CMPMedica
United Business Media

SUPPLEMENT TO

PEER-REVIEWED CONSULTATIONS IN PRIMARY CARE

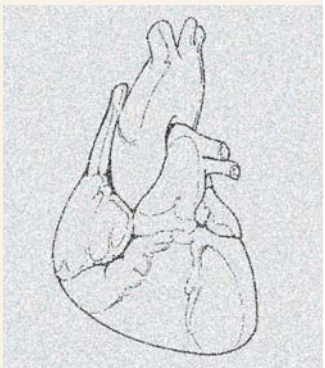
NOVEMBER 2008
VOL.48 NO.12

Consultant®

www.ConsultantLive.com

A CLIGGOTT PUBLICATION

Striking the Right Balance: The Residual Risk of Coronary Artery Disease



FRANK M. SACKS, MD

VERA BITTNER, MD, MSPH

DAVID S. KOUNTZ, MD, FACP

MICHAEL MILLER, MD

1.0 *AMA PRA Category 1 Credit™*

Supported by an educational grant from Abbott Laboratories.

Striking the Right Balance: The Residual Risk of Coronary Artery Disease

Faculty

Frank M. Sacks, MD
Professor of Cardiovascular Disease Prevention
Harvard School of Public Health
Boston, Mass

Vera Bittner, MD, MSPH
Professor of Medicine
University of Alabama at Birmingham
Birmingham, Ala

David S. Kountz, MD, FACP
Associate Professor of Medicine
Robert Wood Johnson Medical School
New Brunswick, NJ

Michael Miller, MD, FACC, FAHA
Associate Professor of Medicine, Epidemiology, and Preventive Medicine
Director, Center for Preventive Cardiology
University of Maryland Medical Center
Baltimore, Md

CONSULTANT (ISSN 0010-7069) is published 14 times a year by the Cliggott Publishing Group, a division of CMPMedica. It is distributed to over 250,000 physicians, MD and DO, in office- and hospital-based general practice, family practice, internal medicine, and cardiology; physician assistants; and nurse practitioners. Subscription rates: $10 per copy; $115 a year in the U.S.; $125 a year (U.S. funds only) for Canada and overseas countries (foreign delivery not guaranteed); $45 a year for students. Visa and MasterCard are accepted. CMP Healthcare Media LLC will honor claims for missing issues only within three months of the issue dates. Back issues are available for $10 per copy ($15, foreign) plus postage and handling. Reprints are available from PARS International at CMPMedicaReprints@parsintl.com or 212-221-9595, ext. 426. Periodicals postage paid at Darien, CT 06820-4027 and additional mailing offices. Postmaster: If undelivered, send form 3579 to CONSULTANT, 330 Boston Post Road, Box 4027, Darien, CT 06820-4027.

Faculty Profiles

FRANK M. SACKS, MD

Frank M. Sacks, MD, is professor of cardiovascular disease prevention, department of nutrition, Harvard School of Public Health; professor of medicine, Harvard Medical School; and senior attending physician, cardiovascular division and Channing Laboratory, Brigham and Women's Hospital, where he has a specialty clinic in hyperlipidemia.

Dr Sacks earned his degree in medicine from Columbia University, College of Physicians and Surgeons.

Dr Sacks is involved in research and public policy in cholesterol disorders, nutrition, hypertension, obesity, and cardiovascular disease. His research program is a combination of laboratory research on human lipoprotein metabolism; the effects of lipoproteins on vascular cells; and clinical trials in hyperlipidemia, nutrition, obesity, and cardiovascular disease. Dr Sacks has contributed over 150 publications of original research, and over 60 reviews, editorials, and chapters. He is a member and vice chair of the American Heart Association Nutrition Committee, and associate editor of *The American Journal of Clinical Nutrition.* ■

VERA BITTNER, MD, MSPH

Vera Bittner, MD, is professor of medicine in the division of cardiovascular disease, department of medicine, University of Alabama at Birmingham (UAB). She is section head of preventive cardiology, director of the cardiovascular disease residency program, and director of cardiac rehabilitation, UAB Hospital. Dr Bittner is also professor of nursing at the School of Nursing (appointed through the Dean's Office), UAB. She is a senior scientist at UAB's Center for Health Promotion, Center for Aging, Clinical Nutrition Research Center, and Center for Outcomes and Effectiveness Research.

Dr Bittner attended medical school at Johann Wolfgang Goethe Universität Frankfurt, Fachbereich Medizin, and received an MD from the University of South Alabama College of Medicine. She completed her internship and residency in internal medicine at North Carolina Baptist Hospital, Bowman Gray School of Medicine, Winston-Salem, and a fellowship in cardiovascular disease at UAB. She has also received an MSPH in epidemiology from the UAB School of Public Health.

Very active in international, national, and local organizations, including the American College of Cardiology and the American Heart Association, Dr Bittner is on the editorial boards of the *Journal of the American College of Cardiology, American Heart Journal, Cardiology Today,* as well as 6 other publications, in addition to having been a reviewer for almost 40 medical journals. She is a board member of the National Lipid Association and a past president of the Southeast Lipid Association and the Birmingham Cardiovascular Society. Dr Bittner has conducted extensive research on a variety of cardiovascular topics, and she has published over 100 journal articles, dozens of reviews and book chapters, and more than 150 abstracts. She has made hundreds of international, national, and regional presentations. ■

DAVID S. KOUNTZ, MD, FACP

David S. Kountz, MD, is associate professor of medicine at Robert Wood Johnson Medical School in New Brunswick, NJ. He also serves as senior vice president at Jersey Shore University Medical Center, an affiliate of the Medical School in Neptune, NJ.

Dr Kountz earned his undergraduate degree at Princeton University and his MD at the State University of New York in Buffalo. He completed house staff training in internal medicine at Hahnemann University Hospital in Philadelphia.

Dr Kountz has published and lectured extensively on cardiovascular issues, especially in minority populations. In 1998, Dr Kountz was funded by the CDC to study the management of diabetes in managed care. This study, called Translating Research Into Action in Diabetes (TRIAD), has resulted in over 60 publications. More recently, he has served as editorial board chair for MetabolicPulse.org, a CME-accredited Web site providing education on diabetes and related disorders to health care providers. ■

MICHAEL MILLER, MD, FACC, FAHA

Michael Miller, MD, serves as tenured associate professor of medicine in the division of cardiology and associate professor of epidemiology and preventive medicine at the University of Maryland School of Medicine. In addition, he is director of the Center for Preventive Cardiology at the University of Maryland Medical System and staff physician at the Veterans Affairs Medical Center in Baltimore.

Dr Miller received his BA from Rutgers College and his MD from the University of Medicine and Dentistry of New Jersey. Following a medical residency at the University of Cincinnati Medical Center, he completed 2 fellowships at The Johns Hopkins Hospital in Baltimore, one in lipoprotein metabolism and the second in cardiovascular disease.

Dr Miller's major research interests are disorders of lipid and lipoprotein metabolism; molecular studies of high-density lipoprotein cholesterol, triglycerides, and the postprandial response to dietary fat; nontraditional coronary risk factors; and clinical trials to reduce atherosclerosis. He has participated in landmark clinical trials, including AVERT, MIRACL, PROVE-IT, TNT, and COURAGE. Dr Miller is a fellow of the American College of Cardiology and the American Heart Association Council on Arteriosclerosis. He is also an active member of the American Heart Association Council on Epidemiology.

Dr Miller has authored more than 200 original articles, book chapters, and other publications. He is the coauthor of *The Practice of Coronary Disease Prevention* and the recently published *AMA Guide to Preventing and Treating Heart Disease.* Dr Miller is on the program faculty for the Complex Lipid Management Self-Assessment Program, which involves preparation for certification by the American Board of Clinical Lipidology. He is also a member of several editorial boards and a reviewer for numerous journals. Dr Miller is past president of the American Society of Preventive Cardiology and has served on the Program Committee of the AHA Epidemiology and Prevention Council. His research has been supported by the NIH, American Heart Association, and Veterans Affairs Administration. ■

Striking the Right Balance: The Residual Risk of Coronary Artery Disease

Supported by an educational grant from Abbott Laboratories.

Overview

A decade ago, it was envisaged that the treatment of hypercholesterolemia and hypertension would eventually eliminate coronary heart disease; however, that goal has not yet been realized. In 2006, the estimated costs associated with coronary heart disease in the United States exceeded $145 billion. Despite the availability of lipid-lowering agents, cardiovascular disease continues to be one of the leading causes of mortality in the United States and worldwide, owing to a rising incidence of obesity and diabetes, among other factors. This exclusive monograph will revisit coronary heart disease, discuss the underlying risks, and present strategies for prevention and treatment.

Learning Objectives

After completion of this program, participants should be able to:

- Recognize the types and levels of lipids that contribute to increased coronary heart disease risk.
- Differentiate the factors that contribute to residual risk, including high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG).
- Assess the effect of therapies that focus on lowering low-density lipoprotein cholesterol versus therapies that are directed toward managing dyslipidemia as a whole (ie, "the lipid triad") in the form of raising HDL-C and lowering serum TG through single-agent and/or combination treatment.

Release Date: November 2008

Expiration Date: November 2009

Method of Participation

Participants should read the learning objectives and review the monograph in its entirety. After reviewing the activity, they should complete and submit the post-test and evaluation. Upon achieving a passing score of 70% or better on the post-test, a statement of credit will be awarded.

Target Audience

This program is intended for the education of cardiologists, primary care physicians, nurse practitioners, physician assistants, as well as other health care providers involved in the treatment of patients with dyslipidemia.

Accreditation and Designation

The Chatham Institute is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. The Chatham Institute designates this educational activity for 1.0 *AMA PRA Category 1 Credit™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Disclosures

It is the policy of The Chatham Institute to ensure balance, independence, objectivity, and scientific rigor in all of its educational activities. All faculty, planners, and managers who affect the content of medical education activities sponsored by The Chatham Institute are required to disclose to the audience any real or apparent conflict of interest related to the activity. Faculty, planners, and managers not complying with the disclosure policy will not be permitted to participate in this activity.

Program faculty and planners have disclosed the financial relationships with commercial interests cited below. All program content has been peer reviewed for balance and any potential bias. The conflict of interest resolution process aims to ensure that financial relationships with commercial interests and resultant loyalties do not supersede the public interest in the design and delivery of continuing medical education activities for the profession.

Frank M. Sacks, MD
Consultant: Abbott Laboratories, AstraZeneca Pharmaceuticals LP, Eli Lilly and Company, Merck & Co., Inc., Genzyme Corporation, Isis Pharmaceuticals, Inc.
Research grants: Isis Pharmaceuticals, Inc.
Advisory board: Lipid Sciences, Inc.
Stock/shareholder: Isis Pharmaceuticals, Inc.

Vera Bittner, MD, MSPH
Consultant: Pfizer Inc
Research grants: Abbott Laboratories, Merck & Co., Inc., Pfizer Inc, Roche Pharmaceuticals, Schering-Plough Corporation

David S. Kountz, MD, FACP
No real or apparent financial relationships to disclose

Michael Miller, MD, FACC, FAHA
Speaker bureaus: Abbott Laboratories, AstraZeneca Pharmaceuticals LP, Merck & Co., Inc., Pfizer Inc, Schering-Plough Corporation
Advisory boards: Abbott Laboratories, Roche Pharmaceuticals
Research grants: AstraZeneca Pharmaceuticals LP, Merck & Co., Inc., Pfizer Inc, Roche Pharmaceuticals, sanofi-aventis U.S. LLC, Schering-Plough Corporation

Dan Duch, PhD
Medical Director, The Chatham Institute
No real or apparent financial relationships to disclose

Bagirathy Ravishankar, PhD
Scientific Director, The Chatham Institute
No real or apparent financial relationships to disclose

Peer Reviewer Disclosure

This monograph case study was peer reviewed by CME Peer Review LLC, which has no relevant financial relationships to disclose.

Sponsorship and Support

This educational activity is sponsored by The Chatham Institute and supported by an educational grant from Abbott Laboratories.

THE CHATHAM INSTITUTE

Abbott
A Promise for Life

FRANK M. SACKS, MD
Harvard School of Public Health

DAVID S. KOUNTZ, MD, FACP
Robert Wood Johnson Medical School

VERA BITTNER, MD, MSPH
University of Alabama at Birmingham

MICHAEL MILLER, MD, FACC, FAHA
University of Maryland

Striking the Right Balance: The Residual Risk of Coronary Artery Disease

Dr Sacks is professor of cardiovascular disease prevention, Harvard School of Public Health, Boston. Dr Bittner is professor of medicine at the University of Alabama at Birmingham. Dr Kountz is associate professor of medicine at Robert Wood Johnson Medical School, New Brunswick, NJ. Dr Miller is associate professor of medicine, epidemiology, and preventive medicine and director, Center for Preventive Cardiology, at the University of Maryland Medical Center, Baltimore.

ABSTRACT: Elevated low-density lipoprotein cholesterol (LDL-C) is a well-established independent risk factor for coronary artery disease and is the principal lipid target for risk reduction. Statins lower LDL and other apo B–containing lipoproteins, thereby leading to a 20% to 35% reduction in major cardiovascular events, but do not comprehensively address the multiple lipid abnormalities of atherogenic dyslipidemia. Combination therapy with available lipid agents (eg, statin plus fibrate or statin plus niacin) has been shown to improve lipid profiles in atherogenic dyslipidemia. Even though small clinical trials have suggested clinical benefit using surrogate end points (less coronary lesion progression, less progression of carotid intima-media thickening), definitive outcomes studies are not yet available. Major trials are in progress to determine whether improvement in the atherogenic dyslipidemia will achieve the projected reduction in cardiovascular events, and which combination is associated with the most favorable outcomes.

More than a decade ago, it was envisaged that treating hypercholesterolemia and hypertension, the 2 major risk factors of cardiovascular disease (CVD), would significantly lower the incidence of CVD.[1] Although, as expected, age-adjusted CVD death rates have declined in developed nations, CVD is estimated to be the leading cause of death worldwide, with a significant increase in disease burden in low-income and middle-income countries.[2]

Low-density lipoprotein cholesterol (LDL-C) is strongly related to development and progression of CVD, and lowering of LDL-C lowers the risk of incident and recurrent cardiovascular events and mortality. Current treatment paradigms for the prevention of CVD recommend the use of statin therapy to achieve cholesterol goals, which have shown a significant 30% to 40% reduction in cardiovascular events, as documented in clinical trials.[3,4] Despite the use of optimal statin therapy to lower LDL-C levels, a significant number of patients continue to be at high risk for cardiovascular events. Thus, some have suggested adopting a more comprehensive approach, which includes modification of other lipoprotein fractions to address this burden of "residual risk."[5] This article will review the pathophysiology of atherosclerosis, and provide a comprehensive evidence-based overview of the available treatment options to manage residual risk in patients with dyslipidemia.

PLASMA LIPIDS AND LIPOPROTEINS

There are 4 major types of lipids that circulate in plasma: cholesterol and cholesteryl esters, phospholipids, and triglycerides (TGs).[6] Cells obtain cholesterol either by intracellular synthesis or by reuptake from the systemic circulation.[7] The function of the lipid transport system is to ferry these hydrophobic fat molecules from their sites of synthesis to points of utilization

through the aqueous environment of the plasma.

Because of their hydrophobic nature, cholesterol and other fatty substances are packaged into lipoprotein particles before secretion into plasma.[7] Typically, a lipoprotein particle is composed of a core of TGs and cholesteryl esters that are covered by an envelope of phospholipids and free cholesterol. Based on size, density, lipid, and apolipoprotein content, lipoprotein particles can be separated into distinct classes: high-density lipoprotein (HDL), LDL, very low-density lipoprotein (VLDL), intermediate density lipoprotein (IDL), and chylomicrons.[6] Apolipoproteins, the protein moieties on the outer surface of lipoproteins, provide structural integrity to lipoproteins, activate enzyme systems, and bind or dock to specific receptors.[6,7]

PHYSIOLOGY OF LIPID TRANSPORT

The lipid transport system has 2 main functions: transporting TGs from the gut and liver to muscles or fat tissue for utilization or storage, and transporting cholesterol to sites of utilization for the synthesis of bile acids, steroid hormones, and membrane synthesis.[8] In the exogenous pathway, dietary fat and cholesterol first pass through the intestinal lymphatic circulation, then through the systemic circulation, and finally to the liver by receptor-mediated uptake of chylomicron remnants. Dietary fat, emulsified by bile salts in the gut, is hydrolyzed by pancreatic lipases into constituent free fatty acids and monoglycerides and diglycerides, which are taken up by intestinal cells, the enterocytes.

To facilitate transportation through lymphatic venous circulation, the constituent free fatty acids and glycerides, which are first reassembled into TGs, are transformed into chylomicrons by the addition of apolipoprotein (apo) B48. As the TG-rich chylomicrons pass through the capillary beds, a part of the TG content is removed by the catabolic activity of lipoprotein lipase, leaving the core of the remnant particles containing cholesterol as well as some of the dietary TG to be re-utilized by the liver.[6] In the endogenous pathway of the lipid transport system, TGs synthesized in the liver are assembled into VLDL particles before their secretion into the systemic circulation. The VLDL particles undergo a partial delipidation in a manner similar to the processing of chylomicrons. The resultant VLDL remnants and IDL particles are smaller and enriched in cholesterol. Approximately 50% of remnants are removed from the circulation, while the remainder is converted into LDL particles.[6,7]

The primary function of HDL particles is to transport cholesterol from peripheral tissue to the liver, a process called *reverse cholesterol transport.* This process begins with the uptake of cholesterol from peripheral cells, such as arterial wall macrophages, by nascent cholesterol-poor HDL, which is then converted to mature HDL_2 through the activity of lecithin-cholesterol acyltransferase (LCAT). In addition, a cholesterol ester transfer protein (CETP) mediates a net exchange of TGs for cholesteryl esters to facilitate the transfer of cholesterol from HDL to VLDL remnants.[8] Such bidirectional transfer of constituents between lipoproteins allows the acquisition of specific apolipoproteins and ensures that unused cholesterol from peripheral tissues is transferred to the liver for re-utilization.[8]

PATHOGENESIS OF ATHEROSCLEROSIS

Atherosclerosis is a chronic inflammatory disorder of blood vessels, which results in asymmetric focal thickenings of the arterial intima.[9] The atheroma is preceded by the formation of a fatty streak consisting of macrophages and some T lymphocytes. The center of the atheroma has a core region with foam cells (cholesterol-rich macrophages) and extracellular lipid droplets, surrounded by a cap of smooth muscle cells and a collagen-rich matrix. T cells, macrophages, and mast cells often infiltrate the lesion and are present around the shoulder region, where the atheroma grows.[9-11]

Myocardial infarction occurs because of complete coronary artery occlusion resulting from atheromatous plaque that is covered by overlying thrombus. It was previously thought that progressive luminal narrowing was the main cause of infarction.[1] However, angiographic studies have identified that destabilization of plaque with overlying occlusive thrombus, rather than progressive stenosis, precipitates ischemia and infarction.[1,12] What might be the cause of coronary thrombosis? Plaque rupture, detectable in 60% to 70% of cases, exposes prothrombotic material from the core of plaques.[13] It is believed that activated immune cells, which are abundant at sites of plaque rupture, produce factors such as inflammatory cytokines, coagulation factors, and vasoactive molecules that destabilize lesions and promote thrombosis.[1]

Endothelial activation. Hypercholesterolemia causes focal activation of the endothelium in large- and medium-sized arteries.[1] The activation of the endothelium starts with the infiltration and retention of LDL, VLDL, and chylomicron remnants in the arterial intima, which initiates an inflammatory response in the arterial wall.[14,15]

There are several mechanisms by which these lipoproteins may cause atherosclerosis. For instance, native LDL can be retained in the intima by aggregation, binding to pro-

teoglycan matrix, and absorption by macrophages. The inflammatory effect of LDL can be modified by glycosylation or oxidation, which facilitates the cholesterol loading of macrophages.[16] Further, it has been recently discovered that apo CIII, a component of some of these lipoproteins, directly stimulates the inflammatory process in vascular tissue.[17,18]

The endothelial cells that are activated by the lipoproteins are responsible for the production of several monocyte adhesion molecules that cause circulating monocytes to adhere at sites of activation.[16] Once recruited, cytokines and other growth factors produced at the site of the inflamed intima induce the differentiation of monocytes into active macrophages—a critical early step in the development of atherosclerosis—and attract collagen-producing smooth muscle cells into the intima.[1]

Formation of atherosclerotic plaques. Scavenger receptors on the surface of activated macrophages enable the uptake of aggregated and modified LDL and remnant VLDL particles.[19] These macrophages transform into foam cells, and accumulate in the intimal space to form a fatty streak.[7] As fatty streaks continue to transform the once-smooth endothelial artery surface into an uneven surface, an *atherosclerotic plaque* is formed. Calcium is also deposited in advanced plaques. However, the pathogenesis of atherosclerosis is much more complex than the initiation and formation of plaques. In an earlier study, Glagov and colleagues[20] have shown that as atherosclerotic plaques develop, arteries enlarge in relation to plaque area due to a compensatory mechanism. Given that lumen stenosis may be delayed until 40% of the internal elastic lamina area is occupied by lesion,[20] evidence of luminal obstruction on coronary angiography is more likely to indicate an advanced lesion. Lower-grade lesions may be more prone to rupture due to intrinsic pro-inflammatory characteristics of the plaque-derived foam cells.[7]

RISK FACTORS FOR ATHEROSCLEROSIS: DYSLIPIDEMIA AND METABOLIC SYNDROME

The *Framingham Heart Study* coined the term "risk factors" for CVD.[8] According to the current NCEP ATP III guidelines, along with elevated LDL-C, a number of lipid and nonlipid factors have been identified that are associated with the development of coronary heart disease (CHD).[21] Two such risk factors, elevated TGs and reduced HDL-C, often occur together and, when both are present, the patient is said to have "atherogenic dyslipidemia." Atherogenic dyslipidemia is prevalent in persons with obesity, insulin resistance, type 2 diabetes, and physical inactivity.[22-24]

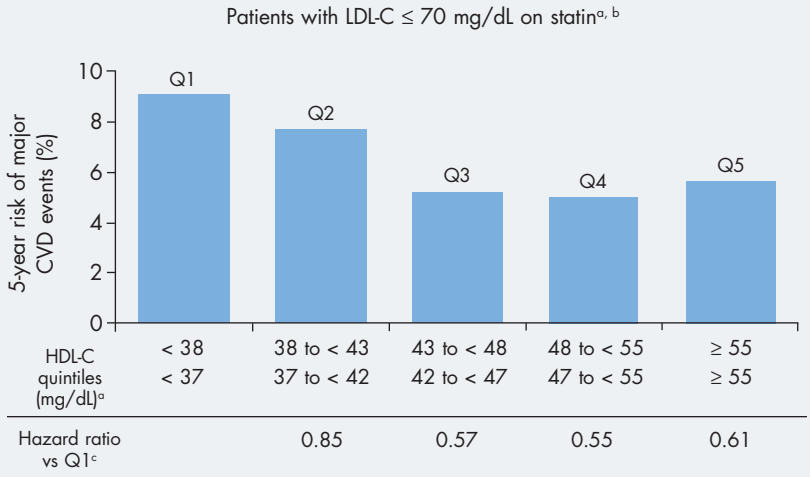
Elevated LDL-C. From the *7-Country Study,* it became evident that cardiovascular mortality was highest in countries with populations that had elevated levels of total serum cholesterol and was lowest in Mediterranean and Asian populations.[25] Furthermore, the study showed a strong and graded relationship between saturated fat intake, serum cholesterol, and the incidence of CHD, whereas dietary cholesterol had a weaker correlation.[25]

In the *Framingham studies,* increased level of LDL-C proved to be a major risk factor for development of CHD. More importantly, however, the Framingham data set showed that a mix of risk factors, when present together, additively increase the risk of CVD.[26]

A contentious issue is the relative strength of LDL-C compared with non-HDL-C and apo B. Non-HDL-C and apo B include not only LDL but also VLDL and VLDL remnants, which are atherogenic and contribute to risk. Thus, non-HDL-C and apo B provide a more complete assessment of risk associated with atherogenic lipoproteins.[27] Nuclear magnetic resonance spectroscopy can be used to estimate lipoprotein particle concentration and measure the size of lipoprotein particles.[27] Although small dense LDL particles are moderately correlated with high TGs, and were thought to contribute independently to CVD,[25] particle size is not an independent predictor of CVD but rather a secondary phenomenon; accumulating data indicate that LDL is related to abnormal TG metabolism.[28]

In this context, data from the *Physician's Health Study* showed that nonfasting TG levels were a better predictor of first myocardial infarction than LDL particle size, and that LDL particle size had no effect beyond that of TGs.[27,28] Moreover, in epidemiological studies that used LDL particle size as a parameter to predict the risk of CHD, there was no consistent pattern that suggested small LDL is an independent contributor of CHD risk, as some have found that large LDL was associated with CVD.[29] This is consistent with the observation that patients with familial hypercholesterolemia have large LDL.

Reduced HDL-C. Population-based studies have consistently shown that a low level of HDL-C is a powerful predictor of increased cardiovascular risk; nonetheless, it remained unclear whether low HDL-C would be a significant risk factor in individuals with LDL-C reduced to very low levels.[30-32] In a post hoc multivariate analysis from the *Treating to New Targets* (TNT) study, HDL-C levels were a significant predictor of major cardiovascular events across the entire study cohort, even when LDL-C was reduced to an on-treatment level of less than 70 mg/dL



[a] On-treatment level (3 months of statin therapy); N = 2661.

[b] Mean LDL-C, 58 mg/dL; mean TG, 126 mg/dL.

[c] *P* = .03 for differences among quartiles of HDL-C.

CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides

Figure 1 – A post hoc multivariate analysis from the Treating to New Targets (TNT) Study showed that low HDL-C increases CVD risk even if LDL-C levels are well controlled.

with statin therapy.[33] According to the multivariate analysis, patients in the highest quintile of HDL-C (≥ 55 mg/dL) had a lower risk of major cardiovascular events compared with those subjects in the lowest quintile (≤ 37 mg/dL) (hazard ratio, 0.61; 95% CI, 0.38 - 0.97) (**Figure 1**).

The biosynthesis of HDL is complex and requires the synthesis of apo AI and apo AII, the 2 major protein components. Interestingly, in the general population, an inverse relationship has been observed between plasma levels of both apo AI and apo AII and CHD risk.[34] Turnover studies that delineate the rate of metabolism of HDL in plasma have indicated that HDL levels are determined mainly by the clearance rate from plasma of both apo AI and apo AII.[35-37] Apo AI is mainly synthesized in the liver, with a minor contribution from the intestine.[38] Newly synthesized HDL particles—also referred to as pre-beta HDL—are secreted into plasma as disk-like structures containing apo AI and phospholipids. As the disks interact with vascular intima, they take up the cholesterol from macrophages to form mature spherical HDL particles. Based on the genetic studies of Tangier disease, it is evident that ABC-A1—a transport protein involved in the efflux of cellular cholesterol—is a critical participant in the cholesterol loading of nascent HDL and reverse cholesterol transport.[39] The genetic absence of ABC-A1 is associated with low levels of HDL-C and apo AI, and consequently the development of atherosclerosis and CVD early in adult life.

Apo B/apo AI ratio. Several studies have now demonstrated that apolipoprotein concentrations predict future cardiovascular events somewhat more strongly than the lipoprotein cholesterol concentrations. The *Apolipoprotein-Related Mortality Risk Study* (AMORIS) investigated whether apo B and apo AI are better predic-

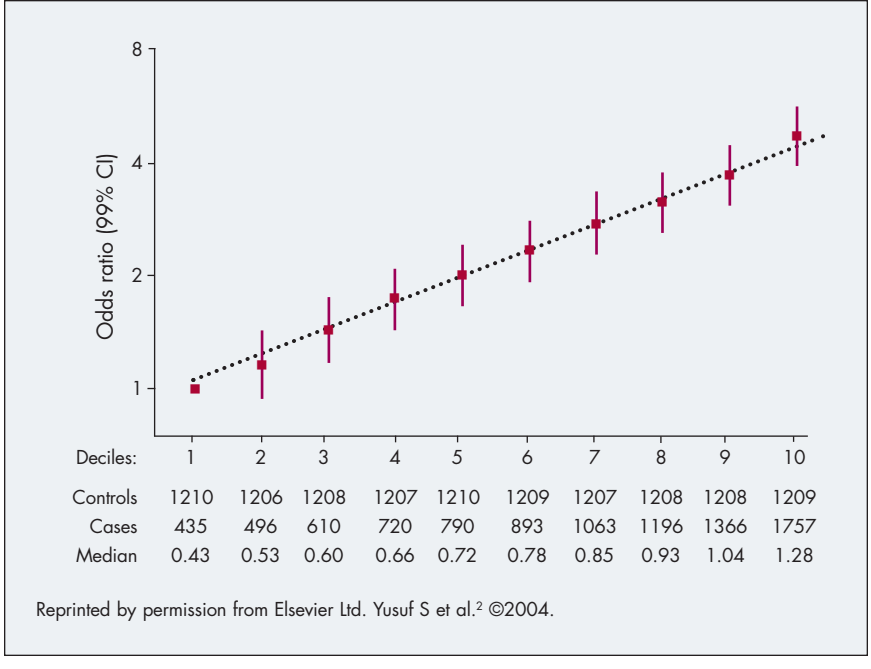
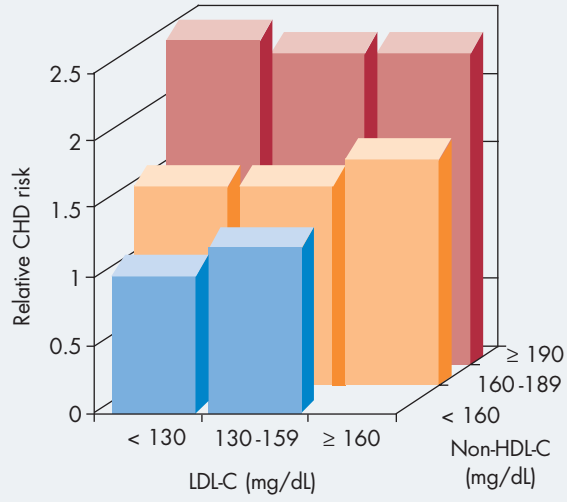


Figure 2 – The INTERHEART study, which assessed the importance of risk factors for coronary heart disease in 52 countries, reported overall odds ratios for individual risk factors in more than 12,000 cases. Raised apo B/AI ratio was found to be one of the strongest risk factors for acute myocardial infarction.

tors of risk of fatal myocardial infarction than total cholesterol and LDL-C.[40] The study, which investigated a large cohort of Swedish men and women, showed that after adjusting for age, cholesterol, and TG content, both apo B and apo B/apo AI ratio were significantly and positively correlated to increased risk of fatal myocardial infarction. In agreement with the Swedish study, data from the *INTERHEART* study clearly identified raised apo B/apo AI ratio as the most important lipoprotein-related risk factor for acute myocardial infarction in men and women across different ethnic groups and geographic regions (**Figure 2**).[2] The *INTERHEART* study, a large, international, case-control study designed to assess the importance of risk factors for CHD in 52 countries, reported overall odds ratios for individual risk factors in 12,461 cases and 14,637 controls after adjusting for age, sex, smoking status, and region. After a multivariate analysis, raised apo B/apo AI ratio emerged as one of the two strongest risk factors for acute myocardial infarction, second only to current smoking status.[2]

Non-HDL-C. Another approach to predict cardiovascular risk is to use non-HDL-C, which is a surrogate estimate of all atherogenic particles in the VLDL, remnants lipoprotein(a), and LDL fractions.[27,41] Thus, non-HDL-C is the cholesterol equivalent of apo B levels, and both parameters are highly correlated to one another and better predictors of CHD risk than LDL-C; the correlation coefficient of non-HDL and apo B is 0.93 - 0.94, compared with 0.84 - 0.85 for LDL-C and apo B.[42] Interestingly, recent prospective studies such as AMORIS[40] and the *Health Professionals Follow-Up Study*[43] have shown that apo B measurement outperforms LDL-C and non-HDL-C in cardiovascular risk stratification. Specifically, in the latter, an increase in CHD was associated with higher apo B levels across all categories of non-HDL-C levels.[43] Given the lack of readily available standardized assays for the measurement of apo B in a clinical setting, non-HDL-C is preferred and recommended as a secondary target of therapy when TG levels are higher than 200 mg/dL.[21] In this context, findings from a recent report by Liu and colleagues, who examined the original data sets from the *Framingham Cohort Study* and the *Framingham Offspring Study,* were in agreement with the earlier findings that non-HDL-C is a better predictor of CHD risk than LDL-C (**Figure 3**).[44]



CHD, coronary heart disease; LDL-C, low-density lipoprotein cholesterol; Non-HDL-C, non–high-density lipoprotein cholesterol

Reprinted by permission from Elsevier Ltd. Liu J et al.[44] ©2006.

Figure 3 – Non-HDL-C is superior to LDL-C in predicting CHD risk. Within non-HDL-C levels, no association was found between LDL-C and the risk of CHD. In contrast, a strong positive and graded association between non-HDL-C and risk of CHD occurred within every level of LDL-C.

Elevated TGs. Many epidemiological studies that employed meta-analyses have reported a positive correlation between elevated serum TGs and the incidence of CHD,[45,46] though previous multivariate analyses did not always identify TGs as an independent risk factor.[47] Recent data from 29 Western prospective studies with more than 260,000 participants and 10,000 CHD cases have indicated that elevated TGs are indeed a significant risk factor for CVD (**Figure 4**).[48] It is notable that NCEP ATP III guidelines recommend the use of lower cut points for the categorization of TG levels than the ATP II guidelines, thus reflecting a growing concern about even moderate TG elevation. Elevated TGs are thought to increase CHD risk through the atherogenic effects of TG-rich remnant lipoproteins, specifically chylomicrons and VLDL remnants and their high apo CIII content.[49]

An elevated TG level (> 150 mg/dL) is also one of the criteria for the diagnosis of metabolic syndrome.[49] The ATP III guidelines define metabolic syndrome as any 3 of the following 5 clinical features: abdominal obesity (waist > 40 inches for men and > 35 inches for women), elevated TG (> 150 mg/dL), low HDL-C (< 40 mg/dL for men and < 50 mg/dL for women), elevated blood pressure (> 130/85 mm Hg), and elevated fasting glucose (> 110 mg/dL).[21] Several factors may elevate TG levels in the general population. These include overweight/obesity,

physical inactivity, cigarette smoking and excess alcohol intake, consumption of high-carbohydrate diets, diabetes, and renal failure, and a number of medications.[50,51] However, the most common contributing factors are related to lifestyle. The current ATP III guidelines recommend treating hypertriglyceridemia according to its severity and the levels of other lipids. For borderline high TG levels (150 - 199 mg/dL), the goal of therapy is to reduce LDL-C levels with therapeutic lifestyle changes and drug therapy if needed.[21] Lifestyle changes that incorporate weight loss programs and increased physical activity have been shown to be effective in improving insulin sensitivity in patients with insulin resistance, a contributor to hypertriglyceridemia.[49] When TG levels continue to remain high (200 - 499 mg/dL) even after achieving LDL-C goals, the guidelines recommend using non-HDL-C levels as the secondary target for therapy. For very high TG levels (≥ 500 mg/dL), the primary goal of therapy is to prevent pancreatitis by lowering TG levels.[52]

MANAGING DYSLIPIDEMIA: TREATMENT GOALS AND RESIDUAL RISK

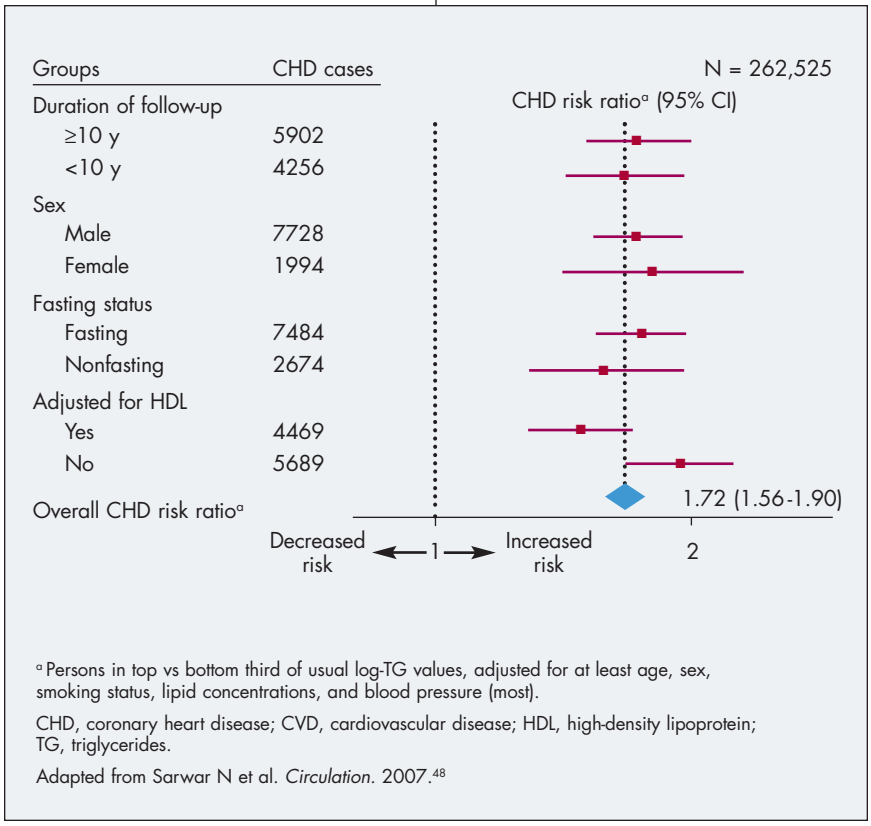
Risk assessment. The NCEP ATP III guidelines recommend risk assessment as the first step in primary prevention of coronary artery disease (CAD). According to the guidelines, individuals are categorized into 3 risk factor groups:

- Those with established CAD or CAD-risk equivalents.
- Those with more than 2 risk factors for CAD.
- Those with no or 1 risk factor.

CAD-risk equivalents include patients with peripheral arterial atherosclerosis, abdominal aortic aneurysm, or diabetes.[53] Others have also included patients with chronic kidney disease in this designation.[53] To estimate the cardiovascular risk, risk factors are first counted, and for those patients with multiple risk factors, the Framingham risk calculator is used to estimate the 10-year cardiovascular risk.[21] Although NCEP ATP III guidelines have recommended a LDL-C goal of less than 100 mg/dL as an optimal level, for those patients who are at very high risk, a further reduction to less than 70 mg/dL is suggested as an option, with a non-HDL-C goal of less than 100 mg/dL. Individuals deemed to be at "very high risk" are those with established CVD and one or more additional risk factors (eg, recent acute coronary syndrome, diabetes, smoking, etc).[52] After LDL-C goals have been met, the guidelines recommend addressing metabolic syndrome as a secondary goal of therapy.

Lifestyle modification. While it is widely accepted that dietary changes can improve LDL-C levels, it is less well appreciated that comprehensive lifestyle modification is critical in the management of patients with multiple metabolic abnormalities or metabolic syndrome. NCEP-ATP III–recommended therapeutic lifestyle changes include reduced intake of saturated fat, trans fat, and cholesterol; increased consumption of plant stanols/sterols and soluble fiber; weight reduction; and increased regular physical activity.[21] Even seemingly modest weight changes can result in significant metabolic benefits.

The importance of lifestyle management is also emphasized in the updated 2006 American Heart Association (AHA) "Diet and Lifestyle Recommendations." Balancing caloric intake and physical activity to achieve and maintain a healthy body weight is a major priority in this scientific statement. The authors recommend a diet rich in vegetables, fruits, and whole



[a] Persons in top vs bottom third of usual log-TG values, adjusted for at least age, sex, smoking status, lipid concentrations, and blood pressure (most).

CHD, coronary heart disease; CVD, cardiovascular disease; HDL, high-density lipoprotein; TG, triglycerides.

Adapted from Sarwar N et al. *Circulation*. 2007.[48]

Figure 4 – TG level is a significant CVD risk factor. Shown here are the results of a recent meta-analysis of 29 studies.

grains that is high in fiber, and consumption of oily fish at least twice a week while limiting the intake of saturated fat to less than 7% of energy, trans fat to less than 1% of energy, and cholesterol to less than 300 mg/d by choosing lean meats, vegetable alternatives, and fat-free (skim) or low-fat (1% fat) dairy products and minimizing intake of partially hydrogenated fats.[54]

In observational studies, both physical fitness and physical activity levels are strongly associated with subsequent cardiovascular events, cardiovascular mortality, as well as noncardiovascular morbidity and mortality. The *Aerobics Center Longitudinal Study* (ACLS) was a prospective study that was designed to examine the association between cardiorespiratory fitness and health, which was broadly defined to encompass all-cause mortality, cause-specific mortality, disease morbidity, and functional health status. The study population included over 14,000 women and 46,000 men who were examined at least once at a preventive medicine clinic from 1970 to 2004. Data from this study evaluated changes in physical fitness and the risk of mortality in men.[55] This analysis, which involved assessment of physical fitness by maximal exercise tests and evaluation of health status at 2 clinical examinations conducted 5 years apart, showed that the highest rate of mortality was observed in men who were unfit at both examinations. As expected, those who were fit at baseline and follow-up had the best prognosis. Importantly, men who improved from unfit to fit status between the first and subsequent assessment had a 44% lower mortality than those who remained unfit at both examinations.[55] While observational in nature, this study suggests that exercise interventions that improve physical fitness could have a major impact on cardiovascular morbidity and mortality.

Another study of relevance is the *Diabetes Prevention Program* (DPP), which was designed to determine whether lifestyle intervention or pharmacotherapy with metformin would prevent or delay the onset of diabetes in persons with impaired glucose tolerance, many of whom had metabolic syndrome. Results from this study showed that lifestyle intervention conferred a marked reduction of 58% in the incidence of type 2 diabetes, a reduction that was significantly greater than that achieved with metformin (31%).[56]

Most recently, the LOOK AHEAD trial published its 1-year results indicating that a comprehensive lifestyle approach is more effective in improving metabolic parameters among patients with diabetes than a traditional diabetes education approach.[57] This study is ongoing and will answer the question whether these metabolic improvements translate into improved morbidity and mortality.

TRADITIONAL PHARMACOLOGICAL APPROACHES

While lifestyle management is critical in all patients at increased cardiovascular risk, many will require pharmacological therapy as well, an approach supported by a large evidence base. Given that the magnitude of reduction in cardiovascular events is related to the extent of LDL lowering, recent intervention trials have used increasing doses of statin therapy to achieve maximal therapeutic benefit. In the *Prospective Study of Pravastatin in the Elderly at Risk* (PROSPER) study, treatment with pravastatin 40 mg/day reduced major coronary events by 19%.[58] In the *Heart Protection Study* (HPS), treatment with simvastatin 40 mg/day resulted in a significant reduction in major cardiovascular events by 24%.[59] In the *Pravastatin or Atorvastatin Evaluation and Infection Therapy (*PROVE-IT), patients hospitalized with acute coronary syndrome were given atorvastatin 80 mg/day or pravastatin 40 mg/day. Death, myocardial infarction, unstable angina, revascularization, or stroke was considered as primary end points. Although both statins were effective in reducing LDL-C levels, atorvastatin at higher dose was more effective in lowering clinical events over two years compared with pravastatin therapy; 26.3% versus 22.4%, respectively.[60] To compare the effects of high and low doses of atorvastatin, in the TNT study, 80 mg/day was compared with 10 mg/day in patients with stable CHD. The study concluded that the higher dose of atorvastatin was significantly effective in providing additional clinical benefits compared with low-dose therapy.[61] To compare the effects of 2 different statins on the risk of cardiovascular events, patients with a history of myocardial infarction in the *Incremental Decrease in End Points Through Aggressive Lipid Lowering* (IDEAL) study received either atorvastatin 80 mg/day or simvastatin 20 mg/day. Interestingly, the intensive lowering of LDL-C with atorvastatin at the highest recommended dose did not yield a significant reduction in the primary outcome of major coronary events compared with the moderate and most widely used dose of simvastatin, although atorvastatin 80 mg did significantly reduce secondary CVD end points.[62]

As recommended LDL cholesterol targets have decreased, it has become increasingly difficult to achieve these goals solely with lifestyle modifications. Of relevance is a recent study that analyzed the data from participants of the 1999 to 2002 NHANES study and demonstrated that 30% of the US adults had LDL-C levels that exceeded their corresponding ATP III goals.[63] More impor-

tantly, 18% of the participants exceeded their LDL-C goal by more than 10%; thus, they were considered unlikely to reach their target LDL without pharmacotherapy.[63] For many, adopting the lower optional LDL-C target would mean large reductions using high-dose statin therapy or combination therapy.

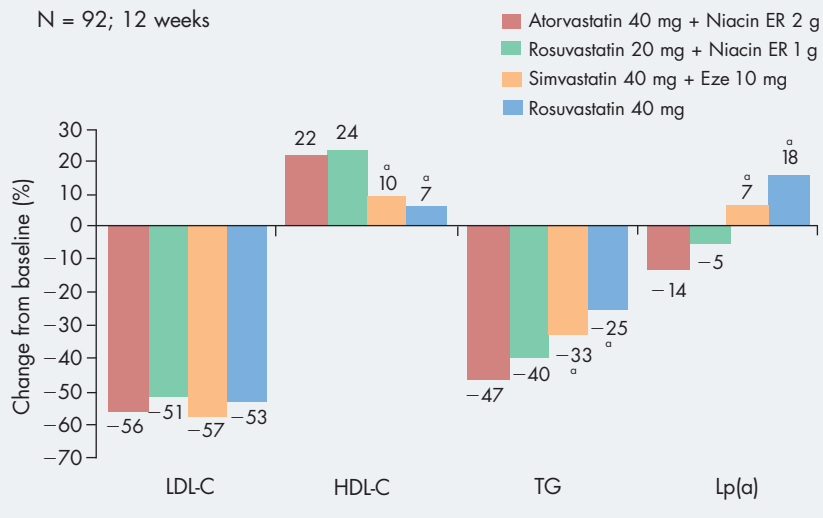
Lowering LDL with statins has significantly reduced CVD risk. A recent meta-analysis of lipid-lowering trials estimated that major coronary events were lowered by 23%, thus leaving a residual risk of 77% for events among treated patients, possibly higher among those at the greatest risk.[4] While high-dose statin therapy may yield additional benefits, a more comprehensive approach targeting other components of the dyslipidemia and addressing non-lipid risk factors is clearly warranted. Additionally, it is important to note that the clinical use of statin therapy depends not only on its ability to reduce LDL-C levels, but also on its tolerability and safety profile. Generally, statins are well tolerated, with myalgias, including rhabdomyolysis, and their effect on liver enzymes the best known and most challenging adverse events.[64] Most statins may occasionally cause myopathy; however, the occurrence has been estimated to be less than 1 in 10,000 patients at standard dose with increasing risk at higher doses.[65]

TARGETING RESIDUAL RISK WITH COMBINATION THERAPY

Combination therapies. In addition to statins, lipid-lowering drugs such as fibrates, niacin, and bile acid sequestrants have proven efficacy in lowering cardiovascular events, although the number of clinical trials that have tested these agents is quite small.[5] Fibrates, which are peroxisome proliferator–activated receptor α (PPAR-α) agonists, affect many genes that influence lipoprotein metabolism and could consequently modulate atherogenesis.[5] Fibrates also exert pleiotropic effects to downregulate proinflammatory genes in vascular cells. While the clinical importance of these effects is speculative, post hoc analyses from some of the fibrate trials do support a role for PPAR-α agonism in patients with diabetes or metabolic syndrome, such as to reduce cerebrovascular disease or microvascular disease of the kidney and retina, vascular conditions that are not related to lipid risk factors.

Analyses of subgroups of patients in several fibrate trials suggest that patients with atherogenic dyslipidemia or diabetes receive greater event reduction compared with those with normal TG and HDL-C levels, or nondiabetics. This effect was especially notable in the older studies such as *Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial* (VA-HIT)[66] and in the *Helsinki Heart Study* (HHS),[67] where a subset of patients with diabetes had a nominally greater risk reduction than patients without diabetes. Furthermore, in the VA-HIT study, the effect of fibrate therapy was less dependent on lipid levels than on the presence or absence of insulin resistance.[66] In the large *Fenofibrate Intervention and Event Lowering in Diabetes* (FIELD) study, patients with type 2 diabetes who were treated with micronized fenofibrate showed significant reduction in total cardiovascular events (a secondary end point) compared with the placebo group.[68] However, it must be noted that fenofibrate treatment did not yield a significant benefit on the primary outcome, which was a combination of CHD events including death or first occurrence of nonfatal myocardial infarction.

Because fibrates appear to have unique benefits in patients with insulin resistance, the combination of statin and fibrate therapy may have the potential to benefit patients with



COMPELL, Comparative Effects on Lipid Levels of Niaspan and Statin Versus Other Lipid-Modifying Therapies Study.

[a] $P < .05$ vs atorvastatin + niacin ER.

ER, extended release; Eze, ezetimibe, LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; Lp(a), lipoprotein(a).

Adapted from McKenney JM et al. *Atherosclerosis.* 2007.[71]

Figure 5 – Shown here are the lipid effects of niacin ER/statin combination therapy in the COMPELL study.

diabetes.[5] The combined effects of simvastatin and fenofibrate on lipid parameters have been investigated in the *Simvastatin Plus Fenofibrate for Combined Hyperlipidemia* (SAFARI) trial.[69] The combination significantly improved the components of atherogenic dyslipidemia compared with monotherapy. For example, combination therapy increased HDL-C levels by 19% compared with 10% with simvastatin monotherapy (19% vs 10%).[69] Although the risk of myopathy is low with statin monotherapy, a significant increase in rhabdomyolysis has been reported when used in combination with fibrates, particularly with gemfibrozil.[70]

Statins have also been combined with niacin. This combination regimen not only significantly lowers LDL-C levels but also TGs and lipoprotein(a) and it concurrently increases HDL-C levels. Thus, the *COMParative Effects on Lipid Levels of Niaspan and Statin Versus Other Lipid-Modifying Agents* (COMPELL) study was designed to investigate whether a low-to-moderate dose of statins with low-dose niacin extended-release (ER) is an effective combination regimen to lower LDL-C levels (>50%) and non-HDL-C.[71] The study concluded that low-dose niacin ER in combination with low doses of either atorvastatin or rosuvastatin was effective in lowering LDL-C by 50%, an efficacy that was comparable to statin/ezetimibe combination therapy or to rosuvastatin monotherapy at moderate-to-high doses.[71] Interestingly, the efficacy of statin/niacin combination therapy on HDL-C, TGs, and lipoprotein(a) was superior to other therapies (**Figure 5**).[71] A limitation of this study was its inability to evaluate the impact of the lipid changes on measurable cardiovascular end points. Nonetheless, limited outcome data exist at this time.

In the *HDL Atherosclerosis Treatment Study* (HATS), patients who were diagnosed with CHD, in addition to having moderately elevated LDL-C and low HDL-C, were randomized to receive simvastatin alone or simvastatin plus niacin for 2.5 years.[72] At the end of the study, significant regression was noted on serial quantitative angiography, accompanied by 60% to 90% risk reduction in cardiovascular events in the combination treatment group compared with half the efficacy observed in the group that received statin alone.[72] Using a similar combination regimen, in the *Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol* (ARBITER) study, treatment with simvastatin plus niacin ER did not result in significant changes in the carotid intima-media thickness from baseline, whereas with statin monotherapy, a significant progression was noted.[73] Interestingly, in the subsequent 1-year follow-up study during which all patients were treated with the combination regimen, an absolute regression was evident in carotid intima-media thickness.[74] The *Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides and Impact on Global Health Outcomes* (AIM HIGH) study, which is still recruiting, is specifically designed to ascertain the impact of statin/niacin combination therapy on cardiovascular outcomes (see www.clinicaltrials.gov).

Niacin therapy induces flushing, raises blood glucose levels, raises uric acid levels, and increase liver enzymes.[75] Although clinical trials have failed to show that niacin therapy increases the rate of myalgias over that of placebo, myopathy has been reported in statin and niacin combination therapy.[75] ■

REFERENCES:

1. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. *N Engl J Med.* 2005;352:1685-1695.

2. Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet.* 2004;364:937-952.

3. Libby P. The forgotten majority: unfinished business in cardiovascular risk reduction. *J Am Coll Cardiol.* 2005;46:1225-1228.

4. Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins. *Lancet.* 2005;366:1267-1278.

5. Davidson MH. Reducing residual risk for patients on statin therapy: the potential role of combination therapy. *Am J Cardiol.* 2005;96:3K-13K.

6. Genest J. Lipoprotein disorders and cardiovascular risk. *J Inherit Metab Dis.* 2003;26:267-287.

7. McKenney JM. Dyslipidemias, atherosclerosis, and coronary heart disease. In: Kradjan WA, ed. *Cardiac and Vascular Disorders.* 2008:13-1, 13-43.

8. Ridker PM, Genest J, Libby P. Risk factors for atherosclerotic disease. In: Braunwald E, Zipes DP, Libby P, eds. *Heart Disease.* 6th ed. Philadelphia: WB Saunders Co; 2001:1010-1017.

9. Stary HC, Chandler AB, Dinsmore RE, et al. A definition of advanced types of atherosclerotic lesions and a histological classification of atherosclerosis. A report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association. *Arterioscler Thromb Vasc Biol.* 1995;15:1512-1531.

10. Jonasson L, Holm J, Skalli O, et al. Regional accumulations of T cells, macrophages, and smooth muscle cells in the human atherosclerotic plaque. *Arteriosclerosis.* 1986;6:131-138.

11. Kovanen PT, Kaartinen M, Paavonen T. Infiltrates of activated mast cells at the site of coronary atheromatous erosion or rupture in myocardial infarction. *Circulation.* 1995;92:1084-1088.

12. Davies MJ. The contribution of thrombosis to the clinical expression of coronary atherosclerosis. *Thromb Res.* 1996;82:1-32.

13. Falk E, Shah PK, Fuster V. Coronary plaque disruption. *Circulation.* 1995;92:657-671.

14. Skalen K, Gustafsson M, Rydberg EK, et al. Subendothelial retention of atherogenic lipoproteins in early atherosclerosis. *Nature.* 2002;417:750-754.

15. Leitinger N. Oxidized phospholipids as modulators of inflammation in atherosclerosis. *Curr Opin Lipidol.* 2003;14:421-430.

16. Eriksson EE, Xie X, Werr J, et al. Direct viewing of atherosclerosis in vivo: plaque invasion by leukocytes is initiated by the endothelial selectins. *FASEB J.* 2001;15:1149-1157.

17. Kawakami A, Aikawa M, Libby P, et al. Apolipoprotein CIII in apolipoprotein B lipoproteins enhances the adhesion of human monocytic cells to endothelial cells. *Circulation.* 2006;113:691-700.

18. Kawakami A, Osaka M, Tani M, et al. Apolipoprotein CIII links hyperlipidemia with vascular endothelial cell dysfunction. *Circulation.* 2008;118:731-742.

19. Peiser L, Mukhopadhyay S, Gordon S. Scavenger receptors in innate immunity. *Curr Opin Immunol.* 2002;14:123-128.

20. Glagov S, Weisenberg E, Zarins CK, et al. Compensatory enlargement of human atherosclerotic coronary arteries. *N Engl J Med.* 1987;316:1371-1375.

21. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation.* 2002;106:3143-3421.

22. Austin MA, Breslow JL, Hennekens CH, et al. Low-density lipoprotein subclass patterns and risk of myocardial infarction. *JAMA.* 1988;260:1917-1921.

23. Grundy SM. Hypertriglyceridemia, atherogenic dyslipidemia, and the metabolic syndrome. *Am J Cardiol.* 1998;81:18B-25B.
24. Krauss RM. Triglycerides and atherogenic lipoproteins: rationale for lipid management. *Am J Med.* 1998;105:58S-62S.
25. Kromhout D. Serum cholesterol in cross-cultural perspective. The Seven Countries Study. *Acta Cardiol.* 1999;54:155-158.
26. Castelli WP. Cholesterol and lipids in the risk of coronary artery disease—the Framingham Heart Study. *Can J Cardiol.* 1988;(4 suppl A):5A-10A.
27. Sacks FM. The apolipoprotein story. *Atheroscler Suppl.* 2006;7:23-27.
28. Sacks FM, Campos H. Clinical review 163: cardiovascular endocrinology: low-density lipoprotein size and cardiovascular disease: a reappraisal. *J Clin Endocrinol Metab.* 2003;88:4525-4532.
29. Campos H, Moye LA, Glasser SP, et al. Low-density lipoprotein size, pravastatin treatment, and coronary events. *JAMA.* 2001;286:1468-1474.
30. Assmann G, Schulte H, von EA, Huang Y. High-density lipoprotein cholesterol as a predictor of coronary heart disease risk. The PROCAM experience and pathophysiological implications for reverse cholesterol transport. *Atherosclerosis.* 1996; 124(suppl):S11-S20.
31. Sharrett AR, Ballantyne CM, Coady SA, et al. Coronary heart disease prediction from lipoprotein cholesterol levels, triglycerides, lipoprotein(a), apolipoproteins A-I and B, and HDL density subfractions: The Atherosclerosis Risk in Communities (ARIC) Study. *Circulation.* 2001;104:1108-1113.
32. Gordon T, Castelli WP, Hjortland MC, et al. High density lipoprotein as a protective factor against coronary heart disease. The Framingham Study. *Am J Med.* 1977;62:707-714.
33. Barter P, Gotto AM, LaRosa JC, et al. HDL cholesterol, very low levels of LDL cholesterol, and cardiovascular events. *N Engl J Med.* 2007;357: 1301-1310.
34. Gotto AM Jr, Brinton EA. Assessing low levels of high-density lipoprotein cholesterol as a risk factor in coronary heart disease: a working group report and update. *J Am Coll Cardiol.* 2004;43: 717-724.
35. Brinton EA, Eisenberg S, Breslow JL. Human HDL cholesterol levels are determined by apo A-I fractional catabolic rate, which correlates inversely with estimates of HDL particle size. Effects of gender, hepatic and lipoprotein lipases, triglyceride and insulin levels, and body fat distribution. *Arterioscler Thromb.* 1994;14:707-720.
36. Brinton EA, Eisenberg S, Breslow JL. Increased apo A-I and apo A-II fractional catabolic rate in patients with low high density lipoprotein-cholesterol levels with or without hypertriglyceridemia. *J Clin Invest.* 1991;87:536-544.
37. Brinton EA, Eisenberg S, Breslow JL. Elevated high density lipoprotein cholesterol levels correlate with decreased apolipoprotein A-I and A-II fractional catabolic rate in women. *J Clin Invest.* 1989;84: 262-269.
38. Lewis GF, Rader DJ. New insights into the regulation of HDL metabolism and reverse cholesterol transport. *Circ Res.* 2005;96:1221-1232.
39. Brooks-Wilson A, Marcil M, Clee SM, et al. Mutations in ABC1 in Tangier disease and familial high-density lipoprotein deficiency. *Nat Genet.* 1999; 22:336-345.
40. Walldius G, Jungner I, Holme I, et al. High apolipoprotein B, low apolipoprotein A-I, and improvement in the prediction of fatal myocardial infarction (AMORIS study): a prospective study. *Lancet.* 2001; 358:2026-2033.
41. Mudd JO, Borlaug BA, Johnston PV, et al. Beyond low-density lipoprotein cholesterol: defining the role of low-density lipoprotein heterogeneity in coronary artery disease. *J Am Coll Cardiol.* 2007; 50:1735-1741.
42. Ballantyne CM, Andrews TC, Hsia JA, et al. Correlation of non-high-density lipoprotein cholesterol with apolipoprotein B: effect of 5 hydroxymethylglutaryl coenzyme A reductase inhibitors on non-high-density lipoprotein cholesterol levels. *Am J Cardiol.* 2001;88:265-269.
43. Pischon T, Girman CJ, Sacks FM, et al. Non-high-density lipoprotein cholesterol and apolipoprotein B in the prediction of coronary heart disease in men. *Circulation.* 2005;112:3375-3383.
44. Liu J, Sempos CT, Donahue RP, et al. Non-high-density lipoprotein and very-low-density lipoprotein cholesterol and their risk predictive values in coronary heart disease. *Am J Cardiol.* 2006;98: 1363-1368.
45. Austin MA. Epidemiologic associations between hypertriglyceridemia and coronary heart disease. *Semin Thromb Hemost.* 1988;14:137-142.
46. Assmann G, Schulte H, Funke H, von Eckardstein A. The emergence of triglycerides as a significant independent risk factor in coronary artery disease. *Eur Heart J.* 1998;19(suppl M):M8-M14.
47. Hulley SB, Rosenman RH, Bawol RD, Brand RJ. Epidemiology as a guide to clinical decisions. The association between triglyceride and coronary heart disease. *N Engl J Med.* 1980;302:1383-1389.
48. Sarwar N, Danesh J, Eiriksdottir G, et al. Triglycerides and the risk of coronary heart disease: 10,158 incident cases among 262,525 participants in 29 Western prospective studies. *Circulation.* 2007;115:450-458.
49. Jacobson TA, Miller M, Schaefer EJ. Hypertriglyceridemia and cardiovascular risk reduction. *Clin Ther.* 2007;29:763-777.
50. Stone NJ. Cardiovascular disease and hyperlipidaemia. *Curr Opin Lipidol.* 1994;5:U16-U21.
51. Chait A, Brunzell JD. Acquired hyperlipidemia (secondary dyslipoproteinemias). *Endocrinol Metab Clin North Am.* 1990;19:259-278.
52. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA.* 2001;285:2486-2497.
53. Gau GT, Wright RS. Pathophysiology, diagnosis, and management of dyslipidemia. *Curr Probl Cardiol.* 2006;31:445-486.
54. Lichtenstein AH, Appel LJ, Brands M, et al. Diet and lifestyle recommendations revision 2006: a scientific statement from the American Heart Association Nutrition Committee. *Circulation.* 2006; 114:82-96.
55. Blair SN, Kohl HW III, Barlow CE, et al. Changes in physical fitness and all-cause mortality. A prospective study of healthy and unhealthy men. *JAMA.* 1995;273:1093-1098.
56. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med.* 2002;346:393-403.
57. Pi-Sunyer X, Blackburn G, Brancati FL, et al. Reduction in weight and cardiovascular disease risk factors in individuals with type 2 diabetes: one-year results of the look AHEAD trial. *Diabetes Care.* 2007;30:1374-1383.
58. Shepherd J, Blauw GJ, Murphy MB, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet.* 2002;360:1623-1630.
59. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet.* 2002;360:7-22.
60. Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med.* 2004;350:1495-1504.
61. LaRosa JC, Grundy SM, Waters DD, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med.* 2005; 352:1425-1435.
62. Pedersen TR, Faergeman O, Kastelein JJ, et al. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. *JAMA.* 2005;294:2437-2445.
63. Persell SD, Lloyd-Jones DM, Baker DW. Implications of changing national cholesterol education program goals for the treatment and control of hypercholesterolemia. *J Gen Intern Med.* 2006;21: 171-176.
64. Escobar C, Echarri R, Barrios V. Relative safety profiles of high dose statin regimens. *Vasc Health Risk Manag.* 2008;4:525-533.
65. Armitage J. The safety of statins in clinical practice. *Lancet.* 2007;370:1781-1790.
66. Rubins HB, Robins SJ, Collins D, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. *N Engl J Med.* 1999;341:410-418.
67. Manninen V, Tenkanen L, Koskinen P, et al. Joint effects of serum triglyceride and LDL cholesterol and HDL cholesterol concentrations on coronary heart disease risk in the Helsinki Heart Study. Implications for treatment. *Circulation.* 1992; 85:37-45.
68. Keech A, Simes RJ, Barter P, et al. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet.* 2005;366:1849-1861.
69. Grundy SM, Vega GL, Yuan Z, et al. Effectiveness and tolerability of simvastatin plus fenofibrate for combined hyperlipidemia (the SAFARI trial). *Am J Cardiol.* 2005;95:462-468.
70. Davidson MH, Robinson JG. Safety of aggressive lipid management. *J Am Coll Cardiol.* 2007;49: 1753-1762.
71. McKenney JM, Jones PH, Bays HE, et al. Comparative effects on lipid levels of combination therapy with a statin and extended-release niacin or ezetimibe versus a statin alone (the COMPELL study). *Atherosclerosis.* 2007;192:432-437.
72. Brown BG, Zhao XQ, Chait A, et al. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. *N Engl J Med.* 2001;345:1583-1592.
73. Taylor AJ, Sullenberger LE, Lee HJ, et al. Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) 2: a double-blind, placebo-controlled study of extended-release niacin on atherosclerosis progression in secondary prevention patients treated with statins. *Circulation.* 2004;110:3512-3517.
74. Taylor AJ, Sullenberger LE, Lee HJ. Atherosclerosis regression during open-label continuation of extended-release niacin following ARBITER 2. *Circulation.* 2005;112(17 suppl):179.
75. Bays H. Safety of niacin and simvastatin combination therapy. *Am J Cardiol.* 2008;101:3B-8B.

CME Assessment/Evaluation/Certificate Request

Striking the Right Balance: The Residual Risk of Coronary Artery Disease

PLEASE PRINT CLEARLY

First name, MI _____

Last name, degree _____

Title _____

Affiliation _____

Specialty _____

Mailing address _____

City _____ State _____ ZIP _____

Daytime telephone (_____) _____ Fax (_____) _____

Email _____

Physicians: This activity is designated for a maximum of 1.0 *AMA PRA Category 1 Credit*™.

Release Date: November 2008

Expiration Date: November 2009

Method of Participation: To receive credit for this activity, you must read the CME monograph. Upon finishing the piece, complete the post-test (located on the inside of the back cover), evaluation, and all required personal information and mail or fax the completed form to:

The Chatham Institute
26 Main Street, 3rd Floor
Chatham, NJ 07928
Fax: (973) 701-2515

Please allow up to 6 weeks for processing.

To receive your CME certificate, you will need to pass the post-test with 70% accuracy or better. If you receive less than 70%, you may review the article and take the test again.

This activity is sponsored by The Chatham Institute and supported by an educational grant from Abbott Laboratories.

Examination: Place an X through the box of the letter that represents the best answer to each question on the post-test.

There is only ONE correct answer per question. Place all answers on this form:

	A	B	C	D	E
1.	☐	☐	☐	☐	☐
2.	☐	☐	☐	☐	☐
3.	☐	☐	☐	☐	☐
4.	☐	☐	☐	☐	☐
5.	☐	☐			
6.	☐	☐	☐	☐	☐
7.	☐	☐	☐	☐	☐
8.	☐	☐			
9.	☐	☐			
10.	☐	☐	☐	☐	☐

T7A50-MG

(continued) ▶

Striking the Right Balance: The Residual Risk of Coronary Artery Disease

Program Evaluation: So that we may assess the value of this self-study program, we ask that you please complete this evaluation form.

Have the objectives for the activity been met?

1. Recognize the types and levels of lipids that contribute to increased coronary heart disease risk.

☐ Yes ☐ No

2. Differentiate the factors that contribute to residual risk, including HDL-C and TG.

☐ Yes ☐ No

3. Assess the effect of therapies that focus on lowering LDL-C versus therapies that are directed toward managing dyslipidemia as a whole (ie, "the lipid triad") in the form of raising HDL-C and lowering serum TG through single-agent and/or combination treatment.

☐ Yes ☐ No

Was this publication fair, balanced, and free of commercial bias?

☐ Yes ☐ No

If no, please explain: _____

_____

Please rate the program on the following parameters using a scale of 1 to 5, where 1 = Never, 2 = Not very often, 3 = Sometimes, 4 = Very often, and 5 = Always.

1. Think about how you ***currently*** treat patients for dyslipidemia. How often do you currently use each of the following strategies?

a. Lifestyle changes (weight loss, diet, exercise) in combination with drug therapy

5 4 3 2 1 N/A

b. Single-agent drug therapies directed at managing "the lipid triad," not just lowering LDL-C

5 4 3 2 1 N/A

c. Combination drug therapies directed at managing "the lipid triad," not just lowering LDL-C

5 4 3 2 1 N/A

d. Fibrate therapy to reduce CVD risk in patients with diabetes and metabolic syndrome

5 4 3 2 1 N/A

e. Addition of niacin to statin therapy to reduce residual CVD risk and slow atherosclerosis

5 4 3 2 1 N/A

2. Based on your completion of this CME supplement, how often do you ***now plan to*** use each of the following strategies when treating patients with dyslipidemia?

a. Lifestyle changes (weight loss, diet, exercise) in combination with drug therapy

5 4 3 2 1 N/A

b. Single-agent drug therapies directed at managing "the lipid triad," not just lowering LDL-C

5 4 3 2 1 N/A

c. Combination drug therapies directed at managing "the lipid triad," not just lowering LDL-C

5 4 3 2 1 N/A

d. Fibrate therapy to reduce CVD risk in patients with diabetes and metabolic syndrome

5 4 3 2 1 N/A

e. Addition of niacin to statin therapy to reduce residual CVD risk and slow atherosclerosis

5 4 3 2 1 N/A

Effectiveness of this method of presentation:

Excellent	Very good	Good	Fair	Poor
5	4	3	2	1

What other topics would you like to see addressed?

_____

_____

_____

Comments: _____

_____

_____

_____

CME Post-Test

Striking the Right Balance: The Residual Risk of Coronary Artery Disease

1. Which of the following mediates the net exchange of triglycerides (TGs) to facilitate the transfer of cholesterol from high-density lipoprotein (HDL) to very low-density lipoprotein (VLDL) remnants?

a. Cholesteryl ester transfer protein

b. Intermediate-density lipoprotein

c. Apo B

d. Apo CIII

e. None of the above

2. Which of the following contribute(s) to atherogenic dyslipidemia?

a. Elevated serum glucose

b. Elevated TGs

c. Elevated HDL

d. Elevated VLDL

e. All of the above

3. In using low-density lipoprotein cholesterol (LDL-C) levels to predict cardiovascular risk, which of the following is (are) true?

a. Apo B is a better predictor of atherogenic risk than LDL-C

b. Apo B is a constituent of VLDL and LDL

c. Small dense LDL particles are moderately correlated with high TGs

d. LDL particle size is not an independent predictor of cardiovascular disease

e. All of the above

4. Which of the following markers is (are) effective predictors of cardiovascular events?

a. Non-HDL-C is a better predictor than LDL-C

b. Non-HDL-C is a better predictor when TGs are elevated > 200 mg/dL

c. Apo B is a better predictor than non-HDL-C

d. Raised apo B/apo AI ratio is a strong predictor of myocardial infarction

e. All of the above

5. In population-based studies, reduced HDL-C is a significant predictor of cardiovascular events only when LDL-C levels are elevated above 160 mg/dL.

a. True

b. False

6. According to the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (NCEP ATP) III guidelines, which of the following clinical features define(s) metabolic syndrome?

a. Elevated TG > 150 mg/dL

b. Reduced HDL-C < 30 mg/dL

c. Abdominal obesity > 40 inches for men

d. Elevated LDL-C > 160 mg/dL

e. Elevated fasting glucose > 110 mg/dL

7. For patients with elevated TG levels (200 - 499 mg/dL) the recommended guidelines are:

a. Achieve LDL-C goals as primary target

b. Achieve non-HDL-C levels as secondary target

c. Prevention of pancreatitis

d. a and b

e. a, b, and c

8. In the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) study, subgroup analysis showed that patients with diabetes benefited significantly more from fibrate therapy than those without diabetes.

a. True

b. False

9. According to the COMParative Effects on Lipid Levels of Niaspan and Statin Versus Other Lipid-modifying Agents (COMPELL) study, statin/niacin combination regimen is effective in lowering LDL-C levels by more than 50%.

a. True

b. False

10. According to the American Heart Association guidelines, the recommended daily intake of cholesterol should not exceed:

a. 100 mg

b. 300 mg

c. 500 mg

d. 1 g

e. 5 g