaly at autopsy; minor criteria include ankle edema, nocturnal cough, dyspnea on ordinary exertion, hepatomegaly, pleural effusion, one third reduction of maximum vital capacity, and heart rate >120 beats/minute). These are, however, inconsistent with other criteria, such as the Cardiovascular Health Study criteria (8). Diagnosis of heart failure with preserved ejection fraction is especially challenging (9).

RISK MODULATION

Currently, heart failure risk modulation is targeted at individual risk factors. This section describes known interventions that directly or indirectly reduce the risk for incident heart failure.

Lifestyle

Healthy weight, avoiding smoking, exercise, and a healthy diet reduce heart failure risk factors such as coronary disease, diabetes mellitus, and hypertension. One study reported a 21.3% risk of heart failure in men adhering to none of these habits and a 10.1% risk in men adhering to 4 or more of them (10).

Obesity

Body mass index is associated with heart failure in a positive and linear fashion in both sexes and obesity is associated with an increased risk for heart failure (1). BMI and waist circumference similarly predict incident heart failure (40). The principal approach to risk reduction in obese patients should include weight control and physical activity as well as attention to risk factors such as hypertension, diabetes mellitus, sleep disorders, and components of the metabolic syndrome (4). Even minor weight loss is efficacious. A 10% weight reduction ameliorates systolic dysfunction, and greater weight loss produces a significant decrease in left ventricular dimensions, mass index, and filling pressures, and improves systolic and diastolic function (4).

Sedentary Lifestyle

Physical inactivity is an important risk factor for heart failure (1). Regular physical activity is a central component of weight reduction and weight maintenance, improved lipoprotein profile, and reduced risk of hypertension, diabetes mellitus, and coronary artery disease (10). However, integration of physical activity into the daily lives of the population has proved challenging. Currently, the recommendations of the American College of Sports Medicine and the American Heart Association for adults aged 18 to 65 years include (11):

a. *Aerobic Activity:* Moderate-intensity aerobic physical activity for a minimum of 30 min on five days or vigorous-intensity aerobic activity for a minimum of 20 min on three days each week.

b. *Muscle-Strengthening Activity*: 8 to 10 exercises should be performed on two or more nonconsecutive days each week using the major muscle groups. To maximize strength development, a resistance (weight) should be used that allows 8 to 12 repetitions of each exercise resulting in volitional fatigue.

c. *Activity Dose:* Vigorous-intensity activities may have greater benefit than moderate-intensity physical activity.

Alcohol Consumption

Excessive alcohol consumption is associated with alcoholic cardiomyopathy (2). Interestingly, other data are consistent with possible benefits of moderate alcohol consumption on the risk of heart failure. Studies have reported a 34% to 57% lower risk of heart failure in patients who consume alcohol at moderate levels (2). Beneficial effects of alcohol have also been reported for hypertension, myocardial infarction, and diabetes mellitus.

Dietary Habits

In the Dietary Approaches to Stop Hypertension (DASH) diet, individuals are encouraged to consume more (a) fruits and vegetables; (b) grains and grain products; (c) lean meats, fish, and poultry; (d) low-fat or nonfat dairy foods; and (e) nuts, seeds, and legumes; and reduce the consumption of red meat, fat, and sugar while maintaining a low sodium intake. Initially,

this was promoted for hypertension; however, recent evidence supports reduction of heart failure risk with an observed 37% lower rate in women who adhere to the DASH diet (12). The DASH diet may contribute to heart failure prevention by reducing blood pressure and coronary heart disease (2). The DASH diet reduces low-density lipoprotein cholesterol levels and oxidative stress, and exerts beneficial physiologic effects such as estrogenic effects of phytochemicals (1). The U.S. Department of Health and Human Services and Department of Agriculture recommend that adults consume no more than 2,300 mg per day of sodium. Individuals with hypertension, middle-aged and older adults, and blacks should consume no more than 1,500 mg per day of sodium. There is overwhelming evidence for a causal relationship between salt intake and blood pressure (2).

Smoking

Smoking is a strong predictor of heart failure in both men and women, with 45% and 88% increased risk, respectively (2). The deleterious effect of tobacco seems to be independent of the form of use; increased risk for cardiovascular diseases is reported in nonsmoking use of tobacco (13). There is no "safe" level of smoking; a single cigarette may stiffen the left ventricle, and as few as 1 to 4 cigarettes a day doubles the risk of myocardial infarction (2). Mechanisms leading to heart failure in smokers include indirect effects, that is, by causing or aggravating comorbidities that are related to heart failure, as well as direct effects on the myocardium (14).

All smokers should be counseled to quit. Current recommended strategies include:

1. *Medications*: Several medications are available for tobacco dependence. Seven first-line medications reliably increase long-term smoking abstinence rates including bupropion SR, nicotine gum or inhaler or lozenge or nasal spray or patch, and varenicline.
2. *Counseling and Psychosocial Support*: Individual, group, and telephone practical counseling and social support are effective, and their effectiveness increases with treatment intensity.
3. *Combination*: The combination of counseling and medications is more effective than either alone and clinicians should encourage all individuals attempting to quit to use both counseling and medication.

HYPERTENSION

Hypertension is an antecedent condition in the majority of individuals who develop heart failure (2). By age 75, almost all hypertensive individuals have isolated systolic hypertension (15). Diastolic blood pressure is a more potent cardiovascular risk factor than systolic blood pressure until age 50 and thereafter systolic blood pressure becomes more important (16). Clinical trials have shown that controlling systolic hypertension reduces heart failure rates (2). The population attributable risk of hypertension for heart failure in the general population is reported to be 39% in men and 59% in women by the Framingham investigators (17), whereas population attributable risk of uncontrolled blood pressure in the elderly was reported to be 21.3% in whites and 30.1% in blacks in one study (3). The lifetime risk for heart failure doubles in subjects with blood pressure $\geq$160/100 compared to those with $<$140/90 mmHg. This gradient of risk is seen in both sexes in every decade of life from 40 to 70 years (1). Clinical trials have demonstrated the benefit of antihypertensive therapy in reducing the incidence of cardiovascular disease (18), and a few studies have specifically focused on prevention of left ventricular hypertrophy and development of heart failure.

Antihypertensive Medications

a. *Diuretics*: Secondary outcomes of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial reported a higher rate of incident heart failure with amlodipine and a nonsignificant increase with lisinopril compared with chlorthalidone. The Joint National Commission 7 recommend that in the absence of any other compelling indications, thiazide diuretics should be used as initial therapy for hypertension.

b. *Renin–angiotensin system modulators*: Meta-analysis of double-blind trials that measured the effects of antihypertensive drugs on left ventricular mass show that the greatest reduction was achieved with angiotensin receptor blockers. A recent meta-analysis on renin–angiotensin system inhibition showed that these agents reduce the risk for heart failure by 19% compared with calcium channel blockers (19).

c. *Beta-blockers*: Although beta-blockers are effective in lowering blood pressure, they are less effective in preventing complications such as coronary artery disease and cardiovascular and all-cause mortality, and in reducing left ventricular mass (20). However, a recent a meta-analysis suggested that beta-blockers are efficacious for primary prevention of heart failure in hypertension and have a similar benefit in the elderly and younger individuals when compared with other agents (20).

d. *Calcium channel blockers*: There are limited experimental data on the effects of calcium antagonists on

left ventricular mass or incident heart failure. A recent meta-analysis suggested that treatment of hypertension with calcium channel blockers is less effective for reducing heart failure for the same reduction of blood pressure (18).

Target Goals of Therapy

In patients with hypertension, systolic and diastolic blood pressure targets are <140/90 mmHg except for patients with diabetes where the goal has been recently revised to <140/80 mmHg. Because most patients with hypertension, especially those over age 50, will reach the diastolic blood pressure goal once systolic blood pressure is at goal, the primary focus should be on systolic blood pressure. Recent trials have demonstrated that the majority of patients will require a combination of two or more medications (1). Data from a recent randomized trial evaluating the effect of usual versus tight control of systolic blood pressure (<130 mmHg) in nondiabetic hypertensive individuals with left ventricular hypertrophy demonstrated additional benefit with tighter control (18).

DIABETES MELLITUS

Diabetes mellitus is an independent risk factor for heart failure in all age groups (21). The relative risk for heart failure among patients with diabetes mellitus ranges from 1.3 to 2.7, increasing to 4 in patients younger than 65 years and 11 in those younger than 45 years. Comorbidities associated with heart failure, including obesity, hypertension, and coronary artery disease, are highly prevalent among individuals with diabetes mellitus. Insulin resistance itself may produce abnormalities in cardiac structure and function (22).

Interventions

Medications

a. *Insulin*: Randomized controlled trials suggest that insulin use in ACC-AHA stage A heart failure does not appear to increase the risk for heart failure (23). Whether insulin use reduces the risk for heart failure is not known.

b. *Sulfonylureas*: Sulfonylurea therapy does not increase the risk of heart failure compared with other oral antidiabetic agents (24).

c. *Metformin*: The risk of new onset heart failure among patients treated with metformin compared with patients treated with other oral antidiabetic medications was reported in ADOPT and the findings were similar as for sulfonylureas (24).

d. *Thiazolidinediones*: Although treatment with thiazolidinediones increased myocardial glucose uptake, and myocardial glucose uptake seems to be positively correlated with left ventricular function, the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) study indicated that thiazolidinedione use is associated with a small but clinically relevant increased risk of heart failure (25).

e. *Other agents*: The available evidence suggests that the alpha-glucosidase inhibitor acarbose may decrease the risk of myocardial infarction (26).

Glucose Control

In the United Kingdom Prospective Diabetes Study (UKPDS) 33, no significant reduction in the development of macrovascular disease or heart failure was demonstrated with intensive blood glucose control (23).

Blood Pressure Control

Because hypertension increases the risk of cardiovascular disease and heart failure in patients with diabetes, aggressive blood pressure management is essential to prevent long-term complications in this population. In UKPDS 38, tight blood pressure control reduced the risk for heart failure by 56% (27). The Seventh Report of Joint National Commission on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) recommended more aggressive blood pressure control (target blood pressure <130/80 mmHg) in patients with diabetes (28).

Targeting Underlying Mechanisms

Medications such as ACEI, ARB, and beta-blockers benefit patients with diabetes and prevent complications of diabetes including heart failure. Trials have shown that treatment with ACEI reduces the relative risk for new onset heart failure and that the benefit of ACEI for heart failure prevention is sustained over time (4). Other studies have shown that treatment reduces the frequency of hospitalization for heart failure.

CORONARY HEART DISEASE

Coronary heart disease confers an increased risk of developing heart failure in both men and women, with reported population attributable risks ranging from 62% in men to 56% in women (29) and from 23.9% in whites to 29.5% in blacks as reported in one study (4). Advances in the treatment of myocardial infarction

has led to increasing numbers of patients surviving with residual myocardial damage and may be partially responsible for the increase in heart failure incidence among men (5).

Acute Myocardial Infarction

Acute myocardial infarction leads to a cascade of adaptive mechanisms that promote left ventricular remodeling. Ventricular remodeling may continue for weeks or months until the distending forces are counterbalanced by the tensile strength of the collagen scar; this balance then determines the size, location, and transmurality of the infarct, the extent of myocardial stunning, ventricular loading conditions, and local trophic factors (29). Reperfusion therapy helps prevent infarct progression but is associated with the generation of reactive oxygen species, local inflammatory and oxidant response to reperfusion, and opening of the mitochondrial permeability transition pore that extends infarct size beyond that observed during equivalent periods of ischemia alone (30). Thus, reperfusion injury is a possible target for interventions to reduce myocardial damage.

Chronic Coronary Artery Disease

Ischemia caused by abnormalities in coronary arteries can produce increases in the concentration of neurohormones, for example, norepinephrine, epinephrine, endothelin, and dopamine, that results in myocardial apoptosis, fibrosis, and susceptibility to ventricular arrhythmias. Thus, ischemia contributes to the progression of left ventricular systolic dysfunction even in the absence of a manifest infarct event. Chronic ischemia can result in hibernation or stunning with further progressive decline in ventricular function. These adaptive–protective mechanisms may result in hypocontractile myocardium and contribute to left ventricular systolic dysfunction (31). Moreover, myocardial ischemia induces diastolic dysfunction through alteration of the myocardial passive compliance from scarring, fibrosis, and compensatory hypertrophy of noninfarcted myocardium (32).

Interventions

Prevention of coronary heart disease and ischemic events is essential to maintaining functional myocyte reserve. In patients with established coronary heart disease, a number of cardioprotective medications and procedures can prevent development of symptomatic heart failure in coronary heart disease. The combination of medications and lifestyle changes should be applied aggressively in all patients to reduce the risk of heart failure.

Revascularization

Mechanical (percutaneous or surgical) or pharmacological revascularization of the infarct-related artery reduces the size of the acute infarct and prevents subsequent heart failure (33) if performed early enough for myocardial salvage. In addition, the "open artery hypothesis" proposes that late reperfusion, beyond the window for myocardial salvage, also reduces left ventricular remodeling (34).

Angiotensin-Converting Enzyme Inhibitors

Angiotensin-converting enzyme inhibitors have favorable properties in reducing left ventricular stress and progression of left ventricle enlargement. Early ACEi therapy in acute infarction has been shown to reduce mortality and left ventricular dysfunction above that of aspirin, thrombolytics, and beta-adrenergic blocking agents alone. The Heart Outcomes Prevention Evaluation study demonstrated a 23% reduction in risk for heart failure by ramipril in individuals with established vascular disease (35), expanding the indication for angiotensin-converting enzyme inhibitor therapy to all patients with documented coronary heart disease, presumed coronary heart disease based on presence of other atherosclerotic vascular disease, or diabetes.

Angiotensin–Receptor Blockers

Angiotensin–receptor blockers are at least equally effective as angiotensin-converting enzyme inhibitors in reducing mortality in patients with myocardial infarction complicated by left ventricular dysfunction or heart failure (29). However, because the overall evidence for the effectiveness of angiotensin–receptor blockers on prevention and attenuation of postmyocardial infarction left ventricular remodeling is weaker compared with angiotensin-converting enzyme inhibitors, they may be limited to individuals who do not tolerate angiotensin-converting enzyme inhibitors.

Beta-Blockers

It is well established that beta-blockers are beneficial after acute myocardial infarction. Notably, long-term beta-blocker use is recommended for secondary prevention in patients at highest risk, for example, those with low ejection fraction or heart failure (36). The Reversal of Ventricular Remodeling with Toprol-XL (REVERT) trial provides further evidence that using beta-blockers to treat asymptomatic left ventricular

dysfunction effectively prevents development of heart failure and can reverse left ventricular remodeling (37).

Aldosterone Antagonists

Spironolactone combined with angiotensin-converting enzyme inhibitors ameliorates left ventricle remodeling after acute myocardial infarction (29). Aldosterone antagonists are recommended in myocardial infarction complicated by left ventricular dysfunction based on the decrease in mortality and cardiovascular hospitalizations seen in the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) (38).

Antiplatelet Agents

Aspirin in patients with established vascular disease has been demonstrated to reduce risk for cardiovascular events and heart failure and is recommended after acute myocardial infarction indefinitely if no contraindications exist (36).

Statins

Statins are of proven benefit in patients with coronary heart disease (31) but their usefulness in the setting of left ventricular dysfunction remains under investigation. Preprocedural treatment with a statin before percutaneous coronary intervention is associated with lower levels of periprocedural creatine kinase elevation, and chronic statin therapy before the onset of an acute event is associated with improved perfusion and reduced myocardial necrosis after intervention (29). Kjekshus et al. showed an 11% lower risk of new-onset heart failure in patients with stable coronary heart disease treated with statins (39).

SUMMARY

Considering the prevalence and worsening epidemiologic trends, costs of care, quality of life, and outcomes for heart failure patients, a focus on prevention is essential. This will require efforts ranging from advocacy to research. Population-level interventions at risk factor prevention and adoption of healthy lifestyle habits are necessary to promote cardiovascular health and reduce heart failure risk. The American Heart Association has now defined a 2020 goal that includes not only achieving reductions in mortality due to cardiovascular diseases, but improving the health of the population based on a comprehensive metric that includes multiple healthy lifestyle parameters. Whether treatment goals of heart failure risk factors should be individualized based on a cumulative risk profile still needs further study.

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Lama Al-Khoury, MD,
Hermelinda G. Abcede, MD,
Vivek Jain, MD,
and Mark Fisher, MD

Prevention of Ischemic Stroke

The incidence of new and recurrent stroke in the United States is 795,000 per year. Stroke is one of the leading causes of disability in adults and the 4th leading cause of mortality (1). Strokes can be either ischemic or hemorrhagic. Ischemic strokes occur in approximately 87% of all stroke patients while hemorrhagic strokes include primary intracerebral hemorrhage (10% of stroke patients) and subarachnoid hemorrhage (3% of stroke patients) (1). Our focus in this chapter will be on ischemic stroke, which may be due to one of the following mechanisms:

■ Atherosclerotic cerebrovascular disease: This constitutes approximately 20% of ischemic strokes (2,3). Extracranial atherosclerotic disease occurs most typically at the bifurcation of the internal carotid arteries, as well as the more proximal segments of vertebral arteries or in the aortic arch (which may produce embolism to the carotid or vertebral arterial system). Subclavian artery atherosclerotic disease proximal to the origin of the vertebral artery may cause subclavian steal syndrome and ischemic stroke in the vertebrobasilar system. The mechanism of stroke in atherosclerotic disease is either (a) cerebral hypoperfusion due to stenosis and reduced flow, with or without superimposed thrombosis of the vessel; or (b) embolism caused by atherosclerotic plaque rupture, or embolization of superimposed thrombus. Intracranial atherosclerotic disease can involve the anterior and posterior circulation arteries. The anterior circulation, supplying the majority of the two cerebral hemispheres, consists of the intracranial portions of the internal carotid arteries and its branches, the main branches being the middle cerebral and the anterior cerebral arteries on each side. The posterior circulation consists of the vertebral arteries, the basilar artery, and their branches. The posterior circulation supplies the brain stem and the cerebellum, as well as the posterior portion of the cerebral hemispheres and the thalamus bilaterally.

■ Small vessel (arterial) disease is the mechanism in approximately 25% of ischemic strokes (2,3). This is due to occlusion of small penetrating arteries and arterioles, typically arising from middle cerebral or basilar arteries. Acute occlusion of small arteries and arterioles (chronically affected by hypertension as well as diabetes and atherosclerosis) leads to small deep infarctions affecting basal ganglia, thalamus, internal capsule, pons, or subcortical white matter, and often is associated with lacunar syndromes. The latter include pure motor hemiparesis (ie, weakness without sensory loss) and pure sensory stroke (ie, sensory loss without weakness). Chronic injury to these small vessels can also lead to an acute rupture and an intracerebral hemorrhage (ICH).

■ Cardioembolic disease (approximately one-third of ischemic strokes):

- Embolism due to atrial fibrillation
- Embolism due to valvular heart disease such rheumatic valvular disease
- Embolism due to ischemic or dilated cardiomyopathy
- Septic embolism due to bacterial endocarditis
- Paradoxical embolism, in which a venous thrombus leads to cerebral embolism via a right-to-left shunt such as a patent foramen ovale (PFO).

- Atypical mechanisms (<5%):
  - Carotid or vertebral artery dissection with stroke caused by hypoperfusion or embolism
  - Cerebral venous thrombosis
  - Thrombophilia
  - Vasculitis (primary CNS vasculitis or systemic vasculitis with secondary CNS involvement)
  - Migraine-associated stroke
- Cryptogenic stroke: This is stroke without an identifiable underlying mechanism despite a thorough work-up. Prolonged cardiac monitoring may be beneficial in this subgroup of patients, in order to identify paroxysmal atrial fibrillation as a possible mechanism.

CLINICAL PRESENTATION

Patients with stroke present with acute (sudden) onset neurologic symptoms and signs, typically the following:

- Unilateral (hemiparesis) limb weakness
- Unilateral facial weakness
- Unilateral sensory impairment
- Difficulty expressing and/or understanding language (aphasia)
- Slurred speech or difficulty producing speech (dysarthria)
- Vision loss, unilateral or bilateral
- Vertigo (spinning sensation) usually combined with impaired balance
- Impaired limb coordination with clumsiness (limb ataxia)
- Double vision (diplopia)
- Confusion
- Altered level of consciousness
- Headache, variably present
- Seizure

PRIMARY AND SECONDARY STROKE PREVENTION

Primary and secondary stroke prevention starts by identifying risk factors for stroke. These risk factors may or may not be modifiable:

- **Nonmodifiable risk factors**:
  - **Age**: The risk of stroke doubles for each successive decade after the age of 55 years (4).
  - **Gender**: Lifetime risk of stroke is higher in women than in men (1of 5 women versus 1 out of 6 men). However, age-adjusted incidence of stroke is lower in women than men. For the age range 45 to 84 years, women have lower incidence of stroke than men; however, the opposite is true after the age of 85, when stroke incidence is higher in women (1).
  - **Race-Ethnicity**: African Americans and Hispanics have higher rates of all stroke types and higher mortality rates than whites (4).
  - **Genetics**: Positive family history increases stroke risk; specific conditions include thrombophilia and spontaneous arterial dissections.
- **Modifiable risk factors**:
  - **Hypertension**: Hypertension is one of the most important modifiable stroke risk factors. Even throughout normal blood pressure range, beginning at systolic pressure of 115 mmHg, higher blood pressure increases stroke risk. Many clinical studies have shown that pharmacologic treatment of hypertension reduces the risk of primary stroke, with a risk reduction of 32% to 42%. The benefits of antihypertensive treatment in primary stroke prevention have also been shown for the elderly (4). Antihypertensive treatment lowers the risk of recurrent stroke. Various clinical studies have shown benefit from different groups of antihypertensive agents in the primary prevention and secondary prevention; however, calcium channel antagonists appear to be particularly useful for long-term blood pressure management in stroke prevention and a target systolic blood pressure below 130 mmHg is reasonable for most patients (5,9). Of note, there is evidence that suggests benefit from antihypertensive treatment with angiotensin receptor blockers and angiotensin converting enzyme inhibitors in diabetic patients with microalbuminuria (4).
  - **Diabetes mellitus**: Diabetes mellitus independently increases vascular risk factors such as hypertension and dyslipidemia. The North Manhattan Study (NOMAS) showed that diabetic patients with fasting blood glucose >126 mg/dL had an increased risk of stroke compared to those with lower levels, and standard glycemic control of diabetes is appropriate for stroke prevention purposes. Note that clinical studies have shown no significant reduction of stroke for patients with intensive glycemic control compared to less intensive glycemic control regimens (4,10,11).
  - **Smoking:** Smoking is a major independent risk factor for stroke, doubling the risk when compared to nonsmokers. Smoking increases risk and progression of atherosclerosis and the risk includes active and passive smoking (environmental exposure to cigarette smoking). Cessation of smoking

and avoidance of environmental exposure to smoking should be recommended to patients. The risk of stroke decreases after cessation of smoking but does not fully normalize to nonsmoker levels (4,10).

- **Dyslipidemia**: Total cholesterol has generally been found to be associated with higher risk of ischemic stroke. There is a consistent association between elevated cholesterol levels and carotid artery atherosclerosis. In contrast, most studies have shown an increased association between lower cholesterol and increased risk of hemorrhagic stroke (ICH). The majority of epidemiological studies show an association between high HDL and lower incidence of stroke, and several studies have suggested that there is an increased risk of ischemic stroke in association with a high nonfasting triglyceride level. Treatment with statins reduces the risk of stroke in patients with atherosclerosis or with risk factors for atherosclerosis. Mechanisms by which statins help include their role in reducing LDL-C levels, reducing inflammatory changes in the atherosclerotic plaque, and antithrombotic effects. Higher dose statins have more pronounced effects on mechanisms other than cholesterol lowering. Nevertheless, stroke prevention correlates best with effectiveness in lowering lipid levels, and effectiveness is uncertain for stroke prevention with lipid lowering by agents other than statins. Treatment strategies with lipid reduction are based on ten year vascular risks (4,10,12–16). Lifestyle modifications and pharmacological therapy with statins for secondary prevention are discussed later in this chapter.

- **Carotid artery disease**:
  - **Severe symptomatic carotid stenosis (>70%)**: Multiple major randomized clinical trials showed significant benefit of carotid endarterectomy (CEA) in secondary stroke prevention in patients with severe internal carotid artery stenosis with ipsilateral ischemic stroke or transient ischemic attack (TIA). For mild <50% stenosis there was no benefit of CEA (17,18,4,10).
  - **Moderate symptomatic carotid stenosis**: Patients who have moderate degree of symptomatic stenosis (50%–69%) may benefit from CEA but the magnitude of benefit is less than for severe stenosis. To prevent one stroke over a five year follow-up, 15 patients would have to undergo CEA; therefore, benefits and risks should be carefully considered, making sure that estimated perioperative mortality and morbidity are <6% (10).
  - **Asymptomatic carotid artery stenosis >60%**: Although there is some benefit of CEA in reducing stroke in asymptomatic disease, the number of CEAs needed to treat is estimated at 40 cases in order to prevent one stroke over five years. Asymptomatic carotid stenosis has a more benign course than symptomatic disease. Therefore caution should be applied in these patients and each case should be individualized (4).
  - **Timing of CEA and patient selection**: Best benefit from CEA in stroke prevention is achieved when surgery is performed between day 2 to day 14 after occurrence of stroke or TIA. Moreover, additional recommendations include CEA in severe carotid stenosis diagnosed by noninvasive imaging in patients with TIA or ischemic stroke within the preceding 6 month period. The decision for CEA should be based on gender, age, and existent comorbidities. For example, women tend to have higher surgical mortality, less favorable outcome, and higher neurologic morbidity and recurrent carotid stenosis compared to men. Carotid artery stenting may be an alternative to CEA, performed in patients who are not surgical candidates due to inability to access severe symptomatic carotid stenosis, or when risk of surgery is high (4,10).
- **Atrial fibrillation**: Atrial fibrillation is associated with a 4- to 5-fold increased risk of ischemic stroke. Atrial fibrillation is estimated to be present in 2.3 million Americans. It accounts for 10% of all ischemic strokes and a higher proportion in the elderly. Mechanism of ischemic stroke is cerebral embolism from thrombi in the left atrial appendage. CHADS2 score assesses the risk of ischemic stroke in relation to atrial fibrillation, whether paroxysmal (excluding a single brief one episode of atrial fibrillation in relation to reversible cause) or persistent atrial fibrillation. Each of the most potent independent risk factors for stroke in atrial fibrillation is given a score: congestive heart failure ("C"), hypertension ("H"), age >75 years ("A"), presence of diabetes mellitus ("D"), and the presence of TIA or stroke ("S"), and then adding the numbers assigned to each risk factor (score of 1 for each of these risk factors except prior TIA or stroke which gets a 2 score) to obtain the CHADS2 score. CHADS2 score ≥ 2 reflects substantial risk for stroke (1.9%–7.6% per year) and should be treated with anticoagulation for either primary of secondary stroke prevention (4,10,19).
  - Treatment with adjusted dose warfarin provides 64% relative risk reduction against stroke if the anticoagulant is adequate (INR 2–3) and reduces all-cause mortality by 26%. Anticoagulation has also been found to reduce stroke severity and stroke mortality. Warfarin and newer anticoagulants have been approved for the prevention of stroke in nonvalvular atrial fibrillation. Each of the newer

agents has been compared head to head to warfarin in randomized placebo controlled blinded studies: dabigatran (thrombin inhibitor) versus warfarin; rivaroxaban (anti-factor Xa) versus warfarin; apixaban (anti-factor Xa) versus warfarin. These new agents are not inferior to warfarin in stroke prevention in atrial fibrillation, are associated with a smaller risk of ICH when compared to warfarin, but lack standard means for reversal of effects. Ongoing studies are addressing reversal agents. Warfarin, on the other hand, should be titrated to a goal INR of 2 to 3, which mandates frequent follow-up. The novel antithrombotic agents have a standard dose without a need to follow up with laboratory testing (4,10,19,24).

- To summarize, detection and screening for atrial fibrillation starts in the primary care setting. The decision for type of antithrombotic treatment is influenced by estimated risk of stroke in association with atrial fibrillation, bleeding risk during such therapy, and access to good monitoring of anticoagulation. This decision should be individualized to each patient. Anticoagulant treatment is superior to platelet therapy and is usually preferred for patients who have moderate to high risk of stroke based on CHADS2 score (≥2). Patients who have mild risk with CHADS2 of 0 or 1 may be placed on platelet treatment alone. Given the devastating nature of stroke due to atrial fibrillation, and the high preventability of these strokes with anticoagulation, strong preference for anticoagulation is advised for patients with CHADS2 scores of 2 or higher.

- **Other cardiac conditions**: Patent foramen ovale (PFO) is present in approximately 25% of the population. The potential mechanism of stroke in association with a PFO is paradoxical embolism from a venous source which traverses the PFO. If paradoxical embolism is shown to be the cause of a patient's stroke and with venous thrombus found in the presence of a PFO, anticoagulation should be initiated. In general, however, there is no advantage of anticoagulation when compared to platelet medications for patients with cryptogenic stroke and PFO. PFO closure in secondary stroke prevention remains of unproven value (4,10).
- **Lifestyle**: Reducing sodium intake generally lowers blood pressure, and it has been found that reducing sodium intake by approximately 1,000 mg per day reduces cardiovascular events by 30%. Accordingly the 2013 AHA/ACC lifestyle management guideline recommends consuming no more than 2,400 mg per day of sodium. LDL lowering may be established by a diet rich in vegetables, fruits, whole grains, low-fat dairy products, poultry, fish, legumes, nontropical vegetable oils, and nuts. Patients are recommended to restrict intake of sweets, sugar-sweetened beverages, and red meat. This may be achieved by either the DASH or AHA diets. Restriction of dietary saturated fat intake from 14% to 15% of calories to 5% to 6% of calories lowers both LDL and HDL, but is beneficial because the effect on LDL is greater. Reducing intake of *trans*-fatty acids is also important in lowering LDL-C. Physical activity has also been shown to lower blood pressure as well as lowering LDL-C. Adults are advised to engage in aerobic physical activity of 3 to 4 sessions a week lasting on average 40 minutes per session and with moderate to vigorous intensity physical activity (16).

PHARMACOLOGIC TREATMENT FOR SECONDARY STROKE PREVENTION

Antithrombotic Therapy in Cerebrovascular Disease

The role of antithrombotic treatment in stroke prevention is mainly in secondary prevention. The approved antiplatelet treatments for secondary prevention of stroke are the following:

1. Aspirin: The relative risk reduction of stroke has been shown to be 15% when aspirin is used in secondary prevention of stroke, with the magnitude of benefit similar at dose range between 50 and 1,500 mg dose. There is a higher risk of GI bleeding and hemorrhagic stroke with higher doses of aspirin, so it is sufficient to use a lower dose of aspirin such as 81 mg daily (10).
2. The combination of aspirin and extended-release dipyridamole, 25mg/200mg twice a day has been shown to be at least as effective if not more effective than aspirin alone in secondary stroke prevention. Dipyridamole inhibits phosphodiesterase and augments prostacyclin-related platelet aggregation inhibition (10).
3. Clopidogrel: Clopidogrel is as effective as the combination of extended-release dipyridamole 200mg/aspirin 25mg BID treatment. The risk of gastrointestinal bleeding tends to be less with clopidogrel compared to aspirin treatments (10).

There are novel platelet agents being investigated in secondary prevention of stroke such as cilostazol and ticagrelor. Choice of platelet treatment depends on patient characteristics including tolerance of specific agents or comorbid illness. Side

effects of gastrointestinal upset and headache with dipyridamole/aspirin combination will sway the treatment to either aspirin or clopidogrel. Acute coronary syndromes or peripheral vascular disease/stent may justify combination aspirin plus clopidogrel (10).

Statin Therapy

Statin therapy is indicated for secondary stroke prevention using intensive lipid-lowering dose of statin and targeting LDL level <70 mg/dL or absolute reduction of LDL< 50% of baseline value (5). Recommendation is periodic laboratory testing with liver and muscle enzymes to screen for potential statin side effects (10).

Additional Risk Factors Applicable to Women

Recently released stroke prevention guidelines in women highlighted some gender differences in risks for stroke that apply to women. In childbearing ages, prepregnancy hypertension increases the risk of preeclampsia or eclampsia and the risk of stroke during pregnancy. Pregnancy in itself is associated with a higher risk of stroke. Moreover, there is an increased risk of stroke and cardiovascular disease in patients with pregnancy-related complications including preeclampsia/eclampsia, gestational diabetes, and gestational hypertension. Treatment of pregnancy-related hypertension should be implemented with antihypertensive agents that appear to be safe during pregnancy such as alpha-methyldopa, calcium channel blockers, and thiazide diuretics. Although some beta-blockers (especially atenolol) may be associated with fetal growth restriction, pindolol and metoprolol appear to be safe. Women with chronic primary or secondary hypertension and women with previous pregnancy-related hypertension should be started on low-dose aspirin from the 12th week of gestation owing to higher risk of stroke and cardiovascular disease. Additional risk factors that apply to women include migraine with aura, which has been found to be an independent risk of stroke in women, as well as oral contraceptives. When those two risk factors coexist with smoking (three risk factors) the risk of stroke in women increases by at least seven-fold (25).

Other Modifiable Risk Factors

Heavy alcohol use may elevate stroke risk, and patients should be advised to reduce alcohol use to a drink or less per day for women and to two or less drinks for men. Illicit drug use can increase risk of ischemic and hemorrhagic strokes, and abstinence is recommended. Obstructive sleep apnea is common in stroke patients, and treatment may improve stroke outcome and should be implemented. Obesity and metabolic syndrome may pose a risk for stroke, and dietary modification and exercise are critical (4,10).

SUMMARY

Primary stroke prevention should be emphasized to patients and starts at the level of primary care, focusing on presence of modifiable and nonmodifiable risk factors. Education of patients at risk for stroke includes alerting them to signs and symptoms of stroke, and addressing risk factors including lifestyle and dietary changes, abstinence from smoking, and the importance of implementing an exercise program and reducing obesity. A vascular neurologist should be consulted for secondary prevention and as needed for primary prevention. Patients should be instructed to monitor blood pressure at home and to be compliant with medications.

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Maya J. Salameh, MD and
Elizabeth V. Ratchford, MD

Peripheral Artery Disease

Peripheral artery disease (PAD) is an arterial occlusive syndrome of the lower extremity arteries most commonly caused by atherosclerosis. The arterial lumen becomes progressively obstructed by plaque, leading to reduced blood flow to the lower extremities. Given the systemic nature of atherosclerosis, PAD is associated with an increased risk of cardiovascular events including myocardial infarction and stroke. PAD can also result in a significant reduction in functional status, impaired quality of life, and increased risk of limb loss. This chapter outlines the causes, epidemiology and natural history, diagnostic approach, and treatment of PAD.

EPIDEMIOLOGY

The most common cause of peripheral artery disease (PAD) is atherosclerosis, which is a systemic process characterized by inflammation and changes in endothelial cells lining the vessel walls. The arterial lumen eventually becomes obstructed by plaque, leading to reduced blood flow to the lower extremities.

Nonatherosclerotic causes of PAD are uncommon and include the following:

- Vasculitis
- Fibromuscular dysplasia (FMD)
- Thromboangiitis obliterans (Buerger's disease)
- Cystic adventitial disease
- Popliteal entrapment syndrome
- Endofibrosis

Risk factors for PAD are similar to those previously identified for atherosclerosis. Nonmodifiable risk factors include:

- Age: The prevalence of PAD increases in older age groups. The National Health and Nutrition Examination Survey (NHANES) demonstrated a PAD prevalence of 14.5% in those aged 70 or older, as compared to 4.3% in the overall population aged 40 or older (1).
- Gender: PAD affects both men and women equally in older age groups.
- Race-Ethnicity: The prevalence of PAD in non-Hispanic blacks is as high as 7.9%, compared to 4.4% in non-Hispanic whites (1).

Modifiable risk factors for PAD are as follows:

- Smoking
  - More than 80% of PAD patients are current or former smokers (2). Smoking is more strongly associated with PAD than with coronary artery disease (3).
- Diabetes
  - Diabetes is associated with a fourfold increase in the risk for PAD (4). Patients with both diabetes and PAD are at increased risk for lower extremity amputation.
- Hypertension
- Dyslipidemia

- Chronic kidney disease
- Hyperhomocysteinemia
- Elevated C-reactive protein

The reported PAD prevalence depends on the selected population as well as diagnostic methods used to detect PAD. The prevalence could be underestimated if PAD is assessed by symptoms alone, whereas use of the ankle-brachial index (ABI) increases detection of PAD by 2 to 7 times (5). Current epidemiologic projections estimate that PAD (as defined by ABI < 0.9) affects up to 21% of those 65 or older (7). In higher risk populations, the prevalence of PAD may be as high as 30% (8).

NATURAL HISTORY

Cardiovascular Outcomes

Due to the systemic nature of atherosclerosis, PAD patients are at risk for polyvascular disease. Multiple studies have shown that PAD overlaps with disease in other vascular beds. For example, the Reduction of Atherothrombosis for Continued Health (REACH) international registry revealed that 63% of patients with PAD have concomitant symptomatic cerebrovascular or coronary disease (9).

Accordingly, PAD patients are at significantly increased risk for myocardial infarction, stroke, and vascular death over a 5-year period compared to age-matched cohorts. The 5-year mortality for PAD patients is as high as 15% to 30% with greater than 75% attributable to cardiovascular causes (10). Medial calcification, or incompressible arteries, common in the elderly and in patients with long-standing diabetes or chronic kidney disease, may also be associated with higher cardiovascular risk (11). Findings from two other landmark prospective studies are summarized below:

- PAD (defined by an ABI <0.9) is associated with a sixfold increase in the risk of cardiovascular death at 10 years compared to the general population (12).
- PAD is associated with a two- to threefold increase in the risk of ischemic stroke (13).
- When combined with the Framingham Risk Score (FRS), an ABI ≤0.9 is associated with a twofold increased risk of cardiovascular events, cardiovascular mortality, and overall mortality across all FRS categories (14).
- Higher mortality and event rates in subjects with ABI 0.91 to 1.10 have also been observed compared to those with ABI 1.11 to 1.40. However, the risk remains less than in those with ABI ≤0.9 (14).

Limb Prognosis

PAD patients who are asymptomatic at baseline will likely experience a degree of functional decline over time. Studies have demonstrated a decline in walking performance over 2 years compared to patients without PAD (15).

For the majority of PAD patients presenting with intermittent claudication, limb symptoms gradually stabilize over time. Only 10% to 20% of patients will experience worsening claudication and a small minority (<2%) will progress to critical limb ischemia (CLI) (10).

CLINICAL MANIFESTATIONS

History

PAD patients present with a variable range of symptoms as shown in Table 24.1. The spectrum includes patients who are asymptomatic or who have atypical leg pain. Only a minority of PAD patients present with classic claudication or critical limb ischemia.

Intermittent claudication is defined as a reproducible pain in the lower extremity muscle groups brought on by exertion and relieved by rest. Blood flow at rest is typically adequate but becomes

TABLE 24.1 Range of Symptoms in Patients with PAD

Asymptomatic
- Some degree of functional impairment usually present.

Intermittent Claudication
- Lower extremity symptoms brought on by exertion and relieved with rest.
- Pain, cramping, fatigue, or heaviness in lower extremity muscle groups.
  - Hip/buttock/thigh pain may indicate aortoiliac disease.
  - Calf pain usually suggests femoral–popliteal disease.

Atypical Leg Pain
- Comorbidities may mask classic claudication symptoms.
  - Neuropathy, osteoarthritis, or spinal stenosis.
- Consider PAD diagnosis if patients are at risk.

Critical Limb Ischemia (CLI)
- Pain at rest that improves when limb is in dependent position.
- Tissue loss.
- Ulcers.
- Gangrene.

insufficient during exercise to meet the increased metabolic demand. Symptoms may include the following:

- Cramping
- Fatigue
- Heaviness
- Weakness

Identifying the affected muscle groups may help in localizing the affected arterial segments.

- Hip, buttock, or thigh pain may indicate aortoiliac disease.
- Calf pain is usually associated with disease in femoral–popliteal segment.

Although intermittent claudication is considered the traditional symptom of PAD, its prevalence remains low among PAD patients. Relying on classic claudication alone for the diagnosis will result in missing a majority of cases (8). A significant number of patients with PAD instead present with atypical leg pain. This observation may be related to the multiple comorbidities often seen in PAD patients, including arthritis, neuropathy, and spinal stenosis, which may mask the symptoms of classic claudication (16). Therefore, PAD should always remain in the differential when assessing patients with atypical leg symptoms who have risk factors for atherosclerosis.

Many patients with PAD are classified as "asymptomatic," but some degree of functional impairment is almost always present. Decreased functional status has been objectively observed in patients with PAD who report no lower extremity symptoms with exertion (16).

Critical limb ischemia occurs when severely compromised arterial flow is insufficient for tissue viability. It usually presents as pain at rest in the forefoot or distal lower extremity which may improve with dependency. Tissue loss, ulcers, and gangrene may develop. If untreated, CLI often results in major limb amputation within 6 months (10).

Acute limb ischemia (ALI) refers to a sudden deterioration in limb perfusion usually due to acute embolism or thrombosis. The common presentation of ALI is manifested by the five Ps of pain, pallor, paresthesias, pulselessness, and poikilothermia. ALI is associated with high mortality and risk of limb loss and should be treated emergently.

Physical Examination

The vascular physical examination should include bilateral arm pressures to screen for subclavian artery disease. A differential of greater than 15 mmHg between the brachial pressures should prompt further investigation for subclavian stenosis.

A thorough examination of the feet and lower extremities is essential. Common skin findings in PAD patients include abnormal color or pallor, hair loss on legs, atrophic nail changes, or the presence of ulcers, cellulitis, or gangrene. Ulcers due to arterial insufficiency are usually painful and located on the toes or lateral malleolus.

A complete arterial examination, including palpation of pulses, arterial signal assessment, and auscultation for bruits should be performed as summarized in Table 24.2.

TABLE 24.2 Arterial Examination in Patients with Suspected PAD

Femoral Artery
• Palpated inferior to the inguinal ligament.
• Absent pulse may indicate disease of distal aorta and/or iliac arteries.
Popliteal Artery
• Palpated in the popliteal fossa behind the knee.
• Absent pulse may indicate proximal stenosis.
• Prominent pulse may suggest popliteal artery aneurysm.
Posterior Tibial Artery
• Palpated posterior to the medial malleolus.
Anterior Tibial/Dorsalis Pedis Artery
• Palpated on the dorsum of the foot.
Arterial Signal Assessment
• Requires a handheld Doppler device and acoustic gel.
• Normal signal is triphasic.
• Altered signal (biphasic or monophasic) suggests disease in proximal arterial segment.
Auscultation for Bruits
• Carotid, subclavian, iliac, femoral, and popliteal arteries.
• Presence of bruit may indicate disease or stenosis.
• Presence of femoral bruit significantly increases likelihood of PAD but absence does not affect probability that PAD is present (17).

DIAGNOSTIC METHODS

Ankle-Brachial Index

The ankle-brachial index is the most effective screening test for PAD. It is easily performed in the office or in the vascular laboratory. The ABI is defined as the ratio of

the higher ankle systolic pressure to the higher brachial systolic pressure. An ABI <0.9 considered up to 95% sensitive and 99% specific for angiographically confirmed lower extremity arterial disease (18).

The following summarizes the technique for obtaining an ABI measurement:

- Have the patient lie supine for at least 5 to 10 minutes.
- Measure pressures at the bilateral brachial, posterior tibial, and dorsalis pedis arteries.
  - Appropriate size sphygmomanometer cuffs should be used (10–12 cm).
  - A hand-held 5 or 10-MHz Doppler probe with acoustic gel is used to detect the arterial signal.
- Calculation
  - Divide the higher of the two ankle pressures in each leg by the higher of the two brachial pressures.
- ABI range
  - Normal: 1.0 to 1.4 (19)
  - Mild: 0.7 to 0.90
  - Moderate: 0.4 to 0.69
  - Severe: <0.4
  - Borderline or indeterminate: 0.91 to 0.99
  - Incompressible vessels: >1.4

The ABI has several limitations. Medial calcification (incompressible vessels) can lead to a falsely high ABI or an inability to occlude the arterial signal. In the case of aortoiliac disease with collaterals, the ABI may be normal at rest and only become abnormal with exercise. If there is high clinical suspicion for PAD and the resting ABI is normal, postexercise ABIs should be obtained. This exam is performed on a treadmill at 1.5 to 2 mph at a 12% grade for a maximum of 5 minutes, with the goal of reproducing the claudication symptoms. A 15% to 20% drop in the ABI after exercise is considered diagnostic of PAD (20).

Table 24.3 summarizes the clinical indications for diagnostic ABI testing. Screening ABIs may be considered for cardiovascular risk assessment in asymptomatic adults at intermediate risk (21,14).

TABLE 24.3 Clinical Indications for Diagnostic ABI Testing

Exertional leg symptoms in high-risk patients • Age ≥65 or • Age ≥50 with a history of smoking and/or diabetes
Resting pain suspected to be ischemic in etiology.
Nonhealing lower extremity ulcers.

Noninvasive Physiologic Testing

Physiologic testing of the lower extremity arteries, available only in the vascular laboratory, provides additional information regarding the location and severity of disease. In addition to the ABI, physiologic testing also includes the following three components (see Figure 24.1):

- Segmental limb pressures: measured using sphygmomanometer cuffs at the thighs, calves, and ankles
- Pulse Volume Recordings (PVRs): obtained using plethysmography
  - Transient volume change after cuff inflation to 65 mmHg is translated into pulsatile waveform
  - Waveform morphology indicates disease severity
  - Especially useful when ABI is falsely elevated due to calcified vessels
- Toe Pressures: measured using photoplethysmography
  - Useful to predict wound healing potential
  - The toe-brachial index (TBI) can be useful when the ABI is unreliable due to medial calcification (10)

Duplex Ultrasonography

Duplex ultrasonography serves as an adjunct to physiologic testing. It is relatively inexpensive and readily available, but it is operator dependent. Ultrasonography can help determine the presence and location of lower extremity arterial stenoses or occlusions and is useful to assess the patency of arterial stents and bypass grafts (10).

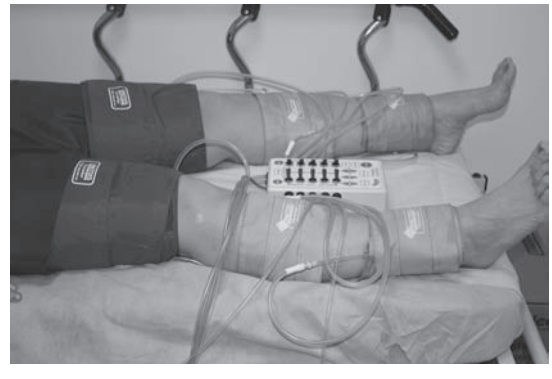

FIGURE 24.1A Arterial noninvasive flow studies. Segmental pressures are measured using sphygmomanometer cuffs at the thigh, calf, and ankle levels. Pulse volume recordings employ plethysmography, a technique whereby each cuff is inflated up to 65 mmHg and the transient change in volume beneath the cuff is translated into a pulsatile waveform.

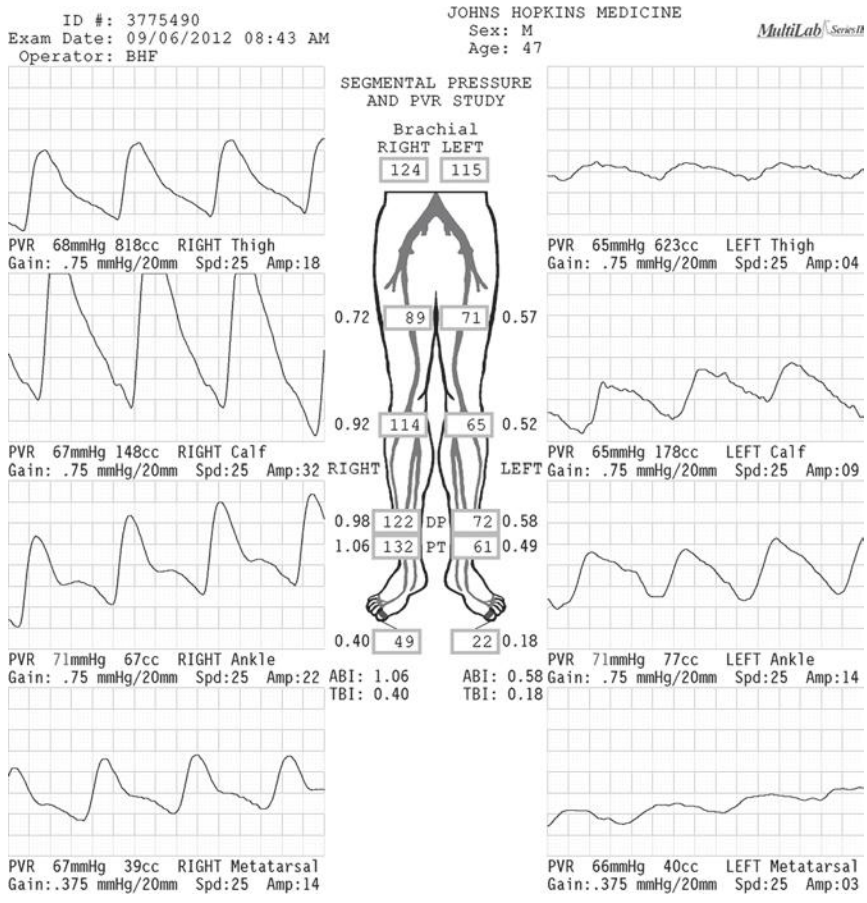

FIGURE 24.1B Abnormal arterial noninvasive flow studies. Segmental pressures and pulse volume recordings suggest moderate iliofemoral disease on the left.

Computed Tomographic Angiography

Computed tomographic angiography (CTA) is useful for visualization of inflow disease, bypass grafts, and arterial stents. It is relatively inexpensive but major disadvantages include radiation exposure and the need for intravenous contrast administration, a particular concern in patients with chronic kidney disease.

Magnetic Resonance Angiography

Magnetic resonance angiography (MRA) is considered comparable to CTA for inflow and surgical bypass evaluation. It is also particularly useful for visualization of runoff vessels. No ionizing radiation exposure is an advantage but drawbacks include cost, inadequate assessment of peripheral stents due to artifact, and contraindications in patients with pacemakers and defibrillators. Furthermore, the risk of nephrogenic systemic fibrosis limits use of MRA with gadolinium for patients with stage 4 or 5 chronic kidney disease.

Digital-Subtraction Angiography

As shown in Figure 24.2, digital-subtraction angiography (DSA) remains the gold standard for lower extremity arterial imaging. A major advantage is the opportunity for revascularization during the diagnostic procedure. However, due to high cost, contrast toxicity, and possible complications resulting from arterial puncture, DSA should not be used as a routine diagnostic method for PAD. Rather it should be reserved for planned revascularization once the PAD diagnosis has been established and the patient has met criteria for endovascular treatment.

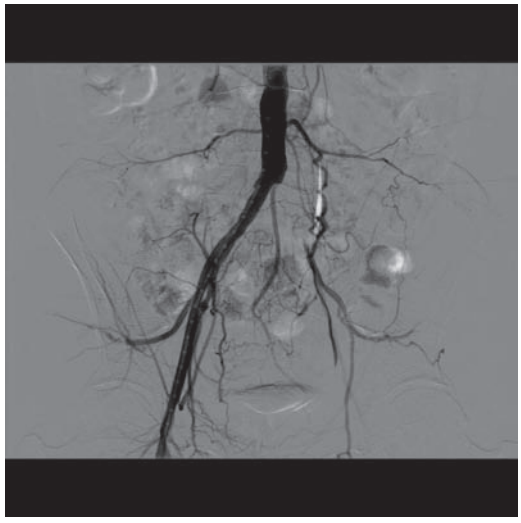

FIGURE 24.2 Abnormal angiogram of the same patient featured in Figure 24.1b. This image shows that the left common iliac and external iliac arteries are occluded.

TREATMENT

The treatment of PAD should focus on cardiovascular risk reduction and improving functional status and quality of life.

Cardiovascular Risk Reduction

Atherosclerosis is a systemic process. Therefore, patients with PAD are at increased risk for vascular events including myocardial infarction and stroke. Reducing this cardiovascular risk is central to the medical management of PAD.

Smoking is the most important modifiable PAD risk factor. In PAD patients who are current smokers, smoking cessation decreases the risk of future cardiovascular events and reduces progression to CLI (22). Conversely, in PAD patients who continue to smoke, the 10-year mortality is as high as 40% to 50%, with the majority of deaths due to cardiovascular events. The approach to smoking cessation in the vascular patient should include education, counseling, and pharmacologic therapy, as no other health intervention offers such a large potential benefit (23). Options for pharmacologic therapy for smoking cessation include:

- Nicotine-replacement therapy including the patch, gum, nasal spray, or inhaler
- Bupropion HCL
- Varenicline

Among these, varenicline is the most effective although patients must be counseled regarding the potential psychiatric side effects (23).

Diabetes is a major risk factor for PAD and increases the risk of lower extremity complications such as CLI and ulcerations. Current guidelines suggest targeting HbA1C to less than 7% in PAD patients to reduce microvascular complications and possibly to improve cardiovascular outcomes (10). Meticulous foot care is essential.

Treatment of dyslipidemia with statins reduces the risk of myocardial infarction, stroke, and vascular death in patients with PAD. Some small studies also suggest statins may improve PAD symptoms.

- The Heart Protection Study found a 22% relative risk reduction at 5 years in PAD patients treated with 40 mg of simvastatin versus placebo (24). Based on this study, statins should be prescribed for PAD patients with a baseline LDL cholesterol level of ≥100 mg/dL (10).
- Treatment of dyslipidemia should be based on the recent ACC/AHA guidelines in which PAD is considered an atherosclerotic cardiovascular disease equivalent (25).
  - For age ≤75, high-intensity statin therapy is recommended, with the goal of lowering LDL-C by ≥50%.
  - For age >75 or for those patients intolerant of high-intensity statin therapy, moderate-intensity statin therapy is recommended, with the goal of lowering LDL-C by approximately 30% to 50%.

Blood pressure control is a key component of cardiovascular risk reduction in PAD patients. The exact target for treatment of hypertension among patients with cardiovascular disease is controversial.

- The target blood pressure should be <140/90 mmHg in patients with PAD (10), including those with concomitant diabetes or chronic kidney disease (26).
- Recent hypertension management guidelines recommend a target BP of <150/90 mmHg for the general population aged 60 years or older (26).
- Current data suggest that angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin receptor blockers (ARBs) may reduce the risk of cardiovascular events in patients with PAD beyond that expected from blood pressure control alone (27,28).

Antiplatelet therapy is prescribed in PAD patients with the goal of reducing the risk of stroke, myocardial infarction, and vascular death.

- Data are derived from Antiplatelet Trialists' Collaboration (29), which was a meta-analysis of 287 studies of antiplatelet agents. The PAD subgroup included 9,214 patients. There was a 22% odds

reduction for adverse cardiovascular events in PAD patients treated with antiplatelet therapy.

- Aspirin in daily doses of 75 mg to 325 mg is recommended (10).
- Clopidogrel 75 mg daily is an effective alternative to aspirin based on the CAPRIE trial (30), in which 19,185 patients with recent myocardial infarction, stroke, or PAD were randomized to clopidogrel 75 mg daily versus aspirin 325 mg daily. In the PAD subgroup (6,452 patients), there was a 23.8% relative risk reduction for vascular events with clopidogrel as compared to aspirin.
- Current data do not support dual antiplatelet therapy (both aspirin and clopidogrel) for patients with PAD.

Functional Status and Quality of Life

Symptoms can range from mildly disabling claudication to severe lifestyle-limiting pain, resulting in decreased functional status and quality of life. For over 50 years, supervised exercise therapy has been well-established as an effective treatment for claudication. Supervised exercise is thus recommended as first-line treatment (10).

- A meta-analysis of 21 randomized and nonrandomized studies revealed a 179% increase in pain-free walking distance and 122% increase in maximum walking distance with supervised exercise compared to placebo (31).
- Supervised exercise is generally considered superior to unsupervised exercise in terms of improving claudication symptoms (32).
- In the recent CLEVER trial (which included 111 patients with symptomatic aortoiliac disease), supervised exercise resulted in superior treadmill walking performance as compared to endovascular therapy (33).

Pharmacologic options for treating claudication symptoms include pentoxifylline and cilostazol. Pentoxifylline is only marginally effective and not typically recommended. Cilostazol (100 mg twice daily) is a phosphodiesterase type 3 inhibitor, but its precise mechanism of action in improving claudication symptoms is unknown.

- Cilostazol inhibits vascular smooth muscle cell proliferation and platelet aggregation and causes vasodilation (22).
- It improves pain-free and maximal walking distance by 40% to 60% compared with placebo based on 5 randomized trials. Side effects are common and include headache, diarrhea, dizziness, and palpitations.
- Cilostazol is contraindicated in heart failure due to the increased mortality observed with oral phosphodiesterase type 3 inhibitors such as milrinone.

Revascularization (endovascular or surgical) should be reserved only for selected cases and the following criteria should be met:

- Response to exercise therapy and/or pharmacologic therapy for at least 3 months has been inadequate to improve symptoms.
- The patient reports a lifestyle-limiting disability due to claudication. Other comorbid conditions that would otherwise limit the patient's functional capacity have been considered.
- The vascular anatomy has been evaluated and considered suitable for intervention with a favorable risk/benefit ratio.

Endovascular treatment is preferred as first-line invasive treatment for short segment (3 cm or less) lesions in the iliac or femoral–popliteal segments. Endovascular patency rates are lower for more distal lesions or for long-segment occlusions, multiple tandem lesions, or poor run-off (10). Surgical treatment is not often performed for claudication but is preferred over endovascular treatment in the case of long-segment occlusions or more distal lesions.

SUMMARY

PAD is highly prevalent and associated with significant cardiovascular morbidity and mortality. PAD patients can present with a range of symptoms including atypical leg pain, intermittent claudication, or critical limb ischemia. However, a significant number of PAD patients may appear asymptomatic, highlighting the importance of maintaining a high index of suspicion in at-risk patients. The diagnostic approach to PAD begins with an ankle-brachial index. Several noninvasive complementary modalities are also readily available in the vascular laboratory. A central component of the medical management of PAD is cardiovascular risk reduction. Supervised exercise training plays a critical role in improving the functional status of patients with PAD. In parallel, endovascular revascularization may be considered in selected patients with lifestyle-limiting symptoms. Comprehensive care of the PAD patient should focus on reducing cardiovascular morbidity and mortality and improving quality of life.

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Seth J. Baum MD, FACC, FAHA, FACPM, FNLA

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Alternative and Complementary Medical Approaches

Complementary and alternative medicine (CAM), also known as integrative medicine, is a group of diverse medical and health care systems, practices, and products that are not presently considered to be part of conventional medicine. Approximately 40% of Americans use CAM, mostly incorporating complementary treatments in conjunction with ordinary care. Therapeutic lifestyle changes are the foundation of many CAM practices. Systems such as Tai Chi, Qi Gong, and Ayurveda emphasize optimal diets, regular exercise, maintenance of optimal weight, and reducing emotional stress. Although some clinical trials have been done involving CAM, evidence is still limited. CAM is now organized mainly into two categories: natural products and mind and body practices. Patient-centered medicine focuses on the patient, the particular needs, concerns, beliefs, and values that each of us has when put in the position of a patient. CAM represents the essence of patient-centered medicine as it permits patients and doctors to consider all reasonable options in averting disease and maintaining health.

BACKGROUND

Complementary and alternative medicine (CAM), as defined by the National Center for Complementary and Alternative Medicine (NCCAM), a branch of the National Institutes of Health (NIH), is a group of diverse medical and health care systems, practices, and products that are not presently considered to be part of conventional medicine. Complementary approaches are used in conjunction with standard care whereas alternative approaches are used in place of approved therapies. Approximately 40% of Americans use CAM, mostly incorporating complementary treatments in conjunction with ordinary care. This practice can also be referred to as integrative medicine.

The notion of prevention, averting a potential clinical event, introduces an uncertainty that is amenable to nontraditional possibilities. We perform a risk–benefit analysis, the basis of all clinical decision making, which is the source of therapeutic recommendations. The core of cardiovascular disease (CVD) prevention is therapeutic lifestyle changes (TLC). TLC is also the foundation of many CAM practices. Systems such as Tai Chi, Qi Gong, and Ayurveda emphasize optimal diets, regular exercise, maintenance of optimal weight, and reducing emotional stress. Although some clinical trials have been done in this realm, the evidence for most CAM disciplines is sparse. Yet, the placebo effect is particularly powerful in CAM (as such practices often address continuous variables such as pain, anxiety, insomnia, and blood pressure). Consequently many university and nonuniversity hospital settings have already incorporated such practices into their standard of care, further blurring the line between CAM and allopathic (or Western) medicine.

CAM is clearly a broad-based definition and one that is therefore constantly in flux. In fact, the arena has changed markedly and although NCCAM divided CAM into five categories in 2007, it now uses only two: natural products and mind and body practices. Some overlap exists between these groups, and consequently assorted disciplines such as Ayurveda and traditional Chinese medicine, for example, do not fit neatly within one group or another. This chapter assesses CAM within the current NCCAM framework. Furthermore, the chapter addresses only the most prevalent of these modalities.

BIOLOGICALLY BASED THERAPIES

Vitamins, minerals, herbs, and dietary advice are the salient biologically based therapies. Dietary advice, however, demands a special place in this section. The frequency and variety of the continuous flow of new diets reflect the elusiveness of the optimal approach.

The 2013 PREDIMED trial demonstrated an approximate 30% CVD event risk reduction with the Mediterranean diet in two groups of patients: high olive oil and high nut consumption (1). Additionally, a review of primitive cultures' diet disparities has demonstrated that in a wide array of diets—from nearly pure protein/fat to vegan—it is the body mass index (BMI) that appears to track best with CVD (2). Cultures with average BMIs <25 have a lower rate of CVD regardless of the dietary constituents.

Below are some basic "food rules" that we should all know and implement in our management of patients.

1. All food is composed of carbohydrate, fat, or protein. In nature, food comes principally in two varieties: predominantly carbohydrate or fat/protein. Vegetables such as broccoli, cauliflower, spinach, and brussels sprouts comprise nearly pure carbohydrate. Chicken, fish, meat, and tree nuts contain chiefly fats and proteins. The latter group contains very little carbohydrate. Our bodies store only about 3,500 calories as carbohydrate. Foods found in nature do not contain a "balanced blend" of all three macromolecules: carbohydrates, proteins, and fat.

2. There has been great emphasis made of the types of carbohydrates we eat, that is, whether they are simple or complex. This issue is best reflected by the glycemic index (GI) and load (GL), metrics that tell us how fast a carbohydrate-containing food is absorbed and assimilated by our bodies. The faster a carbohydrate is absorbed, the more it raises our blood sugar and insulin levels (high GI) and the more efficiently it is then converted into fat for storage. The GI considers a single gram of carbohydrate in a given food, whereas GL reflects the total quantity of carbohydrate in a portion of food.

3. When weight loss is required, GI and GL are relevant. The following is a useful website that provides information regarding the glycemic characteristics of a variety of foods: http://www.health.harvard.edu/newsweek/Glycemic_index_and_glycemic_load_for_100_foods.htm. Three critical points can be made: (1) when trying to help patients maintain a healthful weight, foods with a low GI and GL are recommended; (2) naturally occurring carbohydrates are often healthful. Those in vegetables are satisfactory whereas those in fruits (e.g., fructose) might be detrimental to the metabolically challenged, such as patients with diabetes mellitus, central obesity, high triglycerides, low HDL-C, high apoB, and metabolic syndrome. Fruit juices, stripped of their healthful fiber content, possess high GI and GL and are generally not healthful; and (3) human beings have the capacity to build all the carbohydrates we require and, thus, there are no "essential" carbohydrates.

4. Proteins are built from amino acids of which about half cannot be produced by our bodies and are therefore considered to be *essential*. "Essential" means they must be consumed to sustain life. The best proteins are the most complete because they contain a comprehensive array of all the essential and nonessential amino acids. Egg protein and whey protein are complete; they are the optimal sources for our patients.

5. The preferred grading scale for protein quality is the Protein Digestibility Corrected Amino Acids Score (PDCAAS). A PDCAAS of 1.0 is optimal and anything less than 1.0 is incomplete. Both whey and egg have a PDCAAS of 1.0. The practicing clinician should understand several issues relating to protein consumption. Too much protein can potentially be problematic in medical conditions such as osteoporosis, chronic kidney disease (CKD), and kidney stone formers. The optimal daily intake is considered to be between 0.8 and 1.2 grams/kg of body weight. Protein powders, collagen, and vegetable sources of protein typically have low PDCAAS scores unless they have been "enriched." Because natural food is composed of either carbohydrate or protein/fat, consumption of proteins found in their natural form means there is also consumption of fats.

6. Fats are the third macromolecule in food, and as in the case of proteins (but not carbohydrates), some fats are "essential." It is imperative to distinguish the fats on the basis of their saturation levels. Saturated fats have no double bonds (they are saturated with hydrogen atoms) and they are solid at room temperature. Monounsaturated fats have one double bond (oleic acid prevalent in olive and canola oil is

the best known). Polyunsaturated fats (PUFAs) have more than one double bond and there are multiple examples in nature. The two most important families of PUFAs are the omega-3s and omega-6s. In some respects these two groups of fatty acids compete with each other. The omega-6s tend to promote inflammation and thrombosis, whereas the omega-3s have the opposite tendency. We all need both omega-6s and omega-3s; it's their optimal respective contributions in our diet that remain a source of debate.

7. Linoleic acid (LA) and alpha linolenic acid (ALA) are both essential; we must consume them because we cannot make them. LA is the fundamental omega-6 found in nuts, seeds, vegetables, and the gamut of commercially prepared foods, and ALA is the vital omega-3 found in nuts and seeds, as well as flax and chia. Each of these fatty acids is the purported precursor for longer chain, more highly unsaturated fatty acids in the omega-6 and omega-3 families, respectively. Recently it was recognized that because of the somewhat artificial nature of our modern Western diet, people now lack the ability to effectively convert ALA to two other indispensable omega-3s, EPA and DHA. As EPA and DHA are critical for life, many of us now consider them to be "essential" as well. And so, a side effect of our modern diet mandates us to consume fatty fish or fish oil pills to be "optimally" healthy. In consideration of this, the American Heart Association (AHA) recommends 1,000 mg daily of combined EPA and DHA for people with manifest cardiovascular disease (CVD). As EPA and DHA have important roles in anti-inflammation, they have also been examined and utilized in treating many inflammatory disorders, some of which (e.g., lupus, psoriasis) are now considered to be risk factors for CVD, another inflammatory disease. Consequently, some practitioners recommend high doses of combined EPA and DHA hoping to thwart CVD events. To date this practice has not been studied adequately and therefore remains strictly "alternative." N.B. Although these fatty acids have an antithrombotic effect, at daily doses less than 6 grams they have not been shown to cause an increased risk of bleeding (even in association with anticoagulants and antiplatelet agents).

Dietary Takeaways

1. Eat a balanced natural diet as free from processed foods as possible.

2. Avoid fad diets.

3. For patients already at optimal weight, there is no need to limit calories, but they should be encouraged to consume fatty fish.

4. For patients who need to lose weight, limit their simple carbohydrates and restrict their calories. Portion control is fundamental. Have them consume multiple small meals daily.

5. For metabolically challenged patients, the limitation of sugar and simple carbohydrates is paramount.

6. Use the glycemic index and glycemic load chart: http://www.health.harvard.edu/newsweek/Glycemic_index_and_glycemic_load_for_100_foods.htm.

7. Regardless of the components of diets, keeping patients' body mass indices (BMIs) <25 is essential (2).

8. Nuts and seeds are very calorie dense and very "addictive." In patients attempting to lose weight, nut and seed quantities can be very hard to control. Under such circumstances avoid them despite their beneficial health qualities.

9. At a restaurant have the waiter bring only half your patient's meal to the table. Package the rest for home. Say NO when the waiter tries to put bread on the table. Remember, studies uniformly show that restaurant eating leads to weight gain. Therefore, during periods of intended weight loss, eat predominantly at home.

10. Drink plenty of water. Water prior to meals can also be helpful with weight loss.

11. Ensure adequate daily consumption of fiber: fruits, vegetables, and whole grains. The findings of the PREDIMED trial support the Mediterranean diet as the leader in dietary choices for CVD prevention.

Alcohol

Several of the physiologic benefits inherent in alcohol include decreasing thromboxanes and leukotrienes, increasing tissue plasminogen activator and fibrinolysis, decreasing platelet activity, inducing vasodilation, and something most of us can attest to, reducing stress. However, moderation is vital and there have been no prospective trials on the benefits of alcohol in any form in reducing CVD. All favorable data are observational although consistent with plausible hypotheses based on these data and laboratory studies. It is also well established that the potential benefit of alcohol resides in the alcohol, not in any special form such as red or white wine, beer, or other modality (3).

Nutritional Supplements

Most trials evaluating supplements have done so in a physiologically unsound fashion and have drawn unsupported conclusions. For example, trials that have

assessed high dose vitamin E, beta carotene, and vitamin C have been almost uniformly neutral.

■ *Magnesium:* Magnesium intake of 500 mg/day to 1,000 mg/day may reduce systolic blood pressure (BP) by 5 to 6 mmHg (5).

■ *Fish Oil:* Specifically the omega-3s EPA and DHA, the "active ingredients" in fish oil, have been shown by some studies to be beneficial but in others, not. A difficulty inherent in recent trials relates to the fact that when fish oil (or any other potentially salutary substance) is added to the array of CVD-beneficial medications (statins, ACE inhibitors, antiplatelet agents, and beta blockers) it is difficult to demonstrate incremental benefit. For patients with documented CVD the American Heart Association (AHA) recommends 1,000 mg daily of combined DHA and EPA. Also, purification processes today effectively remove mercury so fish oil supplements are safe.

■ *B6, B12, and Folic Acid:* When these vitamin levels are low, one's homocysteine level can rise. High homocysteine levels are associated with CVD but decreasing homocysteine in clinical trials has had disappointing results, although in younger patients there is some conflicting evidence that homocysteine-lowering may modestly lower CVD events (7). Also, several trials have demonstrated that lowering homocysteine does have a statistically significant advantage for stroke reduction (8).

■ *Vitamin D:* The VITAL Trial is currently in progress and may help answer the vitamin D question regarding primary prevention of cancer and cardiovascular disease by this vitamin (9,10).

■ *Coenzyme Q10 (CoQ10):* This plant-derived antioxidant participates in mitochondrial energy production and is reduced by statins. A few small trials have suggested a modest benefit of CoQ10 supplementation in preventing myalgias and myopathy; larger trials are in progress to provide better data.

■ *L-carnitine:* Found mostly in meats, L-carnitine is a byproduct of the amino acid lysine. It participates in functions involving mitochondrial energy production. L-carnitine appears to improve utilization of oxygen in ischemic tissues and so can be employed in angina and claudication (12,13). Two grams twice daily has been advocated by some for treating claudication. This high dose can be hard to tolerate because of bloating; starting lower and then up-titrating can be helpful.

■ *Bioflavonoids in Green and Black Tea: Camellia sinensis* is the source of both green and black tea. Although purported to have anticarcinogenic qualities, green tea also possesses antioxidant characteristics (14).

■ *Coffee:* Coffee is available in both drink and supplement (caffeine) form. It has been the object of great debate but recent trials definitely favor its beneficial impact on CVD and DM. Some studies show a U-shaped curve supporting either low-dose coffee (one cup per day) or high-dose coffee (> 4 cups per day). Others support up to three or four cups per day as being cardioprotective. The proarrhythmic effect of caffeine at these doses has largely been debunked. Different compounds have been found to produce diverse effects: the chlorogenic acids decrease diabetes mellitus, inflammation, platelet aggregation, and blood pressure, whereas caffeine is felt to decrease weight and increase both fibrinolysis and flow-mediated dilatation (improve endothelial function) (15).

■ *Chocolate:* There is scientific justification for consumption of dark chocolate in small quantities (16). Flavonoids found in chocolate—including the catechins also found in tea and coffee—are antioxidants and anti-inflammatory substances that correlate with lower BP, improved DM, and decreased CVD (17). In comparisons of dark versus other forms of chocolate, dark triumphs, even though its saturated fat content is higher.

■ *Resveratrol:* Resveratrol is a polyphenolic compound found almost exclusively in red wine. Some studies have demonstrated the following effects: anti-inflammatory, antioxidant, endothelial derived nitric oxide stimulation, vascular cell adhesion molecule and platelet inhibition, and inhibition of LDL-peroxidation, an initiating step in atherosclerosis (18). The dose range for resveratrol is under study but it appears that the *trans-* form may impart greater efficacy.

■ *Aromatherapy:* The use of essential oils (aromatic hydrophobic plant-based compounds) for medicinal purposes has been prevalent for the past thousand years but there is no scientific evidence for the claims of benefit versus CVD.

Lipid Altering and Glucose Reducing Supplements

■ *Red Yeast Rice:* Red yeast rice (RYR) is the fermentation product of tthe mold *Monascus purpureus* and rice. The active ingredient, Monacolin K, is identical to lovastatin. Consequently, RYR containing Monacolin K has been banned in the United States. However, some RYR products are available and contain variable concentrations of Monacolin K. As the FDA prohibits products from disclosing their Monacolin K content, consumers are unable to ingest specified quantities of this agent, rendering the use of RYR difficult, and even potentially harmful. Further complicating the issue, some RYR products contain citrinin, a contaminant with potential nephrotoxicity. Thus, although RYR does decrease LDL-C, TG, and total cholesterol, and increases HDL-C, it is a gamble

for patients to consume (20). Its use should be limited to patients who either cannot tolerate statins and other classes of pharmaceutical lipid-altering medications, or refuse to follow the well-established allopathic approach to lipid management.

■ *Gugulipid:* An Ayurvedic herb extracted from the mukul myrrh tree, Gugulipid has been an approved drug for treating hyperlipidemia in India since 1986. The recommended dose to increase HDL-C and decrease total cholesterol and LDL-C is 25 mg tid of the active ingredient gugulsterone. A limitation of this agent is its tid dosing.

■ *Policosanol:* These are sugar cane derived long-chain alcohols. Although trials in Cuba suggest that this substance can decrease LDL-C, subsequent trials have failed to corroborate these initial findings.

■ *Polymethoxilated Flavones (PMF) and Tocotrienols:* These are combined in a commercially available product Sytrinol®. Animal studies have demonstrated hypolipidemic effects of the polymethoxilated flavones (21).

■ *Sterols/Stanols:* These plant-based compounds (both sterols and stanols) lower LDL-C by blocking intestinal absorption of cholesterol and augmenting cholesterol release into the small bowel. They purportedly convey an 11% reduction in LDL-C. Both sterols and stanols enjoy a qualified health claim, meaning manufacturers are permitted by the FDA to state they have a role in reducing CVD risk. To make this claim they must contain a total daily dose of 1.3 grams sterols or 3.4 grams of stanols and be used in combination with a heart-healthful diet.

■ *Pomegranate:* This fruit contains the active ingredients punicalagin, a polyphenolic antioxidant, as well as beta-sitosterol, a phytosterol (22). Both purportedly convey cardiovascular benefit, and pomegranate, both in juice and extract form, has demonstrated significant reductions in both LDL-C and total cholesterol (23). Additional benefits include increased insulin sensitivity, inhibition of alpha-glycosidase, and a favorable impact on glucose transporter type 4 function.

■ *The Portfolio Diet:* This diet represents a natural method for lowering cholesterol (24). Although it was included in guidelines as far back as ATP 2, the Portfolio Diet has been largely disregarded. Its principle is simple: look at a diet as you would your financial portfolio. Replace unhealthful items with those that will increase your "health value" (in this case, by decreasing your cholesterol). Foods containing high quantities of soy protein, viscous fiber, sterols and stanols, and almonds are the bedrock of this program. Here is a website resource: http://www.livestrong.com/article/505699-the-portfolio-diet/

■ *Cinnamon:* This spice has been used for millennia in religious ceremonies and as a highly valued food additive. Current focus is on cinnamon's hypoglycemic properties. In both animal and human trials there is evidence for its efficacy. Mouse studies have shown a reduction in gene expression of both phosphoenolpyruvate carboxykinase and glucose-6-phosphatase, hepatic regulators of gluconeogenesis (25). Human trials have evaluated cinnamon's impact on not only glycemic status, but also body composition and lipid profiles as well (26). Using 3 grams of cinnamon daily in patients with type 2 DM, Vafa demonstrated diminished levels of fasting blood glucose, HbA1c, triglyceride, weight, BMI, and body fat mass.

■ *Bitter Melon: Momordica charantia*, bitter melon, has been studied for its hypoglycemic effects in both animal and human trials. Mechanisms of action that favorably affect glucose control in diabetic patients include protecting pancreatic islet beta cells and inhibiting alpha-glucosidase activity (27,28).

MIND AND BODY PRACTICES

Stress Reduction Techniques

Psychosocial stress contributes to CVD risk, which has been established by numerous studies (29). Stress augments CVD risk by increasing cholesterol, epinephrine, norepinephrine, cortisol, and glucose levels, and activating platelets. We must help our patients (and ourselves) to better manage stress (30). Two major categories of stress reduction techniques that have been effective are "in the moment" and "comprehensive."

■ *In-the-Moment Stress Reduction:* A pragmatic technique to teach our patients is a simple breathing method. When an individual is confronted with a stressor he or she can instantly alter his or her breathing pattern. Deep, slow, purposeful, diaphragmatic breathing will produce instant results. Relax one's abdomen. Inhale deeply and slowly through the nostrils, expanding the belly before the chest. Then exhale through the mouth even more slowly. End the breath with a full collapse of the abdomen to achieve complete exhalation. This is the type of breathing pattern employed in the practice of Yoga, a system that combines exercise and meditative breathing (31). The technique will ensure a very full breath, one that will help shift the autonomic nervous system to a more quiet or more predominantly parasympathetic tone.

■ *Comprehensive Stress Reduction Techniques:* A number of systems have been developed to teach us how to enjoy greater calm in life. Transcendental meditation (TM), the relaxation response, mindfulness-based-stress-reduction, and Freeze Frame® are just a few. TM, a form of meditation, was the first such technique used in the United States and appears to have the

most promise of the meditation techniques for reducing CVD risk. It involves an individual being given a single word or sound (mantra) to repeat over and over as she sits quietly for about 20 minutes, breathing in the fashion described above. As the mind settles down, the body becomes deeply relaxed into a state of "restful alertness." When thoughts enter her mind, the TM practitioner simply lets them pass by, paying them no attention and giving them no credence. In this way, the meditator achieves a peaceful equanimity that can persist for hours after the session. TM instructors advise practitioners to meditate in this fashion twice daily, prior to both breakfast and dinner. TM has been shown to decrease epinephrine and norepinephrine significantly, diminish BP, increase brain alpha waves (the peaceful ones), reduce anxiety, diminish oxygen consumption, and even lower myocardial ischemia. A recent American Heart Association scientific statement, in fact, noted its important ability to lower blood pressure with a class IIb level of evidence B recommendation, while not recommending other meditation techniques for this purpose (32).

Traditional Chinese Medicine

Traditional Chinese medicine (TCM) dates back over two millennia and includes various healing modalities such as acupuncture, Qi Gong, Tai Chi, and herbals. Acupuncture, Qi Gong, and Tai Chi have received the most study and are addressed in this section.

- *Acupuncture* is a system of healing that utilizes 12 pathways, or meridians, that appear to overlie major neural motor and sensory networks. The practitioner stimulates acupoints, specific spots along the meridians, with needles, electricity, pressure, heat, or a combination thereof to achieve a desired result. Both acupoint specificity and the nature of acupuncture's response are vital elements of the practice. Acupoint specificity refers to one's ability to influence a given body system over another, and the nature of the response is determined by the particular modality utilized as well as its duration. In general, the stimulation of afferent pathways back to the central nervous system results in release of neuropeptides such as opioids, serotonin, and the endocannabanoids (33). The end result is an influence on sympathetic and parasympathetic outflow to the heart and elsewhere, depending on the acupoint used. In the realm of cardiovascular disease, hypertension, hyperlipidemia, stress, and even obesity have been most studied. Results are mixed, but some evidence exists to consider the incorporation of this discipline in a comprehensive integrative medicine system.
- *Qi Gong,* literally translated as energy practice, involves deep breathing techniques, slow exercise movements, and a mindfulness-based meditation (34). Similar to acupuncture, Qi Gong lowers catecholamine release and has been studied most in the management of hypertension. The level of data is low, and more studies are required to ascertain the utility of Qi Gong in the management of hypertension.
- *Tai Chi Chuan,* often shortened to Tai Chi, is strictly translated as "the supreme ultimate fist." Though considered a "soft" martial art, Tai Chi is actually a spectrum, which integrates fast-paced hard movements in conjunction with the better-recognized slower movements (35). In the context of CAM, Tai Chi emphasizes deep breathing, slow dancelike movements, and meditation. It has therefore mostly been studied in the context of its impact on hypertension. Results are mixed, but as with Qi Gong it is a practice that may possess merits that extend beyond simply lowering blood pressure.

Ayurvedic Medicine

Dating back over 3,000 years, this Indian system of medicine utilizes a wide range of herbal therapies as well as dietary and lifestyle interventions including the practice of Yoga (36). Ayurvedic systems have not been adequately studied. Particular concern emanates from a 2008 NCCAM-sponsored trial that found 21% of herbal products studied contained heavy metals exceeding the daily-recommended intake (37). This represents a concern for pregnant and lactating women in particular, but all others as well. Small studies of Ayurvedic medicine have evaluated its impact on cardiovascular risk such as hypertension, high cholesterol, and stress. Results have been promising, specifically with regard to the use of Yoga, but larger and better studies are needed.

OTHER COMPLEMENTARY AND ALTERNATIVE THERAPIES

Chelation Therapy

Based upon the principle of chelating (literally "clawing") heavy metals, chelation therapy has been used by alternative health care practitioners as an antiatherosclerosis technique for decades. At the 2012 AHA meetings the first solid clinical trial demonstrated a CVD event reduction from chelation in diabetic patients who had previously experienced anterior wall myocardial infarctions (38). However, this single trial cannot be considered definitive evidence for a therapeutic effect of chelation.

Arrhythmias

Atrial fibrillation has been the focal point of numerous CAM approaches. Several supplements have been suggested, the most popular being the omega-3s and magnesium. Low levels of the omega-3 fatty acid index have been shown to be associated with cardiac arrest (39). Two trials presented at the 2012 AHA meetings, however, evaluated omega-3s and atrial fibrillation, and both failed to demonstrate benefit.

Endothelial Dysfunction

The following section is a brief description of several nutrients that are currently receiving scientific attention regarding their effect on endothelial function, an active area of CV research. In considering the possible benefits of these substances, one must bear in mind the relative doses used in animal studies, which are frequently substantially higher than would be applied in humans.

- *Vitamin C:* Studies of the cardiovascular benefits of vitamin C have reported mixed results. Agarwal et al. found that food-derived vitamin C decreased carotid IMT, whereas supplement-derived vitamin C did not (40). In contrast, Yan et al. found that the combination of 13-Tetrahydrobiopterin, L-arginine, and vitamin C act synergistically to decrease oxidative stress, increase nitric oxide, and improve blood flow after induction of hind limb ischemia (41).
- *Polyphenols:* Found in fruits, vegetables, and wine, polyphenols such as quercetin and resveratrol may have an important role in protecting our endothelium. They function as free radical scavengers, metal chelators, and enzyme modulators. They increase endothelial nitric oxide synthase (eNOS), increase glutathione (an endogenous antioxidant enzyme), and inhibit ROS-producing enzymes. Because of these attributes they are currently the objects of numerous investigations (42).
- *Omega-3 Fatty Acids EPA and DHA:* Discussed earlier, these fatty acids tend to decrease a variety of biologic substances that could lead to endothelial dysfunction. Specifically they are metabolized to by-products that lower proinflammatory cytokines, chemokines, and adhesion molecules (43). The end result is a likely reduction in endothelial dysfunction. A large meta-analysis by Wang et al. demonstrated that these omega-3s improve flow-mediated dilatation (a measure of endothelial function) without affecting endothelium-independent vasodilation (44). Again, further studies are required to validate the clinical significance of supplementing these long-chain, highly unsaturated fatty acids.
- *L-Arginine and Citrulline:* L-arginine is the precursor for nitric oxide (NO). As such, its endothelial impact has been studied in experimental and clinical trials. L-arginine's ability to augment NO has been established. As citrulline is a precursor for L-arginine, it too has been studied as a NO enhancer and it has been found to be effective in that role. The clinical ramifications of these nutrients' ability to increase NO have not been adequately established, but this remains a promising area of research (45).

Person-Centered Medicine (PCM)

PCM is a movement away from the current reductionist medical approach to a systems approach to patient care (46). "Systems" in this context does not refer to cardiovascular, gastrointestinal, neurologic, and the like. Rather, it refers to viewing the patient as a whole, a unique individual with unique issues and needs. Many believe that only through integrative strategies, combining the best of complementary, alternative, and allopathic medicine, can we achieve true PCM. The goal in PCM is to focus on the patient, the particular needs, concerns, beliefs, and values that each of us has when put in the position of a patient. In actuality, CAM represents the essence of PCM as it permits patients and doctors to consider all reasonable options in averting disease and maintaining health.

SUMMARY

Complementary and integrative approaches to prevention of CVD comprise a wide range of practices used extensively by adults in the United States and worldwide. Because of shortcomings and dissatisfaction with current allopathic medical practices, the public has become increasingly interested in CAM and is often exposed to promoted claims of efficacy, despite limited clinical trial evidence regarding the benefits of CAM in prevention or treatment of CVD as well as other ailments. However, increased attention by the National Institutes of Health and other organizations to supporting further research in this area over recent decades has resulted in promising data regarding the efficacy of several areas of CAM, including certain nutritional and mind–body approaches: nutritional supplements, acupuncture, and transcendental meditation to name a few. Evidence has accumulated regarding key CAM therapies that can reduce stress as well as other key CVD risk factors such as hypertension and dyslipidemia. Use of targeted therapies on an individualized basis, consistent with emerging person-centered

approaches to medicine, may serve to complement conventional medical therapies to best achieve optimal cardiovascular health and CVD prevention.

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M. Dominique Ashen, PhD, CRNP,
Christine L. Nell-Dybdahl, NP-C, MPH, MSN,
Laurence Sperling, MD, FACC, FACP, FAHA, and
Roger S. Blumenthal, MD, FACC, FAHA

Development of a Center for Cardiovascular Disease Prevention

Advances in cardiovascular disease (CVD) risk assessment and treatment have improved outcomes for patients, resulting in a 31% reduction in the CVD death rate between 1998 and 2008. However, despite these improvements, CVD is still the leading cause of death and disability in the United States with 1 out of 3, 1 out of 6, and 1 out of 18 deaths the result of CVD, coronary heart disease (CHD), and stroke, respectively (1). Total direct and indirect cost for CVD, projected to rise above $800 billion in 2025, is more than any other diagnostic group and represents $1 of every $6 spent on health care in this country. Further reduction of CVD morbidity and mortality as well as reduction in health care costs associated with CVD is a high priority for both health care providers and the health care industry.

It has been estimated that as much as 84% of the decrease in CVD mortality in the United States between 1980 and 2000 was attributed to reduction in CVD risk factors and the collective CVD preventive effort (2). In addition, adherence to clinical practice guidelines has been shown to reduce CVD morbidity, mortality, and cost (3). The American College of Cardiology (ACC) and the American Heart Association (AHA) have developed clinical practice guidelines for primary and secondary CVD prevention (4,5) and have recently updated guidelines for risk assessment and management of high blood pressure, cholesterol, lifestyle, and overweight and obesity (6–10).

Therefore, the goal should be to adopt guideline-driven, cost-efficient programs that can identify subclinical atherosclerotic vascular disease, prevent its progression, minimize hospitalizations for interventions of acute coronary syndrome, and reduce death from cardiovascular events throughout the adult lifespan. This can be accomplished through the development of centers for CVD prevention.

DEVELOPMENT OF A CENTER FOR CVD PREVENTION

Centers for CVD prevention utilize advances in risk assessment and risk reduction strategies, pharmacologic therapy, and selective use of methodologies to detect advanced subclinical atherosclerosis as a means to inhibit the emergence of CVD risk factors (*primordial prevention*), protect against the development of CVD in those with risk factors (*primary prevention*), identify and detect CVD in its earliest stages and prevent recurrent events (*secondary prevention*), and limit complications and disabilities of CVD in addition to providing rehabilitation (*tertiary prevention*). A premier center for CVD prevention will expand beyond the goal of expert, individualized clinical care to the comprehensive integration of clinical, educational, and research components that focus on population-based strategies.

Essential components of a comprehensive center for CVD prevention include: (a) individualized and comprehensive risk assessment and risk management at all prevention levels; (b)

identification of CVD in high-risk patients, families, and populations; (c) special emphasis on the prevention of CVD risk factors, events, and risk equivalents (eg, diabetes); (d) evidence-based and guideline-driven treatment; (e) cost-effective, economically viable management; and (f) a multidisciplinary approach (clinical, educational, research, and community outreach).

Development of a business plan incorporating these components is the first step in the development of a center for CVD prevention. Although this chapter does not discuss the specific details of a business plan, it includes information that will aid in its development, including discussion of (a) mission statement, goals, and objectives; (b) operational design; (c) clinical design; and (d) financial design.

Mission Statement, Goals, and Objectives

The *mission statement* is the roadmap for the center and should concisely describe what the center for CVD prevention will do and for whom.

■ *Example:* "To improve cardiovascular outcomes in heart disease prevention through the highest quality patient and family centered care, research, and education" (from The Emory Heart Disease Prevention Center, Emory University School of Medicine). The mission statement lays the ground work for *goals* of the preventive CVD center, which are broad statements that describe the short and long term outcomes for patients.
■ *Example:* "We are dedicated to (1) the comprehensive assessment and management of individuals at risk for accelerated atherosclerosis (primary prevention) and those with established CVD (secondary prevention) and (2) to provide the latest information on the prevention of atherosclerotic vascular disease to all patients" (from The Johns Hopkins Ciccarone Center for the Prevention of Heart Disease). In contrast, *objectives* are specific statements that can be clinical or operational.
■ *Example:* "To provide a cost-effective, economically viable, preventive CVD service with direct and indirect profit potential."

Operational Design

Physical Space

Three important considerations include:

■ *Location:* Convenient access with potential for ancillary services (other specialty medical clinics, laboratories, radiology facilities, etc.).
■ *Cost:* This will vary depending on whether the center is newly built, part of a preexisting clinic, or part of a hospital inpatient or outpatient center.
■ *Space requirements:* This should be based on the projected number of patients per day, which will determine the number of providers and staff and the number of days per week of operation. It is important that the physical space include waiting areas, exam rooms, testing areas (stress test, echocardiogram), rest rooms, office space, workstations, a break room, and storage space for office and medical supplies, medical records, and testing equipment. Space for a cardiac rehabilitation facility should also be considered. It is also important to plan for additional space based on predictions of future growth.

Staff

An integral part of a business plan is a personnel plan. The delineation of responsibilities and expectations for each staff member is critical to efficient operation of a center for CVD prevention. Staff and their specific roles may include:

■ *Physicians:* Medical director, clinical provider, spokesperson for the center, medical supervision of other clinical and nonclinical staff, performance and evaluation of clinical testing, and supervision for phase II cardiac rehabilitation.
■ *Advanced-practice provider—nurse practitioner (NP) or physician assistant (PA):* Clinical provider, program coordination, comprehensive patient education of dietary, lifestyle and pharmacologic interventions, evaluation of compliance to treatment plans, and referrals to subspecialists.
■ *Nurses (RN):* Patient care, program coordination, comprehensive patient education of dietary, lifestyle and pharmacologic interventions, evaluation of compliance to treatment plans, and referrals to subspecialists.
■ *Technicians:* Independent performance of clinical testing including EKGs, echocardiograms, stress tests, and so on.
■ *Dietician:* Comprehensive nutrition counseling and medical nutrition therapy (MNT).
■ *Exercise physiologist:* Physical activity evaluation and exercise counseling.
■ *Lifestyle/behavior change specialist:* Comprehensive education of diet, exercise, weight loss, smoking cessation, and behavior change.
■ *Clinical manager:* Management of patient care activities including coordination of clinical space and management of technicians.
■ *Operations manager:* General office management including maintenance of physical space, tracking office supplies, management of administrative

assistants, and management of finances (including billing and budget analyses).

- *Administrative assistant:* Greet and register patients for visit, schedule follow-up visits, manage patient–provider communication.
- *Information technology specialist:* Develop and maintain computer management systems.

Equipment

- *Office:* Photocopy machines, computers, printers, telephones, and so on.
- *Medical:* Machines for blood pressure, EKGs, echocardiograms, stress tests, and heart monitors. Clinic rooms will require chairs, an exam table, a sink, and space to store examination gloves and other supplies.

Some equipment will be purchased and some leased. Other factors to consider include contracts for equipment repair and expendable supplies (e.g., EKG paper, heart monitor leads, etc.).

Information Technology and Management

Specific information technology (IT) services are required for documentation and management of patient medical records, appointment scheduling and notification, prescribing medications, clinical testing, test interpretation, and dissemination of test results. IT specialists are needed for the selection and development of computer systems, maintenance and upgrades, and the training of staff in the use of programs.

Marketing

Although the specifics of a market analysis are not discussed in this chapter, concepts important to the development of a center for CVD prevention include:

- *Referral base:* Source of new patients
  - Current patient population (referral of family, friends, and coworkers).
  - Primary care providers as well as physicians in other specialties
  - Reputation: based on word of mouth, research publications (local and national), and association with other private and/or hospital groups.
- *Direct-to-consumer marketing opportunities:* Attracting and enrolling new patients
  - Lectures at community education programs (local athletic clubs/wellness centers, churches), and organizations (AHA, American Stroke Association)
  - Hosting local CVD risk screening programs
  - Sponsoring local athletic tournaments
  - Partnering with local businesses for CVD prevention of employees and customers (corporate entities, grocery stores)
- *Media resources:* To increase the number of self-referred patients both local and outside the community
  - Television and radio advertisements and presentations
  - Written materials (yearly clinic summaries, pamphlets, and research publications)
  - Clinic website (information about the center as well as CVD health information)

Clinical Design

In the clinical design of a center for CVD prevention, the focus should be to protect against the development of CVD, slow progression of already existing CVD, and decrease risk of CVD events and interventions through risk assessment and risk management. Measurement of clinical outcomes and use of research and teaching will enhance clinical decision making and treatment.

Patient Population

A center for CVD prevention that focuses on all levels of prevention will require clinical decision making and treatment plans that can be applied throughout a wide age range and all stages of CVD. A center for CVD prevention can focus on specific patient groups including: women and ethnic minorities, and individuals with metabolic disorders, premature vascular disease, subclinical and accelerated atherosclerosis, familial lipid disorders, refractory hypertension, family history of coronary heart disease and stroke, recurrent chest pain without established CVD, heart and renal transplant, peripheral arterial disease, nontraditional CVD risk factors (including rheumatoid arthritis, systemic lupus erythematosus, and HIV), a history of radiation therapy for breast cancer or Hodgkin's lymphoma, allergy or intolerance to traditional CVD pharmacotherapy, and multidrug pharmacotherapy unable to meet treatment goals.

Risk Assessment Plan

An individualized and comprehensive risk assessment is the cornerstone for a CVD prevention center. It should include: evaluation of CV symptoms, past medical history, medications, family history, lifestyle behaviors (diet, exercise, and weight), laboratory findings including lipid analyses and indices of glycemic control, and a comprehensive physical exam with special emphasis on the cardiovascular system.

Risk assessment of individuals who present without known heart disease with or without CV risk factors (primary prevention) is a challenge. The ACC/AHA have established New Pooled Cohort Equations

for the estimated 10-year risk of developing atherosclerotic cardiovascular disease (ASCVD), defined as the risk of first ASCVD event including nonfatal myocardial infarction or coronary heart disease death, or fatal or nonfatal stroke (6). Primary prevention patients with no diabetes, an estimated 1-year ASCVD risk of ≥7.5% who are between 40 to 75 years of age with LDL-C between 70 to 189 mg/dL would benefit from statin therapy. However, if after quantitative risk assessment, a risk-based treatment decision is uncertain, assessment of family history, high-sensitivity C-reactive protein, coronary artery calcium score, or ankle-brachial index may be considered to inform treatment decision making. Carotid intima-media thickness is not recommended for routine measurement for risk assessment for a first ASCVD event (7).

Risk Management Plan

Risk management must be individualized, comprehensive, and long term.

- Evidence-based and guideline-driven treatment using the following national guidelines:
  - 2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults (8)
  - 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults (7)
  - 2013 AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk (9)
  - 2013 AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults (10)
  - Treating Tobacco Use and Dependence: 2008 Update (11)
- Additional testing for the management of risk factors, optimization of medication use, and determination of the need for interventions may include: laboratory testing, electrocardiograms, heart monitors, echocardiograms, cardiac CT scans, and stress tests.
- Patient education may include both physical (handouts, packets, and brochures) and online resources. Patient education is an important tool for CVD risk factor modification, lifestyle counseling (diet, exercise, weight loss, and smoking cessation), and behavioral modification counseling (including stages of change, single concept learning, and motivational interviewing).
- A pre-established, specialty referral base may include those with expertise in diabetes, vascular disease, electrophysiology, heart failure, lipid apheresis, and cardiovascular interventions.
- Patient–provider communication (HIPPA compliant) in the form of mailed/e-mailed documents, phone conversations, phone-in sessions, and a protected website to disseminate patient test results, order medication, and so on.

Services Provided

Multidisciplinary programs may be made available as an integrated part of the clinic or through outside specialists. These include heart failure clinics, anticoagulation clinics, peripheral vascular disease programs, chest pain management programs, women's health centers, dieticians, lifestyle coaches, clinical exercise programs, and cardiac rehabilitation.

Clinical Outcomes Plan

A clinical outcomes plan should be developed during the initial design of the center. Clinical outcomes will influence the quality of service provided to patients and determine the extent to which risk assessment and risk management plans are effective in getting patients to therapeutic goal (blood pressure, cholesterol, serum glucose/HbA1C). The outcomes measured must be widely accepted by national guidelines, evidence based, reproducible, and easy to measure. Tools to measure outcomes may be embedded in already existing programs for patient documentation or exist as a separate tool.

Research and Training

Research (clinical, translational, epidemiologic/population-based, or basic) on atherosclerosis and CVD risk factors as well as training of house staff, advanced practice providers, nurses, and researchers will promote identification of patients at risk for CVD and enhance clinical decision making and treatment plans. In addition, both research and training will contribute to marketing for a center for CVD prevention.

Financial Design

Financial Plan

A cost-effective, economically viable preventive CVD center requires a financial plan. An overall plan to estimate net operating income (the difference between total operating revenue and total operating expenses), accounts receivable (actual amount of money received from services), and cash flow (collected revenue minus total operating expenses) over several years will estimate the preventive CVD center's ability to attain predetermined goals and influence investor risk assessment and lending. In the month-to-month management, a detailed profit and loss statement is required to outline monthly and annual year-to-date revenue and expenses compared to those budgeted.

Expenses

Major expenses include: staff salaries and fringe benefits, rent, supplies and materials (computers and programs, copiers, testing machinery and supplies, service and leasing contracts), contractual service (building services, cleaning, telephones, utilities), clinical billing fees, staff education fees, and miscellaneous fees (domestic travel, food costs/catering).

Cost Effectiveness

Important aspects to minimize expenses and maximize profit include:

- *Understanding reimbursement:* Financial success relies on reimbursement for services. Understanding the rules and regulations for reimbursement and the services covered by health insurance programs, including Medicare (Parts A and B), Medicaid, Managed Care Organizations (Health Maintenance Organizations and Preferred Provider Organizations), and Private Fee-for-Service, will maximize reimbursement. It is also important to understand that reimbursement for NP and PA services will vary if billing: "independent" (reimbursed at 85% Medicare allowable fee), "incident to" under the physician's Medicare number (reimbursed at 100% Medicare allowable fee), through Medicaid (reimbursed between 70–100% of Medicaid allowable fee) or through a Managed Care Organization (variable reimbursement based on contracted coverage and state law). An accountant or manager who has expertise in medical billing and reimbursement can be invaluable to ensure remuneration for the services provided.
- Appropriate ICD-9 (diagnostic) and CPT (billing) coding: Accurate and efficient coding leads to appropriate reimbursement. ICD-9 codes, supported by clinical documentation, should be appropriate to the specialty (Table 26.1) and reflect all services provided, not only for the presenting symptoms/disease but also for coexisting conditions. ICD-9 codes identify patient problems and complexity of patient care. Electronic medical records programs are increasingly streamlining this process for the clinical provider. Tables 26.2A,B,C, and D provide CPT coding for new, return, and consultation outpatient visits specifying requirements for history, exam, and medical decision making (MDM). If more than 50% of time was spent for counseling and/or coordination of care, it is not necessary to meet requirements by history, exam and MDM. Total face-to-face time, counseling/coordination time (> 50% of total time), and what was discussed must be documented.
- *Efficient management of staff:* Means to increase cost savings and enhance quality and value of care,

TABLE 26.1 Useful ICD-9 Codes for a Center for CVD Prevention

Category	ICD-9 Codes
Signs and Symptoms	794.31 Abnormal EKG 786.59 Chest Tightness/Pressure 786.09 Dyspnea 780.71 Fatigue/Malaise 785.1 Palpitations 780.4 Dizziness 782.3 Edema
Coronary Artery Disease	413.9 Angina-Stable Exertional 414.00 Coronary Atherosclerosis 414.01 CAD – Native Vessel Disease 440.9 Subclinical Atherosclerosis
Cardiomyopathy Heart Failure/ Myopathy	428.0 Congestive Heart Failure 425.4 Non-Ischemic Cardiomyopathy 414.8 Ischemic Cardiomyopathy
Hypertension	402.10 Hypertension-BN-w/o CHF
Rhythm Irregularities	427.31 Atrial Fibrillation 427.0 SVT 427.9 Cardiac Dysrhythmia, unspecified
Valvular Problems	424.1 Aortic Stenosis or Aortic Insufficiency 424.1 Aortic Valve Disorder 424.0 Mitral Valve Disorder 785.2 Heart Murmur Unspecified
Vascular/ Cerebrovascular	435.9 TIA 436 CVA III Defined
Occlusion and Stenosis	433.1 Carotid 785.9 Bruit
Peripheral Vascular	443.9 Peripheral Vascular Disease
Diabetes/ Metabolic Syndrome	250.00 NIDDM Controlled 250.02 NIDDM Uncontrolled 250.01 IDDM Controlled 250.03 IDDM Uncontrolled 277.7 Metabolic Syndrome 278.00 Obesity 790.21 Impaired Fasting Glucose
Cholesterol	272.0 Hypercholesterolemia 272.1 Hypertriglyceridemia 272.2 Mixed Dyslipidemia
Sleep Disturbances	780.53 Sleep Apnea
Tobacco Use Disorder	305.1 Smoker (Tobacco Abuse)

(*continued*)

TABLE 26.1 Useful ICD-9 Codes for a Center for CVD Prevention (*continued*)

Category	ICD-9 Codes
Testing	794.30 Abnormal Cardiac Study/ Abnormal Stress Test
Personal History	V45.81 Status Post CABG V45.82 Status Post PTCA
Family History	V17.3 Family history of early CVD V18.0 Family history of DM
Screening For	V81.0 Ischemic Heart Disease V81.1 Hypertension
Medications	V58.69 Long-term use high-risk medication

which includes: (a) combining a clinic and operations manager into one role, (b) combining the provider role of an advanced-practice provider (NP or PA) with a lifestyle/behavior change specialist (12) or a stress test technician, (c) the use of NPs or PAs, who are billing "incident to," for management of return patients making available more new patient visits with physicians with 100% reimbursement, referring patients to outside centers for testing, and (d) sending patients needing individualized lifestyle/behavior modification to outside specialists such as dieticians and exercise physiologists.

- *Efficient management of patient volume:* Specifying time limits for new and return patient visits, optimizing the number of patients seen per day per provider, organizing schedules to efficiently combine clinic visits with testing and developing a schedule for long-term follow-up.
- *Efficient use of office space:* Consideration should be given to shared office spaces as well as renting office space during nonclinic hours for community meetings or use by other clinicians.
- *Tracking clinical outcomes:* This will provide data on patient satisfaction and success in patient care (meeting clinical goals, minimizing interventions and mortality) to bolster marketing, provide justification for referrals and coding and billing to support Medicare and Medicaid claims, and fulfill requirements for cardiac rehabilitation certification.

TABLE 26.2A CPT Coding Requirements for New Patient Visits

Level	History Must Meet or Exceed All 3 Elements	1995 Exam Guidelines: Office or Other Oupatient Services	Medical Decision	Usual Time
99201	• **Chief Complaint** • **HPI: 1–3 elements** • **ROS: N/A** • **PFSH: N/A**	1 body area **or** organ system	**STRAIGHTFORWARD**	10 min
99202	• **Chief Complaint** • **HPI: 1–3 elements** • **ROS: 1** • **PFSH: N/A**	2–7 body areas **or** organ systems with limited exam of affected body area/system	**STRAIGHTFORWARD**	20 min
99203	• **Chief complaint** • **HPI: 4 or more elements or the status of 3 chronic or inactive conditions** • **ROS: 2 to 9** • **PFSH: 1**	2–7 body areas **or** organ systems with ***extended exam*** of the affected body area/system	**LOW COMPLEXITY**	**30 min**
99204	• **Chief complaint** • **HPI: 4 or more elements or the status of 3 chronic or inactive conditions** • **ROS: 10+** • **PFSH: 3**	8 or more body areas **or** organ systems	**MODERATE COMPLEXITY**	45 min

(*continued*)

TABLE 26.2A CPT Coding Requirements for New Patient Visits (*continued*)
(http://www.hcmarketplace.com/supplemental/4713_browse.pdf)

Level	History Must Meet or Exceed All 3 Elements	1995 Exam Guidelines: Office or Other Oupatient Services	Medical Decision	Usual Time
99205	• **Chief complaint** • **HPI: 4 or more elements or the status of 3 chronic or inactive conditions** • **ROS: 10+** • **PFSH: 3**	8 or more body areas **or** organ systems	**HIGH COMPLEXITY**	60 min

Modifier 24: indicates an unrelated E&M service by the same physician has taken place during the post-op period.
Modifier 25: indicates a significant, separately identifiable E&M service by the same physician on the same day of a procedure or other service has taken place.
Modifier GC: indicates the service has been performed in part by a resident under the direction and supervision of a teaching physician following Medicare's teaching physician's guidelines.
Billing based on "TIME": If more than 50% of the face-to-face visit is spent on counseling and/or coordination of care, document the total time of encounter, the amount of time spent counseling, as well as summarize the topics discussed.
Source: http://www.hcmarketplace.com/supplemental/4713_browse.pdf.

TABLE 26.2B CPT Coding Requirements for Established Patient Visits

Level	History Must Meet or Exceed 2 of 3 Elements	1995 Exam Guidelines: Established Patient Office Visits	Medical Decision	Usual Time
99211	• Minimal presenting problem • MD supervision, but presence not required	"Nurse's code"—The patient's medication may need to be adjusted or the patient displays symptoms that needs to be addressed.	**MINIMAL**	5 min
99212	• **Chief Complaint** • **HPI: 1–3 elements** • **ROS: N/A** • **PFSH: N/A**	**1** body area **or** organ system	**STRAIGHTFORWARD**	10 min
99213	• **Chief Complaint** • **HPI: 1–3 elements** • **ROS: 1** • **PFSH: N/A**	**2–7** body areas **or** organ systems with limited exam of affected body area/ system	**LOW COMPLEXITY**	15 min
99214	• **Chief complaint** • **HPI: 4 or more elements or the status of 3 chronic or inactive conditions** • **ROS: 2 to 9** • **PFSH: 1**	**2–7** body areas **or** organ systems with extended exam of the affected body area/system	**MODERATE COMPLEXITY**	25 min
99215	• **Chief complaint** • **HPI: 4 or more elements or the status of 3 chronic or inactive conditions** • **ROS: 10+** • **PFSH: 3**	**8 or more** body areas **or** organ systems	**HIGH COMPLEXITY**	40 min

Modifier 24: indicates an unrelated E&M service by the same physician has taken place during the post-op period.
Modifier 25: indicates a significant, separately identifiable E&M service by the same physician on the same day of a procedure or other service has taken place.
Modifier GC: indicates the service has been performed in part by a resident under the direction and supervision of a teaching physician following Medicare's teaching physician's guidelines.
Billing based on "TIME": If more than 50% of the face-to-face visit is spent on counseling and/or coordination of care, document the total time of encounter, the amount of time spent counseling, as well as summarize the topics discussed.

TABLE 26.2C CPT Coding Requirements for Consultation Visits

Level	History Must Meet or Exceed All 3 Elements	1995 Exam Guidelines: Office Consultation Services	Medical Decision	Usual Time
99241	• **Chief Complaint** • **HPI: 1–3 elements** • **ROS: N/A** • **PFSH: N/A**	**1** body area **or** organ system	**STRAIGHTFORWARD**	15 min
99242	• **Chief Complaint** • **HPI: 1–3 elements** • **ROS: 1** • **PFSH: N/A**	**2–7** body areas **or** organ systems with **limited** exam of affected body area/system	**STRAIGHTFORWARD**	30 min
99243	• **Chief complaint** • **HPI: 4 or more elements or the status of 3 chronic or inactive conditions** • **ROS: 2 to 9** • **PFSH: 1**	**2–7** body areas **or** organ systems with ***extended exam*** of the affected body area/system	**LOW COMPLEXITY**	40 min
99244	• **Chief complaint** • **HPI: 4 or more elements or the status of 3 chronic or inactive conditions** • **ROS: 10+** • **PFSH: 3**	**8 or more** body areas **or** organ systems	**MODERATE COMPLEXITY**	60 min
99245	• **Chief complaint** • **HPI: 4 or more elements or the status of 3 chronic or inactive conditions** • **ROS: 10+** • **PFSH: 3**	**8 or more** body areas **or** organ systems	**HIGH COMPLEXITY**	80 min

Modifier 24: indicates an unrelated E&M service by the same physician has taken place during the post-op period.
Modifier 25: indicates a significant, separately identifiable E&M service by the same physician on the same day of a procedure or other service has taken place.
Modifier GC: indicates the service has been performed in part by a resident under the direction and supervision of a teaching physician following Medicare's teaching physician's guidelines.
Billing based on "TIME": If more than 50% of the face-to-face visit is spent on counseling and/or coordination of care, document the total time of encounter, the amount of time spent counseling, as well as summarize the topics discussed.

TABLE 26.2D Medical Decision Making

Medical Decision Making			
Type of Decision Making	**Number of Diagnosis or Management Options**	**Amount and/or Complexity of Data to be Reviewed**	**Risk of Complications and/or Morbidity or Mortality**
STRAIGHTFORWARD	Minimal	Minimal or none	Minimal
LOW COMPLEXITY	Limited	Limited	Low
MODERATE COMPLEXITY	Multiple	Moderate	Moderate

(*continued*)

TABLE 26.2D Medical Decision Making (*continued*)

Medical Decision Making			
Type of Decision Making	**Number of Diagnosis or Management Options**	**Amount and/or Complexity of Data to be Reviewed**	**Risk of Complications and/or Morbidity or Mortality**
HIGH COMPLEXITY	Extensive	Extensive	High

STRAIGHTFORWARD: One self-limited or minor problem ex: cold, insect bite, tinea corporis. **Possible medical tests or procedures:** blood draws, chest x-rays, EKG/EEG, urinalysis, and ultrasounds
LOW COMPLEXITY: Two or more self limited or minor problems, one stable chronic illness (well controlled htn, NIDDM, cataract), acute uncomplicated illness/injury, cystitis, allergic rhinitis, simple sprain. **Possible medical tests:** Physiological test not under stress, Non-cardiovascular imaging w/contrast (barium enema), Superficial needle bx, Clinical lab test requiring arterial puncture, Skin bx.
MODERATE COMPLEXITY: One or more chronic illness w/ mild exacerbation, progression, or side effects of treatment, Two or more stable chronic illness, Undiagnosed new prob. w/ uncertain prognosis (ex: breast lump), Acute illness w/systemic symptoms (ex: pyelonephritis, pneumonitis, colitis), Acute complication injury (ex: head injury with brief LOC). **Possible medical tests:** Physiologic test under stress (cardiac stress test), Diagnostic endoscopy w/no identified risk factors, Deep needle or incisional bx, Cardiovascular imaging w/contrast (ex: cardiac cath), Obtain fluid from body cavity (ex: thoracentesis)
HIGH COMPLEXITY: One or more chronic illness w/ severe exacerbation, progression, or side effects of treatment, Acute or chronic illness or injuries posing a threat to life or body function, Abrupt change in neurologic status (ex: seizure, TIA, weakness, sensory loss). **Possible medical tests:** Cardiovascular imaging w/ identified risk factors, Cardiac EPS tests, Diagnostic endoscopies with identified risk factors, Discography
TEACHING PHYSICIAN (TP) GUIDELINES: The following must be documented by teaching (billing) physicians: they were physically present and participating ***DURING THE KEY COMPONENT*** of the service rendered, that they verify pertinent findings in the resident's note, **AND** personally document modifications/enhancements to the resident's note.

SUMMARY

Development of a center for CVD prevention for patients at all prevention levels requires a business plan that incorporates a mission statement, goals, and objectives as well as designs for the operational, clinical, and financial aspects of the center. Inclusion of the essential components for the prevention of CVD into this business plan will provide a focus on prevention that extends not only to individual clinical care but also to population-based care.

Preventive medicine is being emphasized in health care given the increasing focus on quality initiatives and cost reduction strategies. Evidence supports the cost-effective, prevention strategies utilized in a center for CVD prevention including: (a) use of aspirin, antihypertensive medications, and statins (13–15); (b) screening for diabetes (16); (c) cardiac rehabilitation (17); and (d) counseling for nutrition, weight management, and smoking cessation (18–20). There is also financial incentive for patients to utilize preventive CVD centers as co-pay, co-insurance, or deductibles for blood pressure, diabetes, and cholesterol screening or counseling for smoking cessation, weight loss, and diet may not be required under the Affordable Care Act (21).

Ultimately, it is the focus on prevention of CVD that will influence provider quality of care, patient quality of life, and the economic impact of CVD on our nation's health care system.

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C. Tissa Kappagoda, MD, PhD
and Ezra A. Amsterdam, MD

Exercise-Based Cardiac Rehabilitation

Although there has been suboptimal referral and adherence to these programs in the past, recent trends indicate an encouraging increase in utilization, but not yet at the level of other secondary prevention practices such the use of aspirin, beta blockade, and statins. Exercise-centered cardiac rehabilitation should be considered for secondary prevention in all patients with CHD and other cardiovascular diseases.

The role of physical activity in the management of patients with cardiovascular disease (CVD) has undergone major evolution from mid-twentieth century to the present. Previously proscribed because of fear of adverse effects, exercise has assumed a central position in contemporary cardiac rehabilitation (CR) programs (1–3). Improved understanding of the pathophysiology of CVD and the potential therapeutic and prophylactic benefits of systematic exercise have provided a sound clinical basis for this development. Recognition of the detrimental effects of inactivity (deconditioning) has also endorsed physical activity in both health and disease.

Contemporary CR comprises a comprehensive program which, in addition to the key element of exercise, also addresses cardiac risk factors, diet, patient education, lifestyle, and stress; monitors clinical signs and symptoms; and assesses pharmacologic and nonpharmacologic therapy. As these factors are the subjects of separate sections in this manual, this chapter focuses on the role of exercise in CR. The goals of CR are, as is true of virtually all medical therapy, to: (a) reduce symptoms, (b) enhance capacity for recreation and occupation, (c) decrease morbidity, and (d) improve survival. These objectives are feasible in the majority of cardiac patients, most of whom are capable of a CR program to enhance their cardiovascular and general health.

In the American Heart Association (AHA)/American College of Cardiology (ACC) guidelines for secondary prevention, referral to a CR program has a class I recommendation (1); it is further stated that all patients who have recovered from a MI, who are post-CABG surgery, or have undergone a percutaneous coronary intervention (PCI) should be referred to an outpatient CR program either before discharge from hospital or during their first follow-up visit. In 2007, referral to a CR program after acute MI was designated a performance measure by several professional societies (3). In addition, CR has been applied at some centers to patients without coronary heart disease but with high coronary risk profiles reflected by their coronary risk factors. However, there are no current practice guidelines that include these patients.

The documented and potential benefits that may result from an exercise program in patients with atherosclerosis are multiple (5) and are summarized in the Table 27.1. In the case of low-risk patients, a home-based plan can be substituted for a supervised, center-based program (4). The degree of medical supervision required is related to the level of individual patient risk and ranges from direct on-site monitoring to nonsupervised exercise after "graduating" from a formal CR program.

TABLE 27.1 Potential Benefits of Aerobic Exercise Training

Atherosclerotic risk factors
Increased high density lipoprotein cholesterol
Reduced triglycerides (possibly reduced low-density lipoprotein cholesterol)
Increased insulin sensitivity, reduced blood glucose
Improved endothelial function
Decreased blood pressure
Decreased psychological stress
Cardiovascular
Increased maximal functional capacity
Reduced submaximal myocardial oxygen demand
Reduced myocardial ischemia at submaximal exertion
Decreased atherosclerosis
Decreased morbidity and rehospitalization
Hematologic
Increased blood volume
Increased fibrinolytic activity

PHYSIOLOGIC EFFECTS OF EXERCISE TRAINING AND THERAPEUTIC APPLICATION

Appreciation of the therapeutic potential of exercise in CVD is predicated on an understanding of the physiologic alterations conferred by systematic physical training. Habitual exercise training (ET) is defined as the performance of repetitive activity for the purpose of improving physical performance. ET can include several physiologic modalities (4): aerobic (e.g., walking, running), resistance (e.g., weight training), or a combination of these methods (e.g., cycling, rowing). The most common form of ET in patients with CVD is aerobic and it usually comprises walking or jogging. The other exercise modalities are also applicable; selection is based on the specific goal of training.

The fundamental effects of aerobic ET are an increase in maximal functional capacity, that is, total body oxygen consumption (VO_2 max) (6) (Figure 27.1) and a reduction in cardiac work, that is, myocardial oxygen demand (MVO_2), most simply reflected by the heart rate $\times$ systolic blood pressure, in response to a given submaximal external workload (4) (Figure 27.2). These adaptations result from the induction of an array of complex, beneficial physiologic and anatomic alterations in multiple organ systems (4–11): increased capillary density and oxidative enzyme activity in the trained skeletal muscles; vagotonia and sympatholysis, resulting in inhibition of excessive exercise-induced adrenergic drive at submaximal levels of stress; improved ventilatory function (ventilatory threshold); and favorable effects on risk factors such as lipids, glycaemia, obesity, and blood pressure. Reduction in adrenergic drive contributes to decreased peripheral arterial resistance and thereby an increase in stroke volume (10,11). Although at the usual submaximal training intensities of cardiac patients, ET has little or no direct effects on the heart (4,12,13), the aforementioned physiologic and metabolic alterations have a salutary influence on clinical outcomes that include improved quality of life, less functional impairment, decreased angina symptoms, and fewer repeat hospitalizations (4–6,14–16) (Table 27.1, Figures 27.1 and 27.2). However, because ET is typically administered as one component of comprehensive CR, it has been a challenge to determine to what extent favorable outcomes in CR are attributable to any single one of the multiple interventions utilized.

It is also important to recognize that, in addition to the benefits conferred by a formal ET program, even low levels of physical activity in hospitalized patients can avert the detrimental deconditioning effects of enforced bed rest such as loss of muscle mass and strength, reduced exercise capacity, impaired bowel and bladder function, and depressed morale, as well as multiple unfavorable metabolic actions. In fact, current comprehensive CR programs are an outgrowth of initial approaches to early, low-level activity in patients managed in the cardiac care unit (CCU). The rapid reduction of functional capacity induced by relatively short periods of bed rest and the activity-related recovery are depicted in Figure 27.1.

THE EXERCISE PRESCRIPTION AND TRAINING PROGRAM

As we have previously described (4), the exercise prescription and training program are tailored to the capability and needs of the individual patient. The prescription is usually based on a formal exercise test which is the key element in formulating the exercise prescription. ET is introduced at a relatively low level and progressively advanced at a suitable rate. Thus, the period over which this progression takes place may be weeks or months. The effects of ET on functional capacity and the relation between cardiac work and external performance are depicted in Figures 27.1 and 27.2, respectively. It can be seen that after ET there is an increase in total aerobic capacity (functional capacity, Figure 27.1) and a decrease in MVO_2 (ie, cardiac work) for a given external workload, expressed as exercise "Intensity" in Figure 27.2. It can be readily appreciated that the latter result simulates that of pharmacologic beta adrenergic blockade; however, of

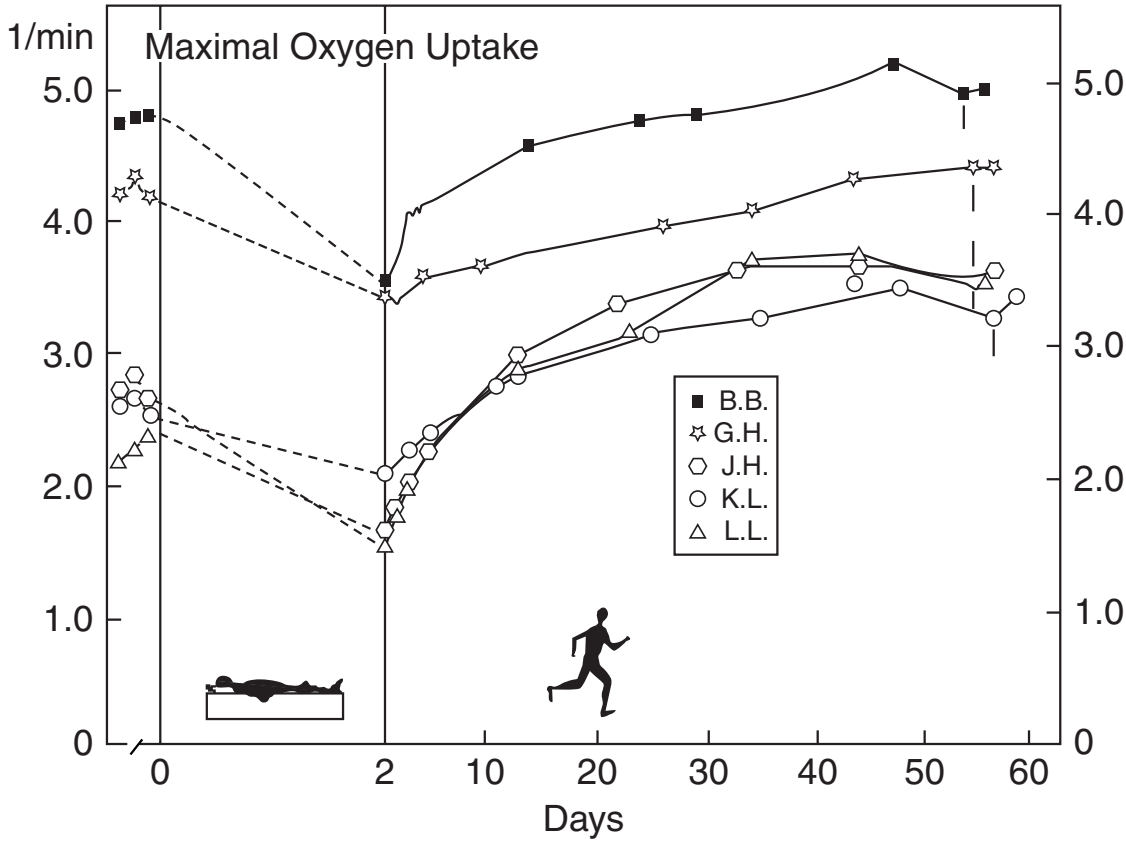

FIGURE 27.1 Effect of bed rest and exercise training on maximal oxygen consumption in five healthy men. The small vertical bars in the linear data of each subject indicate the point at which maximal oxygen consumption returned to the control value prior to bed rest

Source: From Ref. (6). Saltin B, Blomquist G, Mitchell JH, Johnson RL Jr, Wildenthal K, Chapman CB. Response to exercise after bed rest and training. *Circulation*. 1968;38(5 suppl):VIII-78.

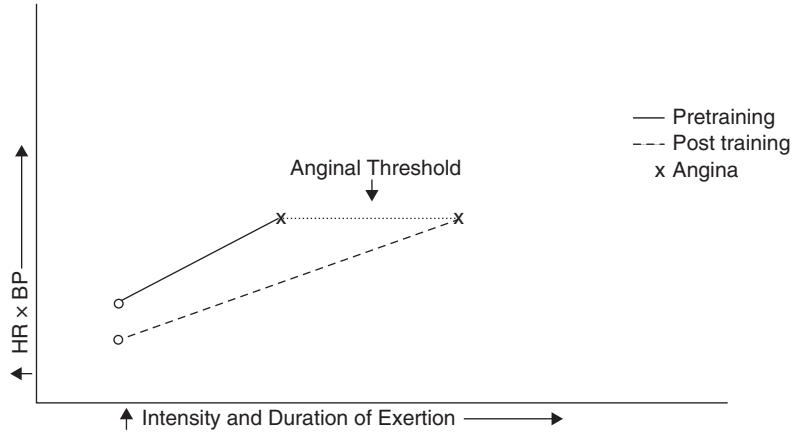

FIGURE 27.2 Effect of exercise training on resting and exertional cardiac work (represented by heart rate [HR] and blood pressure [BP]), which are directly related to myocardial oxygen demand. After training, HR and BP are lower than pretraining at the same level of submaximal exertion, indicating lower myocardial oxygen demand at these levels. The angina threshold is not altered but angina occurs after a longer and more intense level of exertion. These effects are similar to those of beta blockade and of rate-limiting calcium channel blockers.

considerable importance, it is achieved without drug therapy.

The training effect is induced by an aerobic exercise intensity of 60% to 80% of an individual's maximum work capacity (determined from the exercise test) for at least 20 min per exercise session, at least 3 to 4 times per week for at least 12 weeks, but greater longevity is associated with enhanced physiologic alterations. In patients who are clinically stable and several weeks or more posthospitalization, or those who start as outpatients, a formal exercise program is usually prescribed.

The exercise test is typically performed on a treadmill using a procedure such as the Balke–Naughton protocol which starts at a low intensity suitable for a cardiac patient's entry level and utilizes small increments of increased exercise intensity and grade during the test. The endpoint of the test is either symptom onset or a heart rate of 70% to 75% of age-predicted maximum. Age-predicted maximum heart rate is estimated as 200 minus age. (This number is inexact and has a standard deviation of ±10 beats/min; true maximum heart rate is that achieved on a maximum exercise test, which is not appropriate for cardiac patients at initiation into an ET program.) If there are no signs or symptoms (e.g., no ischemic ST-segment shift, arrhythmia, angina, excessive rise in blood pressure (systolic pressure >180 mmHg, fall in pressure, excessive dyspnea) at this level, it can serve as the intensity for the exercise prescription: ~70% of age-predicted maximum heart rate, which can be performed on a treadmill under supervision on beginning the program. The minimum frequency and duration of each session and longevity over which ET is performed are noted above; session should be preceded by a 5 to 10 minute warm-up and followed by a 5 to 10 minute cool-down. ET performed according to these criteria results in a reduction of resting heart rate of ~1 beat/min each week, with progressive alterations in exercise capacity toward goal. At completion of the duration of the patient's program, a repeat exercise test can be performed and the prescription adjusted based on the new exercise performance. The patient who was in a supervised program can be considered for continuation in an unsupervised home-based program. If, on the initial intake exercise test, abnormalities occur at the target heart rate or lower, the exercise prescription is based on the heart rate at which the abnormality occurred and the training intensity is 70% to 75% of that heart rate with ET performed under medical supervision. If it is judged that the patient is not stable enough for ET, the patient will be referred to his or her primary care physician and/or cardiologist for further management.

It was previously considered that only aerobic ET was appropriate for cardiac patients. However, it is now recognized that prudent strength training is both safe and beneficial for appropriately selected patients. We have reported that in patients with coronary artery disease (CAD) who can perform a symptom-limited treadmill test without abnormalities, resistance training with a load that allows 20 repetitions (e.g., bicep curls) without straining is safe and results in increased strength (15). The value of this approach is that tasks of daily living involving strength are associated with reduced cardiac work after strength training and thereby less propensity for cardiac symptoms.

TRADITIONAL AND CONTEMPORARY CARDIAC REHABILITATION PROGRAMS

CR in patients following an acute coronary syndrome (ACS) is typically implemented in three phases.

Phase I: Inpatient hospital phase beginning in the CCU

Phase II: Outpatient hospital-based phase for 2 to 4 months

Phase III: Maintenance phase for 4 to 6 months (or up to12 months)

In Phase III, which is also referred to as long-term CR, patients continue an exercise program (which may be expanded to cycling, jogging, swimming, calisthenics, weight training, and endurance sports) and health-related behavior modification procedures, at home or in a community-based facility.

Initiated in stable post-MI CCU patients in the 1960s, physical activity in the CCU usually begins on day 2 and continues in a gradual and progressive manner through the remainder of hospitalization. (The admonition regarding clinical stability cannot be overemphasized prior to initiation of physical activity.) Consisting initially of low-energy functions such as self-care, activity progresses to bedside chair and ambulation within the patient's room, and then to further ambulation outside the room. These activities avert the deleterious effects of enforced immobilization. Response to activity is scrutinized by symptoms, vital signs, and electrocardiogram (ECG) monitoring, Progressive activity continues after discharge, such as walking one-half to one block one or two times daily for the first week or two and increasing toward normal nonstrenuous physical functions. Two to three weeks following hospital discharge, stable patients may be referred to evaluation for a formal comprehensive CR program, as described earlier in this chapter, that includes the full complement of risk reduction aspects in addition to ET.

ACCESS TO PROGRAMS

In spite of the demonstrated benefits of secondary prevention, between 2000 and 2007, only 56% of eligible patients were referred to CR, based on the American Heart Association's "Get With the Guidelines Program" (17). These low rates of participation appeared to be related to factors such as the cost of the programs, lack of access to services, absence of social support, patient anxiety, excessive travel time, failure to obtain release from work, patients' lack of knowledge regarding the benefits of rehabilitation services, and poor patient motivation. Failure to receive rehabilitation services was associated with both lower educational levels and income, and women were also less frequent participants. To enhance utilization of secondary prevention programs for post-MI patients, the AHA developed the "Get With The Guidelines Initiative" (18), but despite a referral rate of 53% to cardiac rehabilitation programs, actual enrollment was only 19%. However, since its designation as a quality measure in 2007, we have found that referral to CR has significantly increased and was most recently greater than 80% in eligible patients in one large database (19). Nevertheless, referral to CR is lower than other recommended measures such as prescription of aspirin, beta-blockers, and counseling for smoking cessation, all of which have adherence rates greater than 95%.

The low level of participation and/or enrollment in CR programs was attributed to both physician inertia in referring patients and the "natural" reluctance of patients to undertake health-promoting behaviors (20), coupled with absence of an effective strategy to transition patients from hospital to organized long-term programs. These issues require optimal coordination of caregivers (nurses, resident staff, attending physicians) in hospitals and by primary care physicians in their own practices. In the United States, secondary prevention services are largely determined by the realities imposed by patients' insurance coverage. The latter includes one of three basic categories of health care coverage: (a) third party payers (i.e., private insurance plans), (b) Medicare, and (c) Medicaid. In addition, a significant number of patients have some form of dual coverage coupled with a copayment for which they are responsible.

SUMMARY

Exercise training is a central component of contemporary cardiac rehabilitation programs. Referral to cardiac rehabilitation has a class I recommendation in the secondary prevention guidelines of the American Heart Association and American College of Cardiology and has been designated a quality measure for patients following myocardial infarction. It has also been extended to a spectrum of cardiovascular disease. The benefits of appropriately applied exercise training include numerous favorable physical and metabolic alterations that contribute to improved cardiovascular risk factors, reduced symptoms, enhanced functional capacity, and less morbidity. Although there has been suboptimal referral and adherence to these programs, recent trends indicate an encouraging increase in utilization. Exercise-centered cardiac rehabilitation should be considered for secondary prevention in all patients with cardiovascular disease.

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