Journal of Clinical Lipidology (2014) 8, 29–60

Journal of Clinical Lipidology

Original Articles

An International Atherosclerosis Society Position Paper: Global recommendations for the management of dyslipidemia—Full report

Expert Dyslipidemia Panel of the International Atherosclerosis Society*

KEYWORDS:
Cholesterol;
Dyslipidemia;
Lifestyle therapies;
Lifetime risk;
Metabolic syndrome;
Statins

Abstract: An international panel of the International Atherosclerosis Society has developed a new set of recommendations for the management of dyslipidemia. The panel identifies non—high-density lipoprotein cholesterol as the major atherogenic lipoprotein. Primary and secondary prevention are considered separately. Optimal levels for atherogenic lipoproteins are derived for the two forms of prevention. For primary prevention, the recommendations emphasize lifestyle therapies to reduce atherogenic lipoproteins; drug therapy is reserved for subjects at greater risk. Risk assessment is based on estimation of lifetime risk according to differences in baseline population risk in different nations or regions. Secondary prevention emphasizes use of cholesterol-lowering drugs to attain optimal levels of atherogenic lipoproteins.
Published by Elsevier Inc. on behalf of National Lipid Association.

Introduction

The International Atherosclerosis Society (IAS) has developed a guide for intervention regarding dyslipidemia. This guide is based on deliberations of an IAS committee with international representation. Its recommendations are based on an interpretation of available data from a majority of the panel members. The Position Paper was developed as follows. Fifteen committee members were nominated by the IAS Executive Committee and were invited to participate on the writing panel. They were both experts and representative of different regions of the world. Timely questions relating to lifestyle and drug management of dyslipidemia were selected and shared with the panel. Responses were organized as IAS panel deliberations. From the deliberations, key recommendations were abstracted. Before each deliberation, a background section was developed for perspective. A draft document was constructed and shared with IAS panel members. Responses were incorporated, and a revised draft was again shared. The second draft was also provided to the IAS Executive Board. All comments were collated and incorporated into a final draft; this was provided to the IAS Executive Committee for approval. Finally, the document was shared with IAS member societies for their comment and ratification. Many member organizations provided useful comments that led a final modification of the document.

The recommendations are based on international consensus. Three major lines of evidence underpinned the recommendations: epidemiologic studies, genetic studies, and clinical trials. Where appropriate, the recommendations were further informed by pathologic studies, pharmacology, metabolic studies, smaller clinical trials, meta-analyses of clinical trials, animal studies, and the basic sciences. Each line of evidence contains strengths and weakness. Epidemiologic studies are worldwide in scope. A vast database of population research relates cholesterol and lipoproteins to atherosclerotic cardiovascular diseases (ASCVDs). The consistency and strength of these relationships make it

For a list of the International Atherosclerosis Society Panel members, see the Appendix.

* Corresponding author: Scott M. Grundy
E-mail address: scott.grundy@utsouthwestern.edu

Submitted December 9, 2013. Accepted for publication December 9, 2013.

1933-2874/$ - see front matter Published by Elsevier Inc. on behalf of National Lipid Association.
http://dx.doi.org/10.1016/j.jacl.2013.12.005

possible to determine optimal cholesterol levels for the prevention of ASCVDs. Although epidemiology is subject to confounding factors, consistency of results from many studies helps to overcome this weakness. Genetic epidemiology reduces the possibility of confounding factors by having single variables—genetic mutations. Although genetic data are limited, they are highly informative for linking cholesterol levels to risk for ASCVD. Finally, clinical trials, especially randomized clinical trials (RCTs), allow the testing of single variables—usually drug therapies. This fact has led many guideline panels to give priority to RCTs over other lines of evidence. However, most RCTs are drug trials. Allowing RCTs to dominate guideline development largely restricts them to drug recommendations; reliable RCTs for lifestyles therapies are few. Drug RCTs, moreover, have not been carried out in a diversity of populations. Volunteers for RCTs commonly do not reflect the population at large. And finally, RCTs are mostly sponsored by the pharmacological industry. They are designed primarily to obtain regulatory registration, not to answer critical questions in clinical intervention. The IAS panel recognized the enormous fund of useful information provided by RCTs but it also has placed RCTs in the context of epidemiologic and genetic findings.

Most investigators in the field of lipid research contend that atherosclerosis is largely a lifestyle problem. This belief derives from epidemiology and not RCTs. Creating guidelines exclusively from drug RCTs makes pharmacology a solution to unhealthy life habits. Drug treatment may of necessity supersede lifestyle in secondary prevention, but a drug paradigm may not be the best for primary prevention. Some investigators are promoting the concept that drugs should be used as public health measures in primary prevention. The IAS panel instead favored the use of lifestyle intervention to reverse unhealthy life habits. Drugs are reserved for patients at greater risk.

Although RCTs are limited, their results are largely congruent with epidemiologic evidence. Epidemiology shows that high levels of serum cholesterol impart increased risk for coronary heart disease (CHD), whereas low levels coincide with low rates of CHD.[1–4] In accordance, RCTs demonstrate that reducing serum cholesterol lowers risk for both CHD and stroke.[5–24] These congruent findings are the cornerstone of cholesterol guidelines.

The writing panel recognized different populations can differ in many important ways. Although the panel attempted to make the recommendations as uniform as possible, adjustments were made as needed for particular countries or populations.

Other organizations likewise have crafted treatment guidelines for dyslipidemia. For more than 25 years, the US National Heart Lung and Blood Institute has sponsored a National Cholesterol Education Program. Its major product has been the reports of the Adult Treatment Panel (ATP). The most recent report is ATP III.[25,26] ATP IV preparation has been suspended. The American Heart Association (AHA) and American College of Cardiology Foundation also issues guidelines; among these, secondary prevention guidelines are the most recent.[27] The European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) publish joint dyslipidemia guidelines.[28] Organizations in other countries have developed guidelines both on lipid management and on cardiovascular risk reduction. The IAS stores all of these guidelines on its website (www.athero.org/); they provide a treasure trove of information for those interested.

Primary prevention

Introduction

Primary prevention seeks to prevent new-onset ASCVDs. These diseases include CHD, stroke, and other atherosclerotic vascular diseases. ASCVD constitutes the leading cause of death in the world[29]; moreover, morbidity and mortality from ASCVD increase when countries become urbanized and industrialized.[30] Because the prevalence of ASCVD increases with advancing age, the reduction in early deaths from infections and malnutrition increases ASCVD prevalence later in life. To reduce the worldwide burden of ASCVD, new onset disease must be decreased.

Pathogenesis of atherosclerosis

Some elevation of LDL seemingly is required for atherogenesis and hence ASCVD.[26,31,32] LDL accounts for more than 75% of atherogenic lipoproteins, the others being cholesterol-enriched remnants of triglyceride-rich lipoproteins. The latter play a larger role when triglycerides are increased. When LDL infiltrates into the arterial wall, it initiates and promotes atherosclerosis; indeed, an increased LDL level acting alone can cause ASCVD. The role of LDL is best exemplified in patients with familial hypercholesterolemia (FH).[33] Persons with FH commonly develop premature atherosclerosis and clinical ASCVD even in the absence of other risk factors.[34] No other risk factor can do the same. In populations with low levels of LDL, the presence of other risk factors—cigarette smoking, hypertension, low HDL, or diabetes—does not lead to premature ASCVD.[35] These other risk factors appear to accelerate atherogenesis when LDL is high enough to initiate atherosclerosis. For this reason, the prime focus of prevention of ASCVD must be on lowering LDL and keeping it low throughout life. LDL promotes atherosclerosis in several ways. After entering the arterial wall, LDL is trapped and modified in a variety of ways; this leads to its uptake by macrophages.[36] Lipid-engorged macrophages are called foam cells. Expansion of regions of foam cells creates a fatty streak. The latter initiates smooth muscle proliferation, and this response forms a fibrous cap (fibrous plaque).[37] Continued LDL infiltration, however, creates

superficial lipid-rich areas in fibrous plaques. These areas are prone to breaking though the surface of the plaque; this breakage is called plaque rupture.[38] When rupture occurs, plaque contents exude and precipitate a thrombosis. Plaque rupture and thrombosis in coronary arteries are responsible for acute coronary syndromes. Ruptures of carotid artery plaques produce strokes. All of these steps occur in patients with FH and demonstrate how increased levels of LDL alone can cause clinical ASCVD.

Because LDL is the predominant cholesterol-carrying lipoprotein, it has received the most attention in the atherosclerosis field. Yet very-low-density lipoproteins (VLDLs) also are cholesterol enriched and have atherogenic potential.[39–44] The most atherogenic form of VLDL consists of partially degraded VLDL, called remnants. The atherogenic component of VLDL is its cholesterol, not its triglyceride. VLDL remnants are particularly enriched in cholesterol. The importance of VLDL as an atherogenic lipoprotein is greatest in persons with hypertriglyceridemia.[45]

Risk factors for ASCVD accelerate the process described previously. The *major risk factors* include cigarette smoking, hypertension, low HDL-C, and diabetes.[26] They act at one or more steps in atherogenesis to enhance the formation of plaques or cause plaque rupture. The *emerging risk factors* are those that relate to atherosclerosis or its complications, although their mechanistic linkage to ASCVD is less well understood. These factors include proinflammatory and prothrombotic states, and some forms of dyslipidemia. *Underlying risk factors* are atherogenic diets, obesity, physical inactivity, and genetic tendencies. They underlie the development of major and emerging risk factors. *Advancing age* is usually listed as a major risk factor, but age per se is not a cause of atherosclerosis. Because atherogenesis progresses throughout life, a person's age commonly reflects atherosclerotic burden; importantly, however, the extent of atherosclerotic burden at a given age varies greatly from one individual to another. Age, therefore, is an imprecise indicator of risk for individuals.

Besides cholesterol lowering, primary prevention aims to reduce the accelerating risk factors—both major and emerging risk factors. Public health approaches to prevention focus on identifying and treating individuals with risk factors, especially smoking and hypertension. Primary prevention promotes lifestyle behaviors to prevent the development of accelerating risk factors as well as elevated LDL-C.[46] When any of the major risk factors are identified, they too become targets for clinical intervention.

Lipoprotein classes

Three major classes of lipoproteins are LDL, VLDL, and high-density lipoproteins (HDLs). VLDL, derived from liver, carries both triglycerides and cholesterol. An elevated VLDL occurs with hypertriglyceridemia. Clinically, LDL is identified as LDL cholesterol (LDL-C). Calculation of LDL-C is as follows: L = C–H–kT, where L is LDL cholesterol, C is total cholesterol, H is HDL cholesterol, T is triglycerides, and k is 0.20 if the quantities are measured in mg/dL and 0.45 if in mmol/L.[47] LDL is derived from the catabolism of VLDL and exits the circulation mainly via LDL receptors on the surface of liver cells. Another triglyceride-rich lipoprotein is the chylomicron; this lipoprotein carries triglycerides derived from dietary fat. Although chylomicrons apparently are not atherogenic, chylomicron remnants may be. The sum of LDL-C and VLDL-C is called non-HDL-C (calculated as non-HDL-C = total-C–HDL-C). Several studies show that non-HDL-C is more strongly related to risk for ASCVD than LDL-C.[48–53] In this document, the term *atherogenic cholesterol* can be applied to either LDL-C or non-HDL-C. It should be noted that total cholesterol is often used in risk assessment algorithms. Total cholesterol is less reliable as a target of therapy, but it can be used if lipoprotein cholesterol values are not available.

HDL is derived in part through products released during triglyceride catabolism; other components are made by liver and gut. Epidemiologic evidence suggests that HDL may protect against ASCVD.[54–56] A low HDL-C is widely recognized as a major risk predictor for ASCVD.[26,29,57] Several mechanisms are proposed whereby a high HDL-C may protect against ASCVD.[58] Clinical trials are currently underway to determine whether HDL-increasing drugs will reduce the risk of ASCVD. Regardless of outcome, HDL is a powerful indicator of risk and plays a key role in global risk assessment.

Lifestyle influence on lipoproteins and ASCVD risk

The prevalence of ASCVD differs greatly in different regions of the world.[30] Although these differences may be due in part to genetic/racial factors, most investigators believe that lifestyle influences predominate.[59–66] These influences include the composition of diet, total caloric intake and body weight, physical activity levels, and smoking habits.[46,67] The former three affect LDL or other lipoproteins. If healthy life habits were to be adopted in high-risk populations, the prevalence of ASCVD almost certainly would decline.

Dietary lipids

Dietary fats in particular affect lipoprotein levels.[68] Diets rich in saturated fatty acids and trans-fatty acids increase LDL-C levels, as does a high cholesterol intake.[26] In populations in which dietary saturated fatty acids and cholesterol are high, serum cholesterol levels are 10%–25% greater than where intakes are low.[69,70] Unsaturated fatty acids (monounsaturated and polyunsaturated) do not increase LDL-C levels and represent an alternative to saturated fatty acids.[71] Diets high in carbohydrates will cause mild-to-moderate increases in VLDL and often reduce HDL levels. Unsaturated fatty acids do not affect LDL-C levels relative to carbohydrates. Replacement of

Table 1 Criteria for clinical diagnosis of the metabolic syndrome

Measure	Categorical cut points
Increased waist circumference*	Population- and country-specific definitions
Increased triglycerides (drug treatment for increased triglycerides is an alternate indicator†)	≥150 mg/dL (1.7 mmol/L)
Reduced HDL-C (drug treatment for reduced HDL-C is an alternate indicator†)	<40 mg/dL (1.0 mmol/L) in men <50 mg/dL (1.3 mmol/L) in women
Increased blood pressure (antihypertensive drug treatment in a patient with a history of hypertension is an alternate indicator)	Systolic ≥130 and/or diastolic ≥85 mm Hg
Increased fasting glucose‡ (drug treatment of elevated glucose is an alternate indicator)	≥100 mg/dL

HDL-C, high-density lipoprotein cholesterol.

*It is recommended that the International Diabetes Federation cut points be used for non-Europeans and either the IDF or American Heart Association/National Heart, Lung, and Blood Institute cut points used for people of European origin until more data are available (See Table 2).

†The most commonly used drugs for increased triglycerides and reduced HDL-C are fibrates and nicotinic acid. A patient taking 1 of these drugs can be presumed to have high triglycerides and low HDL-C. High-dose n-3 fatty acids presume high triglycerides.

‡Most patients with type 2 diabetes mellitus will have the metabolic syndrome by the proposed criteria.

carbohydrates with monounsaturated fatty acids has the advantage that it does not lower HDL-C.[72] However, there is little evidence that a greater VLDL and lower HDL-C on high carbohydrate diets are atherogenic; populations consuming low-fat, high-carbohydrate diets often have low rates of ASCVD, especially CHD.

Epidemiologic studies indicate that countries having high intakes of saturated fats and cholesterol carry an increased prevalence of CHD.[73–75] In contrast, when intakes of saturated fats and cholesterol are low, whether from diets low in total fats or high in unsaturated fats, rates of CHD are relatively low. A few RCTs have evaluated the effects of saturated fats and unsaturated fats on incidence of CHD; those on a diet high in unsaturated fats had fewer CHD events.[76–78]

Cardioprotective foods and food patterns

Other dietary factors have been implicated in ASCVD risk (or protection there from). These include fruits and vegetables, fish, n-3 fatty acids, nuts, seeds, moderate alcohol intake, and low sodium/high potassium intakes.[67,79–85] In particular, available evidence indicates that increased consumption of some natural foods, such as tree nuts and peanuts, legumes, whole grains rich in soluble fiber like oats and barley, and cocoa products like chocolate, can reduce blood cholesterol by themselves, independently of the background diet.[86] Part of the cholesterol-lowering effects of seeds may be due to fiber content. It is has been demonstrated that high intakes of soluble fiber will reduce serum cholesterol levels.[87,88] Another category of plant products that reduce cholesterol levels are the plant sterols/stanols.[89–93] Intakes of approximately 2 g per day of these products will reduce serum LDL-C levels about 10%.

None of these factors have been subjected to rigorous RCTs except for n-3 fatty acids. In the Japan eicosapentaenoic acid (EPA) lipid intervention study, a primary and secondary prevention study in patients with hypercholesterolemia, EPA reduced the risk for major coronary events when combined with a statin.[94] Recently, an important RCT has tested the effects of a Mediterranean-type diet on CHD risk.[95] This was enriched with virgin olive oil or mixed nuts, thus high in unsaturated fats. A test of this diet showed that it protected against ASCVD.[95]

Obesity

Excess body fat adversely affects all of the lipoproteins. In some people, obesity increases LDL-C levels but it more consistently increases VLDL and lowers HDL-C.[96] HDL-C can decrease during active weight loss, with a typical return to baseline, or increase above baseline longer term if weight loss is maintained. In addition to improvement in lipid blood levels with nutritional and physical activity interventions, overweight, dyslipidemic patients may simultaneously experience improvement in lipid blood levels with fat weight loss promoted by weight management drug therapies as well as bariatric surgery.[97] Epidemiologic studies show that obesity is an underlying risk factor for ASCVD[98,99]; this risk is mediated largely through major risk factors but possibly through emerging risk factors as well.

Physical inactivity

Epidemiologic studies indicate that physical inactivity associates with increased risk for ASCVD.[100] Regular physical activity helps to prevent obesity with the accompanying beneficial effects on lipoproteins.[97] Vigorous physical activity appears to independently lower triglycerides and increase HDL-C.[101] Beyond effects on plasma lipids, physical activity may protect against ASCVD in a variety of ways.[102,103]

Metabolic syndrome

Adverse risk factors induced by obesity and physical inactivity can aggregate to produce a multiplex risk factor for ASCVD and diabetes called the metabolic syndrome. This syndrome consists of atherogenic dyslipidemia (high

triglyceride and low HDL-C), high blood pressure, elevated plasma glucose, a prothrombotic state, and a proinflammatory state. In many countries, the prevalence of the metabolic syndrome ranges between 20% and 30% of the adult population; in some populations, the prevalence can be even greater.[104] A clinical diagnosis of the metabolic syndrome based on consensus was recently published.[105] The criteria are shown in Table 1.

Table 2 lists country specific recommendations for waist circumference thresholds for abdominal obesity. The presence of the metabolic syndrome essentially doubles the risk for ASCVD.[106,107] Of clinical importance, all of the risk factors associated with syndrome can be improved by lifestyle intervention.[108–111]

Tobacco use

Another lifestyle consideration is tobacco use, particularly cigarette smoking. This is a major cause of ASCVD worldwide and a high priority must be given to prevention or cessation of cigarette smoking as a lifestyle intervention.[30]

Lipid-lowering drugs and ASCVD risk

Statins are powerful LDL lowering drugs. They block cholesterol synthesis in the liver and increase LDL receptors, which remove LDL from the blood stream. Statins also lower VLDL, the other atherogenic lipoprotein. These agents reduce LDL-C by 25%–55%. A wealth of RCT evidence demonstrates that statins decrease risk for ASCVD events in both primary and secondary prevention.[20,121,122] In 5-year RCTs, they reduced risk for ASCVD events by 25%–45%; it is estimated that long-term treatment will produce even greater risk reduction.[123] Statins are first-line drug treatment in both primary and secondary prevention.

Statins have proven to be safe for most patients.[124–126] They do not cause liver disease, cataracts, or hemorrhagic stroke. Rare patients experience muscle damage characterized by marked elevations of creatine kinase, rhabdomyolysis, hemoglobinuria and acute renal failure. This is most likely to occur in who have complex medical problems and/or who are taking multiple medications. Predisposing medications are cyclosporine, fibrates, macrolide antibiotics, certain antifungal drugs. The combination of gemfibrozil with a statin is more likely to cause myopathy than is fenofibrate.

The most common side effect of statins is myalgia. Up to 10% of patients taking statins complain of muscle aches, weakness or other symptoms[127,128]; consequently, some people are unable or unwilling to continue their statin. The extent to which myalgias are actually due to statins is disputed.[129,130] For patients who complain of myalgias on statin therapy, alternative approaches thus must be used to obtain the needed LDL reduction. These include maximizing lifestyle therapies or using other lipid-lowering drugs. In some patients, statins can cause moderate rises in transaminases, which are not a sign of true hepatoxicity but may require reassurance.[131] Recently, statins have been linked to new-onset diabetes.[132,133] The risk seems small, is of questionable clinical relevance, and is far outweighed by benefit of risk reduction for ASCVD. Most cases of diabetes appear in to occur in patients who already

Table 2 Current recommended waist circumference thresholds for abdominal obesity by organizations

		Recommended waist, cm	
Population	Organization (reference)	Men	Women
Caucasian	WHO, 2000[112]	≥94 (increased risk) ≥102 (still greater risk)	≥80 cm (increased risk) ≥88 (still greater risk)
United States	AHA/NHLBI (ATP III*) (NCEP 2002)[26]	≥102	≥88
Canada	Health Canada (Health Canada 2003[113]; Khan et al 2006)[114]	≥102	≥88
European	European Cardiovascular Societies (Graham et al 2007)[115]	≥102	≥88
Asian	WHO (Hara et al 2006)[116]	≥90	≥80
Japanese	Japanese Obesity Society (Oka et al 2008)[117,118]	≥85	≥90
China	Cooperative Task Force (Zhou 2002)[119]	≥85	≥80
Middle Eastern, Mediterranean	IDF (Alberti et al 2005)[120]	≥94	≥80
Sub-Saharan African	IDF (Alberti et al 2005)[120]	≥94	≥80
Ethnic Central and South American	IDF (Alberti et al 2005)[120]	≥90	≥80
Europid	IDF (Alberti et al 2005)[120]	≥94	≥80
Asian (including Japanese)	IDF (Alberti et al 2005)[120]	≥90	≥80

AHA, American Heart Association; ATP, Adult Treatment Panel; IDF, International Diabetes Federation; NCEP, National Cholesterol Education Program; WHO, World Health Organization.

*Recent American Heart Association/NHLBI guidelines for metabolic syndrome recognize an increased risk for cardiovascular disease and diabetes at waist-circumference thresholds of ≥94 cm in men and ≥80 in women and identify these as optional cut points for individuals or populations with increased insulin resistance.[112,121]

have borderline diabetes. Occasional patients complain of cognitive dysfunction while taking statins.[134–136] The possibility of these side effects indicates that statin therapy must balance benefit versus risk. Fortunately, the risk for serious side effects is low, whereas the benefit for patients at risk for ASCVD can be great.

Ezetimibe is another LDL-lowering drug. It blocks the absorption of cholesterol by the intestine. This only moderately lowers LDL-C (15%–25%).[137] Ezetimibe appears to be safe but has not been tested in RCTs against placebo in monotherapy for either safety or for efficacy to reduce ASCVD. The rationale for use of ezetimibe therefore is predicated on its ability to lower LDL levels. One use of the drug is for LDL lowering in patients with statin intolerance. Another is in combination with statins in patients with FH. It can further be used with statins to achieve very low LDL-C levels in very-high-risk patients.[138] Recently, the combination of ezetimibe and simvastatin was shown to reduce cardiovascular events in patients with chronic kidney disease.[139]

Fibrates are primarily triglyceride-lowering agents that also lower VLDL-C. Clinical experiences attests to their utility for treatment of severe hypertriglyceridemia to prevent development of acute pancreatitis. They also have been tested in many RCTs for prevention of CHD. A meta-analysis of these trials shows reduction for CHD morbidity of about 10%[140]; however, there was not a reduction in total mortality. Another meta-analysis in patients with hypertriglyceridemia found a CHD risk reduction of approximately 25%.[141] Moreover, RCTs have shown that fibrates, specifically gemfibrozil, reduce risk when used as the sole lipid-lowering drug[142,143]; they therefore represent an alternative in people who cannot tolerate statins. The combination of a statin + a fibrate is attractive for mixed hyperlipidemia because of a favorable effect on the lipoprotein pattern; however, evidence in RCTs of incremental risk reduction when a fibrate if added to a statin is lacking. There is a need for a specific clinical trial to test the efficacy of add-on fibrate therapy in patients with mixed hyperlipidemia.

Niacin effectively lowers triglycerides and moderately increases HDL-C. It also moderately reduces LDL-C. In one secondary prevention trial niacin reduced CHD events and total mortality.[144,145] Imaging studies further show that niacin combined with a statin reduces subclinical atherosclerosis.[146,147] In two large secondary RCTs, however, addition of niacin to maximal statin therapy failed to further reduce ASCVD events.[148,149] It is well known that niacin is accompanied by a variety of side effects; of note, in Heart Protection Study 2: Treatment of HDL to Reduce the Incidence of Vascular Events (HPS-2 THRIVE), the combination of niacin and simvastatin was accompanied by an increased risk of myopathy in the Chinese population.[150] On the other hand, for patients with statin intolerance, the combination of niacin + ezetimibe can effectively lower LDL-C levels[151]; this represents an alternative to statin therapy but without proof of risk reduction.

LDL cholesterol and Non-HDL cholesterol as major targets of therapy

Background

Most guidelines for dyslipidemia recognize LDL as the major atherogenic lipoprotein and consequently identify LDL-C as the primary target of therapy.[26,28] In addition strong evidence points to VLDL as being atherogenic like LDL[26,44]; thus, the claim can be made that combining LDL and VLDL makes non-HDL-C a preferred target in patients with dyslipidemia. Because the major apolipoprotein of both LDL and VLDL is apolipoprotein B (apoB), some investigators propose the use of total apoB as an alternative to non-HDL-C.[152] These investigators cite studies suggesting that total apoB (or lipoprotein particle number) is more highly correlated with ASCVD risk than is LDL-C,[153–162] and other reports suggest that apoB is more strongly correlated with ASCVD risk than is non-HDL-C.[163–165] Therefore, some workers contend that total apoB is the preferred target of lipid-lowering therapy. Other reports suggest that non-HDL-C equals or exceeds the predictive power of apoB.[50,166,167] Thus, if total apoB is more predictive than non-HDL-C, the difference is small. A recent analysis of contemporary statin trials moreover demonstrated that on-treatment levels of non-HDL-C are more strongly associated with future risk of ASCVD events than either apoB or LDL-C.[166] In the same analysis non-HDL-C explained a larger proportion of the atheroprotective effects of statin therapy than either apoB or LDL-C.[166] These findings favor the use of non-HDL-C over LDL-C as targets of therapy. Other reasons to place primacy on non-HDL-C are that it is less expensive to measure than apoB and does not require fasting as does LDL-C.

As for HDL-C, epidemiologic studies show that levels of this lipoprotein are inversely associated with risk for ASCVD.[54] These studies suggest that HDL may be protective. Clinical trial evidence indicates that risk for ASCVD is modulated by HDL-C levels even when statin treatment has reduced LDL-C levels to below 70 mg/dL (1.8 mmol/L).[168] But because of a lack of evidence that raising HDL-C reduces risk for ASCVD, current treatment guidelines do not make a low HDL-C concentration a primary target of drug therapy. They do however support maximizing lifestyle therapies in an effort to raise HDL-C concentrations.

IAS panel deliberations

For historical and conceptual reasons, most panel members recognized LDL-C as the first target of clinical intervention for reducing the risk of ASCVD. Non-HDL-C (reflecting all atherogenic lipoproteins) was considered an equal target in patients with or without hypertriglyceridemia. Several panel members in fact favored replacing LDL-C with non-HDL-C as the primary treatment target. Others found apoB attractive as an alternative to non-HDL-C. They nonetheless recognized the increased cost of measuring

apoB; most felt that any superiority of apoB over non-HDL-C is not sufficient to justify its routine measurement in either risk assessment or as a target of therapy.[169] An optimal apoB level for primary prevention remains to be defined. According to one study, in untreated, high-risk patients, an apoB level of <90 mg/dL is roughly equivalent to an LDL-C level <100 mg/dL and a non-HDL-C level <130 mg/dL; during statin therapy, however, to consistently reach an apoB target of <90 mg/dL, it is necessary to reduce non-HDL-C to <100 mg/dL or to reduce LDL-C to <70 mg/dL.[170] A final issue with apoB in routine clinical management is a lack of standardization.[171] Because the measurement of apoB is an immunoassay, it suffers from inconsistencies in measurement technique. Finally, the panel counted a low HDL-C as a major risk factor and recommended it be a component of global risk assessment; moreover, a low HDL-C was considered a reasonable target of lifestyle intervention but not of drug therapy.

Recommendation

Because LDL is the major atherogenic lipoprotein, LDL-C is accepted as the major target of lipid-lowering therapy. Non-HDL-C nonetheless is an alternate target and has growing advantages. Notably it includes atherogenic cholesterol-rich VLDL remnants and it does not require fasting for accurate measurement. Thus, in this document, the term *atherogenic* cholesterol is used interchangeably with LDL-C and non-HDL-C. It is expected that in future guidelines non-HDL-C will replace LDL-C as the better target of treatment. Total apoB is an optional target, but is not recommended as a primary target treatment. Issues of cost, lack of standardization, and lack of consensus on its use stand in the way of making apoB the primary treatment target. A low HDL-C is a target of intervention, but predominately through lifestyle therapies. Because HDL-C is independently and inversely related to ASCVD risk, it is useful as a component of global risk assessment.

Other lipid measures in primary prevention

Background

Other lipid-related measures are either predictors of ASCVD or they are potential targets of therapy. Among these are triglycerides, lipoprotein subfractions, total cholesterol/HDL-C ratios, triglyceride/HDL-C ratios, lipoprotein (a) (Lp[a]), and lipoprotein-associated phospholipase A(2) (Lp-PLA2). Elevated serum triglycerides are a positive risk predictor for ASCVD[45,172–174]; however, except in cases of severe hypertriglyceridemia, they are not a direct target of therapy. High triglycerides are associated with increased non-HDL-C, and for risk prediction and therapy, they are subsumed by the latter. Small, dense LDL particles likely carry ASCVD prediction.[156,157,175–178] Although positive prediction is undeniable, more small LDL particles occur in the presence of greater non-HDL-C. Effective treatment of the latter probably is sufficient. The total cholesterol/HDL-C ratio was previously promoted by Framingham investigators as a predictor of CHD.[179] Similarly, the apoB/apoA1 ratio has been shown to be a strong predictor of CHD.[180,181] Both total cholesterol and HDL-C appear in Framingham global risk assessment, and so the predictive power of the ratio adds nothing to risk assessment. To date apolipoproteins and their ratios have not been incorporated into Framingham risk scoring. The triglyceride/HDL-C ratio has been shown to correlated with insulin resistance and risk for ASCVD[182–187]; its major usefulness is as a component of the metabolic syndrome. An elevated Lp(a) almost certainly is associated with a greater risk for ASCVD; thus, Lp(a) may have some utility in risk assessment.[188] Except for a modest effect of niacin, there are no efficacious drugs currently available for reducing Lp(a). Lp-PLA2 is an inflammatory enzyme expressed in atherosclerotic plaques. A collaborative meta-analysis of 32 prospective studies showed that Lp-PLA2 is positively correlated with risk for ASCVD.[189] At present, however, its use as a predictor of ASCVD has not been fully developed.

IAS panel deliberations

The panel recognized that a variety of other lipid risk factors have predictive power for ASCVD. To date, however, these factors have not been incorporated into standard risk assessment tools such as the Framingham risk scoring. Their utility thus is either limited or uncertain. Furthermore, their measurements add expense to routine risk assessment. Consequently, they cannot be recommended for routine testing. In the hands of lipid specialists some of these tests may provide useful information. For example the panel recognized that the EAS recommends screening for elevated Lp(a) in those at moderately high or high ASCVD risk, and in selected patients, niacin therapy can be employed.

Recommendations

Estimation of fasting triglycerides is useful for calculating LDL-C levels; increased triglycerides further support use of non-HDL-C as a treatment target. Determination of small dense lipoproteins is an option, but usefulness in prediction or therapy is largely subsumed by non-HDL-C. The total cholesterol/HDL-C ratio adds nothing to global risk assessment because the ratio is already part of the latter. Similarly, the triglyceride/HDL-C ratio is contained in the metabolic syndrome. An elevated Lp(a) signifies a greater risk in patients with multiple risk factors; its presence points to a need for more intensive management of other risk factors, notably atherogenic cholesterol. A high Lp-PLA2 appears to be predictive of ASCVD; but at present the test is not widely available.

Nonlipid emerging risk factors

Background

There are several so-called emerging risk factors for ASCVD.[28,190–192] Among these are C-reactive protein (CRP), fibrinogen, plasma insulin, Lp-PLA2, homocysteine,

and microalbuminuria. Among these, CRP has received the most attention. Without a doubt, CRP carries predictive power. Some investigators contend that elevated CRP signifies need for statin therapy in a person otherwise at borderline risk.[193] One algorithm uses CRP along with other risk factors to calculate absolute risk; this is the Reynolds risk algorithm (http://www.reynoldsriskscore.org/).[194] Other researchers contend that emerging risk factors carry little utility in global risk assessment.[195] They argue that even if risk prediction with CRP (or other biomarkers of risk) is positive, the number of people who would benefit from screening is too small to justify the financial investment into routine measurement.[195]

IAS panel deliberations

Among the several nonlipid risk factors, only CRP was considered worthy of use in risk-assessment algorithms. There was not full agreement on its value, although it was acknowledged that an elevated CRP associates with increased risk for ASCVD. Measurement of CRP is an option in moderate risk patients as a guide the risk-reduction therapy. If CRP is to be measured, use of the Reynolds risk score deserves consideration.

Recommendations

CRP measurement is an option in patients at moderate lifetime risk. If CRP is used, the most acceptable risk assessment tool is the Reynolds risk score.

Identifying persons at risk for ASCVD

Short-term risk assessment with major risk factors

Most guidelines adjust intensity of LDL-lowering therapy (and LDL-C goals) to absolute, short-term risk as determined by major risk factors and age. For primary prevention, several categories of risk are defined. Most algorithms estimate 10-year risk for CHD or ASCVD. In the United States, ASCVD is approximately one-third greater than CHD (2012 NHLBI Morbidity and Mortality Chart Book; http://www.nhlbi.nih.gov/resources/docs/chtbook.htm). Although risk categories vary somewhat in different guidelines, risk typically is divided into three categories of 10-year risk: high, intermediate, and low. ATP III guidelines defined *high risk* as 10-year risk for CHD to be >20%, *intermediate risk* is 5–20%, and *low risk,* <5%. Intermediate risk was subdivided into *moderately high risk* (10–20) and *moderate risk* (2+ risk factors or ~ 5–9%). The EAS/ESC[28] classifies risk according to 10-year risk for fatal cardiovascular disease: *very high* (>10%), *high* (5%–10%), *moderate* (intermediate) (≥1% and <5%), and *low* (<1%). The high risk of EAS/ESC corresponds approximately to 10-year risk for ASCVD events of 15%–30%. The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice propose similar risk assessment.[196] In recent Canadian guidelines, risk categories were defined in terms of 10-year risk for CHD: high: ≥20%; intermediate: 10%–19%; and low: <10%. Brazilian guidelines used the same classification. Other countries propose similar although not identical categories. Australian guidelines categorized risk for CHD as high: > 15%/5 years (>~30%/10 years); moderate: 10%–15%/5 years (~20–30%/10 years); and low: <10%/5 years (<~20%/10 years). Japanese guidelines defined three categories of 10-year risk for CHD death: high: >2.0%, moderate: 0.5 to <2.0%; and low: <0.5%.

ATP guidelines have used the Framingham risk algorithm to classify risk for hard CHD (myocardial infarction and coronary death).[26] The prevalence in the United States of three categories of 10-year risk for CHD (≥20%; 10%–19%; and <10%) by age is shown in Figure 1.

The EAS/ESC uses an algorithm called Systematic COronary Risk Evaluation (SCORE) to determine risk for fatal CVD. Another risk algorithm available in Europe is PROCAM.[197] The latter is similar to Framingham, except that it is adjusted for the European population (http://www.chd-taskforce.de/). The question has been raised whether Framingham scoring and SCORE overestimate the risk for CHD.[198] This is a reasonable question because of the decrease in CHD rates in greater-risk populations. Available evidence indicates that Framingham scoring overestimates risk in many countries (see below).

Risk assessment with major + emerging risk factors

As discussed previously, a host of emerging lipid and nonlipid risk factors has been studied. Surprisingly few studies attempted to incorporate them into global risk assessment (including major risk factors). One exception is the metabolic syndrome, which includes both emerging and major risk factors. In US populations, patients with the metabolic syndrome appear to be at moderately high risk for CHD.[199] In fact, postmenopausal women with metabolic syndrome appear to be at greater risk than predicted by Framingham scoring.[200] Several authors have emphasized the need to incorporate the metabolic syndrome into global risk assessment.[201–204] Framingham investigators have further reported that the trajectory for increasing risk is greater in persons with the metabolic syndrome than in those without.[205] Thus, the presence of the metabolic syndrome may signify greater lifetime risk for a given Framingham risk score for 10-year risk. In a word, it is doubtful that risk associated with the metabolic syndrome is entirely subsumed by Framingham risk scoring. Moreover, there is little doubt that the metabolic syndrome is a stronger predictor of type 2 diabetes than is Framingham risk scoring.[206,207]

Framingham risk scoring does not include triglycerides as one of its components. Another risk assessment tool (Prospective Cardiovascular Münster study tool) does in fact include triglycerides in global risk assessment (http://www.chd-taskforce.com/procam_interactive.html).[208] Prospective Cardiovascular Münster investigators have reported that unadjusted Framingham scoring overestimates risk in European populations.[209] This seems to be a

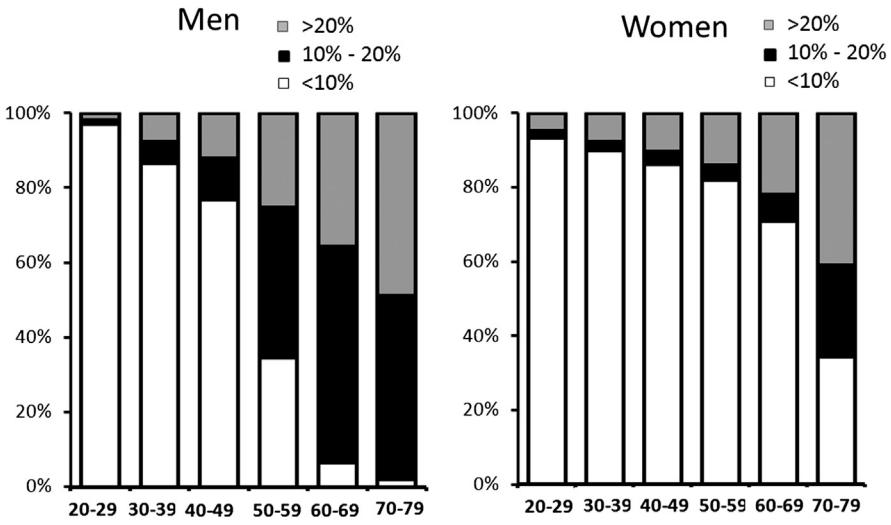

Figure 1 Ten-year risk for CHD by age decade based on National Health and Nutrition Examination Survey III data. Risk levels include high (>20%), intermediate (10%–20%), and low (<10%). Modified from Ford et al.[346]

well-defined discrepancy between the populations of some European countries and that of the United States.

Small LDL particles associate with risk for ASCVD.[175,176,210] Framingham investigators have examined the relation between small LDL particles and ASCVD risk in their population.[211] They found small LDL particle number is increased in the patients with the metabolic syndrome, with increases with the number of metabolic syndrome components, and most prominently with triglycerides and HDL-C. Whereas increased small LDL particle number identified the metabolic syndrome with high sensitivity, a higher number of small LDL particle number was not associated with greater CVD event rates in those with the metabolic syndrome. They made no attempt to integrate LDL particle number into Framingham risk scoring.

Finally, there has been much interest in integrating CRP into Framingham risk assessment. One approach has been to use CRP as a "tie-breaker" to decide whether to use cholesterol-lowering drugs for a given Framingham risk score. Framingham investigators indicate that this approach has promise.[193] But perhaps more promising is the inclusion of CRP values into multivariate analysis so as to produce a risk assessment tool that incorporates this measure. The Reynolds risk score is the best example of this approach (http://www.reynoldsriskscore.org/).[194]

In summary, there is promise for combining emerging risk factors with the major risk factors for estimating risk. To date, however, no consensus has gelled on how best to merge the two categories of risk factors. Consequently, until a consensus has developed, it is preferable to use algorithms that incorporate only the major risk factors. This does not detract from the usefulness of metabolic syndrome as a long-term predictor of ASCVD and type 2 diabetes. Moreover for those who desire to use CRP as a component of risk assessment, Reynolds risk scoring is an option.

Risk assessment by atherosclerosis imaging

One promising approach to improved risk assessment is through atherosclerosis imaging. Measurement of coronary artery calcium (CAC) is the most widely used approach.[212] CAC is strongly correlated with coronary artery plaque burden.[213–217] Carotid artery sonography is another methodology, although it does not have as much predictive power for CHD events as does CAC.[218–220] Nonetheless, carotid artery imaging with ultrasound and other imaging modalities can be useful for identification at high risk for stroke.[221,222] These modalities can be a useful guide for stroke prevention. There is little doubt that CAC adds predictive power when combined with Framingham risk scoring.[223–230]

According to a recent expert committee report, CAC testing can be used as an adjunct to risk-factor scoring in intermediate risk (moderate-to-moderately high risk) patients.[212] CAC measurement in these patients could be a guide to intensity of statin therapy. Nonetheless, CAC testing is not widely available and is relatively expensive. How to use it appropriately in risk assessment is not well understood by most physicians. Therefore, CAC testing has not become a part of routine risk assessment.

Long-term risk assessment

The use of 10-year risk assessment as a sole indicator of risk is problematic because the purpose of primary prevention is to reduce lifetime risk, not 10-year risk. Estimates of 10-year risk, of course, underestimate lifetime risk except in the elderly population. This fact has led to increased interest in estimating lifetime risk.[231–235] Donald Lloyd-Jones has spear-headed interest in lifetime risk estimation.[231,235–243] A seminal report by[238] was based on Framingham data. Risk factors included total cholesterol, systolic blood pressure, cigarette smoking, and diabetes. Four risk levels of cholesterol and blood pressure were

identified. Cigarette smoking and diabetes were named major risk factors. Atherosclerotic CVD events were defined by the occurrence of myocardial infarction, coronary insufficiency, death resulting from CHD, angina pectoris, atherothrombotic stroke, intermittent claudication, or other cardiovascular death. This risk-assessment tool will hence be designated the Lloyd-Jones/Framingham algorithm (Table 3).

Table 4 provides an estimation of total CVD morbidity by age 80 from age 50 based on these four risk factors in the Framingham Heart Study.[238] A potential weakness of this algorithm is that it is based on estimated risk from age 50. However, it can reasonably be assumed that an individual's risk factors (other than age) will remain constant throughout middle age and into older years. Consequently basing the estimate of long-term risk starting at age 50 should give a fairly good estimate of absolute long-term risk.

In a more recent publication from The Cardiovascular Lifetime Risk Pooling Project,[235] the same risk factors were used to estimate CVD mortality by age 80 from age 55 based on these same four risk factors as in the Lloyd-Jones/Framingham Risk Algorithm.

In another long-term risk predictor from the Framingham Heart Study, investigators[233] related the number of major risk factors to 10-year and 30-year risk for CVD morbidity and mortality in 45-year-old men and women. This algorithm is similar to that developed by Lloyd-Jones.[238]

Another risk predictor to estimate lifetime risk of ASCVD is the QRISK model.[234,244,245] This model was derived from a prospective cohort study with data collected from 563 general practices in the United Kingdom between 1994 and 2010. The study included 2,343,759 subjects in the derivation dataset and 1,267,159 in the validation dataset. Measures included smoking status, ethnic group, systolic blood pressure, total cholesterol/high density lipoprotein cholesterol ratio, body mass index (BMI), and family history of CHD disease in first degree relative aged <60 years. CVD was defined as CHD, stroke, and transient ischemic attack. The QRISK2 lifetime risk calculator is available at www.qrisk.org/lifetime/. This calculator has the advantage that it is ethnic specific, at least for the ethnicities represented in the UK.

Table 3 Lloyd-Jones/Framingham risk algorithm

Risk factor	Minor*	Moderate*	Major
Cholesterol, mg/dL	180–199	200–239	≥240
Systolic blood pressure, mmHg	120–139	140–159	≥160
Cigarette smoking	0	0	+++
Diabetes	0	0	+++

*The term minor refers to *not desirable* and moderate refers to the *elevated* used by Lloyd-Jones et al.[238]

Table 4 Risk for CVD morbidity by age 80

Risk factor	Men, %	Women, %
None	5	8
≥1 minor	25	10
≥1 moderate	38	22
1 major	45	25
≥2 major	60	45

CVD, cardiovascular disease.

Risk assessment calibration

Risk factors affect total risk differently in various populations. This is because of differences in baseline population risk. The latter can be defined as the inherent risk of a population beyond traditional risk factors. A multitude of factors likely contribute to baseline population risk. In an effort to adjust risk scoring for different populations, Framingham Heart Study investigators and others have attempted to recalibrate Framingham scoring for several populations.[209,246–260] Recalibration coefficients derived from available data are shown in Table 5.[249,252,255–259] In the United States, D'Agostino et al[249] found that Framingham scoring similarly predicted CHD risk in white and black patients. However, the Framingham algorithm overestimated risk in Japanese-Americans. Likewise, in several studies, Framingham scoring overpredicted risk in several European countries and in China. It correctly estimated risk in rural Indians but underpredicted risk in Indians living in urban settings. It further correctly predicted risk in other Asians, including a predominance of Koreans.[256] Relative to QRISK scoring, Framingham generally overpredicts risk.[244,245] These findings emphasize the importance of not using Framingham scoring without recalibration for determining who is a candidate for cholesterol-lowering drugs. When using one of the long-term, risk-assessment algorithms based on Framingham risk scores, the absolute risk can be approximated by multiplying the estimated risk by the recalibration coefficient (Table 5).

In some countries (eg, Italy, China, and Japan), baseline population risk appears to be unusually low.[261–263] This may be due in part to a lifetime of relatively low LDL-C levels, but other poorly defined factors likely account for the low population risk. In Asian countries, hypertension appears to be the dominant risk factor, and stroke incidence rivals that of CHD.[264] Nonetheless, all of the major risk factors contribute to risk and all deserve clinical attention in proportion to their severity.

IAS panel deliberations

For primary prevention, the panel generally favored moving to a lifetime (long-term) risk prediction for clinical intervention on LDL-C (and atherogenic lipoproteins). At least four algorithms are available: two from Framingham,

Table 5 Framingham Heart Study recalibration coefficients for coronary heart disease

Reference	Cohort	Men	Women	Combined
Eichler et al (2007)[257]	Italy			0.37
	Scotland			0.91
	Germany			0.43
	France			0.41
	UK			0.76
	Ireland			0.76
	Australia			0.90
	New Zealand			1.15
Marques-Vidal et al (2009)[259]	Switzerland	0.48	0.44	
Brindle et al (2003)[252]	Britain	0.57		
Chow et al (2009)[258]	Rural India	1.0	0.8	
	Urban India	1.81	1.54	
Asia Pacific Cohort Studies Collaboration (2007)[256]	"Asian" (enriched in Korean)	1.02	0.96	
Liu et al (2004)[255]	China	0.36		
D'Agostino et al (2001)[249]	Japanese American	0.50		
	Native American	0.80	0.70	

The Cardiovascular Lifetime Risk Pooling Project, and QRISK. With QRISK, risk can be estimated on-line. QRISK is attractive because it is ethnic specific. The committee identified the following categories of risk for ASCVD to age 80 years. Outcomes are those defined by Framingham (myocardial infarction, coronary insufficiency, death resulting from CHD, angina pectoris, atherothrombotic stroke, intermittent claudication, or other cardiovascular death). QRISK should slightly underpredict these outcomes because it includes fewer endpoints than Framingham.

The panel emphasized that without absolute risk projections for different populations, absolute risk estimations for individuals will be open to some question. It is clear from Framingham studies in different populations that the relative impact of risk factors on absolute risk is highly consistent. Since European risk assessment is based on CVD mortality, the results of Berry et al[235] could be used to classify long-term CVD mortality risk as follows: low risk (<10%), moderate risk (10%–15%), moderately high >15%–29%, and high risk (≥30%). However, the IAS panel favored using the Framingham total CVD data to estimate long-term risk.[238] Because risk factors worsen the risk of ASCVD, attention must always be given to the management of risk factors themselves, particularly when risk factors are present in young adults; standard risk algorithms underestimate the long-term impact of major risk factors present in young adults. Indeed, regardless of age, all accelerating risk factors—whether cigarette smoking, hypertension, or diabetes—deserves clinical intervention. The same is true for increased LDL-C. Once intervention is initiated, global risk will change. Therefore, global risk calculations are not fixed entities. For example, treatment of any risk factor will lower the risk and can downgrade a person to a lower risk category. There is a tendency to pigeon-hole a person based on a single risk assessment. The fact that risk category is modifiable along with changes in risk factors illustrates the weakness of global risk assessment for defining a person's true risk status. One advantage of the QRISK algorithm is that it allows for adjustment of absolute risk based on changes in risk factor status.

Recommendation

For primary prevention, risk to age 80 for ASCVD can be stratified into high (≥45%), moderately high (30%–44%), moderate (15–29%), and low (<15%) (Table 6). Four risk assessment tools are available in Table 6. Three estimate long-term risk for CVD morbidity (QRISK[233,238]), and one estimates the risk for CVD mortality.[235] The QRISK has the advantage that it is ethnic specific (at least for the United Kingdom). QRISK may be reliable for all of Western Europe. Estimation of Framingham long-term risk allows for recalibration of risk in many countries. Therefore, for world populations, the IAS recommends using the Lloyd-Jones/Framingham algorithm[237] for estimating absolute risk for total ASCVD to age 80. The calculated risk should then be recalibrated on the basis of the coefficients determined by national comparisons with Framingham estimates. If recalibration values are not available, it

Table 6 Long-term risk for ASCVD by age 80 (from age 50)

Long-risk category	Absolute risk for ASCVD, %
Low	<15%
Moderate	15%–30%
Moderately high	30%–44%
High	≥45%

ASCVD, atherosclerotic cardiovascular disease.

may be more prudent to focus treatment on individual risk factors.

Optimal levels of LDL-C (or non-HDL-C) for primary prevention

Background

What constitutes an optimal LDL-C (or non-HDL-C) for lifetime prevention of ASCVD? Cholesterol-lowering RCTs were not specifically designed to test efficacy at various goals for LDL-C (or non-HDL-C); according to some researchers the optimal LDL-C for lifetime prevention in persons without ASCVD therefore cannot be known. Some thus propose eliminating LDL-C goals altogether from treatment recommendations.[265] Considerable data can be used to inform optimal cholesterol ranges. Epidemiological studies in several populations show that risk for CHD decreases progressively down to a total cholesterol of approximately 150 mg/dL (3.9 mmol/L)[2,4] (Fig. 2). In populations, a total cholesterol of 150 mg/dL corresponds to an LDL-C of about 100 mg/dL (2.6 mmol/L) or non-HDL-C of 130 mg/dL (3.4 mmol/L).[26]

Genetic studies further show that genetic variants causing lifetime LDL-C levels of approximately 100 mg/dL (2.6 mmol/L) associate with very low rates of CHD (Fig. 3).[266–268] Third, clinical trials demonstrate that reducing LDL-C levels to near 100 mg/dL (2.6 mmol/L) or less over 5 years substantially reduces ASCVD events in primary prevention (Fig. 4). On the basis of evidence of these types, ATP III[25] defined an LDL-C level <100 mg/dL (2.6 mmol/L) as being optimal, whereas 100–129 mg/dL was called near optimal.

Most evidence for optimal LDL-C comes from greater-risk populations. Some lower-risk populations may well tolerate somewhat-greater levels of LDL-C. In the Seven Countries Study, for example, baseline risk varied greatly from one country to another. Rates of CHD were much greater in northern Europe and USA than in southern Europe and Japan.[261] Lower CHD rates in the latter areas

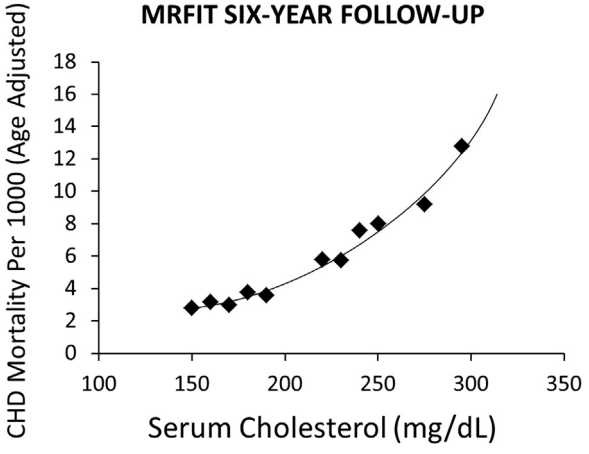

Figure 2 Mortality from CHD in the MRFIT study after 6 years of follow-up. Shown is the curvilinear relationship between serum cholesterol levels and CHD mortality.[2]

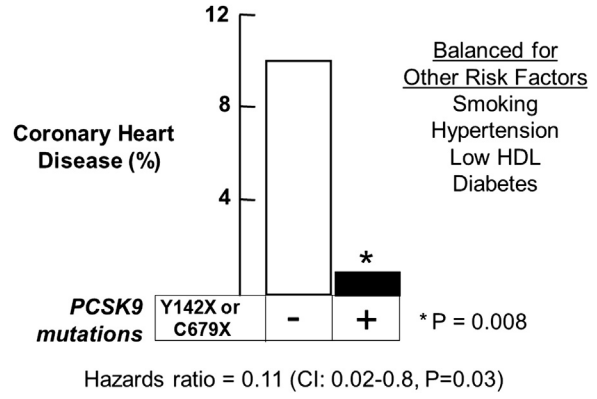

Figure 3 Benefit of lifetime of low LDL levels in patients with and without mutations in proprotein convertase subtilisin/kexin type 9. Those with mutations (+) had low LDL levels (<100 mg/dL) and those without mutations (−) had greater levels (138 mg/dL). Otherwise they were balanced for risk factors—smoking, hypertension, low HDL, and diabetes. Those with mutations were virtually free of CHD whereas those without mutations had the expected prevalence of CHD.[266]

may have been due in part to a paucity of ASCVD risk factors, or in the case of Japan, to racial as well as environmental factors. Regardless, low-risk populations may be able to sustain ATP III's near-optimal LDL-C (100–129 mg/dL; 2.6–3.4 mmol/L) without greater ASCVD rates.[57]

Beyond the concept of an optimal LDL-C, various guideline committees have set LDL-C goals according to risk category. For primary prevention, ATP III[26] set an LDL-C treatment goal of <160 mg/dL (4.1 mmol/L) for persons at low risk; of <130 mg/dL (3.4 mmol/L) for moderate or moderately high risk, and of <100 mg/dL

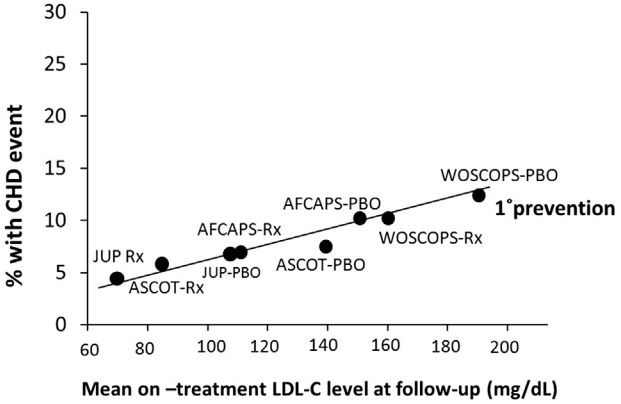

Figure 4 Relation between LDL-C levels and prevalence of CHD in RCTs. Results are shown for placebo (PBO) vs. on-treatment (Rx) for the West of Scotland Coronary Prevention Study (WOSCOPS), Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS), *Anglo-Scandinavian Cardiac Outcomes Trial* (ASCOT), and Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUP). Although reduction of LDL-C to near 70 mg/dL appears to reduce lower risk compared with 100 mg/dL, the absolute beneficial effect of the lower level compared with 100 mg/dL is small (abstracted from major primary prevention trials).

(2.6 mmol/L) for high risk. For Japanese, who have a lower population risk, national guidelines set LDL-C goals for three categories of risk are <160 mg/dL (low risk), <140 mg/dL (moderate to moderately high risk), and <120 mg/dL (high risk).[57] In 2004, an ATP III subpanel[20] modified the LDL-C goal for moderately high-risk individuals to be <100 mg/dL (2.6 mmol/L). EAS/ESC guidelines[28] recommend an LDL-C goal of <100 mg/dL (2.6 mmol/L) for high-risk subjects and a goal of <115 mg/dL (3.0 mmol/L) for moderate (intermediate) risk individuals. Recent Canadian guidelines recommended an LDL-C goal of < 80 mg/dL (2.0 mmol/L) for patients at moderately high-risk or high risk[269]; these guidelines, however, are heavily weighted to pharmacotherapy and do not discuss the relative benefits of different lower goals for LDL-C in primary prevention.

It is important to distinguish between optimal levels and goals of therapy. For primary prevention, the former refer to levels that minimize risk for ASCVD over a lifetime; the latter refer to concentrations that impart an acceptably lower risk at any given risk level. The concept of optimal level places the emphasis on strategies to maintain low cholesterol concentrations over a lifetime. Therapeutic goals are for persons who are already at a defined risk level. Existing epidemiologic and genetic evidence support an optimal LDL-C of < 100 mg/dL. RCT evidence is congruent with this level even though trials were not designed to test for specific goals. Different national guidelines have identified various LDL-C goals in primary prevention at different risk levels. For persons at high risk, it is possible that goals of therapy will be even lower than optimal levels for lifetime prevention, eg, for secondary prevention or high-risk primary prevention.[269] Less-than-optimal goals may be set for reasons of cost; in some countries it may not be practical to achieve optimal levels in spite of their desirability.

IAS panel deliberations

The majority of the IAS panel favored setting an optimal LDL-C for primary prevention to be a level of <100 mg/dL (2.6 mmol/L; or non-HDL-C of < 130 mg/dL [3.4 mmol/L]). This position is based on evidence from epidemiology and genetics augmented by limited RCT data. This, conclusion, however does not rule out the acceptability of attaining near-optimal LDL-C levels in people at low-lifetime risk caused by either a paucity of other risk factors or because of a low baseline population risk. Neither does it rule out the setting of still lower cholesterol goals in patients with high accumulated risk, as is done in some national guidelines.[269]

Recommendation

The optimal LDL-C level for lifetime primary prevention is <100 mg/dL (2.6 mmol/L) (or non-HDL-C of <130 mg/dL). This level is especially desirable in high-risk populations. Near-optimal LDL-C levels (100–129 mg/dL [2.6–3.3 mmol/L]) (or non-HDL-C of < 130–159 mg/dL [3.4–4.1 mmol/L]) may be acceptable in low-risk populations or in individuals with a paucity of other risk factors. The IAS does not specifically prescribe "treatment goals" for atherogenic lipoproteins for different circumstances. Instead it identifies optimal levels and makes the general statement that the intensity of lipid-lowering therapy should be adjusted to long-term risk. Because of the great variety of circumstances affecting use of lipid-lowering therapy, these guidelines leave to clinical judgment and national recommendations on intensities of therapies.

Statin therapy vs treatment to LDL-C goals

Background

Some authors dispute the use of LDL-C goals because of alleged lack of RCT evidence-specific goals.[270] They assert that LDL-C goals should be eliminated altogether; decisions about cholesterol-lowering drugs instead should depend entirely on estimated risk. This view makes statins the be-all and end-all of risk management. Non-statin RCTs are considered insufficient to serve as the basis of recommendations.[271]

Another view holds the following: The introduction of statins has created a "crisis" in preventive strategies. Potent statins are now inexpensive and largely safe. Would it not be better to ignore lifestyle factors and instead employ statins widely in the population?[272] This idea is known as the "polypill" approach because it includes drugs to lower both LDL and blood pressure.[273–275] The use of the polypill as a public health measure remains a possible approach for the future. Preliminary trials to test the strategy have been initiated.[276,277] Still, it is too soon to know whether the public and medical profession will accept the polypill model. Among unresolved issues are costs, drug side effects, and long-term compliance. The polypill idea casts the benefits of lifestyle interventions in a dim light. Many investigators in the atherosclerosis community do not share this pessimism towards lifestyle efficacy.

A commonly held view is that statins exert risk reduction through multiple actions (pleiotropic actions).[278–281] Yet their primary mechanism of action is to reduce LDL (and atherogenic lipoproteins). RCTs with statins show that ASCVD reduction is proportional to LDL lowering (Fig. 5).[282] Statins seemingly are like other LDL-lowering agents and are not unique except in LDL-lowering potency. Other dietary and drug cholesterol-lowering agents show a similar risk reduction for a given degree of LDL cholesterol lowering (Fig. 6). The strong relation between reductions in LDL reduction and ASCVD risk allows for the defining of optimal LDL-C levels; and this relation justifies defining treatment efficacy in terms of LDL-C levels achieved.

IAS panel deliberations

The majority of the IAS panel favored defining therapeutic efficacy in terms of the lipoprotein response and relative to an optimal atherogenic cholesterol level. The

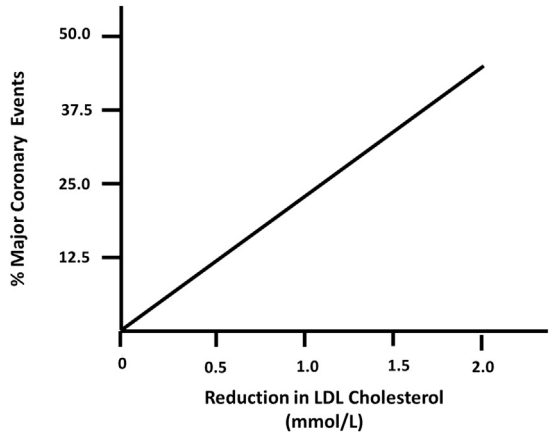

Figure 5 Proportional reduction in event rate. Abstracted results from the Cholesterol Treatment Trialists' Collaboration. The data show that an absolute reduction in LDL-C levels produces a constant risk reduction in major coronary events across all absolute levels of LDL-C.[282]

panel concluded that use of the polypill as a public health measure is premature.

Recommendations

For clinical cholesterol guidelines, levels of atherogenic cholesterol are the cornerstone for defining efficacy of therapy. Statin therapy undoubtedly represents first-line therapy when risk is high enough to warrant cholesterol-lowering drugs.

IAS lifestyle recommendations

The prime aim of lifestyle intervention is to reduce levels of atherogenic cholesterol. A secondary aim is to decrease other risk factors. The IAS panel made the following recommendations for maximal lifestyle therapy to be used in the clinical setting.

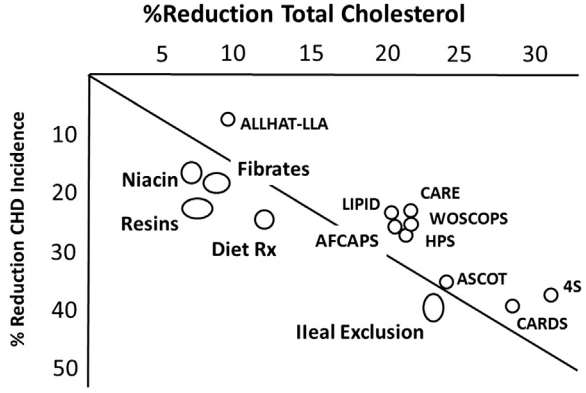

Figure 6 Comparison of percent reduction in total cholesterol and percent reduction in CHD incidence. Data abstracted from RCTs of statin trials and non-statin therapies for cholesterol lowering.[6,26,78]

LDL-increasing lipids

Reduce intake of saturated fatty acids to <7% of total calories, and at least to <10%. Lower intake of trans-fatty acids to <1% of total calories (or even more) and dietary cholesterol to <200 mg/day.

Other dietary factors

Maintain a relatively high intake of fruits, vegetables, and fiber. Replace excess saturated fatty acids with either complex, fiber-rich carbohydrates (with emphasis on whole grains) or monounsaturated/polyunsaturated fatty acids. The latter can be obtained through vegetable oils and nuts. Consume some fish rich in omega-3 fatty acids. Eat foods low in sodium and high in potassium. Processed meats and sugar-sweetened beverages, sweets, grain-based desserts and bakery foods should be limited. For individuals who choose to consume alcohol up to 2 servings daily for men and 1 serving daily for women is advised.

Consider using plant sterols/stanols (2 g/day) as a dietary adjunct along with soluble/viscous fiber (10–25 g/day) to further lower LDL-C levels. Several nations place limits on amounts of plant sterols/stanols that are allowed as nutritional supplements (because of questions about potential benefits vs. possible side effects). However, if plant sterols/stanols are available, they are a useful adjunct to lowering of LDL-C by dietary means.

Total fat

The IAS recommends flexibility in the intake of total fat depending on cultural preferences; alternatives are lower fat intakes of 20%–25% of calories or even lower (as is typical in Pacific Rim countries), or higher fat intakes of 30%–35% of calories or even greater (as is typical in Mediterranean countries). Any fat intake above that recommended for saturated and *trans* fatty acids should be in the form of unsaturated fatty acids. In addition, irrespective of the total fat content of the diet, nutrient needs must be met and energy intake be appropriate for maintenance of a healthy body weight.

Total calories

One ideal aim of dietary intervention is to achieve and maintain a desirable weight. The latter can be defined by either BMI or waist circumference. The World Health Organization defines 2 categories of overweight/obesity: BMI 25–29.9 kg/m^2 (overweight) and ≥30 kg/m^2 (obesity) (http://www.who.int/mediacentre/factsheets/fs311/en/). However, in some populations, such as South Asians, lower BMI cutpoints for overweight/obesity are recommended.[283] For South Asians, normal BMI was defined as 18–22.9 kg/m^2, overweight as 23–24.9 kg/m^2, and obesity as ≥25 kg/m^2. These same thresholds may apply to other areas of Asia. If a normal BMI cannot be achieved in obese

individuals, achieving a 10% reduction in body weight is desirable. The latter has been shown to reduce the risk for diabetes and to improve the metabolic syndrome in patients with pre-diabetes.[108,109,284–287]

An alternate indicator of obesity status is waist circumference. As noted before, waist circumference thresholds to define abdominal obesity have been identified for different countries. Weight reduction can be facilitated by professional nutritional assistance when such is available.

Physical activity

Engage in approximately 30 minutes of moderate intensity physical activity daily. The activity should be aerobic, 40%–75% of aerobic capacity, for 5–7 days a week, for 30–60 minutes per day. For individuals trying to lose weight, it is recommended that these individuals eventually progress to higher amounts of exercise (eg, 250–300 min/week or >2000 kcal/week of leisure-time physical activity).[288]

The metabolic syndrome is a multiplex risk factor for ASCVD and type 2 diabetes.[289] It is becomingly increasingly common throughout the world.[104] It essentially doubles the risk for ASCVD.[106,107] The syndrome deserves identification in routine clinical practice.[105] Patients with metabolic syndrome should receive maximal lifestyle therapy with increased emphasis on weight reduction and increased physical activity.

Tobacco use

The goal of clinical intervention is complete cessation of tobacco use. Quit rates are related to intensity of counseling. Components of effective counseling include problem-solving guidance for smokers and provision of social support. More intense practices are motivational interviewing, assessing readiness to change, referrals to smoking-cessation clinics, telephone "quit lines," and pharmacotherapy. Detailed national guidelines are available in many countries or can be obtained through the internet.

Practical suggestions for a healthy lifestyle[290] has created a table of suggestions for a healthy lifestyle. The following is a summary of their suggestions (Table 7).

IAS cholesterol-lowering drug recommendations

When a decision is made to initiate LDL-lowering drugs, *statins* are first-line therapy. The choice of statins depends on availability and costs. The dose of statins should be adequate to achieve optimal levels of atherogenic cholesterol. In patients who are intolerant to statins, several options are available: switching to an alternate statin, reducing statin dose, every other day statins, use of alternate drugs (ezetimibe, bile acid resins, niacin) alone or in combination, and maximizing lifestyle changes. Combined drug therapy, ie statin + other cholesterol-lowering drug (ezetimibe and/or bile acid resin) is a reasonable option in patients with severe hypercholesterolemia.

Specific forms of dyslipidemia in primary prevention

The IAS panel made the following consensus recommendations for special circumstances. *Very high LDL-C levels* constitute a greater risk condition and deserve more intensive LDL lowering therapy. Approximately 1 in 500 patients has a monogenic cause for of hypercholesterolemia. Most such patients will have a mutation in one of three genes: LDL receptors (FH); PCSK-9; or apoB. Because of the high lifetime risk of patients with FH, attention must be given from an early age to effective cholesterol lowering.[291–294] Other cases of severe hypercholesterolemia likely will have polygenic hypercholesterolemia. In some patients with severe hypercholesterolemia, it may not be possible to achieve optimal LDL-C concentrations with the combination of lifestyle and statin therapies; in this circumstance, combination drug therapy (eg, statins + ezetimibe and/or bile acid resins and/or niacin) may prove efficacious. In patients with extremely high LDL-C, eg, homozygous FH, LDL apheresis may be required to retard atherogenesis.[295,296] Finally, recently in the United States, the FDA approved use of lomitapide and mipomersen as adjunct to diet and drugs in severe familial hypercholesterolemia. Both of these drugs inhibit the production of lipoproteins containing atherogenic cholesterol.

Hypertriglyceridemia

Observational evidence strongly suggests that mixed hyperlipidemia (elevated LDL-C + elevated VLDL-C) increases risk more than high LDL-C alone.[142,297] Therapy of mixed hyperlipidemia is simplified by making non-HDL-C the treatment target. This is particularly so when the serum triglycerides is <500 mg/d (5.7 mmol/L). An optimal non-HDL-C for primary prevention will be a level of <130 mg/dL (3.4 mmol/L). Statins lower non-HDL-C as effectively as they lower LDL-C. Whether the combination of statins with fibrates or niacin is efficacious in primary prevention is uncertain.

Patients with severe hypertriglyceridemia (TG > 500 mg/dL; 5.7 mmol/L) are at increased risk for acute pancreatitis.[298] The greater the triglyceride level, the greater is the risk. Clinical experience shows that use of fibrates or niacin in patients with severe hypertriglyceridemia will reduce risk for acute pancreatitis. High intakes of omega-3 fatty acids are an alternative to drug therapy for treatment of severe hypertriglyceridemia.

Adjusting intensity of cholesterol-lowering therapy to absolute risk

Background

As mentioned previously, some researchers hold that decisions about lipid treatment should be based exclusively on calculated risk for ASCVD; accordingly LDL-C levels

Table 7 Practical tips for a healthy lifestyle*

- Limit your intake of saturated fat to 7% of energy, trans-fat to 1% of energy, and cholesterol to 300 mg per day by
  - — choosing lean meats and vegetable alternatives;
  - — selecting fat-free (skim), 1% fat, and low-fat dairy products; and
  - — minimizing intake of partially hydrogenated fats.
- Know your caloric needs to achieve and maintain a healthy weight.
- Know the calorie content of the foods and beverages you consume.
- Track your weight, physical activity, and calorie intake.
- Prepare and eat smaller portions.
- Track and, when possible, decrease screen time (eg, watching television, surfing the Web, playing computer games).
- Incorporate physical movement into habitual activities.
- Do not smoke or use tobacco products.
- If you consume alcohol, do so in moderation (equivalent of no more than 1 drink in women or 2 drinks in men per day).
- Food choices and preparation

Use the nutrition facts panel and ingredients list when choosing foods to buy.

- Eat fresh, frozen, and canned vegetables and fruits without high-calorie sauces and added salt and sugars.
- Replace high-calorie foods with fruits and vegetables.
- Increase fiber intake by eating beans (legumes), whole-grain products, fruits, and vegetables.
- Use liquid vegetable oils in place of solid fats.
- Limit beverages and foods high in added sugars. Common forms of added sugars are sucrose, glucose, fructose, maltose, dextrose, corn syrups, concentrated fruit juice, and honey. Some investigators contend that high fructose intakes are a risk factor for fatty liver disease and type 2 diabetes.
- Choose foods made with whole grains. Common forms of whole grains are whole wheat, oats/oatmeal, rye, barley, corn, popcorn, brown rice, wild rice, buckwheat, triticale, bulgur (cracked wheat), millet, quinoa, and sorghum.
- Cut back on pastries and high-calorie bakery products (eg, muffins, doughnuts).
- Select milk and dairy products that are either fat free or low fat.
- Reduce salt intake by
  - — comparing the sodium content of similar products (eg, different brands of tomato sauce) and choosing products with less salt;
  - — choosing versions of processed foods, including cereals and baked goods, that are reduced in salt; and
  - — limiting condiments (eg, soy sauce, ketchup).
- Use lean cuts of meat and remove skin from poultry before eating.
- Consume fish, especially oily fish, at least twice a week.
- Limit processed meats that are high in saturated fat and sodium.
- Grill, bake, or broil fish, meat, and poultry.
- Incorporate vegetable-based meat substitutes into favorite recipes.
- Encourage the consumption of whole vegetables and fruits in place of juices.

*American Heart Association Nutrition Committee, 2006.[290]

should be ignored both at baseline and on-treatment.[299–301] In this opinion, risk itself is the target of therapy. An alternate view identifies elevations of atherogenic cholesterol as the underlying cause of ASCVD. If true, treatment intensity should not be independent of atherogenic-cholesterol levels. Hence all persons without ASCVD ideally would achieve optimal atherogenic-cholesterol levels. Because most people in high-risk populations have atherogenic-cholesterol levels above optimal, most should benefit by some form of cholesterol-lowering intervention. Whether to drive atherogenic cholesterol to optimal levels depends on cost-benefit-safety factors. Available therapeutic options are therapeutic lifestyle changes and cholesterol-lowering drugs (ie statins or other drugs). Most agree that lifestyle intervention is the first option of therapy and is universally needed for maximum risk reduction; nonetheless drug therapy will be warranted in some persons to attain optimal atherogenic-cholesterol levels. Once the decision is made to use drugs, the aim should be to achieve optimal atherogenic-cholesterol concentrations. Considerations for each risk category can be briefly reviewed.

For practical purposes, high risk can be defined as one of the following: (1) a risk for ASCVD ≥45% up to age 80, (2) diabetes plus other risk factors,[302] (3) FH,[303] and possibly chronic kidney disease.[304] For primary prevention, current guidelines generally agree cholesterol levels in high-risk persons should be lowered to the optimal range.[20,28,269] Although drug therapy may be required to achieve optimal atherogenic-cholesterol levels, use of maximal lifestyle intervention will make it possible to use lower doses of drugs and will reduce risk in ways other than cholesterol reduction.

Moderately high risk can be defined as (1) a risk for ASCVD to age 80 of 30%–44%, (2) diabetes without other risk factors,[305,306] (3) chronic kidney disease,[307] and (4) metabolic syndrome in higher risk populations.[199,308] For

persons at moderately high risk, several guidelines endorse reduction of atherogenic cholesterol to the optimal range, ie LDL-C of <100 mg/dL (2.6 mmol/L).[20,28,269] These same guidelines allow use of cholesterol-lowering drugs combined with lifestyles therapies to achieve these low levels. Even so, use of cholesterol-lowering drugs in moderately high risk persons to achieve a low LDL-C is not universally accepted.[309] In some countries, use of drugs in this risk category is considered too expensive for the health care system to support.

Moderate risk is here defined as risk for ASCVD to age 80 year of 15%–29%. Maximal lifestyle therapy is generally advocated for this risk range. Whether to recommend cholesterol-lowering drugs is disputed. Some investigators oppose treatment of lower risk individuals with statins.[310,311] A recent meta-analysis of RCTs nonetheless suggests some benefit can be attained in moderate risk persons.[122] Long-term treatment of such people moreover might magnify benefit.[312,313] To resolve this question to everyone's satisfaction, a clinical trial may be required.[314] One factor to consider in persons at moderate risk is the baseline level of atherogenic cholesterol. There is almost universal agreement that those with very high LDL-C concentrations (>190 mg/dL) should be treated with drug therapy; in these individuals, LDL-C should be reduced as much as possible.[26,28] For those with high LDL-C (160–190 mg/dL), treatment with cholesterol-lowering drugs seems reasonable. Whether statin treatment in moderate-risk individuals with marginally high LDL-C (130–159 mg/dL) is warranted is uncertain. Although such individuals might achieve some risk reduction from statin therapy, maximizing lifestyle therapies should provide a similar benefit.

Some investigators have questioned whether statins will reduce risk in women without ASCVD; they note a lack of benefit in reducing total mortality.[315–317] Even reports that LDL-lowering therapy does not reduce ASCVD mortality note that morbidity is decreased. Evidence for reduction in ASCVD morbidity with statin therapy has been strengthened by the Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin trial and follow-up meta-analysis of all primary prevention trials in women.[318,319] On the basis of RCT data it is reasonable to treat women similarly to men, provided they fall into the same risk categories. By these criteria, many fewer women will quality for cholesterol-lowering drugs than men.

Next must be considered the question of employing statin therapy in older persons (>65 years). Risk assessment tools for older persons are limited. A reasonable approach is to estimate 10-year risk using Framingham scoring (recalibrated for country). The on-line calculator (http://hp2010.nhlbihin.net/atpiii/calculator.asp?usertype=prof) estimates risk for hard CHD. The resulting value can be elevated by approximately one-third to obtain total ASCVD. The resulting estimate will give a rough estimate of long-term risk category. The result should assist in deciding whether to use statin therapy. There is RCT evidence that statin therapy will reduce ASCVD risk in older persons.[15]

IAS panel deliberations

The IAS panel favored efforts to achieve optimal levels of atherogenic cholesterol in primary prevention. However, the intensity of this effort should be conditioned by considerations of long-term risk, costs of intervention, and safety. The panel emphasized that all persons at risk deserve maximal lifestyle therapy. Use of statins generally should be reserved for persons at high or moderately high risk. The judicious use of lifestyle therapies plus the availability of generic statins nonetheless will make it possible to inexpensively attain optimal LDL-C levels in most patients. Whether to use statins in moderate-risk individuals depends on clinical judgment and national policies. Their use should be considered for persons with high or very high LDL-C concentrations. Women should be treated similarly to men when long-term risk is similar. Statin therapy has been shown to reduce risk in older persons; they should not be excluded from therapy when risk is moderately high or high. Nonetheless, clinical judgment is required for decisions about drug therapy in older persons. They frequently are treated with multiple drugs, and the costs and possibilities of drug interaction must be kept in mind.[320]

Recommendations

To reduce long-term risk for ASCVD in primary prevention it is ideal to achieve atherogenic cholesterol in the optimal range. Several factors must be kept in mind when deciding how low to drive atherogenic cholesterol. Lifestyle therapies are first-line intervention; but depending on risk status, drug therapies may be necessary. A general recommendation for adjusting intensity of therapy to absolute risk is shown in Table 8.

Management of nonlipid risk factors in primary prevention

Every major risk factor deserves clinical attention. Nonlipid risk factors either accelerate atherogenesis or predispose to thrombotic events. It is true that cholesterol-lowering therapy will reduce risk for ASCVD events in the presence of all other risk factors. This fact is behind the concept of treating "risk" with LDL-lowering therapy. In primary prevention, however, attempting to treat nonlipid risk factors with LDL lowering alone fails to achieve the benefit that can be obtained by therapy directed at other major risk factors. For instance, using cholesterol-lowering drugs to treat cigarette smoking or hypertension in young adults is inappropriate management.

Cigarette smoking is a major risk factor for ASCVD but has many other adverse effects (eg, lung cancer, chronic obstructive pulmonary disease and other cancers). The World Health Organization (WHO) gives a grim picture of tobacco-induced illness worldwide (WHO Fact sheet No. 339May 2012).[321] Tobacco kills approximately 6 million people per year. Approximately half of those who use tobacco are killed by it. The world has approximately

Table 8 IAS Recommendations for cholesterol-lowering therapy at different risk levels

Risk level to age 80 years	Low (<15%)	Moderate (15%–24%)	Moderately high (25%–40%)	High (>40%)
Therapeutic intensity		Moderate	Moderately high	High
Specific therapy	Public health recommendation*	MLT+CLD optional†	MLT+CLD consideration‡	MLT+CLD indicated§

ASCVD, atherosclerotic cardiovascular disease; CLD, cholesterol-lowering drug; MLT, maximal lifestyle therapies.

*Persons at low risk for ASCVD should be treated according to national recommendation for the general public. These recommendations should accord with IAS recommendations for lifestyle therapies.

†Cholesterol-lowering drug therapy usually reserved for patients with high levels of atherogenic cholesterol.

‡Statin therapy is widely recommended for this risk category, although it is not accepted in many countries because of cost considerations. If drugs are employed, the dose should be adequate to achieve optimal atherogenic-cholesterol levels.

§Cholesterol-lowering drug therapy is usually indicated in this category. The dose should be adequate to achieve optimal atherogenic-cholesterol levels.

one billion smokers, and most live in low- and middle-income countries. Tobacco use is increasing throughout the world. Thus clinical management of cardiovascular risk must stress smoking cessation or preventing tobacco use. Cessation of tobacco use should be an integral part of maximal lifestyle therapy.

Hypertension

Increased blood pressure is a major risk factor for CHD, stroke, peripheral vascular disease, and kidney failure (http://www.who.int/gho/ncd/risk_factors/blood_pressure_prevalence_text/en/index.html). Hypertension causes about 13% of all deaths (7.5 million deaths per year). It occurs in approximately 40% of people older than 25 years of age. Almost 1 billion people have uncontrolled hypertension. Among the major risk factors for ASCVD, hypertension is the foremost cause of disability.[322] Lifestyle factors (obesity, high salt intakes, alcohol) contribute importantly to development of hypertension; but once hypertension takes hold, it can usually be controlled by judicious use of inexpensive anti-hypertensive agents.

Diabetes is widely recognized as a major contributor to ASCVD. According to the WHO, 347 million people have diabetes; and in 2004, 3.4 million died from this disease. Most diabetes occurs in low- and middle-income countries; but high-income countries with a high prevalence of obesity are by no means immune. The WHO projects that the presence of diabetes will increase by two-thirds in the next 20 years. An elevation of plasma glucose predisposes to microvascular disease, notably kidney failure and blindness; but there is considerable evidence that hyperglycemia either accelerates atherosclerosis or underlies ASCVD events. Most diabetes is type 2 and is often accompanied by other cardiovascular risk factors. The combination of hyperglycemia and other risk factors is commonly designated a high-risk condition for ASCVD events. In some populations the risk associated with type 2 diabetes approaches that of established ASCVD.[26] But, in other populations this is not true. Whereas hyperglycemia per se may be a risk factor, it cannot be universally identified as a CHD risk equivalent. When combined with other risk factors, the combination clearly enhances risk. Because the relation of diabetes and ASCVD is complex for different populations throughout the world, it is difficult to simplify the connection. To date there is limited evidence that treatment of hyperglycemia will reduce risk for macrovascular ASCVD.[323,324] Even so, control of hyperglycemia will reduce microvascular disease. The most effective means to reduce ASCVD events in patients with diabetes is though the use of LDL-lowering drugs.[325] Patients with type 1 diabetes are at increased risk for ASCVD.[326] Current guidelines indicate that patients with type 1 diabetes should be treated with cholesterol-lowering drugs similarly to those with type 2 diabetes when their risk factor profiles are similar.[327]

Chronic kidney disease is associated with increased likelihood for ASCVD events and is generally considered to be a higher risk condition.[307] The efficacy of statin therapy for reducing risk has been a subject of some uncertainty. However, a recent clinical trial showed clearly the benefit of intensive LDL-lowering therapy in patients with chronic kidney disease.[139] The value of statin therapy in patients with chronic kidney disease is supported by two recent meta-analyses.[328,329] Whether statins are useful in patients on hemodialysis is uncertain. For example, in the 4D trial, atorvastatin therapy showed no benefit in patients with diabetes who were undergoing hemodialysis.[330] This report however may not be the last word on the question; another trial suggested benefit in end-stage renal disease.[139]

Secondary prevention

Secondary prevention extends to all patients with established ASCVD. These conditions include a history of CHD, stroke, peripheral arterial disease, carotid artery disease, and other forms of atherosclerotic vascular disease.

Identifying optimal levels of atherogenic cholesterol in secondary prevention

Background

In patients with existing ASCVD there is a wealth of RCT evidence showing that statin therapy reduces recurrent cardiovascular events.[20,26,27,121,281] The CTT collaboration

consisted mainly of secondary prevention trials (Fig. 5). The relationship between LDL-C levels and CHD incidence is summarized in Figure 7. This fact has led some researchers to hold that statins should be used in secondary prevention without reference to baseline levels of atherogenic cholesterol or to goals of therapy. Nonetheless most evidence supports the view that the major benefit of statin therapy is achieved through lowering of LDL-C (or non-HDL-C). Earlier statin RCTs showed substantial CHD risk reduction following lowering LDL-C to the range of 100-125 mg/dL.[331]

More recent RCTs reported that further reduction of LDL-C to a mean of 70–80 mg/dL causes additional falls in CHD events.[13,21,22,332–335] These results are summarized in Figures 8–10.

It is important to note that a portion of patients with acute coronary syndromes have baseline LDL-C levels less than 100 mg/dL (2.6 mmol/L).[336] Investigators from The Heart Protection Study[13] showed that patients of this type benefit from starting statin therapy even though their LDL-C levels are already low. Another trial demonstrated that lowering LDL-C to very low levels significantly reduced stroke.[337] In none of these trials was there evidence that very low LDL-C levels produced adverse events.

To summarize, evidence supporting a lower level for optimal LDL-C in secondary prevention comes from clinical trials in ASCVD patients: TNT, IDEAL, PROVE-IT, HPS, and their subgroup analyses. These trials all are consistent with "the lower, the better" for LDL-C. Because patients with ASCVD carry high-risk for future events and death, prudence favors a more aggressive preventive strategy than a more conservative one. Cholesterol-lowering drugs are generally safe; therefore, greater danger comes from under treatment than over treatment. If a precise optimal LDL-C level cannot be identified, the decision will have to be made whether LDL lowering should be more intensive or less intensive.

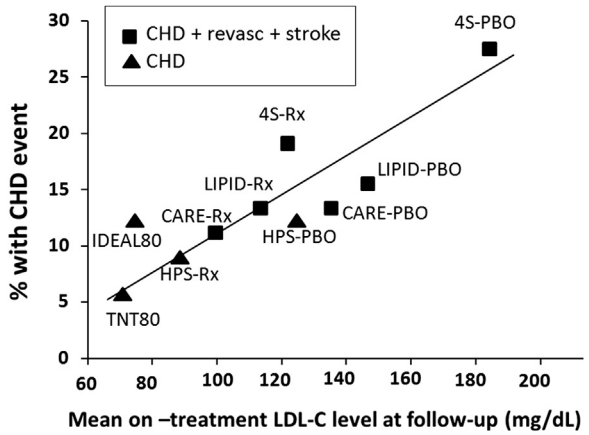

Figure 7 Relation between LDL-C lowering and percent CHD in secondary prevention trials. The finding supports a constant relationship, even to LDL-C levels <80 mg/dL. Rx = on-treatment arm of study; PBO = placebo arm. 80 = 80 mg atorvastatin. These data support an optimal LDL-C being near to or below 70 mg/dL in secondary prevention. Abstracted from secondary prevention trials.

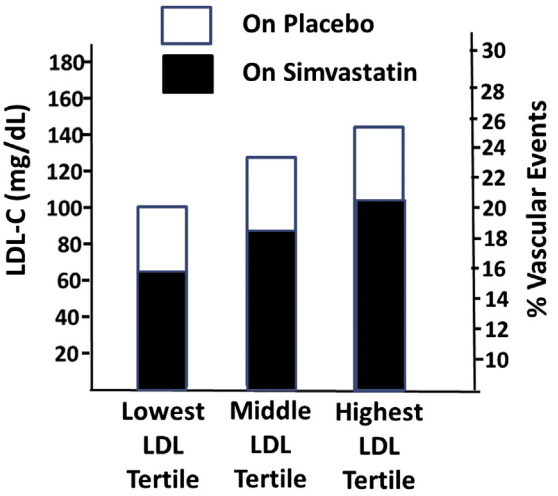

Figure 8 Risk reduction in the Heart Protection Study with simvastatin therapy at 3 levels of baseline LDL-C. The total height of the bars gives the LDL-C level and percentage of vascular events on placebo by LDL-C tertile. The heights of the black bars give the LDL-C levels and percentage of vascular events on simvastatin therapy. In the lowest tertile, starting simvastatin therapy with baseline level of 100 mg/dL lowered LDL-C to near 60 mg/dL and produced a corresponding lower percent of vascular events. This finding supports an optimal LDL-C of < 70 mg/dL in secondary prevention (from Heart Protection Study[13]).

To determine whether other lipid targets might be superior to LDL-C for predicting ASCVD events in secondary prevention, investigators from TNT and IDEAL compared the relationships of on-treatment levels of LDL-C, non-HDL-C, and apoB as well as ratios of total/HDL cholesterol, LDL/HDL cholesterol, and apoB/A-I, with the occurrence of cardiovascular events in patients receiving statin therapy.[338] In this study, on-treatment levels of non-HDL-C and apoB were more closely associated with cardiovascular outcomes than were levels of LDL-C. These

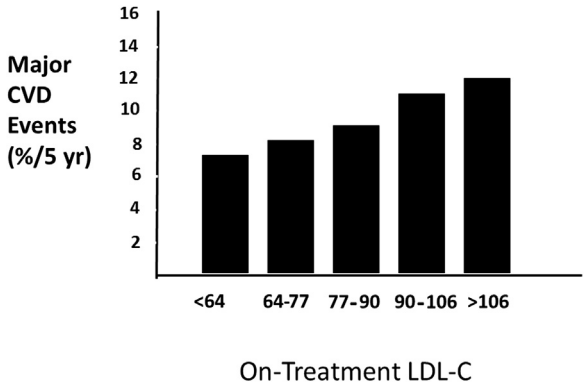

Figure 9 Subgroup analysis of TNT trial. Percentage of major CVD events is shown for different levels of on-treatment LDL-C. The lowest percentage of events occurred in patients who achieved an LDL-C <70 mg/dL. This finding supports an optimal LDL-C of <70 mg/dL in secondary prevention. From LaRosa et al.[332]

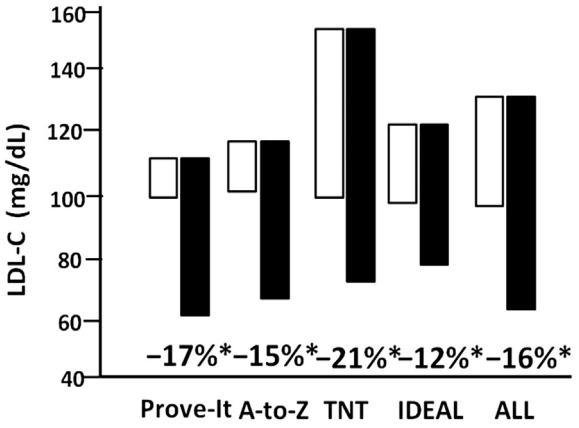

Figure 10 Meta-analysis of RCTs with high-dose statins compared with moderate dose. On-treatment LDL-C levels attained with moderate dose (open bars) and high dose (black bars). Percent risk reduction on high vs. moderate dose shown for each trial. ALL includes average results from meta-analysis. The best results were obtained on high-does statins. Modified from Cannon et al.[335] * Percent risk reduction

data supported use of non-HDL-C or apoB targets of therapy in secondary prevention. A larger meta-analysis gave precedence to non-HDL-C over apoB as therapeutic targets in secondary prevention.[166]

IAS panel deliberations

The panel was aware that some investigators believe that patients with ASCVD should be treated with high-dose statins without regard to LDL-C concentrations.[271] The argument in favor of such a recommendation is that RCTs have not identified an optimal LDL-C in secondary prevention. The panel did not agree with this line of reasoning. Instead, the panel found convincing evidence from RCTs and subgroups analysis of major RCTs for an optimal LDL-C in the range of 70 mg/dL (1.8 mmol/L) or lower. Future RCTs using highly efficacious LDL-lowering drugs could uncover a still lower optimal range. In the meantime, an optimal LDL-C in the range of <70 mg/dL seems acceptable. The panel further identified an optimal non-HDL-C as being <100 mg/dL. The panel is aware that Ballantyne et al[339] reported that on treatment non-HDL-C levels of 90 mg/dL correspond to LDL-C levels of 70 mg/dL; but in large epidemiological studies, non-HDL-C concentrations generally are 30 mg/dL greater than LDL-C. Moreover, non-HDL-C has its greatest utility in patients with elevated triglyceride; in this population, the likelihood is that there will be a somewhat greater differential between LDL-C and non-HDL-C than observed by Ballantyne et al.[339] for all patients. In the latter study, the differential between LDL-C and non-HDL-C in patients with hypertriglyceridemia averaged 24 mg/dL.

Recommendation

Optimal levels for LDL-C and non-HDL-C in secondary prevention are < 70 mg/dL (1.8 mmol/L) and < 100 mg/dL (2.6 mmol/L), respectively.

Cholesterol-lowering drugs in secondary prevention

Background

There is abundant RCT evidence that statins are first-line therapy in secondary prevention. High-dose statins, which produced the greatest LDL lowering, gave the greatest risk reductions. Although RCT data support an optimal LDL-C for secondary prevention being <70 mg/dL (1.8 mmol/L), these RCTs showed that the majority of patients receiving high-dose statins fail to reach this levels. An example is shown for the TNT and IDEAL trials in Figure 11. This figure shows the need for use of add-on drugs to achieve an optimal LDL-C level for secondary prevention.

Five classes of lipid-lowering drugs are available as potential add-on to statin therapy. These are bile acid resins, ezetimibe, nicotinic acid, fibrates (ie, fenofibrate), and n-3 fatty acids. The only drug to be tested as add-on to maximal statin therapy in secondary prevention is niacin. In AIM-HIGH and HPS-2 THRIVE, adding niacin to maximal statin therapy failed to produce a further reduction in risk for ASCVD events. It might be noted, however, that combining statins with niacin produced a favorable effect on subclinical atherosclerosis; but clinical end-point trials have failed to document a reduction in clinical events. Although bile acids resins reduce CHD events in patients with very high LDL-C levels[5] they have not been tested as add-ons to maximal statin therapy. Ezetimibe is currently being testing as add-on to high dose statin in IMPROVE-IT[138]; however, the results of this trial have not been reported. Recently it was reported that the combination of statin + fenofibrate failed to reduce ASCVD risk more than statin alone in patients with diabetes[340]; nonetheless, subgroup analysis of this trial suggested risk reduction in patients with hypertriglyceridemia and low HDL-C.[341] Subgroup meta-analysis of other fibrate trials suggests that these drugs reduce risk for ASCVD events in patients with elevated triglycerides and reduced HDL-C.[141] In a

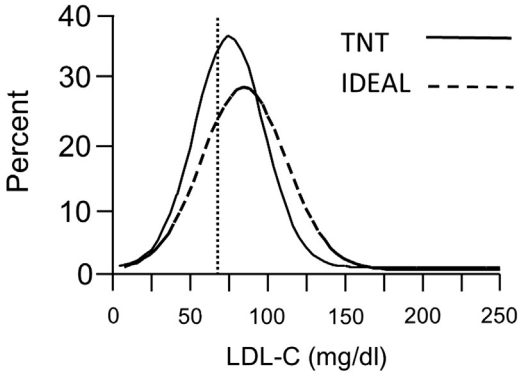

Figure 11 Distribution of on-treatment LDL-C levels for patients on high-dose atorvastatin (80 mg/day) in TNT and IDEAL studies. The majority of patients failed to achieve an LDL-C level of < 70 mg/dL (1.8 mmol/L).[21,22]

sizable secondary prevention trial, the addition of n-3 fatty acids to statin therapy (along with effective therapy of other risk factors) failed to produce an incremental reduction in ASCVD events.[342] Moreover in the ORIGIN trial, daily supplementation with 1 g of n-3 fatty acids did not reduce the rate of cardiovascular events in patients at high risk for cardiovascular events.[343] On the other hand, the Japan EPA lipid intervention study trial showed a beneficial effect of EPA add-on in secondary prevention.[94]

IAS panel deliberations

The IAS panel recognized a lack of evidence for incremental risk reduction from adding a second cholesterol-lowering drug to maximal statin therapy. Further, considering the curvilinear relationship between LDL-C and CHD risk, it is not known how much additional benefit can be obtained by lowering LDL-C to well below 70 mg/dL (1.8 mmol/L). The failure of combining niacin with high-dose statin to reduce ASCVD events in AIM-HIGH[148] and HPS-2 THRIVE is sobering. On the other hand, most panel members felt that if statin therapy alone does not achieve an LDL-C <70 mg/dL (1.8 mmol/L), adding a second cholesterol-lowering drug is warranted. Two recent clinical trials have cast doubt on the benefit of supplementation of the diet with n-3 fatty acids.[342,343]

Recommendations

When statin therapy fails to achieve an LDL-C goal of <70 mg/dL (1.8 mmol/L) on maximal therapy, consideration should be given to use of either a bile acid resin or ezetimibe as an add-on drug to achieve this level. If non-HDL-C and triglycerides remain elevated when the LDL-C goal is achieved, consideration can be given to adding a fibrate, niacin, or high doses of n-3 fatty acids for triglyceride lowering. Any statin add-on therapy must be used with the recognition that risk-reduction efficacy has not been documented on combined-drug RCTs. Further, low doses of n-3 fatty acids seemingly do not reduce risk in routine secondary prevention.

Treatment of nonlipid risk factors in secondary prevention

Because ASCVD is a multifactorial condition, preventive therapy must be directed to all of the risk factors. The most recent inclusive guideline for secondary prevention has been published by the American Heart Association/American College of Cardiology Foundation.[27] These guidelines have been recently endorsed by the World Heart Federation. Recommendations for hemoglobin A1C have recently been modified by the American Diabetes Association and the European Association for Study of Diabetes.[344,345]

Smoking: The goal is complete cessation. No exposure to environmental tobacco smoke.

Blood pressure: Should be reduced to levels <140/90 mm Hg.

Physical activity: At least 30 minutes, 7 days per week (minimum 5 days per week).

Weight management: Achieve a body mass index of 18.5–24.9 kg/m^2.

Type 2 diabetes mellitus: Achieve a hemoglobin A1C appropriate to a patient's clinical condition.

Antiplatelet agents/anticoagulants: Aspirin 75–162 mg daily is recommended in all patients with coronary artery disease unless contraindicated. For other antiplatelet/anticoagulant agents, see national guidelines.

Renin-angiotensin-aldosterone system blockers: See national guidelines.

β-Blockers: See national guidelines.

Influenza vaccination: patients with cardiovascular disease should have an annual influenza vaccination.

Other considerations: Identify and treat mental depression; employ cardiac rehabilitation when appropriate.

References

1. Pooling Project Research Group. Relationship of blood pressure, serum cholesterol, smoking habit, relative weight and ECG abnormalities to incidence of major coronary events: final report of the Pooling Project. *J Chronic Dis*. 1978;31:201–306.
2. Stamler J, Wentworth D, Neaton JD. Is the relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356,222 primary screenees of the Multiple Risk Factor Intervention Trial (MRFIT). *JAMA*. 1986;256:2823–2828.
3. Anderson KM, Castelli WP, Levy D. Cholesterol and mortality: 30 years of follow-up from the Framingham Study. *JAMA*. 1987;257:2176–2180.
4. Law MR, Wald NJ, Thompson SG. By how much and how quickly does reduction in serum cholesterol concentration lower risk of ischaemic heart disease? *BMJ*. 1994;308:367–372.
5. Lipid Research Clinics Program. The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease. *JAMA*. 1984;251:351–364.
6. Rossouw JE, Lewis B, Rifkind BM. The value of lowering cholesterol after myocardial infarction. *N Engl J Med*. 1990;323:1112–1119.
7. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet*. 1994;344:1383–1389.
8. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med*. 1995;333:1301–1307.
9. Lewis SJ, Moye LA, Sacks FM, et al. Effect of pravastatin on cardiovascular events in older patients with myocardial infarction and cholesterol levels in the average range. Results of the Cholesterol and Recurrent Events (CARE) trial. *Ann Intern Med*. 1998;129:681–689.
10. Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS: Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA*. 1998;279:1615–1622.
11. The Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med*. 1998;339:1349–1357.

12. Schwartz GG, Olsson AG, Ezekowitz MD, et al, Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) Study Investigators. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. *JAMA*. 2001;285:1711–1718.
13. 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.
14. Serruys PW, de Feyter P, Macaya C, et al, Lescol Intervention Prevention Study (LIPS) Investigators. Fluvastatin for prevention of cardiac events following successful first percutaneous coronary intervention: a randomized controlled trial. *JAMA*. 2002;287:3215–3222.
15. Shepherd J, Blauw GJ, Murphy MB, et al, PROSPER Study Group. PROspective Study of Pravastatin in the Elderly at Risk. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet*. 2002;360:1623–1630.
16. Holdaas H, Fellström B, Jardine AG, et al, Assessment of LEscol in Renal Transplantation (ALERT) Study Investigators. Effect of fluvastatin on cardiac outcomes in renal transplant recipients: a multicentre, randomised, placebo controlled trial. *Lancet*. 2003;361:2024–2031.
17. Sever PS, Dahlöf B, Poulter NR, et al, ASCOT Investigators. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower than-average cholesterol concentrations, in the ANGLO-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA): a multicenter randomised controlled trial. *Lancet*. 2003;361:1149–1158.
18. Colhoun HM, Betteridge DJ, Durrington PN, et al, CARDS Investigators. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicenter randomised placebo-controlled trial. *Lancet*. 2004;364:685–696.
19. de Lemos JA, Blazing MA, Wiviott SD, et al, Investigators. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. *JAMA*. 2004;292:1307–1316.
20. Grundy SM, Cleeman JI, Merz CN, et al, National Heart, Lung, and Blood Institute; American College of Cardiology Foundation; American Heart Association. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines [Erratum in: *Circulation*. 2004;110:763]. *Circulation*. 2004;110:227–239 Review.
21. Pedersen TR, Faergeman O, Kastelein JJ, et al, Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) Study Group. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial [Erratum in: *JAMA*. 2005;294:3092]. *JAMA*. 2005;294:2437–2445.
22. LaRosa JC, Grundy SM, Waters DD, et al, Treating to New Targets (TNT) Investigators. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med*. 2005;352:1425–1435.
23. Ray KK, Cannon CP, McCabe CH, et al, PROVE IT-TIMI 22 Investigators. Early and late benefits of high-dose atorvastatin in patients with acute coronary syndromes: results from the PROVE IT-TIMI 22 trial. *J Am Coll Cardiol*. 2005;46:1405–1410.
24. Amarenco P, Bogousslavsky J, Callahan A 3rd, et al. High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med*. 2006;355:549–559.
25. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. 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.
26. NCEP. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). 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.
27. Smith SC Jr., Benjamin EJ, Bonow RO, et al, World Heart Federation and the Preventive Cardiovascular Nurses Association. AHA/ACCF Secondary Prevention and Risk Reduction Therapy for Patients with Coronary and other Atherosclerotic Vascular Disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation. *Circulation*. 2011;124:2458–2473.
28. Catapano AL, Reiner Z, De Backer G, et al, European Society of Cardiology (ESC); European Atherosclerosis Society (EAS). ESC/EAS Guidelines for the management of dyslipidaemias The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). *Atherosclerosis*. 2011;217:3–46.
29. Bonow RO, Smaha LA, Smith SC Jr., Mensah GA, Lenfant C. World Heart Day 2002: the international burden of cardiovascular disease: responding to the emerging global epidemic. *Circulation*. 2002;106:1602–1605.
30. Mendis S, Puska P, Norrving B, editors. Global Atlas on Cardiovascular Disease Prevention and Control. Geneva: World Health Organization, 2011.
31. De Backer G, Ambrosioni E, Borch-Johnsen K, et al. European guidelines on cardiovascular disease prevention in clinical practice. Third Joint Task Force of European and other Societies on Cardiovascular Disease Prevention in Clinical Practice. *Eur Heart J*. 2003;24:1601–1610.
32. Genest J, Frohlich J, Fodor G, McPherson R, , Working Group on Hypercholesterolemia and Other Dyslipidemias. Recommendations for the management of dyslipidemia and the prevention of cardiovascular disease: summary of the 2003 update. *Can Med Assoc J*. 2003;169:921–924.
33. Brown MS, Goldstein JL. Familial hypercholesterolemia: A genetic defect in the low-density lipoprotein receptor. *N Engl J Med*. 1976;294:1386–1390.
34. Goldstein JL, Hobbs HH, Brown MS. Familial hypercholesterolemia. In: Scriver CR, Sly WS, Childs B, et al., editors. The Metabolic and Molecular Bases of Inherited Disease. New York, NY: McGraw-Hill Companies, Inc, 2001. p. 2863–2914.
35. Grundy SM, Wilhelmsen L, Rose G, Campbell RW, Assmann G. Coronary heart disease in high-risk populations: lessons from Finland. *Eur Heart J*. 1990;11:462–471.
36. Tabas I, Williams KJ, Borén J. Subendothelial lipoprotein retention as the initiating process in atherosclerosis: update and therapeutic implications. *Circulation*. 2007;116:1832–1844 Review.
37. Wang J, Razuvaev A, Folkersen L, et al. The expression of IGFs and IGF binding proteins in human carotid atherosclerosis, and the possible role of IGF binding protein-1 in the regulation of smooth muscle cell proliferation. *Atherosclerosis*. 2012;220:102–109.
38. Falk E, Nakano M, Bentzon JF, Finn AV, Virmani R. Update on acute coronary syndromes: the pathologists' view. *Eur Heart J*. 2013;34:719–728.
39. Chung BH, Tallis G, Yalamoori V, Anantharamaiah GM, Segrest JP. Liposome-like particles isolated from human atherosclerotic plaques are structurally and compositionally similar to surface remnants of triglyceride-rich lipoproteins. *Arterioscler Thromb*. 1994;14:622–635.
40. Rapp JH, Lespine A, Hamilton RL, et al. Triglyceride-rich lipoproteins isolated by selected-affinity anti-apolipoprotein B immunoadsorption from human atherosclerotic plaque. *Arterioscler Thromb*. 1994;14:1767–1774.
41. Havel RJ. Remnant lipoproteins as therapeutic targets. *Curr Opin Lipidol*. 2000;11:615–620.
42. Veniant MM, Sullivan MA, Kim SK, et al. Defining the atherogenicity of large and small lipoproteins containing apolipoprotein B100. *J Clin Invest*. 2000;106:1501–1510.

43. Twickler T, Dallinga-Thie GM, Chapman MJ, Cohn JS. Remnant lipoproteins and atherosclerosis. *Curr Atheroscler Rep*. 2005;7: 140–147.
44. Varbo A, Benn M, Tybjærg-Hansen A, et al. Remnant cholesterol as a causal risk factor for ischemic heart disease. *J Am Coll Cardiol*. 2013;61:427–436.
45. Jeppesen J, Hein HO, Suadicani P, Gyntelberg F. Triglyceride concentration and ischemic heart disease: an eight-year follow-up in the Copenhagen Male Study. *Circulation*. 1998;97:1029–1036.
46. Lloyd-Jones DM, Hong Y, Labarthe D, et al, on behalf of the American Heart Association Strategic Planning Task Force and Statistics Committee. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic impact goal through 2020 and beyond. *Circulation*. 2010;121:586–613.
47. Friedewald WT, Levy RI, Frederickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem*. 1972;18: 499–502.
48. Cui Y, Blumenthal RS, Flaws JA, et al. Non-high-density lipoprotein cholesterol level as a predictor of cardiovascular disease mortality. *Arch Intern Med*. 2001;161:1413–1419.
49. Farwell WR, Sesso HD, Buring JE, Gaziano JM. Non-high-density lipoprotein cholesterol versus low-density lipoprotein cholesterol as a risk factor for a first nonfatal myocardial infarction. *Am J Cardiol*. 2005;96:1129–1134.
50. Ridker PM, Rifai N, Cook NR, Bradwin G, Buring JE. Non-HDL cholesterol, apolipoproteins A-I and B100, standard lipid measures, lipid ratios, and CRP as risk factors for cardiovascular disease in women. *JAMA*. 2005;294:326–333.
51. Liu J, Sempos CT, Donahue RP, Dorn J, Trevisan M, Grundy SM. 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.
52. Holme I, Aastveit AH, Jungner I, Walldius G. Relationships between lipoprotein components and risk of myocardial infarction: age, gender and short versus longer follow-up periods in the Apolipoprotein MOrtality RISk study (AMORIS). *J Intern Med*. 2008;264: 30–38.
53. Robinson JG, Wang S, Smith BJ, Jacobson TA. Meta-analysis of the relationship between non-high-density lipoprotein cholesterol reduction and coronary heart disease risk. *J Am Coll Cardiol*. 2009;53: 316–322.
54. Gordon DJ, Probstfield JL, Garrison RJ, et al. High-density lipoprotein cholesterol and cardiovascular disease: four prospective American studies. *Circulation*. 1989;79:8–15.
55. Fruchart JC, Sacks F, Hermans MP, et al. The Residual Risk Reduction Initiative: a call to action to reduce residual vascular risk in patients with dyslipidemia. *Am J Cardiol*. 2008;102:1K–34K.
56. Chapman MJ, Ginsberg HN, Amarenco P, et al, for the European Atherosclerosis Society Consensus Panel. Triglyceride-rich lipoproteins and high-density lipoprotein cholesterol in patients at high risk of cardiovascular disease: evidence and guidance for management. *Eur Heart J*. 2011;332:1345–1361.
57. Teramoto T, Sasaki J, Ishibashi S, et al. Executive Summary of the Japan Atherosclerosis Society (JAS) Guidelines for the Diagnosis and Prevention of Atherosclerotic Cardiovascular Diseases in Japan - 2012 Version. *J Atheroscler Thromb*. 2013;20:517–523.
58. Barter P. HDL-C: role as a risk modifier. *Atheroscler Suppl*. 2011;12: 267–270.
59. Keys A, editor. Seven Countries: A Multivariate Analysis of Death and Coronary Heart Disease. Cambridge, MA: Harvard University Press, 1980.
60. Stamler J. Diet and coronary heart disease. *Biometrics*. 1982; 38(Suppl):95–118.
61. Blackburn H, Watkins LO, Agras WS, Carleton RA, Falkner B. Primary prevention of coronary heart disease. *Circulation*. 1987; 76(1 Pt 2):I164–I167.
62. Pietinen P, Vartiainen E, Seppänen R, Aro A, Puska P. Changes in diet in Finland from 1972 to 1992: impact on coronary heart disease risk. *Prev Med*. 1996;25:243–250.
63. Zhou BF, Stamler J, Dennis B, et al, INTERMAP Research Group. Nutrient intakes of middle-aged men and women in China, Japan, United Kingdom, and United States in the late 1990s: the INTERMAP study. *J Hum Hypertens*. 2003;17:623–630.
64. Knoops KT, de Groot LC, Kromhout D, et al. Mediterranean diet, lifestyle factors, and 10-year mortality in elderly European men and women: the HALE project. *JAMA*. 2004;22:1433–1439.
65. Menotti A, Lanti M, Kromhout D, et al. Homogeneity in the relationship of serum cholesterol to coronary deaths across different cultures: 40-year follow-up of the Seven Countries Study. *Eur J Cardiovasc Prev Rehabil*. 2008;15:719–725.
66. Fung TT, Rexrode KM, Mantzoros CS, et al. Mediterranean diet and incidence of and mortality from coronary heart disease and stroke in women. *Circulation*. 2009;119:1093–1100.
67. Mozaffarian D, Appel LJ, Van Horn L. Components of a cardioprotective diet: new insights. *Circulation*. 2011;123:2870–2891.
68. Baum SJ, Kris-Etherton PM, Willett WC, et al. Fatty acids in cardiovascular health and disease: a comprehensive update. *J Clin Lipidol*. 2012;6:216–234.
69. Pietinen P, Lahti-Koski M, Vartiainen E, Puska P. Nutrition and cardiovascular disease in Finland since the early 1970s: a success story. *J Nutr Health Aging*. 2001;5:150–154 Review.
70. Kok FJ, Kromhout D. Atherosclerosis–epidemiological studies on the health effects of a Mediterranean diet. *Eur J Nutr*. 2004;43(Suppl 1): I/2–I/5 Review.
71. Mensink RP, Zock PL, Kester AD, Katan MB. Effects of dietary fatty acids and carbohydrates on the ratio of serum total to HDL cholesterol and on serum lipids and apolipoproteins: a meta-analysis of 60 controlled trials. *Am J Clin Nutr*. 2003;77:1146–1155.
72. Grundy SM. Comparison of monounsaturated fatty acids and carbohydrates for lowering plasma cholesterol. *N Engl J Med*. 1986;314: 745–748.
73. Keys A, Menotti A, Aravanis C, et al. The seven countries study: 2,289 deaths in 15 years. *Prev Med*. 1984;13:141–154.
74. Peoples Republic of China-United States Cardiovascular and Cardiopulmonary Epidemiology Research Group. An epidemiological study of cardiovascular and cardiopulmonary disease risk factors in four populations in the Peoples Republic of China: baseline report from the P.R.C.-U.S.A. [Collaborative Study]. *Circulation*. 1992;85: 1083–1096.
75. Kromhout D, Bloemberg B, Feskens E, Menotti A, Nissinen A. Saturated fat, vitamin C and smoking predict long-term population allcause mortality rates in the Seven Countries Study. *Int J Epidemiol*. 2000;29:260–265.
76. Dayton S, Pearce ML, Hashimoto S, Dixon WJ, Tomiyasu U. A controlled clinical trial of a diet high in unsaturated fat in preventing complications of atherosclerosis. *Circulation*. 1969;40(suppl II): II1–II62.
77. Miettinen M, Karvonen MJ, Turpeinen O, Elosuo R, Paavilainen E. Effect of cholesterol-lowering diet on mortality from coronary heart-disease and other causes: a twelve-year clinical trial in men and women. *Lancet*. 1972;2:835–838.
78. Gordon DJ. Cholesterol lowering and total mortality. In: Rifkind BM, editor. Lowering Cholesterol in High-Risk Individuals and Populations. New York: Marcel Dekker, Inc., 1995. p. 333–348.
79. Jenkins DJ, Kendall CW, Axelsen M, Augustin LS, Vuksan V. Viscous and nonviscous fibres, nonabsorbable and low glycaemic index carbohydrates, blood lipids and coronary heart disease. *Curr Opin Lipidol*. 2000;11:49–56.
80. Kris-Etherton PM, Hu F, Ros E, Sabaté J. The role of tree nuts and peanuts in the prevention of coronary heart disease: multiple potential mechanisms. *J Nutr*. 2008;138:1746S–1751S.
81. Banel DK, Hu FB. Effects of walnut consumption on blood lipids and other cardiovascular risk factors: a meta-analysis and systematic review. *Am J Clin Nutr*. 2009;90:56–63.

82. Fraser GE. Vegetarian diets: what do we know of their effects on common chronic diseases? *Am J Clin Nutr*. 2009;89:1607S–1612S.
83. Sabaté J, Oda K, Ros E. Nut consumption and blood lipid levels: a pooled analysis of 25 intervention trials. *Arch Intern Med*. 2010; 170:821–827.
84. Sofi F, Abbate R, Gensini GF, Casini A. Accruing evidence on benefits of adherence to the Mediterranean diet on health: an updated systematic review and metaanalysis. *Am J Clin Nutr*. 2010;92:1189–1196.
85. van den Brandt PA. The impact of a Mediterranean diet and healthy lifestyle on premature mortality in men and women. *Am J Clin Nutr*. 2011;94:913–920.
86. Ros E, Hu FB. Consumption of plant seeds and cardiovascular health: epidemiologic and clinical trial evidence. *Circulation*. 2013; 128:553–565.
87. Jenkins DJ, Wolever TM, Rao AV, et al. Effect on blood lipids of very high intakes of fiber in diets low in saturated fat and cholesterol. *N Engl J Med*. 1993;329:21–26.
88. Brown L, Rosner B, Willett WW, Sacks FM. Cholesterol-lowering effects of dietary fiber: a meta-analysis. *Am J Clin Nutr*. 1999;69: 30–42.
89. Grundy SM, Ahrens EH Jr., Davignon J. The interaction of cholesterol absorption and cholesterol synthesis in man. *J Lipid Res*. 1969;10:304–315.
90. Miettinen TA, Puska P, Gylling H, Vanhanen H, Vartiainen E. Reduction of serum cholesterol with sitostanol-ester margarine in a mildly hypercholesterolemic population. *N Engl J Med*. 1995;333: 1308–1312.
91. Gylling H, Miettinen TA. Cholesterol reduction by different plant stanol mixtures and with variable fat intake. *Metabolism*. 1999;48: 575–580.
92. Blair SN, Capuzzi DM, Gottlieb SO, Nguyen T, Morgan JM, Cater NB. Incremental reduction of serum total cholesterol and low-density lipoprotein cholesterol with the addition of plant stanol ester-containing spread to statin therapy. *Am J Cardiol*. 2000;86:46–52.
93. Katan MB, Grundy SM, Jones P, Law M, Miettinen T, Paoletti R. Stresa Workshop Participants: Efficacy and safety of plant stanols and sterols in the management of blood cholesterol levels. *Mayo Clin Proc*. 2003;78:965–978.
94. Yokoyama M, Origasa H, Matsuzaki M, et al, Japan EPA lipid intervention study (JELIS) Investigators. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis [Erratum in: *Lancet*. 2007 Jul 21;370:220]. *Lancet*. 2007;369:1090–1098.
95. Estruch R, Ros E, Salas-Salvadó J, et al, the PREDIMED Study Investigators. Primary prevention of cardiovascular disease with a Mediterranean diet. *N Engl J Med*. 2013;368:1279–1290.
96. Wolf RN, Grundy SM. Influence of weight reduction on plasma lipoproteins in obese patients. *Arteriosclerosis*. 1983;3:160–169.
97. Bays HE, Toth PP, Kris-Etherton P, et al. Obesity, adiposity, and dyslipidemia: a consensus statement from the National Lipid Association. *J Clin Lipidol*. 2013;7:304–383.
98. Hubert HB, Feinleib M, McNamara PM, Castelli WP. Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study. *Circulation*. 1983; 67:968–977.
99. Park YS, Kim JS. Obesity phenotype and coronary heart disease risk as estimated by the Framingham risk score. *J Korean Med Sci*. 2012; 27:243–249.
100. Thompson PD, Buchner D, Pina IL, et al, American Heart Association Council on Clinical Cardiology Subcommittee on Exercise, Rehabilitation, and Prevention; American Heart Association Council on Nutrition, Physical Activity, and Metabolism Subcommittee on Physical Activity. Exercise and physical activity in the prevention and treatment of atherosclerotic cardiovascular disease: a statement from the Council on Clinical Cardiology (Subcommittee on Exercise, Rehabilitation, and Prevention) and the Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity). *Circulation*. 2003;107:3109–3116.
101. Vanhees L, Geladas N, Hansen D, et al, on behalf of the EACPR Writing Group. Importance of characteristics and modalities of physical activity and exercise in the management of cardiovascular health in individuals with cardiovascular risk factors: recommendations from the EACPR (Part II). *Eur J Prev Cardiol*. 2012;19: 1005–1033.
102. Physical Activity Guidelines Advisory Committee report, 2008. To the Secretary of Health and Human Services. Part A. Executive summary. *Nutr Rev*. 2009;67:114–120.
103. Li J, Siegrist J. Physical activity and risk of cardiovascular disease—a meta-analysis of prospective cohort studies. *Int J Environ Res Public Health*. 2012;9:391–407.
104. Grundy SM. Metabolic syndrome pandemic. *Arterioscler Thromb Vasc Biol*. 2008;28:629–636.
105. Alberti KG, Eckel RH, Grundy SM, et al, International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; International Association for the Study of Obesity. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation*. 2009;120:1640–1645.
106. Gami AS, Witt BJ, Howard DE, et al. Metabolic syndrome and risk of incident cardiovascular events and death: a systematic review and meta-analysis of longitudinal studies. *J Am Coll Cardiol*. 2007;49: 403–414.
107. Mottillo S, Filion KB, Genest J, et al. The metabolic syndrome and cardiovascular risk a systematic review and meta-analysis. *J Am Coll Cardiol*. 2010;56:1113–1132.
108. Orchard TJ, Temprosa M, Goldberg R, et al, Diabetes Prevention Program Research Group. The effect of metformin and intensive lifestyle intervention on the metabolic syndrome: the Diabetes Prevention Program randomized trial. *Ann Intern Med*. 2005;142: 611–619.
109. Goldberg RB, Mather K. Targeting the consequences of the metabolic syndrome in the Diabetes Prevention Program. *Arterioscler Thromb Vasc Biol*. 2012;32:2077–2090.
110. Grundy SM, Cleeman JI, Daniels SR, et al, American Heart Association; National Heart, Lung, and Blood Institute. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement [published corrections arrear in Circulation. 2005; 112:3297 and Circulation. 2005;112:e298]. *Circulation*. 2005;112:2735–2752.
111. National Institutes of Health. Clinical guidelines on the identification, evaluation and treatment of overweight and obesity in adults: the evidence report [published correction appears in *Obes Res*. 1998;6:464]. *Obes Res*. 1998;6(suppl2):51S–209S.
112. World Health Organization. Obesity: Preventing and Managing the Global Epidemic: Report on a WHO Consultation (WHO Technical Report Series 894). Geneva, Switzerland: World Health Organization; 2000.
113. Health Canada. Canadian Guidelines for Body Weight Classification in Adults. Ottawa, Canada: Health Canada Publications Centre; 2003 Publication ID No. 4645. ISBN 0-662-33431-0.
114. Khan NA, McAlister FA, Rabkin SW, et al, Canadian Hypertension Education Program. The 2006 Canadian Hypertension Education Program recommendations for the management of hypertension: part II—therapy. *Can J Cardiol*. 2006;22:583–593.
115. Graham I, Atar D, Borch-Johnsen K, et al, ESC Committee for Practice Guidelines. European guidelines on cardiovascular disease prevention in clinical practice: executive summary. *Atherosclerosis*. 2007;194:1–45.
116. Hara K, Matsushita Y, Horikoshi M, et al. A proposal for the cutoff point of waist circumference for the diagnosis of metabolic syndrome in the Japanese population. *Diabetes Care*. 2006;29:1123–1124.

117. Oka R, Kobayashi J, Yagi K, et al. Reassessment of the cutoff values of waist circumference and visceral fat for identifying Japanese subjects at risk for the metabolic syndrome. *Diabetes Res Clin Pract*. 2008;79:474–481.
118. Examination Committee of Criteria for "Obesity Disease" in Japan; Japan Society for the Study of Obesity. New criteria for "obesity disease" in Japan. *Circ J*. 2002;66:987–992.
119. Zhou BF, , Cooperative Meta-Analysis Group of the Working Group on Obesity in China. Predictive values of body mass index and waist circumference for risk factors of certain related diseases in Chinese adults: study on optimal cut-off points of body mass index and waist circumference in Chinese adults. *Biomed Environ Sci*. 2002;15:83–96.
120. Alberti KG, Zimmet P, Shaw J, IDF Epidemiology Task Force Consensus Group. The metabolic syndrome—a new worldwide definition. *Lancet*. 2005;366:1059–1062.
121. Cholesterol Treatment Trialists' (CTT) CollaborationBaigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet*. 2010;376:1670–1681.
122. Cholesterol Treatment Trialists' (CTT) CollaboratorsMihaylova B, Emberson J, Blackwell L, et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *Lancet*. 2012;380:581–590.
123. Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. *BMJ*. 2003;326:1423.
124. Pasternak RC, Smith SC Jr., Bairey-Merz CN, et al, American College of Cardiology; American Heart Association; National Heart, Lung and Blood Institute. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. *J Am Coll Cardiol*. 2002;40:567–572.
125. McKenney JM, Davidson MH, Jacobson TA, Guyton J, National Lipid Association Statin Safety Assessment Task Force. Final conclusions and recommendations of the National Lipid Association Statin Safety Assessment Task Force. *Am J Cardiol*. 2006;97:89C–94C.
126. LaRosa JC, Pedersen TR, Somaratne R, Wasserman SM. Safety and effect of very low levels of low-density lipoprotein cholesterol on cardiovascular events. *Am J Cardiol*. 2013;111:1221–1229.
127. Bruckert E, Hayem G, Dejager S, Yau C, Bégaud B. Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients—the PRIMO study. *Cardiovasc Drugs Ther*. 2005;19:403–414.
128. Rosenbaum D, Dallongeville J, Sabouret P, Bruckert E. Discontinuation of statin therapy due to muscular side effects: a survey in real life. *Nutr Metab Cardiovasc Dis*. 2013;23:871–875.
129. Thompson PD, Clarkson P, Karas RH. Statin-associated myopathy. *JAMA*. 2003;289:1681–1690.
130. Parker BA, Capizzi JA, Grimaldi AS, et al. Effect of statins on skeletal muscle function. *Circulation*. 2013;127:96–103.
131. Bader T. The myth of statin-induced hepatotoxicity. *Am J Gastroenterol*. 2010;105:978–980.
132. Sattar N, Preiss D, Murray HM, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. *Lancet*. 2010;375:735–742.
133. Preiss D, Seshasai SR, Welsh P, et al. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. *JAMA*. 2011;305:2556–2564.
134. Wagstaff LR, Mitton MW, Arvik BM, Doraiswamy PM. Statin-associated memory loss: analysis of 60 case reports and review of the literature. *Pharmacotherapy*. 2003;23:871–880.
135. Golomb BA, Evans MA. Statin adverse effects: a review of the literature and evidence for a mitochondrial mechanism. *Am J Cardiovasc Drugs*. 2008;8:373–418.
136. Rojas-Fernandez CH, Cameron JC. Is statin-associated cognitive impairment clinically relevant? A narrative review and clinical recommendations. *Ann Pharmacother*. 2012;46:549–557.
137. Bays HE, Moore PB, Drehobl MA, et al, Ezetimibe Study Group. Effectiveness and tolerability of ezetimibe in patients with primary hypercholesterolemia: pooled analysis of two phase II studies [Erratum in: *Clin Ther*. 2001;23:1601]. *Clin Ther*. 2001;23:1209–1230.
138. Cannon CP, Giugliano RP, Blazing MA, et al, IMPROVE-IT Investigators. Rationale and design of IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial): comparison of ezetimibe/simvastatin versus simvastatin monotherapy on cardiovascular outcomes in patients with acute coronary syndromes. *Am Heart J*. 2008;156:826–832.
139. Baigent C, Landray MJ, Reith C, et al, SHARP Investigators. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet*. 2011;377:2181–2192.
140. Jun M, Foote C, Lv J, et al. Effects of fibrates on cardiovascular outcomes: a systematic review and meta-analysis. *Lancet*. 2010;375:1875–1884.
141. Lee M, Saver JL, Towfighi A, Chow J, Ovbiagele B. Efficacy of fibrates for cardiovascular risk reduction in persons with atherogenic dyslipidemia: a meta-analysis. *Atherosclerosis*. 2011;217:492–498.
142. Frick MH, Elo O, Haapa K, et al. Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N Engl J Med*. 1987;317:1237–1245.
143. 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.
144. Canner PL, Berge KG, Wenger NK, et al. Fifteen year mortality in Coronary Drug Project patients: long-term benefit with niacin. *J Am Coll Cardiol*. 1986;8:1245–1255.
145. Canner PL, Furberg CD, Terrin ML, McGovern ME. Benefits of niacin by glycemic status in patients with healed myocardial infarction (from the Coronary Drug Project). *Am J Cardiol*. 2005;95:254–257.
146. 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.
147. Taylor AJ, Sullenberger LE, Lee HJ, Lee JK, Grace KA. 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 [Epub 2004 Nov 10. Erratum in: *Circulation*. 2005;111:e446. *Circulation*. 2004;110:3615]. *Circulation*. 2004;110:3512–3517.
148. AIM-HIGH Investigators. Boden WE, Probstfield JL, Anderson T, et al. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med*. 2011;365:2255–2267.
149. ClinicalTrials.gov. HPS II THRIVE. Available at: http://clinicaltrials.gov/ct2/show/NCT00461630. Accessed January 6, 2014.
150. HPS2-THRIVE Collaborative Group. HPS2-THRIVE randomized placebo-controlled trial in 25 673 high-risk patients of ER niacin/laropiprant: trial design, pre-specified muscle and liver outcomes, and reasons for stopping study treatment. *Eur Heart J*. 2013;34:1279–1291.
151. Jelesoff NE, Ballantyne CM, Xydakis AM, Chiou P, Jones PH, Guyton JR. Effectiveness and tolerability of adding ezetimibe to niacin-based regimens for treatment of primary hyperlipidemia. *Endocr Pract*. 2006;12:159–164.

152. Barter PJ, Ballantyne CM, Carmena R, et al. Apo B versus cholesterol in estimating cardiovascular risk and in guiding therapy: report of the thirty-person/ten-country panel. *J Intern Med*. 2006;259: 247–258.
153. Lamarche B, Moorjani S, Lupien PJ, et al. Apoprotein A-1 and B levels and the risk of ischemic heart disease during a 5 year follow-up of men in the Québec Cardiovascular Study. *Circulation*. 1996;94:273–278.
154. Moss AJ, Goldstein RE, Marder VJ, et al. Thrombogenic factors and recurrent coronary events. *Circulation*. 1999;99:2517–2522.
155. Walldius G, Jungner I, Holme I, Aastveit AH, Kolar W, Steiner E. High apolipoprotein B, low apolipoprotein A-1, and improvement in the prediction of fatal myocardial infarction (AMORIS study): a prospective study. *Lancet*. 2001;358:2026–2033.
156. Blake GJ, Otvos JD, Rifai N, Ridker PM. Low-density lipoprotein particle concentration, and size as determined by nuclear magnetic resonance spectroscopy as predictors of cardiovascular disease in women. *Circulation*. 2002;106:1930–1939.
157. Rosenson RS, Otvos JD, Freedman DS. Relations of lipoprotein subclass levels and low-density lipoprotein size to progression of coronary artery disease in the Pravastatin Limitation of Atherosclerosis in the Coronary Arteries (PLAC-I) trial. *Am J Cardiol*. 2002;90: 89–94.
158. Talmud PJ, Hawe E, Miller GJ, Humphries SE. Non-fasting apolipoprotein B and triglyceride levels as a useful predictor of coronary heart disease risk in middle-aged UK men. *Arterioscler Thromb Vasc Biol*. 2002;22:1918–1923.
159. Corsetti JP, Zareba W, Moss AJ, Sparks CE. Apolipoprotein B determines risk for recurrent coronary events in postinfarction patients with metabolic syndrome. *Atherosclerosis*. 2004;177: 367–373.
160. Jiang R, Schulze MB, Li T, et al. Non-HDL cholesterol and apolipoprotein B predict cardiovascular disease events among men with type 2 diabetes. *Diabetes Care*. 2004;27:1991–1997.
161. Shai I, Rimm EB, Hankinson SE, et al. Multivariate assessment of lipid parameters as predictors of coronary heart disease among postmenopausal women. Potential implications for clinical guidelines. *Circulation*. 2004;110:2824–2830.
162. St-Pierre AC, Cantin B, Dagenais GR, et al. Low-density lipoprotein subfractions and the long-term risk of ischemic heart disease in men. 13-year follow-up data from the Quebec Cardiovascular Study. *Arterioscler Thromb Vasc Biol*. 2005;25:553–559.
163. Sniderman A, Williams K, de Graaf J. Non-HDL C equals apolipoprotein B: except when it does not!. *Curr Opin Lipidol*. 2010;21: 518–524.
164. Sniderman AD, Williams K, Contois JH, et al. A meta-analysis of low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, and apolipoprotein B as markers of cardiovascular risk. *Circ Cardiovasc Qual Outcomes*. 2011;4:337–345.
165. Sniderman AD, Islam S, Yusuf S, McQueen MJ. Discordance analysis of apolipoprotein B and non-high density lipoprotein cholesterol as markers of cardiovascular risk in the INTERHEART study. *Atherosclerosis*. 2012;225:444–449.
166. Boekholdt SM, Arsenault BJ, Mora S, et al. Association of LDL cholesterol, non-HDL cholesterol, and apolipoprotein B Levels with risk of cardiovascular events among patients treated with statins. *JAMA*. 2012;307:1302–1309.
167. Robinson JG, Wang S, Jacobson TA. Meta-analysis of comparison of effectiveness of lowering apolipoprotein B versus low-density lipoprotein cholesterol and non high-density lipoprotein cholesterol for cardiovascular risk reduction in randomized trials. *Am J Cardiol*. 2012;110:1468–1476.
168. Barter P, Gotto AM, LaRosa JC, et al, Treating to New Targets Investigators. HDL cholesterol, very low levels of LDL cholesterol, and cardiovascular events. *N Engl J Med*. 2007;357:1301–1310.
169. Ramjee V, Sperling LS, Jacobson TA. Non-high-density lipoprotein cholesterol versus apolipoprotein B in cardiovascular risk stratification: do the math. *J Am Coll Cardiol*. 2011;58:457–463.
170. Ballantyne CM, Raichlen JS, Cain VA. Statin therapy alters the relationship between apolipoprotein B and low-density lipoprotein cholesterol and non-high-density lipoprotein cholesterol targets in high-risk patients: the MERCURY II (Measuring Effective Reductions in Cholesterol Using Rosuvastatin) trial. *J Am Coll Cardiol*. 2008;52:626–632.
171. Grundy SM, Vega GL, Tomassini JE, Tershakovec AM. Comparisons of apolipoprotein B levels estimated by immunoassay, nuclear magnetic resonance, vertical auto profile, and non-high-density lipoprotein cholesterol in subjects with hypertriglyceridemia (SAFARI Trial). *Am J Cardiol*. 2011;108:40–46.
172. Austin MA. Plasma triglyceride and coronary heart disease. *Arterioscler Thromb*. 1991;11:2–14.
173. Assmann G, Schulte H, von Eckardstein A. Hypertriglyceridemia and elevated levels of lipoprotein(a) are risk factors for major coronary events in middle-aged men. *Am J Cardiol*. 1996;77:1179–1184.
174. Iso H, Naito Y, Sato S, et al. Serum triglycerides and risk of coronary heart disease among Japanese men and women. *Am J Epidemiol*. 2001;153:490–499.
175. Austin MA, Breslow JL, Hennekens CH, Buring JE, Willett WC, Krauss RM. Low-density lipoprotein subclass patterns and risk of myocardial infarction. *JAMA*. 1988;260:1917–1921.
176. Gardner CD, Fortmann SP, Krauss RM. Association of small low-density lipoprotein particles with the incidence of coronary artery disease in men and women. *JAMA*. 1996;276:875–881.
177. St-Pierre AC, Ruel IL, Cantin B, et al. Comparison of various electrophoretic characteristics of LDL particles and their relationship to the risk of ischemic heart disease. *Circulation*. 2001;104:2295–2299.
178. Kuller L, Arnold A, Tracy R, et al. Nuclear magnetic resonance spectroscopy of lipoproteins and risk of coronary heart disease in the Cardiovascular Health Study. *Arterioscler Thromb Vasc Biol*. 2002;22: 1175–1180.
179. Castelli WP, Anderson K, Wilson PW, Levy D. Lipids and risk of coronary heart disease. The Framingham Study. *Ann Epidemiol*. 1992;2:23–28.
180. Yusuf S, Hawken S, Ounpuu S, et al, INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet*. 2004;364:937–952.
181. O'Donnell MJ, Xavier D, Liu L, et al, INTERSTROKE investigators. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. *Lancet*. 2010;376:112–123.
182. McLaughlin T, Abbasi F, Cheal K, Chu J, Lamendola C, Reaven G. Use of metabolic markers to identify overweight individuals who are insulin resistant. *Ann Intern Med*. 2003;139:802–809.
183. Bhalodkar NC, Blum S, Enas EA. Accuracy of the ratio of triglycerides to high-density lipoprotein cholesterol for predicting low-density lipoprotein cholesterol particle sizes, phenotype B, and particle concentrations among Asian Indians. *Am J Cardiol*. 2006;97: 1007–1009.
184. Bittner V, Johnson BD, Zineh I, et al. The triglyceride/high-density lipoprotein cholesterol ratio predicts all-cause mortality in women with suspected myocardial ischemia: a report from the Women's Ischemia Syndrome Evaluation (WISE). *Am Heart J*. 2009;157: 548–555.
185. Hadaegh F, Khalili D, Ghasemi A, Tohidi M, Sheikholeslami F, Azizi F. Triglyceride/HDL-cholesterol ratio is an independent predictor for coronary heart disease in a population of Iranian men. *Nutr Metab Cardiovasc Dis*. 2009;19:401–408.
186. Gasevic D, Frohlich J, Mancini GB, Lear SA. The association between triglyceride to high-density-lipoprotein cholesterol ratio and insulin resistance in a multiethnic primary prevention cohort. *Metabolism*. 2012;61:583–589.
187. Kang HT, Yoon JH, Kim JY, et al. The association between the ratio of triglyceride to HDL-C and insulin resistance according to waist circumference in a rural Korean population. *Nutr Metab Cardiovasc Dis*. 2012;22:1054–1060.

188. Nordestgaard BG, Chapman MJ, Ray K, et al. European Atherosclerosis Society Consensus Panel: Lipoprotein(a) as a cardiovascular risk factor: current status. *Eur Heart J*. 2010;31:2844–2853.
189. Lp-PLA(2) Studies CollaborationThompson A, Gao P, Orfei L, et al. Lipoprotein-associated phospholipase A(2) and risk of coronary disease, stroke, and mortality: collaborative analysis of 32 prospective studies. *Lancet*. 2010;375:1536–1544.
190. Ridker PM. C-reactive protein and the prediction of cardiovascular events among those at intermediate risk: moving an inflammatory hypothesis toward consensus. *J Am Coll Cardiol*. 2007;49:2129–2138.
191. Casas JP, Shah T, Hingorani AD, Danesh J, Pepys MB. C-reactive protein and coronary heart disease: a critical review. *J Intern Med*. 2008;264:295–314.
192. Davidson MH, Ballantyne CM, Jacobson TA, et al. Clinical utility of inflammatory markers and advanced lipoprotein testing: advice from an expert panel of lipid specialists. *J Clin Lipidol*. 2011;5:338–367.
193. Wilson PW, Pencina M, Jacques P, Selhub J, D'Agostino R Sr, O'Donnell CJ. C-reactive protein and reclassification of cardiovascular risk in the Framingham Heart Study. *Circ Cardiovasc Qual Outcomes*. 2008;1:92–97.
194. Cook NR, Paynter NP, Eaton CB, et al. Comparison of the Framingham and Reynolds Risk scores for global cardiovascular risk prediction in the multiethnic Women's Health Initiative. *Circulation*. 2012;125:1748–1756.
195. Emerging Risk Factors Collaboration. C-reactive protein, fibrinogen, and cardiovascular disease prediction. *N Engl J Med*. 2012;367:1310–1320.
196. Perk J, De Backer G, Gohlke H, et al. European guidelines on cardiovascular disease prevention in clinical practice (version 2012). *Eur Heart J*. 2012;33:1635–1701.
197. Assmann G, Schulte H, Cullen P, Seedorf U. Assessing risk of myocardial infarction and stroke: new data from the Prospective Cardiovascular Münster (PROCAM) study. *Eur J Clin Invest*. 2007;37:925–932.
198. Ramsay SE, Morris RW, Whincup PH, Papacosta AO, Thomas MC, Wannamethee SG. Prediction of coronary heart disease risk by Framingham and SCORE risk assessments varies by socioeconomic position: results from a study in British men. *Eur J Cardiovasc Prev Rehabil*. 2011;18:186–193.
199. Lorenzo C, Williams K, Hunt KJ, Haffner SM. The National Cholesterol Education Program - Adult Treatment Panel III, International Diabetes Federation, and World Health Organization definitions of the metabolic syndrome as predictors of incident cardiovascular disease and diabetes. *Diabetes Care*. 2007;30:8–13.
200. Pelletier P, Lapointe A, Laflamme N, et al. Discordances among different tools used to estimate cardiovascular risk in postmenopausal women. *Can J Cardiol*. 2009;25:e413–e416.
201. Patt MR, Yanek LR, Moy TF, Becker DM. Assessment of global coronary heart disease risk in overweight and obese African-American women. *Obes Res*. 2003;11:660–667.
202. Correll CU, Frederickson AM, Kane JM, Manu P. Metabolic syndrome and the risk of coronary heart disease in 367 patients treated with second-generation antipsychotic drugs. *J Clin Psychiatry*. 2006;67:575–583.
203. Jaumdally JR, Lip GY, Varma C. Traditional risk factors for coronary atherosclerosis in Indo Asians: the need for a reappraisal. *Curr Pharm Des*. 2006;12:1611–1621.
204. Arsenault BJ, Rana JS, Stroes ES, et al. Beyond low-density lipoprotein cholesterol: respective contributions of non-high-density lipoprotein cholesterol levels, triglycerides, and the total cholesterol/high-density lipoprotein cholesterol ratio to coronary heart disease risk in apparently healthy men and women. *J Am Coll Cardiol*. 2009;55:35–41.
205. Franco OH, Massaro JM, Civil J, Cobain MR, O'Malley B, D'Agostino RB Sr. Trajectories of entering the metabolic syndrome: the Framingham Heart Study. *Circulation*. 2009;120:1943–1950.
206. Wannamethee SG. The metabolic syndrome and cardiovascular risk in the British Regional Heart Study. *Int J Obes (Lond)*. 2008;32(Suppl 2):S25–S29.
207. Wannamethee SG, Shaper AG, Lennon L, Morris RW. Metabolic syndrome vs Framingham Risk Score for prediction of coronary heart disease, stroke, and type 2 diabetes mellitus. *Arch Intern Med*. 2005;165:2644–2650.
208. Assmann G, Cullen P, Schulte H. Simple scoring scheme for calculating the risk of acute coronary events based on the 10-year follow-up of the prospective cardiovascular Munster (PROCAM) study. *Circulation*. 2002;105:310–315.
209. Hense HW, Schulte H, Lowel H, Assmann G, Keil U. Framingham risk function overestimates risk of coronary heart disease in men and women from Germany—results from the MONICA Augsburg and the PROCAM cohorts. *Eur Heart J*. 2003;24:937–945.
210. Arai H, Kokubo Y, Watanabe M, et al. Small dense low-density lipoproteins cholesterol can predict incident cardiovascular disease in an urban Japanese cohort: the Suita study. *J Atheroscler Thromb*. 2013;20:195–203.
211. Kathiresan S, Otvos JD, Sullivan LM, et al. Increased small low-density lipoprotein particle number: a prominent feature of the metabolic syndrome in the Framingham Heart Study. *Circulation*. 2006;113:20–29.
212. Greenland P, Bonow RO, Brundage BH, et al, American College of Cardiology Foundation Clinical Expert Consensus Task Force (ACCF/AHA Writing Committee to Update the 2000 Expert Consensus Document on Electron Beam Computer Tomography); Society of Atherosclerosis Imaging and Prevention; Society of Cardiovascular Computer Tomography. ACCF/AHA 2007 clinical expert consensus document on coronary artery calcium scoring by computed tomography in global cardiovascular risk assessment and in evaluation of patients with chest pain: a report of the American College of Cardiology Foundation Clinical Expert Consensus Task Force (ACCF/AHA Writing Committee to Update the 2000 Expert Consensus Document on Electron Beam Computed Tomography). *Circulation*. 2007;115:402–426.
213. Rumberger JA, Schwartz RS, Simons DB, Sheedy PF III, Edwards WD, Fitzpatrick LA. Relation of coronary calcium determined by electron beam computed tomography and lumen narrowing determined by autopsy. *Am J Cardiol*. 1994;73:1169–1173.
214. Rumberger JA, Simons DB, Fitzpatrick LA, Sheedy PF, Schwartz RS. Coronary artery calcium area by electron-beam computed tomography and coronary atherosclerotic plaque area. A histopathologic correlative study. *Circulation*. 1995;92:2157–2162.
215. Budoff MJ, Georgiou D, Brody A, et al. Ultrafast computed tomography as a diagnostic modality in the detection of coronary artery disease: a multicenter study. *Circulation*. 1996;93:898–904.
216. Guerci AD, Spadaro LA, Popma JJ, et al. Relation of coronary calcium score by electron beam computed tomography to arteriographic findings in asymptomatic and symptomatic adults. *Am J Cardiol*. 1997;79:128–133.
217. Schmermund A, Baumgart D, Gorge G, et al. Measuring the effect of risk factors on coronary atherosclerosis: coronary calcium score versus angiographic disease severity. *J Am Coll Cardiol*. 1998;31:1267–1273.
218. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK Jr. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study Collaborative Research Group. *N Engl J Med*. 1999;340:14–22.
219. Folsom AR, Kronmal RA, Detrano RC, et al. Coronary artery calcification compared with carotid intima-media thickness in the prediction of cardiovascular disease incidence: the Multi-Ethnic Study of Atherosclerosis (MESA). *Arch Intern Med*. 2008;168:1333–1339.
220. Nambi V, Chambless L, Folsom AR, et al. Carotid intima-media thickness and presence or absence of plaque improves prediction of

coronary heart disease risk: the ARIC (Atherosclerosis Risk In Communities) study. *J Am Coll Cardiol*. 2010;55:1600–1607.
221. Wardlaw JM, Stevenson MD, Chappell F, et al. Carotid artery imaging for secondary stroke prevention: both imaging modality and rapid access to imaging are important. *Stroke*. 2009;40:3511–3517.
222. U-King-Im JM, Young V, Gillard JH. Carotid-artery imaging in the diagnosis and management of patients at risk of stroke. *Lancet Neurol*. 2009;8:569–580.
223. Grundy SM. Age as a risk factor: you are as old as your arteries. *Am J Cardiol*. 1999;83:1455–1457.
224. Greenland P, LaBree L, Azen SP, Doherty TM, Detrano RC. Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals. *JAMA*. 2004;291:210–215.
225. Sung J, Lim SJ, Choe Y, et al. Comparison of the coronary calcium score with the estimated coronary risk. *Coron Artery Dis*. 2008;19:475–479.
226. Elias-Smale SE, Proença RV, Koller MT, et al. Coronary calcium score improves classification of coronary heart disease risk in the elderly: the Rotterdam study. *J Am Coll Cardiol*. 2010;56:1407–1414.
227. Okwuosa TM, Greenland P, Ning H, et al. Distribution of coronary artery calcium scores by Framingham 10-year risk strata in the MESA (Multi-Ethnic Study of Atherosclerosis) potential implications for coronary risk assessment. *J Am Coll Cardiol*. 2011;57:1838–1845.
228. Tota-Maharaj R, Blaha MJ, McEvoy JW, et al. Coronary artery calcium for the prediction of mortality in young adults $<$ 45 years old and elderly adults $>$ 75 years old. *Eur Heart J*. 2012;33:2955–2962.
229. Yeboah J, Carr JJ, Terry JG, et al. Computed tomography-derived cardiovascular risk markers, incident cardiovascular events, and all-cause mortality in nondiabetics: the Multi-Ethnic Study of Atherosclerosis. *Eur J Prev Cardiol*. 2013 [E-pub ahead of print].
230. Youssef G, Kalia N, Darabian S, Budoff MJ. Coronary calcium: new insights, recent data, and clinical role. *Curr Cardiol Rep*. 2013;15:325.
231. Lloyd-Jones DM, Wilson PW, Larson MG, et al. Framingham risk score and prediction of lifetime risk for coronary heart disease. *Am J Cardiol*. 2004;94:20–24.
232. Pencina MJ, D'Agostino RB, Beiser AS, Cobain MR, Vasan RS. Estimating lifetime risk of developing high serum total cholesterol: adjustment for baseline prevalence and single-occasion measurements. *Am J Epidemiol*. 2007;165:464–472.
233. Pencina MJ, D'Agostino RB Sr, Larson MG, Massaro JM, Vasan RS. Predicting the 30-year risk of cardiovascular disease: the Framingham Heart Study. *Circulation*. 2009;119:3078–3084.
234. Hippisley-Cox J, Coupland C, Robson J, Brindle P. Derivation, validation, and evaluation of a new QRISK model to estimate lifetime risk of cardiovascular disease: cohort study using Q Research database. *BMJ*. 2010;341:c6624.
235. Berry JD, Dyer A, Cai X, et al. Lifetime risks of cardiovascular disease. *N Engl J Med*. 2012;366:321–329.
236. Lloyd-Jones DM, Larson MG, Beiser A, Levy D. Lifetime risk of developing coronary heart disease. *Lancet*. 1999;353:89–92.
237. Lloyd-Jones DM, Wilson PW, Larson MG, et al. Lifetime risk of coronary heart disease by cholesterol levels at selected ages. *Arch Intern Med*. 2003;163:1966–1972.
238. Lloyd-Jones DM, Leip EP, Larson MG, et al. Prediction of lifetime risk for cardiovascular disease by risk factor burden at 50 years of age. *Circulation*. 2006;113:791–798.
239. Lloyd-Jones DM, Dyer AR, Wang R, Daviglus ML, Greenland P. Risk factor burden in middle age and lifetime risks for cardiovascular and non-cardiovascular death (Chicago Heart Association Detection Project in Industry). *Am J Cardiol*. 2007;99:535–540.
240. Marma AK, Berry JD, Ning H, Persell SD, Lloyd-Jones DM. Distribution of 10-year and lifetime predicted risks for cardiovascular disease in US adults: findings from the National Health and Nutrition Examination Survey 2003 to 2006. *Circ Cardiovasc Qual Outcomes*. 2010;3:8–14.
241. Allen N, Berry JD, Ning H, Van Horn L, Dyer A, Lloyd-Jones DM. Impact of blood pressure and blood pressure change during middle age on the remaining lifetime risk for cardiovascular disease: the Cardiovascular Lifetime Risk Pooling Project. *Circulation*. 2012;125:37–44.
242. Wilkins JT, Ning H, Berry J, Zhao L, Dyer AR, Lloyd-Jones DM. Lifetime risk and years lived free of total cardiovascular disease. *JAMA*. 2012;308:1795–1801.
243. Karmali KN, Lloyd-Jones DM. Adding a life-course perspective to cardiovascular-risk communication. *Nat Rev Cardiol*. 2013;10:111–115.
244. Hippisley-Cox J, Coupland C, Vinogradova Y, et al. Predicting cardiovascular risk in England and Wales: prospective derivation and validation of QRISK2. *BMJ*. 2008;336:1475–1482.
245. Collins GS, Altman DG. Predicting the 10 year risk of cardiovascular disease in the United Kingdom: independent and external validation of an updated version of QRISK2. *BMJ*. 2012;344:e4181.
246. Laurier D, Nguyen PC, Cazelles B, Segond P. Estimation of CHD risk in a French working population using a modified Framingham model. The PCV-METRA Group. *J Clin Epidemiol*. 1994;471:1353–1364.
247. Liao Y, McGee DL, Cooper RS, Sutkowski MB. How generalizable are coronary risk prediction models? Comparison of Framingham and two national cohorts. *Am Heart J*. 1999;137:837–845.
248. Menotti A, Puddu PE, Lanti M. Comparison of the Framingham risk function-based coronary chart with risk function from an Italian population study. *Eur Heart J*. 2000;21:365–370.
249. D'Agostino RB Sr, Grundy S, Sullivan LM, Wilson P, , CHD Risk Prediction Group. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. *JAMA*. 2001;286:180–187.
250. Thomsen TF, Davidsen M, Ibsen H, Jørgensen T, Jensen G, Borch-Johnsen K. A new method for CHD prediction and prevention based on regional risk scores and randomized clinical trials; PRECARD and the Copenhagen Risk Score [Erratum in: J Cardiovasc Risk. 2001;8:391]. *J Cardiovasc Risk*. 2001;8:291–297 Review.
251. Diverse Population Collaborative Group. Prediction of mortality from coronary heart disease among diverse populations: is there a common predictive function? *Heart*. 2002;88:222–228.
252. Brindle P, Emberson J, Lampe F, et al. Predictive accuracy of the Framingham coronary risk score in British men: prospective cohort study. *BMJ*. 2003;327:1267.
253. Empana JP, Ducimetière P, Arveiler D, et al, PRIME Study Group. Are the Framingham and PROCAM coronary heart disease risk functions applicable to different European populations? The PRIME Study. *Eur Heart J*. 2003;24:1903–1911.
254. Marrugat J, D'Agostino R, Sullivan L, et al. An adaptation of the Framingham coronary heart disease risk function to European Mediterranean areas. *J Epidemiol Community Health*. 2003;57:634–863.
255. Liu J, Hong Y, D'Agostino RB Sr, et al. Predictive value for the Chinese population of the Framingham CHD risk assessment tool compared with the Chinese Multi-Provincial Cohort Study. *JAMA*. 2004;291:2591–2599.
256. Asia Pacific Cohort Studies Collaboration. Barzi F, Patel A, Gu D, et al. Cardiovascular risk prediction tools for populations in Asia. *J Epidemiol Community Health*. 2007;61:115–121.
257. Eichler K, Puhan MA, Steurer J, Bachmann LM. Prediction of first coronary events with the Framingham score: a systematic review. *Am Heart J*. 2007;153:722–731.
258. Chow CK, Joshi R, Celermajer DS, Patel A, Neal BC. Recalibration of a Framingham risk equation for a rural population in India. *J Epidemiol Community Health*. 2009;63:379–385.
259. Marques-Vidal P, Rodondi N, Bochud M, et al. Predictive accuracy of original and recalibrated Framingham risk score in the Swiss population. *Int J Cardiol*. 2009;133:346–353.

260. Rodondi N, Locatelli I, Aujesky D, et al. Health ABC Study. Framingham risk score and alternatives for prediction of coronary heart disease in older adults. *PLoS One*. 2012;7:e34287.
261. Menotti A, Keys A, Kromhout D, et al. Inter-cohort differences in coronary heart disease mortality in the 25-year follow-up of the Seven Countries Study. *Eur J Epidemiol*. 1993;9:527–536.
262. Campbell TC, Parpia B, Chen J. Diet, lifestyle, and the etiology of coronary artery disease: the Cornell China study. *Am J Cardiol*. 1998;82:18T–21T.
263. Yokokawa H, Yasumura S, Tanno K, et al. Serum low-density lipoprotein to high-density lipoprotein ratio as a predictor of future acute myocardial infarction among men in a 2.7-year cohort study of a Japanese northern rural population. *J Atheroscler Thromb*. 2011;18:89–98.
264. Singh RB, Suh IL, Singh VP, et al. Hypertension and stroke in Asia: prevalence, control and strategies in developing countries for prevention. *J Hum Hypertens*. 2000;14:749–763.
265. Hayward RA, Krumholz HM, Zulman DM, Timbie JW, Vijan S. Optimizing statin treatment for primary prevention of coronary artery disease. *Ann Intern Med*. 2010;152:69–77.
266. Cohen JC, Boerwinkle E, Mosley TH Jr., Hobbs HH. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. *N Engl J Med*. 2006;354:1264–1272.
267. Kathiresan S. A PCSK9 missense variant associated with a reduced risk of early-onset myocardial infarction. *N Engl J Med*. 2008;358:2299–2300.
268. Ference BA, Yoo W, Alesh I, et al. Effect of long-term exposure to lower low-density lipoprotein cholesterol beginning early in life on the risk of coronary heart disease: a Mendelian randomization analysis. *J Am Coll Cardiol*. 2012;60:2631–2639.
269. Anderson TJ, Grégoire J, Hegele RA, et al. 2012 update of the Canadian Cardiovascular Society guidelines for the diagnosis and treatment of dyslipidemia for the prevention of cardiovascular disease in the adult. *Can J Cardiol*. 2013;29:151–167.
270. Hayward RA, Krumholz HM. Three reasons to abandon low-density lipoprotein targets: an open letter to the Adult Treatment Panel IV of the National Institutes of Health. *Circ Cardiovasc Qual Outcomes*. 2012;5:2–5.
271. Ledford H. Cholesterol limits lose their luster. Revised guidelines for heart health are set to remove from target-based approach. *Nature*. 2013;494:410–411.
272. Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80% [Erratum in: *BMJ*. 2003;327:586. *BMJ*. 2006;60:823]. *BMJ*. 2003;326:1419.
273. Lonn E, Bosch J, Teo KK, Pais P, Xavier D, Yusuf S. The polypill in the prevention of cardiovascular diseases: key concepts, current status, challenges, and future directions. *Circulation*. 2010;122:2078–2088.
274. Elley CR, Gupta AK, Webster R, et al. The efficacy and tolerability of 'polypills': meta-analysis of randomised controlled trials. *PLoS One*. 2012;7:e52145.
275. Wald DS, Morris JK, Wald NJ. Randomized polypill crossover trial in people aged 50 and over. *PLoS One*. 2012;7:e41297.
276. Indian Polycap Study (TIPS)Yusuf S, Pais P, Afzal R, et al. Effects of a polypill (Polycap) on risk factors in middle-aged individuals without cardiovascular disease (TIPS): a phase II, double-blind, randomised trial. *Lancet*. 2009;373:1341–1351.
277. PILL Collaborative Group. Rodgers A, Patel A, Berwanger O, et al. An international randomised placebo-controlled trial of a four-component combination pill ("polypill") in people with raised cardiovascular risk. *PLoS One*. 2011;6:e19857.
278. Milhos CG, Salas MJ, Santana O. The pleiotropic effects of the hydroxy-methyl-glutaryl-CoA reductase inhibitors in cardiovascular disease: a comprehensive review. *Cardiol Rev*. 2010;18:298–304.
279. Ma S, Ma CC. Recent development in pleiotropic effects of statins on cardiovascular disease through regulation of transforming growth factor-beta superfamily. *Cytokine Growth Factor Rev*. 2011;22:167–175.
280. Porter KE, Turner NA. Statins and myocardial remodelling: cell and molecular pathways. *Expert Rev Mol Med*. 2011;13:e22.
281. Davignon J. Pleiotropic effects of pitavastatin. *Br J Clin Pharmacol*. 2012;73:518–535.
282. Baigent C, Keech A, Kearney PM, et al, Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins [Erratum in: *Lancet*. 2008;371:2084. *Lancet*. 2005;366:1358]. *Lancet*. 2005;366:1267–1278.
283. Misra A, Chowbey P, Makkar BM, et al, Consensus Group. Consensus statement for diagnosis of obesity, abdominal obesity and the metabolic syndrome for Asian Indians and recommendations for physical activity, medical and surgical management. *J Assoc Physicians India*. 2009;57:163–170.
284. Eriksson KF, Lindgarde F. Prevention of type 2 (non-insulin-dependent) diabetes mellitus by diet and physical exercise: the 6-year Malmo feasibility study. *Diabetologia*. 1997;34:891–898.
285. Pan XR, Li GW, Hu YH, et al. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance: the Da Qing IGT and Diabetes Study. *Diabetes Care*. 1997;20:537–544.
286. Tuomilehto J, Lindström J, Eriksson JG, et al, Finnish Diabetes Prevention Study Group. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med*. 2001;344:1343–1350.
287. Knowler WC, Barrett-Connor E, Fowler SE, et al, Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002;346:393–403.
288. American College of Sports Medicine. ACSM's Guidelines for Exercise Testing and Prescription. 9th Ed. Philadelphia: Lippincott Williams and Wilkins; 2013.
289. Grundy SM. Metabolic syndrome: a multiplex cardiovascular risk factor. *J Clin Endocrinol Metab*. 2007;92:399–404.
290. American Heart Association Nutrition Committee. 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.
291. National Institute for Health and Clinical Excellence, The National Collaborating Centre for Primary Care. NICE Clinical Guideline 71: Identification and management of familial hypercholesterolaemia. London: Royal College of General Practitioners; 2008.
292. Daniels SR, Gidding SS, de Ferranti SD , National Lipid Association Expert Panel on Familial Hypercholesterolemia. Pediatric aspects of familial hypercholesterolemias: recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. *J Clin Lipidol*. 2011;5:S30–S37.
293. Goldberg AC, Hopkins PN, Toth PP, et al. Familial hypercholesterolemia: screening, diagnosis and management of pediatric and adult patients: clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. *J Clin Lipidol*. 2011;5:133–140.
294. Watts GF, Sullivan DR, Poplawski N, et al, Familial Hypercholesterolaemia Australasia Network Consensus Group (Australian Atherosclerosis Society). Familial hypercholesterolaemia: a model of care for Australasia. *Atheroscler Suppl*. 2011;12:221–263.
295. Thompson GR. Lipoprotein apheresis. *Curr Opin Lipidol*. 2010;21:487–491.
296. Stefanutti C, Julius U. Lipoprotein apheresis: state of the art and novelties. *Atheroscler Suppl*. 2013;14:19–27.
297. Wiesbauer F, Blessberger H, Azar D, et al. Familial-combined hyperlipidaemia in very young myocardial infarction survivors (< or = 40 years of age). *Eur Heart J*. 2009;30:1073–1079.
298. Murphy MJ, Sheng X, MacDonald TM, Wei L. Hypertriglyceridemia and acute pancreatitis. *JAMA Intern Med*. 2013;173:162–164.
299. Hayward RA, Hofer TP, Vijan S. Narrative review: lack of evidence for recommended low-density lipoprotein treatment targets: a solvable problem. *Ann Intern Med*. 2006;145:520–530.

300. Krumholz HM, Hayward RA. Shifting views on lipid lowering therapy. *BMJ*. 2010;341:c3531.
301. Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013 [Epub ahead of print].
302. Solano MP, Goldberg RB. Lipid management in type 2 diabetes. *Clin Diabetes*. 2006;24:27–32.
303. Civeira F, International Panel on Management of Familial Hypercholesterolemia. Guidelines for the diagnosis and management of heterozygous familial hypercholesterolemia. *Atherosclerosis*. 2004;173:55–68.
304. Polonsky TS, Bakris GL. Chronic kidney disease: a coronary heart disease equivalent? *Lancet*. 2012;380:783–785.
305. Adler AI. UKPDS-modelling of cardiovascular risk assessment and lifetime simulation of outcomes. *Diabetes Med*. 2008;25(Suppl 2):41–46.
306. Wannamethee SG, Shaper AG, Whincup PH, Lennon L, Sattar N. Impact of diabetes on cardiovascular disease risk and all-cause mortality in older men: influence of age at onset, diabetes duration, and established and novel risk factors. *Arch Intern Med*. 2011;171:404–410.
307. Tonelli M, Muntner P, Lloyd A, et al, Alberta Kidney Disease Network. Risk of coronary events in people with chronic kidney disease compared with those with diabetes: a population-level cohort study. *Lancet*. 2012;380:807–814.
308. Hoang KC, Ghandehari H, Lopez VA, Barboza MG, Wong ND. Global coronary heart disease risk assessment of individuals with the metabolic syndrome in the U.S. *Diabetes Care*. 2008;31:1405–1409.
309. Teramoto T, Sasaki J, Ueshima H, et al. Executive summary of Japan Atherosclerosis Society (JAS) guideline for diagnosis and prevention of atherosclerotic cardiovascular diseases for Japanese. *J Atheroscler Thromb*. 2007;14:45–50.
310. Mascitelli L, Goldstein MR. Statins for people at low risk of cardiovascular disease. *Lancet*. 2012;380:1816.
311. Newman DH, Saini V, Brody H, et al. Statins for people at low risk of cardiovascular disease. *Lancet*. 2012;380:1814.
312. Brown MS, Goldstein JL. Biomedicine. Lowering LDL–not only how low, but how long? *Science*. 2006;311:1721–1723.
313. Steinberg D, Grundy SM. The case for treating hypercholesterolemia at an earlier age: moving toward consensus. *J Am Coll Cardiol*. 2012;60:2640–2642.
314. Domanski M, Lloyd-Jones D, Fuster V, Grundy S. Can we dramatically reduce the incidence of coronary heart disease? *Nat Rev Cardiol*. 2011;8:721–725.
315. Walsh JM, Pignone M. Drug treatment of hyperlipidemia in women. *JAMA*. 2004;291:2243–2252.
316. Kendrick M. Should women be offered cholesterol lowering drugs to prevent cardiovascular disease? *BMJ*. 2007;334:983.
317. Bukkapatnam RN, Gabler NB, Lewis WR. Statins for primary prevention of cardiovascular mortality in women: a systematic review and meta-analysis. *Prev Cardiol*. 2010;13:84–90.
318. Ridker PM, Danielson E, Fonseca FA, et al, Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med*. 2008;359:2195–2207.
319. Mora S, Glynn RJ, Hsia J, MacFadyen JG, Genest J, Ridker PM. Statins for the primary prevention of cardiovascular events in women with elevated high-sensitivity C-reactive protein or dyslipidemia: results from the Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) and meta-analysis of women from primary prevention trials. *Circulation*. 2010;121:1069–1077.
320. Grundy SM. Drug therapy of the metabolic syndrome: minimizing the emerging crisis in polypharmacy. *Nat Rev Drug Discov*. 2006;5:295–309.
321. World Health Organization. Tobacco. Available at: http://www.who.int/mediacentre/factsheets/fs339/en/index.html. Accessed January 6, 2014.
322. Ezzati M, Lopez AD, Rodgers A, Vander Hoorn S, Murray CJ, Comparative Risk Assessment Collaborating Group. Selected major risk factors and global and regional burden of disease. *Lancet*. 2002;360:1347–1360.
323. Action to Control Cardiovascular Risk in Diabetes Study Group. Gerstein HC, Miller ME, Byington RP, et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med*. 2008;358:2545–2559.
324. Skyler JS, Bergenstal R, Bonow RO, et al, American Diabetes Association; American College of Cardiology Foundation; American Heart Association. Intensive glycemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA diabetes trials: a position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology Foundation and the American Heart Association. *Diabetes Care*. 2009;32:187–192.
325. Jellinger PS, Smith DA, Mehta AE, et al. American Association of Clinical Endocrinologists' guidelines for management of dyslipidemia and prevention of atherosclerosis. *Endocr Pract*. 2012;18(Suppl 1):1–78.
326. Orchard TJ, Costacou T, Kretowski A, Nesto RW. Type 1 diabetes and coronary artery disease. *Diabetes Care*. 2006;29:2528–2538.
327. American Diabetes Association. Standards of medical care in diabetes–2012. *Diabetes Care*. 2012;35(Suppl 1):S11–S63.
328. Barylski M, Nikfar S, Mikhailidis DP, et al, Lipid and Blood Pressure Meta-Analysis Collaboration Group. Statins decrease all-cause mortality only in CKD patients not requiring dialysis therapy-A meta-analysis of 11 randomized controlled trials involving 21,295 participants. *Pharmacol Res*. 2013;72:35–44.
329. Hou W, Lv J, Perkovic V, et al. Effect of statin therapy on cardiovascular and renal outcomes in patients with chronic kidney disease: a systematic review and meta-analysis. *Eur Heart J*. 2013;34:1807–1817.
330. Wanner C, Krane V, März W, et al, German Diabetes and Dialysis Study Investigators. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med*. 2005;353:238–248.
331. Sacks FM, Tonkin AM, Shepherd J, et al. Effect of pravastatin on coronary disease events in subgroups defined by coronary risk factors: the Prospective Pravastatin Pooling Project. *Circulation*. 2000;102:1893–1900.
332. LaRosa JC, Grundy SM, Kastelein JJ, Kostis JB, Greten H. Safety and efficacy of atorvastatin-induced very low-density lipoprotein cholesterol levels in patients with coronary heart disease (a post hoc analysis of the treating to new targets [TNT] study). *Am J Cardiol*. 2007;100:747–752.
333. Cannon CP, Braunwald E, McCabe CH, et al, Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 Investigators. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med*. 2004;350:1495–1504.
334. Cannon CP. The IDEAL cholesterol: lower is better. *JAMA*. 2005;294:2492–2494.
335. Cannon CP, Steinberg BA, Murphy SA, Mega JL, Braunwald E. Meta-analysis of cardiovascular outcomes trials comparing intensive versus moderate statin therapy. *J Am Coll Cardiol*. 2006;48:438–445.
336. Sachdeva A, Cannon CP, Deedwania PC, et al. Lipid levels in patients hospitalized with coronary artery disease: an analysis of 136,905 hospitalizations in Get With The Guidelines. *Am Heart J*. 2009;157:111–117.e2.
337. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators. High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med*. 2006;355:549–559.
338. Kastelein JJ, van der Steeg WA, Holme I, et al, TNT Study Group; IDEAL Study Group. Lipids, apolipoproteins, and their ratios in

relation to cardiovascular events with statin treatment. *Circulation*. 2008;117:3002–3009.
339. Ballantyne CM, Pitt B, Loscalzo J, Cain VA, Raichlen JS. Alteration of relation of atherogenic lipoprotein cholesterol to apolipoprotein B by intensive statin therapy in patients with acute coronary syndrome (from the Limiting UNdertreatment of lipids in ACS With Rosuvastatin [LUNAR] Trial). *Am J Cardiol*. 2013;111:506–509.
340. ACCORD Study Group. Ginsberg HN, Elam MB, Lovato LC, et al. Effects of combination lipid therapy in type 2 diabetes mellitus [Erratum in *N Engl J Med*. 2010;6;362:1748]. *N Engl J Med*. 2010;362:1563–1574.
341. Elam M, Lovato LC, Ginsberg H. Role of fibrates in cardiovascular disease prevention, the ACCORD-Lipid perspective. *Curr Opin Lipidol*. 2011;22:55–61.
342. Kromhout D, Giltay EJ, Geleijnse JM, Alpha Omega Trial Group Collaborators (73). n-3 fatty acids and cardiovascular events after myocardial infarction. *N Engl J Med*. 2010;363:2015–2026.
343. ORIGIN Trial Investigators. Bosch J, Gerstein HC, Dagenais GR, et al. n-3 fatty acids and cardiovascular outcomes in patients with dysglycemia. *N Engl J Med*. 2012;367:309–318.
344. Inzucchi SE, Bergenstal RM, Buse JB, et al, American Diabetes Association (ADA); European Association for the Study of Diabetes (EASD). Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. 2012;35:1364–1379.
345. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia*. 2012;55:1577–1596.
346. Ford ES, Giles WH, Mokdad AH. The distribution of 10-Year risk for coronary heart disease among US adults: findings from the National Health and Nutrition Examination Survey III. *J Am Coll Cardiol*. 2004;43:1791–1796.

Appendix

IAS panel for global recommendations for the management of dyslipidemia

Scott M. Grundy—Chair of the IAS Panel for Global Recommendations for the Management of Dyslipidemia, Professor of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, Texas, USA. Consultant: Merck, Johnson and Johnson, Pfizer, Sanofi Aventis.

Hidenori Arai—Professor, Department of Human Health Sciences, Kyoto University Graduate School of Medicine, Kyoto, Japan. Honoraria: Daiichi Sankyo, Kowa and Merck Sharp & Dohme.

Philip Barter—President, International Atherosclerosis Society. Research Grants: Merck, Pfizer. Honoraria: Amgen, AstraZeneca, ISIS, Kowa, Merck, Novartis, Pfizer, Roche. Advisory board: AstraZeneca, CSL, Kowa, Lilly, Merck, Novartis, Pfizer, Roche.

Thomas P. Bersot—Associate Investigator and Professor of Medicine, J. David Gladstone Institutes, University of California San Francisco, San Francisco, California, USA. Consultant: AbbVie, Aegerion Pharmaceuticals, Genzyme Pharmaceuticals, Merck and Co., Stock Ownership: Merck and Co. (spouse). Honoraria: AbbVie, Aegerion, AstraZeneca, Merck and Co.

D. John Betteridge—Consultant Physician, University College Hospital London and Emeritus Professor of Endocrinology and Metabolism, University College London, London, UK. Honoraria: Amgen, Merck Sharp & Dohme, Pfizer and Kowa, Sanofi, Takeda.

Rafael Carmena—Professor Emeritus of Internal Medicine and Endocrinology, University of Valencia, Spain, General Director of the Clinical Research Institute (INCLIVA), University Hospital, Valencia, Spain. No conflict of interests.

Ada Cuevas—Department of Nutrition, Clínica Las Condes, Santiago, Chile. Advisory boards: Amgen, Merck Sharp & Dohme. Honoraria: Merck, Sanofi, Merck Sharp & Dohme.

Michael H. Davidson—Professor, Director of the Lipid Clinic, The University of Chicago, Pritzker School of Medicine, Chicago, IL, USA. Speakers' Bureau: Merck. Advisory board/consultant: Abbvie, Amgen, AstraZeneca, Daiichi-Sankyo, Esperion, Lipidemx, Merck, Vindico.

Jacques Genest—Cardiologist, Professor, Faculty of Medicine, McGill University, Novartis Chair in Medicine at McGill, Scientific Director, Center for Innovative Medicine, McGill University Health Center/Royal Victoria Hospital, Montreal, QC, Canada. Advisory board: Amgen, Merck, Roche, Sanofi. Speakers Bureau: Amgen, Merck. Steering Committee: AstraZeneca (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin), Merck (IMPROVE-IT), Novartis Pharmaceuticals (CANTOS). Involved in Clinical trials: Amgen (AMG145), Merck Sharp & Dohme (REVEAL), Novartis (ACCELERATE).

Y. Antero Kesäniemi—Professor of Internal Medicine, Emeritus, Institute of Clinical Medicine, Department of Medicine, University of Oulu and Clinical Research Center, Oulu University Hospital, Oulu, Finland. Research Grant: Merck Sharp & Dohme. Honoraria: Abbott, Merck Sharp & Dohme, Novo Nordisk. Ownership: some Orion Pharma stocks. Advisory board: Merck Sharp & Dohme.

Shaukat Sadikot—Diabetes India, Mumbai, India. No conflict of interest.

Raul D. Santos—Director Lipid Clinic Heart Institute (InCor), University of Sao Paulo Medical School Hospital, Associate Professor of Cardiology, University of Sao Paulo, Brazil. Consultant/advisory board: Abbott, Aegerion, Amgen, AstraZeneca, Biolab, Bristol-Myers Squibb, Eli Lilly, Merck, Novo Nordisk, Pfizer, Roche. Honoraria speaker engagements: AstraZeneca, Biolab, Bristol-Myers Squibb, Eli Lilly, Merck, Pfizer.

Andrey V. Susekov—Associate Professor, Laboratory of Clinical Lipidology, Department of Atherosclerosis, Cardiology Research Complex, Moscow, Russia. Honoraria: Abbott, Amgen, AstraZeneca, Merck Sharp & Dohme, Pfizer, Krka and Gedeon Richter.

Rody G. Sy—Professor and Chair, Department of Medicine, University of the Philippines College of Medicine,

Manila, Philippines. Honoraria: Abbott, Astra, LRI-Therapharma, Merck Sharp & Dohme, Novartis, Pfizer and Sanofi. Advisory Committee: Amgen, Astra, GSK, Merck Sharp & Dohme, Pfizer and Sanofi.

S. LaleTokgözoglu—Professor of Cardiology, Hacettepe University, Ankara, Turkey. Cad: 9, Ankara, Turkey. Honoraria: Abbott, Actelion, Astra, Bayer, Boehringer, Daiichi-Sankyo, Novartis, Pfizer, Roche, SanofiServier. Advisory board: Kowa and Merck Sharp & Dohme.

Gerald F. Watts—Winthrop Professor, Cardiometabolic Medicine, Cardiometabolic Clinic, Royal Perth Hospital, School of Medicine and Pharmacology, The University of Western Australia, Australia. Honoraria: Abbott, Amgen and Sanofi, Genfit, Kowa, Merck Sharp & Dohme.

Dong Zhao—Deputy Director & Professor, Beijing Institute of Heart, Lung & Blood Vessel Diseases, Capital Medical University Beijing Anzhen Hospital, Beijing, China. Honoraria: Kowa, Pfizer.