Lipoprotein Management in Patients With Cardiometabolic Risk

Consensus statement from the American Diabetes Association and the American College of Cardiology Foundation

JOHN D. BRUNZELL, MD, FACP[1]
MICHAEL DAVIDSON, MD, FACC[2]
CURT D. FURBERG, MD, PHD[3]
RONALD B. GOLDBERG, MD[4]
BARBARA V. HOWARD, PHD[5]
JAMES H. STEIN, MD, FACC, FACP[6]
JOSEPH L. WITZTUM, MD[7]

Risk factors for type 2 diabetes and cardiovascular disease (CVD) often cluster, including obesity (particularly central), insulin resistance, hyperglycemia, dyslipoproteinemia, and hypertension. These conditions can also occur in isolation, and they are exaggerated by physical inactivity and smoking. Since each of these factors increases risk of CVD, the concept of global cardiometabolic risk (CMR) (Fig. 1) is of value (1). Lipoprotein abnormalities, including elevated triglycerides, low HDL cholesterol, and increased numbers of small dense LDL particles, are common findings in patients with CMR. Clinical entities with increased CMR include type 2 diabetes, familial combined hyperlipidemia, familial hypoalphalipoproteinemia, and polycystic ovary syndrome (2). These disorders often share the CMR characteristics of central obesity, insulin resistance, dyslipoproteinemia, and hypertension.

There are stringent lipid treatment goals for patients with type 2 diabetes or CVD; however, guidelines for treatment of dyslipoproteinemia in high-risk subjects without diabetes or CVD are less intense and are based primarily on LDL cholesterol concentrations, with non-HDL concentrations a secondary consideration in some subjects. Numerous trials have demonstrated that therapies (primarily statins) directed at LDL cholesterol lowering clearly reduce risk of CVD events in patients with diabetes and in those without diabetes but with other CVD risk factors; yet, a number of questions remain. Even with adequate LDL cholesterol lowering, many patients on statin therapy have significant residual CVD risk. It is unclear whether lipoprotein parameters other than LDL or non-HDL cholesterol provide clinically significant additional prognostic information regarding CVD risk, yield more information about the effectiveness of therapy, or indicate more appropriate treatment targets. Many patients with CMR or diabetes have relatively normal levels of LDL cholesterol but increased numbers of small dense LDL particles and other atherogenic lipoproteins. Some have advocated that assessment of other lipoprotein parameters might be more helpful than assessment limited to LDL or non-HDL cholesterol in these populations. In addition, treatment targets and the best approach for CVD risk reduction in this population need to be better defined.

To address these issues, the American Diabetes Association convened a consensus development conference on 18–20 July 2007 focusing on lipoprotein management in patients with CMR. Following presentations of invited speakers and in-depth discussions, a seven-member panel of experts in endocrinology and metabolism, cardiology, epidemiology, and public health developed a consensus position, addressing the following questions in relation to patients with CMR:

1. To what extent do lipoproteins contribute to CVD?
2. What are the clinically important lipoprotein parameters?
3. In the evaluation and treatment of patients with lipoprotein abnormalities, are there other factors that should be considered?
4. What are the principles and objectives of treatment of lipoprotein abnormalities?
5. What new information would help improve lipoprotein management?

TO WHAT EXTENT DO LIPOPROTEINS CONTRIBUTE TO CVD?

— CVD (defined here as coronary artery disease [CAD], cerebrovascular disease, and peripheral arterial disease) is the major cause of morbidity and mortality in the Western world. This is true despite dramatic improvements in therapy over the last few decades. The prevalence of CVD and its associated morbidity is high. Importantly, the initial presentation of CAD in up to one-third of patients is sudden

From the [1]Division of Metabolism, Endocrinology and Nutrition, Department of Medicine, and the Northwest Lipid Laboratory, University of Washington, Seattle, Washington; the [2]University of Chicago Pritzker School of Medicine, Chicago, Illinois; the [3]Department of Public Health Sciences, Wake Forest University, Winston-Salem, North Carolina; the [4]Division of Endocrinology, Department of Medicine, University of Miami, Miami, Florida; the [5]MedStar Research Institute, Hyattsville, Maryland; the [6]Cardiovascular Medicine Division, Department of Medicine, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin; and the [7]Department of Medicine, University of California, San Diego, La Jolla, California.

Address correspondence and reprint requests to M. Sue Kirkman, MD, American Diabetes Association, 1701 N. Beauregard St., Alexandria, VA 22311. E-mail: skirkman@diabetes.org.

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A complete list of the authors' dualities of interest can be found in the APPENDIX.

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Abbreviations: Apo, apolipoprotein; ATP III, Adult Treatment Panel III; CAD, coronary artery disease; CHD, coronary heart disease; CMR, cardiometabolic risk; CRP, C-reactive protein; CVD, cardiovascular disease; IDL, intermediate-density lipoprotein; Lp(a), lipoprotein(a); MI, myocardial infarction; NMR, nuclear magnetic resonance; VA-HIT, Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial.

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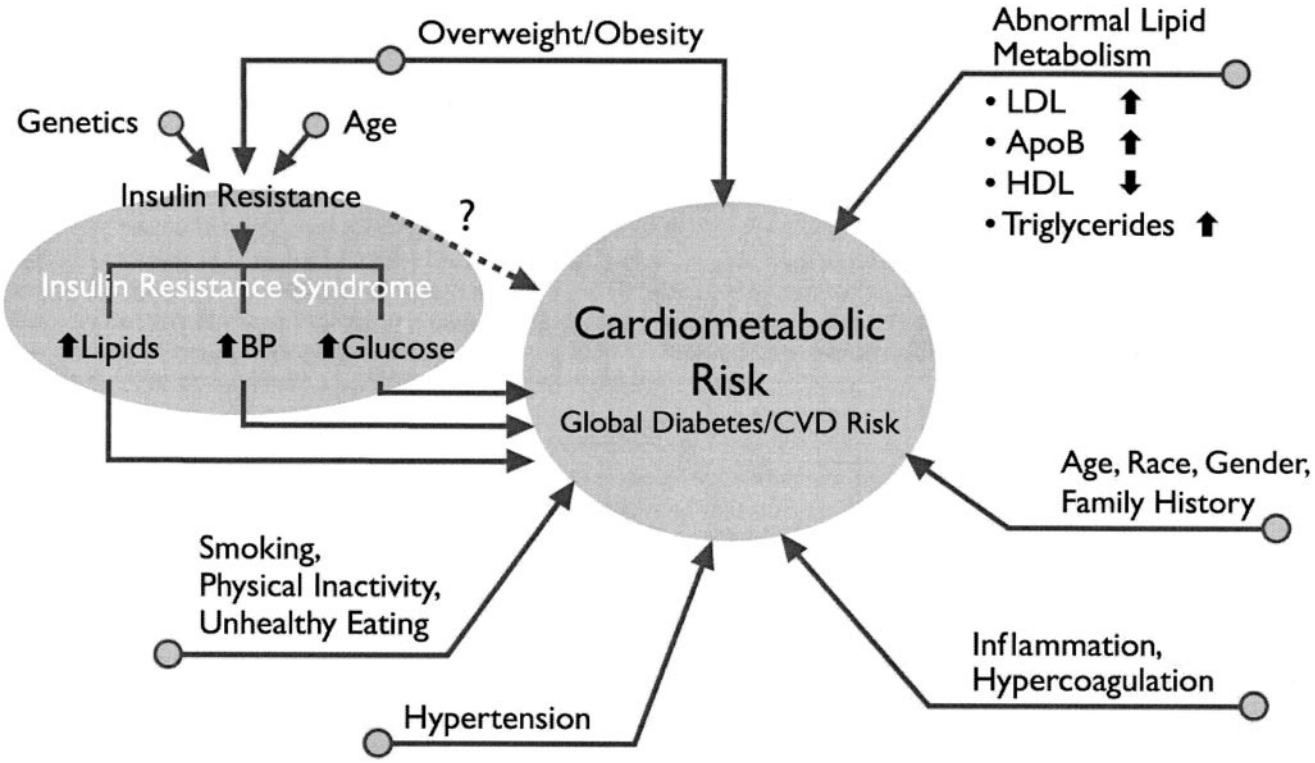

Figure 1—*Factors contributing to cardiometabolic risk.*

death. Thus, a detailed knowledge of the atherosclerotic process is necessary in order to design interventions to prevent atherosclerosis or reduce its rate of progression once the process has been initiated.

Lipoproteins are the particles that transport cholesterol and triglycerides, two compounds essential to cell structure and metabolism that are not soluble in aqueous solutions. Lipoproteins are comprised of proteins (apolipoproteins), phospholipids, triglycerides, and cholesterol. The classes of lipoproteins vary in the major apolipoproteins present and the relative contents of all of the lipid components.

Chylomicrons are primarily triglyceride-bearing lipoproteins produced after a meal during the process of lipid absorption. VLDLs are produced by the liver with a primary function of supplying free fatty acids to tissues and are normally the predominant carriers of circulating triglycerides. LDLs are by-products of VLDL metabolism and, in the normal state, are the primary carriers of plasma cholesterol. Chylomicrons, VLDL, and LDL all carry apoB, among other apolipoproteins. HDLs carry apoAI and apoAII. Nascent HDL particles are produced by the liver and intestine and then mature and become enriched with other apolipoproteins and lipids by exchanges with chylomicrons and VLDL. The size and density of the lipoprotein categories vary, from the largest and least dense chylomicrons to the smallest and most dense HDL. Within each category, there is also a spectrum of particles that vary in size, density, and relative proportions of lipid and protein.

Atherosclerosis is a form of chronic inflammation resulting from complex interactions between modified lipoproteins, monocyte-derived macrophages, components of innate and adaptive immunity, and the normal cellular elements of the arterial wall. This process can ultimately lead to the development of complex lesions or plaques that protrude into the arterial lumen, causing abnormal flow patterns and clinical symptoms such as angina or claudication. In addition, vulnerable areas within plaques can rupture or erode, leading to intravascular thrombosis resulting in the acute clinical complications of myocardial infarction and stroke.

Central role of LDL in atherogenesis

Among the many contributing factors, elevated cholesterol levels play a dominant role in both the initiation and progression of atherosclerosis, as well as in the clinical consequences such as myocardial infarction, stroke, peripheral vascular disease, and heart failure. Although a myriad of different genetic and environmental factors have been identified that modulate lesion formation in animal models, atherogenesis will not occur in these models in the absence of greatly elevated plasma cholesterol levels (>800 mg/dl) except by direct arterial injury. Hypercholesterolemia also appears to be obligatory for atherogenesis in humans, but in humans, where lesion formation usually occurs over many decades, the threshold level of plasma total cholesterol that must be exceeded to produce clinically relevant disease appears to be much lower than that in animal models. Atherosclerotic clinical events are uncommon in humans with lifelong very low plasma cholesterol levels (3). In general, however, there appears to be a curvilinear relationship between increasing plasma cholesterol and increasing incidence of CVD.

The dramatic success of cholesterol-lowering therapy might suggest that low cholesterol levels would be all that is required to prevent the development of atherosclerotic disease or halt or reverse established disease. This might be true if plasma cholesterol concentration could be reduced to very low levels long before the usual time of development of clinical disease. However, available hypolipidemic therapy may not lower cholesterol levels to very low values in all patients. In addition, drug therapy is often initiated

only after clinical disease is noted, and such therapy may not be sufficient to prevent the progression of atherosclerosis.

The totality of evidence overwhelmingly supports the centrality of elevated plasma cholesterol levels as a predictor of the development of atherosclerosis, though a complex set of genetic and environmental factors strongly influences the extent of atherogenesis and the expression of clinical events at any given plasma cholesterol level. It must be recognized, however, that it is lipoproteins that interact with the arterial wall and set in motion the cascade of events that leads to atherosclerosis. Measurements of total cholesterol are indirect estimates of the lipoproteins that transport the bulk of cholesterol in plasma and are the most atherogenic. In most circumstances, these are LDLs; however, in patients with CMR, VLDL and other apoB100-containing lipoproteins also may contribute to atherosclerosis.

Experimental studies directly support the central role of LDL in atherogenesis. Current concepts suggest that higher plasma levels of LDL lead to increased transport into the intima, where LDL becomes bound to proteoglycans, greatly prolonging its residence time. This makes LDL susceptible to a variety of modifications, including oxidation, enzymatic modification, nonenzymatic glycation, aggregation, and immune complex formation. All of these lead to enhanced macrophage uptake, foam cell formation, and initiation of the cascade of events resulting in progression of the atherosclerotic lesion.

The LDL receptor regulates plasma LDL levels. When human fibroblasts are grown in cell culture, they take up media LDL via the LDL receptor pathway until sufficient cholesterol is internalized to meet cellular needs, leading to the downregulation of LDL receptors. The amount of LDL cholesterol that is needed in such cultures is only 2.5 mg/dl. Because there is a 10:1 gradient between plasma and interstitial fluid LDL levels, this implies that a plasma level of 25 mg/dl LDL cholesterol would be sufficient to supply peripheral cholesterol needs (4). Indeed, examination of plasma LDL cholesterol levels in a variety of nonhuman species reveals that their levels cluster around this value. Human newborns have similarly low LDL cholesterol values, in the range of 40–50 mg/dl. In contrast, healthy adult LDL cholesterol levels are 3–4 times higher (5). People with heterozygous mutations in the LDL receptor have LDL cholesterol levels two times normal levels at birth and many develop CAD by age 50. Children homozygous for this disorder have LDL cholesterol levels 10-fold higher than normal and will, if untreated, have CAD in the first decade of life (4). These data strongly suggest that high levels of LDL cause atherosclerosis, as well as the significant dose-response relationship between atherogenic lipoproteins and development of disease.

Animal and human trials of dietary and pharmacological interventions that reduce LDL cholesterol are associated with stabilization and regression of atherosclerosis in proportion to the cholesterol lowering achieved, supporting the validity of "the lower the cholesterol the better" notion, especially in individuals with established CVD. Theoretically, all humans should maintain "newborn" LDL cholesterol levels of about 50 mg/dl to prevent atherosclerosis, and those with existing CVD should be treated to similarly low levels. The lower limit to safe and effective cholesterol lowering has not been established. Individuals with genetic mutations causing lifelong very low LDL cholesterol levels appear not only to avoid CVD but also to be free of other abnormalities that might conceivably be linked to their very low plasma cholesterol levels (6).

The role of other lipoproteins in atherosclerosis

Other abnormalities in lipoprotein components have been hypothesized to be involved in the atherosclerotic process. There is a specific dyslipoproteinemia in individuals with insulin resistance—and exacerbated in those with diabetes—characterized by elevated VLDL, lower HDL cholesterol, and altered distributions of particles in all lipoprotein classes. The increase in plasma VLDL, caused by both increased hepatic production and decreased clearance, is paired with a shift in particle distribution such that there are higher levels of large and intermediate-sized VLDL particles. It is not clear to what extent these changes stimulate atherosclerosis or are simply a marker of a more atherogenic milieu, since larger VLDLs are usually not able to penetrate the endothelium to enter the vascular wall. Individuals with benign hypertriglyceridemias characterized by large VLDL do not have increased risk of CVD. On the other hand, the smaller VLDLs and their catabolic product, intermediate-density lipoproteins (IDLs), can enter the subendothelial space and could contribute substantially to atherosclerosis. They may also increase prothrombotic factors, thus triggering CVD events.

Lower HDL cholesterol is consistently observed in individuals with CMR or diabetes, related in part to abnormalities in VLDL metabolism. HDL protects against atherosclerosis, in part by virtue of its ability to promote reverse cholesterol transport from cells in the vessel wall to the liver for disposal. It also has anti-inflammatory properties and can protect LDL from oxidation. Population studies and clinical trials of patients on statin therapy have demonstrated a strong inverse association between HDL cholesterol levels and CVD risk.

Alterations in the particle distribution within lipoprotein classes in patients with CMR or diabetes may be pertinent to atherosclerosis. Of particular relevance are changes observed in the LDL fraction, with increased numbers of small dense LDL particles. Smaller particles have increased endothelial permeability, are more easily oxidized and glycated, and are more able to bind to proteoglycans in the vessel wall.

WHAT ARE THE CLINICALLY IMPORTANT LIPOPROTEIN PARAMETERS?

— To intervene to prevent, halt, or reverse atherosclerosis, it is important to identify which lipoproteins, or lipoprotein components, are most clinically relevant. This includes the following considerations: whether they can be easily, precisely, and cost-effectively measured in a clinical setting; whether there are readily available treatment strategies that can alter them; and whether the treatment strategy is effective in reducing cardiovascular events.

LDL cholesterol

A large body of research, ranging from molecular to population studies, indicates that elevated LDL cholesterol is a major predictor of CVD, including in populations with CMR or diabetes. Mean LDL cholesterol levels are similar in diabetic, insulin-resistant, and nondiabetic populations, but levels vary widely among individuals within any population, due to a variety of genetic and environmental causes. In the UK Prospective Diabetes Study trial of patients with type 2 diabetes, LDL cholesterol was the most powerful risk factor predicting cardiovas-

cular risk (7). Data from several studies suggest that elevated levels of LDL cholesterol may have even more adverse effects in individuals with insulin resistance and diabetes than in individuals without insulin resistance or diabetes (8). There do not appear to be meaningful sex differences in the predictive value of elevated LDL cholesterol in individuals with diabetes or CMR. Age effects have not been thoroughly examined in the diabetic population, although data from predominantly nondiabetic populations suggest that LDL cholesterol is not a strong predictor of CVD in the elderly (9,10).

In addition to the robust data indicating the usefulness of LDL cholesterol as a predictor of CVD in individuals with diabetes, there are a number of large randomized controlled trials that have established that lowering LDL cholesterol in individuals with diabetes or with multiple cardiovascular risk factors lowers CVD event rates for both primary (11–14) and secondary prevention (15–21).

Despite the usefulness of LDL cholesterol for CVD prediction on a population level, the measure may have limitations for individual risk assessment. The reference method, beta quantitation, is complex and expensive. LDL cholesterol is typically estimated using the Friedewald equation, but this equation progressively underestimates LDL cholesterol as triglyceride levels increase. Available "direct" methods to measure LDL cholesterol are not well standardized (22). Measurement of LDL cholesterol (the cholesterol within LDL particles) has been the standard approach to approximate LDL levels. However, the cholesterol content of LDL particles varies from person to person and is influenced by metabolic abnormalities such as insulin resistance and hyperglycemia. Hence, measurement of LDL cholesterol may not accurately reflect the true burden of atherogenic LDL particles, especially in those with the typical lipoprotein abnormalities of CMR: elevated triglycerides, low HDL cholesterol, and increased numbers of small LDL particles.

LDL particle number

A more accurate way to capture the risk posed by LDL may be to measure the number of LDL particles directly using nuclear magnetic resonance (NMR) (23). Many cross-sectional (24) and prospective (25–29) studies show that LDL particle number is a better discriminator of risk than is LDL cholesterol.

The size of LDL particles can also be measured. As small dense LDL particles seem to be particularly atherogenic (30), assessment of particle size has intuitive appeal. Both LDL particle concentration and LDL size are important predictors of CVD (31). However, the Multi-Ethnic Study of Atherosclerosis suggested that on multivariate analyses, both small and large LDL were strongly associated with carotid intima-media thickness (24), while the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) showed that both were significantly related to coronary heart disease (CHD) events (28). The association of small LDL and CVD may simply reflect the increased number of LDL particles in patients with small LDL. Hence, it is unclear whether LDL particle size measurements add value to measurement of LDL particle concentration.

Limitations of the clinical utility of NMR measurement of LDL particle number or size include the facts that the technique is not widely available and that it is currently relatively expensive. In addition, there is a need for more independent data confirming the accuracy of the method (32) and whether its CVD predictive power is consistent across various ethnicities, ages, and conditions that affect lipid metabolism.

Lipoprotein(a)

Lipoprotein(a) [Lp(a)], an apoB-containing LDL-like particle with enhanced binding to intimal proteoglycans and prothrombotic effect, also predicts CVD. There is little evidence that insulin resistance or diabetes influences Lp(a) concentrations. The clinical utility of routine measurement of Lp(a) is unclear, although more aggressive control of other lipoprotein parameters may be warranted in those with high concentrations of Lp(a).

Non-HDL cholesterol

Non-HDL cholesterol (total cholesterol minus HDL cholesterol) reflects the concentration of cholesterol within all lipoprotein particles currently considered atherogenic. The Adult Treatment Panel III (ATP III) proposed that in individuals with hypertriglyceridemia (which would include many with CMR or diabetes), non-HDL cholesterol levels are a secondary goal of therapy after targeting LDL cholesterol levels. Many studies have demonstrated that non-HDL cholesterol is a better predictor of CVD risk than is LDL cholesterol (33–35), and this may be especially true of statin-treated patients (36). Additional benefits of non-HDL cholesterol measurement are its lack of additional expense in patients already getting lipid panel measurements and that it can be calculated from nonfasting samples.

ApoB-100

ApoB is found in chylomicrons, VLDL, IDL, LDL, and Lp(a) particles. Since each of these particles contains a single apoB molecule, measurements of apoB represent the total burden of particles considered most atherogenic (37,38). ApoB measurements do not require a fasting sample, and the assay has been standardized (39,40), but is not yet widely available. As with non-HDL cholesterol and NMR-based measurements of LDL particle number, in several epidemiological studies and in post hoc analyses of clinical trials, apoB has been found to be a better predictor of CVD risk than LDL cholesterol (41,42), particularly the on-treatment LDL cholesterol level (15,17,36,42). These analyses suggest that once LDL cholesterol is lowered, apoB may be a more effective way to assess residual CVD risk and to determine the need for medication adjustments. However, not all studies agree: in some studies, apoB did not outperform LDL cholesterol and non-HDL cholesterol as risk predictors (44–46). Discrepancies between studies may be due to the inclusion of different proportions of subjects with CMR. In individuals with CMR, the discrepancies between apoB, LDL cholesterol, and non-HDL cholesterol are greater, suggesting that apoB may be a more useful risk predictor among these individuals (47).

Triglyceride-rich lipoproteins

In the fasting state, plasma triglycerides are primarily found in VLDL, so plasma triglyceride measurements are used as a surrogate measure of VLDL. Triglycerides are a univariate predictor of CVD in many studies but often not an independent predictor in multivariate analyses. This may be because triglycerides are highly linked to abnormalities in HDL and LDL and because of high biological and laboratory variability. Similarly, there are no clinical trial data establishing that lowering triglycerides in individuals with or without diabetes independently leads to lower CVD event rates when one adjusts for changes in HDL cholesterol.

Chylomicron remnants may be atherogenic in a manner similar to VLDL remnants. There is little population-based evidence that chylomicron remnants are linked to CVD, but several studies show consistent elevations of chylomicron remnants in individuals with familial combined hyperlipidemia and diabetes, conditions associated with atherosclerosis. Measures of chylomicron remnants are not readily available.

HDL cholesterol

HDL cholesterol levels are strong inverse predictors of CVD events in both diabetic and nondiabetic populations (48,49). It has been difficult to determine whether raising HDL cholesterol independently reduces CVD events, because all interventions that raise HDL cholesterol also affect the concentration of other lipoproteins (50). The VA-HIT was conducted in a population that was largely comprised of individuals with CAD and low HDL cholesterol, including 625 with diabetes. Therapy with gemfibrozil reduced CVD events, and a post hoc analysis showed a modest association of the reduction in CVD with the extent of HDL increase (51). Strategies to raise HDL cholesterol remain a promising area of research that may be particularly valuable for preventing CVD in individuals with CMR and diabetes. Measurements of HDL subfractions or apoA1 appear to provide little clinical value beyond measurements of HDL cholesterol (49).

IN THE EVALUATION AND TREATMENT OF PATIENTS WITH LIPOPROTEIN ABNORMALITIES, ARE THERE OTHER FACTORS THAT SHOULD BE CONSIDERED? — In patients with lipoprotein abnormalities, good clinical practice calls for a comprehensive evaluation of their current vascular health, factors contributing to the observed dyslipoproteinemia, and other factors that may alter the global risk of first or recurrent CVD event. The objectives of the evaluation are as follows: *1*) to determine, to the extent possible, the magnitude of the future risk of CVD events; *2*) to identify the presence of prognostic factors that may be modifiable; and *3*) to establish a treatment plan both in terms of scope and intensity. An integral part of this process should be the active involvement of the patient because a better informed patient is more likely to adhere to the treatment plan.

A major objective of the risk evaluation is to ascertain the patient's current vascular health to determine whether the patient already has CVD. Stratification by the presence or absence of clinical CVD is important for decisions about the type of intervention and its intensity. The presence of so-called subclinical vascular disease may be determined by measuring coronary calcification, carotid intima-media thickness, or the ankle-brachial index. Patients with documented subclinical atherosclerosis are at increased CVD risk and may be considered candidates for more aggressive therapy (52–54). Whether such tests improve prediction or clinical decision making in patients with diabetes or CMR is unclear.

The presence and severity of other major prognostic factors besides lipoprotein abnormalities should also be ascertained. Modifiable risk factors include high blood pressure, smoking, hyperglycemia, obesity, adverse dietary habits, and physical inactivity. The main nonmodifiable prognostic factors are age, sex, ethnicity, and family history; other risk factors such as chronic kidney disease may also be present. Two components of age contribute to the risk of CVD. The aging process per se leads to vascular changes in a manner similar to that associated with age-related changes in other organs. Additionally, age is an indicator of duration of exposure to adverse prognostic factors. For example, a person exposed to the toxic effects of a one pack/day smoking habit over 30 years is more likely to have smoking-related arterial lesions than another person who has smoked one pack/day for 3 years. Sex differences lead to an earlier onset of CVD in men than in women by about 10 years. Young men have more CVD than premenopausal women; however, women's rates catch up with men's after menopause. There are racial differences in the prevalence of certain prognostic factors, such as increased rates of hypertension in African Americans. Family history of premature CAD, especially in siblings, also is a powerful prognostic factor.

Additional biomarkers (e.g., C-reactive protein [CRP], fibrinogen, and homocysteine) have been evaluated to determine their prognostic significance; however, their independent predictive power and clinical utility are still unclear. In particular, CRP is often elevated in people with CMR, but here, too, the utility of its measurement in individuals already known to be at high risk is unknown.

Risk assessment and strategies in primary prevention

Some global risk assessment tools estimate an individual's risk of a major coronary heart disease event (such as fatal or nonfatal myocardial infarction) over 10 years (55). There is a general consensus that a 10-year risk of ≥20% requires aggressive intervention directed at the abnormal prognostic factors. Those with a 10-year risk <20% are given interventions based on the number and magnitude of their risk factors. Although such tools are helpful, they underestimate lifetime risk, especially in youth and women. Assessments of lifetime global risk may be more valuable guides to treatment in subjects at intermediate or low 10-year risk. Risk assessment models often have the limitation that continuous prognostic factors are dichotomized, which reduces their statistical power. The American Diabetes Association has developed a risk assessment model that addresses global risk over a longer time frame (30 years) and does not dichotomize continuous risk factors (http://www.diabetes.org/diabetesphd/default.jsp).

The treatment plan for primary prevention may include antihypertensive and glucose-lowering medications and lifestyle interventions directed at smoking cessation, weight loss, improved dietary habits, and increased physical activity. Such lifestyle interventions have major potential benefits on cardiovascular health and are often overlooked. There is strong scientific evidence for CVD risk reduction for antihypertensive, lipid-lowering, and smoking cessation therapies. An aggressive approach to prevent multiple comorbidities is warranted. Disappointingly, a large proportion of high-risk individuals are not receiving optimal preventive care or fail to adhere to treatment recommendations.

Risk assessment and strategies in secondary prevention

The prognostic factors for the secondary prevention of CVD include those for primary prevention but also include several related to myocardial injury. For example, myocardial ischemia, left ventricular dysfunction, and ventricular arrhythmias are powerful prognostic indicators after myocardial infarction (MI). Treatments with lipid-lowering therapy (statins), aspirin, β-blockers, and ACE inhibitors

have well-documented benefits in secondary prevention. In addition, antihypertensive treatment, smoking cessation counseling, and advice about dietary choices and physical activity are also beneficial.

WHAT ARE THE PRINCIPLES AND OBJECTIVES OF TREATMENT OF LIPOPROTEIN ABNORMALITIES?

— Dyslipoproteinemia implies the presence of an increased number of atherogenic lipoproteins and/or a reduced protective capacity of HDL beyond what is considered optimal. It is present when levels of triglycerides are high, HDL cholesterol is low, and/or there is atherogenic particle excess, such as high LDL cholesterol or an increased number of small LDL particles. Cut points have been developed to define values associated with increased CVD risk. However, these cut points are arbitrary because the relationship of each of these measures with cardiovascular events is continuous and because the lipoprotein fractions are metabolically connected in a complex fashion.

LDL cholesterol

There is widespread consensus (54,56,57) that for patients with elevated CMR, the primary objective in reducing risk for CVD events through modification of lipid and lipoprotein risk factors is to lower LDL cholesterol values. This consensus is driven by the evidence that LDL is an important component of the atherogenic process and that treatments that lower LDL cholesterol have been convincingly demonstrated to reduce risk of CHD and stroke. The major issues to be considered in translating this paradigm into practice are as follows: *1*) At what LDL cholesterol level should treatment be initiated? *2*) Through what mechanisms should LDL cholesterol be lowered? *3*) Is LDL cholesterol the best measure to assess the response to treatment? *4*) What are the goals of treatment?

Determining cut points for initiating therapy. Based on the curvilinear relationship between LDL cholesterol and CHD in the general population, from a public health standpoint it has been suggested that LDL cholesterol values <100 mg/dl are optimal. Lifestyle recommendations targeted at reduction of saturated and *trans* unsaturated fat and cholesterol intake, lowering of excess body weight, and increasing intake of soluble fiber should be emphasized as first-line therapy for those with LDL cholesterol values >100 mg/dl. It is clear that the absolute benefit that can be achieved by LDL cholesterol lowering is proportional to the underlying global risk for CVD in a given individual. Thus, guidelines for initiating both medical nutrition therapy as well as pharmacologic treatment aimed at LDL cholesterol lowering have been stratified by level of risk (54).

The panel agrees with the general recommendations to start lifestyle and pharmacologic therapy concurrently in subjects with CVD (secondary prevention) and in those with diabetes and multiple CVD risk factors, regardless of baseline LDL cholesterol. In addition, we recommend pharmacologic therapy for moderately high-risk primary prevention patients (those with two or more CMR risk factors and a 10-year risk >10%) if LDL cholesterol levels remain >100 mg/dl after several months of lifestyle changes.

Therapeutic options for LDL cholesterol lowering. With respect to dietary principles, the standard recommendations for LDL cholesterol lowering have focused on lowering saturated and *trans* fat to <7% of calories and dietary cholesterol to <200 mg/day, lowering excess body weight by at least 5–10%, and increasing soluble fiber consumption. In addition, increasing plant sterol and stanol intake modestly lowers LDL cholesterol. Weight reduction and weight maintenance are best achieved by a combination of caloric reduction and increased physical activity.

As a result of the strong evidence base for the benefits of statin treatment on CVD outcomes, this class of drugs provides the primary pharmacologic modality for LDL cholesterol lowering. Although statins' beneficial effects are thought to be mediated predominantly through lowering of LDL cholesterol, their effects on HDL cholesterol and possibly other lipoproteins explain some of their benefit, and the possibility of nonlipoprotein-mediated (pleiotropic) effects cannot be excluded. However, significant CVD benefit has been directly linked to LDL cholesterol lowering using other modalities of treatment including diet, bile acid sequestrants, and ileal bypass surgery.

For patients who cannot tolerate a statin, or in whom maximal dose statin therapy does not achieve treatment goals, other LDL cholesterol-lowering drugs include ezetimibe, bile-acid sequestrants, or niacin. As monotherapy, these drugs are less effective at lowering LDL cholesterol than statins, but each enhances the LDL-lowering effect of statins. Bile-acid binding drugs, when used alone, can aggravate the dyslipidemia seen with insulin resistance by increasing triglycerides (58). Bile-acid resins in combination with a statin or nicotinic acid with a statin selectively decrease small dense LDL particles (59).

Assessing response to therapy. LDL cholesterol is the established primary target of treatment. In patients with hypertriglyceridemia or the metabolic syndrome, the ATP III (54) introduced non-HDL cholesterol as a secondary treatment target, recognizing that in this patient population, LDL cholesterol underestimates the burden of atherogenic, cholesterol-carrying lipoproteins. Non-HDL cholesterol adds no additional expense to a lipid profile and is easy to calculate, but use of the measure has not been widely adopted.

Although numerous studies have affirmed the superiority of non-HDL cholesterol over LDL cholesterol as a marker of CVD risk in patients with combined hyperlipidemia (elevated triglycerides and LDL cholesterol) or in those with a propensity for small dense LDL particles (patients with multiple CMR factors), both measures essentially focus on cholesterol as the agent of atherogenic risk. However, the measurement of cholesterol is a surrogate measure of atherogenic risk, given that atherosclerosis is the result of a complex interaction between lipoproteins and the vessel wall.

Measurements of apoB or LDL particle number by NMR may more closely quantitate the atherogenic lipoprotein load. Some studies suggest that both are better indices of CVD risk than LDL cholesterol or non-HDL cholesterol and more reliable indexes of on-treatment residual CVD risk (26,27,36,37,42,60–67). ApoB and LDL particle number also appear to be more discriminating measures of the adequacy of LDL-lowering therapy than are LDL cholesterol or non-HDL cholesterol. Statins lower non-HDL cholesterol more than they lower apoB (37), and several studies have shown that reaching the apoB target usually requires more intensive therapy than achieving the equivalent level for non-HDL cholesterol (68,69). ApoB and LDL particle concentration also appear to be more closely associated with obesity, diabetes, insulin resistance, and

Table 1—*Suggested treatment goals in patients with CMR and lipoprotein abnormalities*

	Goals		
	LDL cholesterol (mg/dl)	Non-HDL cholesterol (mg/dl)	ApoB (mg/dl)
Highest-risk patients, including those with *1*) known CVD or *2*) diabetes plus one or more additional major CVD risk factor	<70	<100	<80
High-risk patients, including those with *1*) no diabetes or known clinical CVD but two or more additional major CVD risk factors or *2*) diabetes but no other major CVD risk factors	<100	<130	<90

Other major risk factors (beyond dyslipoproteinemia) include smoking, hypertension, and family history of premature CAD.

other markers of CMR than are LDL cholesterol or non-HDL cholesterol (70–72).

When both non-HDL cholesterol and apoB are measured, the two are highly correlated but only moderately concordant (35,47,65,68,73,74). Although a change in non-HDL cholesterol is closely related to a change in apoB, at any given level of non-HDL cholesterol there will be considerable variation in apoB levels and vice versa, indicating that the correlation is of limited clinical value for assessing individual risk. This lack of concordance is particularly marked in patients with elevated triglyceride levels, a common finding in patients with CMR.

The consensus panel concludes that routine calculation and use of non-HDL cholesterol constitute a better index than LDL cholesterol for identifying high-risk patients. That does not mean, however, that LDL cholesterol should not be measured and used to guide therapy. The many years of public and professional education geared toward measurement of LDL cholesterol has resulted in its successful integration into the fabric of CVD prevention and treatment, and it would be a mistake to discontinue its use. On the other hand, the calculation of non-HDL cholesterol should be provided on all laboratory reports and should also be used to ascertain risk in patients with low to moderate LDL cholesterol levels (i.e., LDL cholesterol <130 mg/dl). Because apoB appears to be a more sensitive index of residual CVD risk when LDL cholesterol or non-HDL cholesterol are <130 mg/dl or <160 mg/dl, respectively, measurement of apoB, using a standardized assay, is warranted in patients with CMR on pharmacologic treatment. In particular, apoB levels should be used to guide adjustments of therapy. While LDL particle number as measured by NMR appears equally informative as apoB, the concerns expressed above with regard to this assay limit its widespread adoption at this time.

Treatment goals for adults with CMR and lipoprotein abnormalities. By definition, patients with CMR have high lifetime risk for CVD. Among patients with CMR and lipoprotein abnormalities, there are patients whom we define as at highest risk for CVD over the short or intermediate term: those with known clinical CVD and those who do not have clinical CVD but who have diabetes and one or more other CMR factors beyond their dyslipidemia. We recommend that these highest-risk individuals be treated to an LDL cholesterol goal <70 mg/dl, a non-HDL cholesterol goal <100 mg/dl, and an apoB goal <80 mg/dl.

Among patients with CMR and lipoprotein abnormalities, there are patients whom we define as high (but not highest) risk over the short or intermediate term: those without diabetes or clinical CVD but with two or more major CVD risk factors such as smoking, hypertension, and family history of premature CAD and those with diabetes but no other CMR risk factors. We recommend that these high-risk individuals be treated to an LDL cholesterol goal <100 mg/dl, a non-HDL cholesterol goal <130 mg/dl, and an apoB goal <90 mg/dl.

These treatment goal recommendations (Table 1) represent the panel's consensus based on evaluation of the available evidence. As is the case with any treatment recommendations, clinicians should recognize that individual patient factors and preferences may reasonably lead to alteration of these goals (to higher or lower levels) in some patients. These factors might include age, life expectancy, desire for pregnancy in the near future in women, severity of risk factors, medication interactions, and provider and patient assessment of individual risks and benefits of treatment.

Other lipids and lipoproteins

Elevated triglyceride and reduced HDL cholesterol levels are the most common abnormalities of the standard lipid profile in subjects with obesity and insulin-resistance–related CMR. Although increased triglycerides are modestly associated with increased CVD risk, especially in women (75), it has been difficult to demonstrate that lowering of triglyceride levels is independently associated with a reduction in CVD events. While the HDL cholesterol level is a powerful risk predictor, the clinical trial evidence supporting treatment of low HDL cholesterol values is modest compared with that for LDL cholesterol lowering. For these reasons, approaches directed at lowering triglyceride-rich lipoproteins and raising reduced HDL cholesterol levels have been assigned secondary levels of therapeutic importance.

For subjects with mildly or moderately elevated triglyceride levels (>200 mg/dl), we support the ATP III recommendations to target LDL cholesterol first and then use non-HDL cholesterol as a secondary target for treatment, with a goal 30 mg/dl higher than the patient's LDL cholesterol goal, but we further recommend that the population- equivalent apoB goal be reached. The exception to not targeting triglycerides initially is the relatively small proportion of patients with severe hypertriglyceridemia in whom the initial treatment priority is to reduce the risk of pancreatitis by combining dietary fat restriction with fibrate, niacin, or high-dose n-3 fatty acid therapy. All patients with low HDL cholesterol should receive lifestyle counseling focusing on weight reduction, increased physical activity, avoidance of very high carbohydrate diets, and discontinuing smoking.

A statin is the initial drug of choice for the vast majority of people with CMR who have elevated triglycerides and low HDL cholesterol. In individuals on statin therapy who continue to have low HDL cholesterol or elevated non-HDL cholesterol, especially if apoB levels remain elevated, combination therapy is recommended.

The preferred agent to use in combination with a statin is nicotinic acid because there is somewhat better evidence for reduction in CVD events with niacin, as monotherapy or in combination, than there is for fibrates. Nicotinic acid decreased CVD in the Coronary Drug Project (76) and total mortality in extended follow-up (77). Nicotinic acid in combination with a bile-acid binding resin or a statin was associated with regression of atherosclerosis and reduced CVD events in several studies (78–81). Although nicotinic acid has been associated with insulin resistance, in diabetes the use of low-dose nicotinic acid (1,500 mg/day) does not significantly increase A1C levels (82,83).

Fibrates have been shown to reduce CVD events in some studies but not mortality. In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial of patients with type 2 diabetes, the primary outcome of overall CHD events was not significantly reduced by the drug. The secondary outcome of nonfatal MI was decreased by 24% ($P = 0.01$), but fatal MI increased by 19% ($P = 0.22$) (84). Similar decreases in nonfatal MI, but not fatal MI or total mortality, were seen in the WHO trial with clofibrate (85), in the Helsinki Heart Study with gemfibrozil (86), in the VA-HIT trial with gemfibrozil (87), and in the Bezafibrate Infarction Prevention (BIP) trial with bezofibrate (88).

n-3 fatty acid therapy lowers plasma triglyceride levels at high doses (≥4 g/day) and may be another option to consider to lower non-HDL cholesterol in patients on statin therapy, but CVD outcome data are lacking for hypertriglyceridemic patients treated with these doses of n-3 fatty acids. In diabetic subjects, enhanced glycemic control may improve lipid and lipoprotein abnormalities, particularly hypertriglyceridemia. Specific antihyperglycemic agents may have advantages in this respect. For example, metformin has modest triglyceride-lowering properties. Both peroxisome proliferator–activated receptor-γ agonists increase LDL particle size, but they have differing effects on other lipoprotein fractions. Pioglitazone raises HDL cholesterol to a greater extent than rosiglitazone and lowers triglycerides, while rosiglitazone leads to a modest increase in triglycerides. Furthermore, pioglitazone lowers whereas rosiglitazone increases LDL particle number (89).

WHAT NEW INFORMATION WOULD HELP IMPROVE LIPOPROTEIN MANAGEMENT?

Residual risk on statin therapy

While statin therapy has proven to reduce cardiovascular risk, there remains substantial residual risk in treated patients. Studies are needed to determine whether very low LDL cholesterol levels are beneficial and safe and to define which types of patients receive the most benefit. We need to determine whether residual risk can be decreased by interventions that impact other lipoproteins, such as increasing HDL cholesterol or decreasing small dense LDL. In addition, studies are needed to directly determine whether apoB or other lipoproteins are better therapeutic targets than LDL cholesterol.

Triglycerides

Although patients with elevated triglycerides are at increased CVD risk, there is a lack of data regarding the benefits of strategies directly targeting elevated triglyceride levels. Therefore, it is unclear whether or at what level triglycerides should be treated and what should be the goal of therapy. This will not be an easy question to answer because of the complexities of triglyceride and lipoprotein metabolism (90).

HDL cholesterol

In observational studies, low HDL cholesterol is a powerful risk factor for CVD and remains a risk factor even in patients with low LDL cholesterol. Because a recent trial with a cholesteryl ester transfer protein inhibitor to raise HDL cholesterol was terminated as a result of excess cardiovascular events, it remains unclear whether raising HDL cholesterol per se reduces cardiovascular risk (91). It may be that increasing HDL cholesterol by modifying the reverse cholesterol pathway would paradoxically increase risk, while other mechanisms to increase HDL cholesterol may lead to a reduction in risk. Strategies to safely and effectively raise HDL cholesterol remain a promising area of research that is particularly relevant to CMR patients whose dyslipoproteinemia is often characterized by low levels of HDL cholesterol.

Combination therapy

Monotherapy with statins, fibrates, niacin, and bile acid sequestrants has been shown to reduce cardiovascular events in clinical trials, but there is not yet robust evidence for incremental benefits or risks of combination therapy compared with those of monotherapy. Results of ongoing and future trials of statin-niacin, statin-fibrate, and statin–n-3 fatty acids will, it is hoped, help answer these questions.

Benefits of lipoprotein management in other high-risk subsets

Although statin therapy is highly effective in reducing CVD risk in primary and secondary prevention, there remain subsets of patients regarding whom more data are needed. These include the elderly, those with chronic kidney disease, and young patients with CMR.

Utility of biomarkers

Biomarkers such as CRP have been shown to identify patients at higher risk for CVD events. However, their additive value as a clinical tool is unclear, especially among patients with CMR (92). At least one ongoing trial (93) is addressing the issue of whether prospectively selecting patients based on an elevated CRP will identify a high-risk group that will benefit from statin treatment.

SUMMARY — Patients with cardiometabolic risk factors represent a group at high lifetime risk for CVD. These patients frequently have dyslipoproteinemia (low HDL cholesterol, increased triglycerides, and/or an increased number of small LDL particles). We recommend an assessment of global risk followed by a multifactorial risk reduction strategy for such individuals targeting each risk factor and emphasizing both lifestyle and pharmacologic therapy. In terms of dyslipoproteinemia, we recommend the following:

- Statin therapy for the majority of dyslipoproteinemic adult patients with CMR
- For patients with CMR on statin therapy, guiding therapy with measurements of apoB and treatment to apoB goals in addition to LDL cholesterol and non-HDL cholesterol assessments
- Treatment goals, summarized in Table 1, that address the high lifetime risk of patients with dyslipoproteinemia and CMR.
- Clinical trials to determine whether the pharmacologic therapy required to achieve very low levels of atherogenic lipoproteins is safe and cost-effective
- A concerted, multifaceted, public health effort, focused on lifestyle mod-

ification, to reduce mean population levels of atherogenic lipoproteins to values well below current ones.

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