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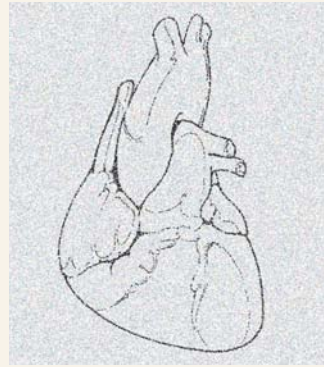
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Striking the Right Balance: The Residual Risk of Coronary Artery Disease



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

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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.

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

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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 re-assembled 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 HDL₂ 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 colleagues²⁰ 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 le-

sions 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 rem-

nants, 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

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

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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