Emerging Therapies for Residual Risk

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The role of statins in reducing the risk of coronary artery disease is well established. The use of statins in patients at high risk for cardiovascular disease has reduced the incidence of major clinical events by 25% to 40%. However, despite aggressive statin therapy and the achievement of target low-density lipoprotein cholesterol levels, the residual risk of cardiovascular events remains high. This review investigates emerging therapies to target the residual risk of cardiovascular events with concurrent statin therapy.

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KEY WORDS

Statins • Residual risk • Cardiovascular disease • Benchmark

The 2004 National Cholesterol Education Program report suggests an optional low-density lipoprotein cholesterol (LDL-C) goal of < 70 mg/dL for those at highest risk for coronary artery disease. Statins have been shown to reduce the risk of cardiovascular morbidity and mortality in patients at risk or with coronary heart disease (CHD). Statins are a class of drugs that inhibit 3-hydroxy-3-methylglutaryl coenzyme A reductase and thereby block the formation of mevalonate, a precursor of cholesterol. The lipid-lowering efficacy of statins and their role in reducing the risk of CHD has been well studied and established. The Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial evaluated effects of statin therapy in 17,802 subjects without CHD, stroke, or diabetes, and with an LDL-C level < 130 mg/dL. Subjects randomized to rosuvastatin therapy showed a 54% reduction in myocardial infarction (MI), 46% in revascularization, and 20% in all-cause mortality compared with subjects randomized to placebo treatment.[1]

Need for Alternatives and Supplements to Statins

The role of statins in reducing risk of coronary artery disease is well established. Nichols and colleagues[2] performed a retrospective study to evaluate the impact of lipid-modifying therapy (96% on statin monotherapy and 3% on fibrates with or without a statin) in 5158 subjects who were started on lipid therapy between 2004 and 2006. Results revealed that the percentage of patients not at LDL-C goals, as set forth by the 2004 update to the National Cholesterol Education Program Adult Treatment Panel III guidelines on cholesterol management, decreased from 77% to 22%, and subjects with high triglycerides fell from 34% to 20%. However, the percentage of subjects with low high-density lipoprotein cholesterol (HDL-C; < 40 mg/dL in men and < 45 mg/dL in women) remained high, at 50% after and 49% before starting therapy (Figure 1).

A significant number of subjects were incompletely treated despite more than 1 year on statin therapy; 49% of subjects at baseline had low levels of HDL-C (< 40 mg/dL in men and < 45 mg/dL in women) and 50% had a similar picture after follow-up.[2] The take-home point from this study is that lipid-modifying therapy, which was almost exclusively statin therapy, resulted in little effect on lipid fractions other than LDL. Based on the epidemiological relationship between cardiovascular disease (CVD) and LDL-C, and abundant data suggesting definite benefit of LDL-C reduction, LDL-C has been defined as a primary target in management guidelines. Other lipoprotein measurements have been treated as secondary targets due to a paucity of results from large studies. Low HDL-C, high triglycerides, or both in CHD patients are associated with increased risk of cardiovascular events.

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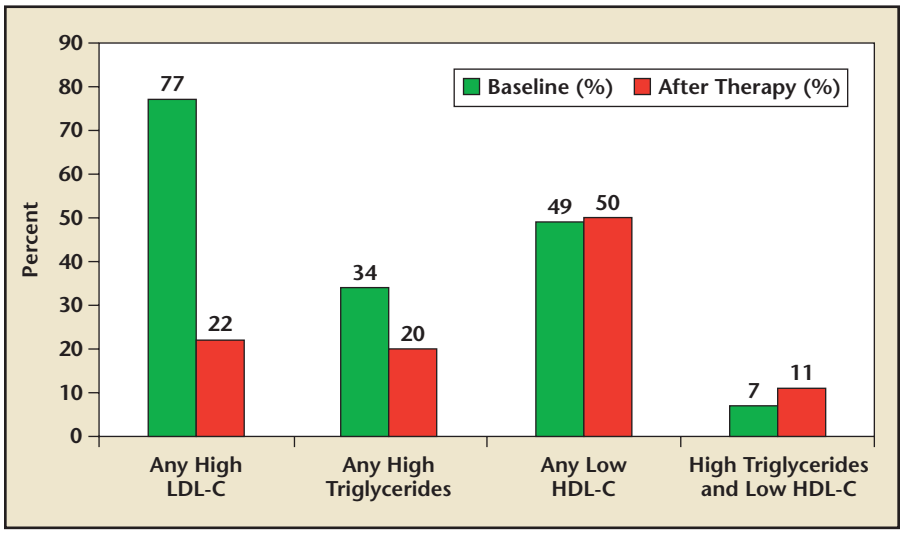
Figure 1. Lipid profile of subjects at baseline and after lipid-modifying therapy. HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol. Data from Nichols GA et al.[2]



The Bezafibrate Infarction Prevention (BIP) study group[3] performed a double-blind trial with 3090 patients with history of MI or stable angina and HDL-C < 45 mg/dL, triglycerides < 300 mg/dL, LDL-C < 180 mg/dL, and total cholesterol 180-250 mg/dL. Subjects were assigned randomly to receive either placebo or bezafibrate, 400 mg/d. Subjects were followed for 6.2 years, with the primary endpoint being fatal or nonfatal MI or sudden death. Results revealed that bezafibrate therapy increased HDL-C by 18% and lowered triglycerides by 21%. The frequency of the primary endpoint in subjects on placebo was 15% and of those on bezafibrate was 13.6% ($P = .24$). This study demonstrates the safety and efficacy of bezafibrate therapy in lowering triglycerides and increasing HDL-C with a corresponding decrease in frequency of fatal/nonfatal MI or sudden death.[3]

An assessment of event rates by HDL-C response to therapy in the 16-year follow-up of BIP showed mortality to be significantly lower among individuals in the upper tertile of on-treatment HDL-C change (> 8 mg/dL). Those with an HDL-C increase > 8 mg/dL had a 22% lower risk of death at 16 years compared with those treated with placebo. The risk of death at 16 years was similar among bezafibrate-treated patients with a limited cholesterol response and those treated with placebo (Table 1).[4]

Taylor and colleagues[5] performed a double-blind, randomized, placebo-controlled study involving 167 patients with known CHD and low HDL-C who were started on extended-release niacin, 1000 mg/d, in addition to statin therapy. The primary endpoint studied was the change in carotid intima-media thickness (CIMT) after 1 year. The study revealed that niacin

TABLE 1

Adjusted Risk for Long-Term Mortality by HDL-C Response

HDL-C Response	Hazard Ratio (95% CI)
Upper tertile (> 8 mg/dL increase) vs placebo	0.78 (0.65-0.94)
Lower tertiles (< 8 mg/dL increase) vs placebo	0.95 (0.83-1.08)

CI, confidence interval; HDL-C, high-density lipoprotein cholesterol.

significantly reduced the rate of CIMT progression in subjects without insulin resistance ($P = .026$). This study demonstrates the effect of niacin addition to statin therapy in slowing progression of atherosclerosis in patients with CHD and low HDL-C.

HDL-C < 35 mg/dL is regarded as an independent risk factor and HDL-C > 60 mg/dL as protective based on data from the Framingham Heart Study.[5] HDL has the ability to remove cholesterol from peripheral cells and transport it to the liver for biliary excretion. Other antiatherogenic effects of HDL are inhibition of LDL oxidation, improvement of endothelial function, promotion of endothelial repair, and inhibition of monocyte binding to endothelium, in addition to antithrombotic and anti-inflammatory properties.[6] α-1 and α-2 are the two largest HDL particles and they have the ability to deliver cholesterol directly to the liver. Patients with CHD have been shown to have low levels of α-1 and α-2. Asztalos and colleagues[7] observed that, in men with or without CHD, there was a 26% increase in CHD risk for every 1-mg/dL decrease in α-1 HDL level. HDL particles have been found to be better predictors of CHD events than HDL-C itself.

Statin use in patients at high risk for CVD has reduced the incidence of major clinical events by 25% to 40%. However, up to 50% of patients treated with statins continue to have CVD events.[8] Rosenson and colleagues[9] have proposed that LDL-C is an inadequate predictor of cardiovascular risk among patients with disorders of insulin resistance. LDL-C is the cholesterol packaged in the LDL particle (LDL-P); it varies widely among individuals and is apt to change due to medications or lifestyle changes. LDL-Ps contain a core of cholesterol and triglycerides, surrounded by a phospholipid shell and surface proteins on top, the chief one of which is apolipoprotein B (Apo B). In nearly all clinical trials, LDL-P or Apo B measurement has been shown to be more predictive of cardiovascular events when compared with LDL-C. The variation in size of LDL-Ps and their cholesterol and triglyceride content leads to the presence of discordance in values of LDL-C and LDL-P in individuals. Among individuals with discordant LDL-C and LDL-P values in the Framingham Offspring Study, the 15-year risk of CVD events was related to LDL-P and not LDL-C. The American Association for Clinical Chemistry has suggested a LDL-P goal of < 1100 nmol/L and LDL-C goal of < 100 mg/dL.[9-13] In the Women's Health Initiative Hormone Trial, increase in early coronary events was associated with increased levels of LDL-P ($P = .02$). There was a lowering of LDL-C observed with postmenopausal hormone therapy but not of LDL-P.[14]

A residual risk of CVD events has been observed when LDL-C is used alone as a benchmark for evaluation of antihyperlipidemic therapy. Sniderman[15] performed an analysis of eight studies involving patients on various statin therapies and observed a reduction of LDL-C to the 27th percentile of the population. However, LDL-P was reduced only to the 51st percentile. Considering LDL-C as the benchmark for evaluation of statin therapy, a residual risk for CVD events would remain despite an impressive lowering of LDL-C. Another study that stresses this point is the Pravastatin Limitation of Atherosclerosis in the Coronary Arteries trial (PLAC-1), in which the effect of pravastatin, 40 mg, on coronary luminal change was studied using angiography. Results of the study revealed reduction of LDL-C by 28% compared with a decrease in LDL-P by 24%. However, angiographic progression was only related to changes in LDL-P.[16,17]

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Need for a New Benchmark

These studies underscore the need to address abnormalities in lipid fractions other than LDL that are significantly associated with increased

risk of CVD, especially low HDL-C and elevated triglycerides. Studies have shown benefit from the addition of fibrates or niacin to statin therapy to help elevate HDL-C and decrease triglycerides, in addition to lowering LDL-C. Robins and colleagues[18] observed that subjects with low HDL-C and average LDL-C treated with gemfibrozil had a decrease in CAD events proportional to the increase in HDL-C when compared with subjects on placebo.

A population-based study of 25,668 men and women between ages 45 and 79 years was conducted by Arsenault and colleagues[19] to evaluate the relative contributions of different indexes of the lipid-lipoprotein profile to the risk of CHD in a contemporary western population. Subjects completed detailed health and lifestyle questionnaires at baseline, in addition to measurement of serum total cholesterol, HDL-C, and triglycerides, and LDL-C was calculated with the Friedewald formula. Non–HDL-C was calculated by subtracting HDL-C from total cholesterol levels. Subjects were classified into four groups based on their LDL-C levels. Study results revealed that, at any LDL-C level, individuals with elevated non–HDL-C, elevated triglycerides, or with increased total cholesterol to HDL-C ratio were still at an increased risk of developing CHD. Figure 2 illustrates the relationship of future risk of CHD in subjects with LDL-C < 100 mg/dL in relation to other components of the lipid-lipoprotein profile.

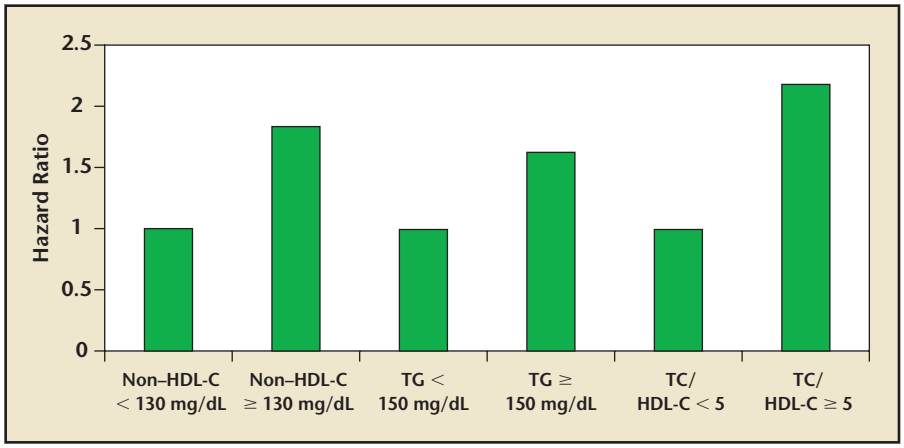

Figure 2. Hazard ratios for future CHD in subjects with LDL < 100 mg/dL in relation to non–HDL-C, TG, and TC/HDL. CHD, coronary heart disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides. Data from Arsenault BJ et al.[19]

Despite the success of statins and their widespread use in the management of lipid disorders, their adverse side-effect profile and the fact that patients on statin therapy have still been found to be at risk for CHD events warrants a need for additional and alternative treatment options. Various therapeutic options and drugs are under development or have been developed that target the various stages of lipid metabolism in humans.

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Inhibition of Intestinal Absorption of Cholesterol

Ezetimibe selectively inhibits intestinal absorption of cholesterol by binding to a critical mediator of cholesterol absorption in the brush border of intestines and hepatocytes.[20-22] At a dose of 10 mg/d, ezetimibe inhibits cholesterol absorption by 50%,[23] which leads to compensatory upregulation of LDL receptors and increased cellular uptake of LDL-C, thereby decreasing blood LDL-C content.[24] When used alone, ezetimibe reduces plasma total and LDL-C by 17% to 22% in patients with primary hypercholesterolemia.[25-28] In combination with statins, an additive effect of a 25% decrease in LDL-C has been observed compared with statin therapy alone.[29-32] No significant differences have been observed in hepatic impairment and muscle complaints with use of an ezetimibe/statin combination compared with statins alone. A slight elevation in liver transaminases has been observed with ezetimibe, especially in combination with statins. Another limitation is the lack of data on the use of ezetimibe in patients with severe hepatic insufficiency.[33]

Increase in HDL-C

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the anti-atherogenic HDL-C level in the blood. The beneficial effect of niacin has been observed in dosages of 100 to 2000 mg/d. Adverse effects limiting its use include flushing, hyperglycemia, and culminant hepatic failure. Severe liver damage can occur when switching from an immediate-release niacin to a long-acting niacin.[34-36]

The Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6-HDL and LDL Treatment Strategies in Atherosclerosis (ARBITER 6-HALTS) trial[37] compared the efficacy addition of ezetimibe or extended-release niacin on CIMT in high-risk patients on stable, chronic statin monotherapy. Niacin resulted in significant regression in mean CIMT and maximal CIMT compared with ezetimibe, which did not reduce mean or maximal CIMT.[37]

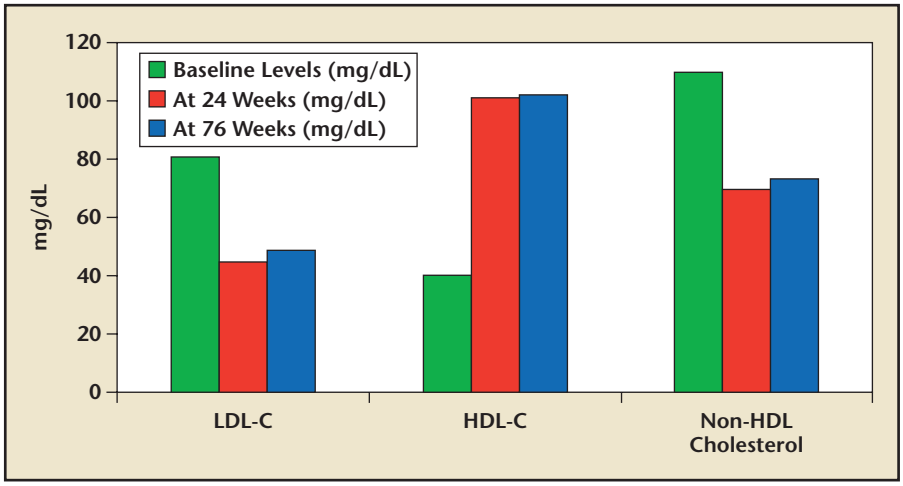

Figure 3. Changes in lipid profile in the anacetrapib group. HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol. Data from Cannon CP et al.[43]

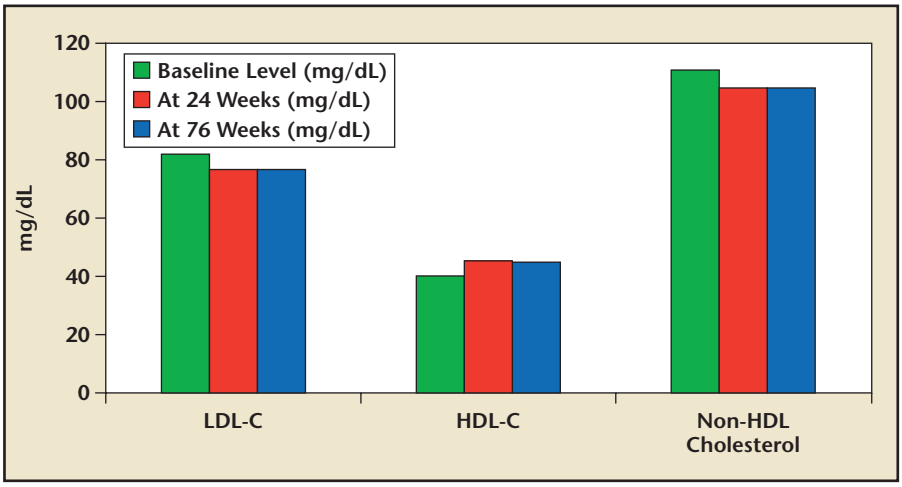

Figure 4. Changes in lipid profile in the placebo group. HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol. Data from Cannon CP et al.[43]

Cholesteryl Ester Transfer Protein Inhibition

Cholesteryl ester transfer protein (CETP) facilitates transport of triglycerides and cholesteryl esters between lipoproteins, which leads to an increase in HDL-C levels and a decrease in very low-density lipoprotein cholesterol/LDL-C levels.[17,38,39] Currently, two drugs in this class, dalcetrapib and anacetrapib, are in development. Huang and associates[40] observed a $>$ 30% increase in HDL-C levels with dalcetrapib in a phase II trial. Similarly, anacetrapib has been shown to provide a substantial increase in HDL-C and reduce LDL-C when used alone or in combination with a statin.[41,42]

Cannon and colleagues[43] performed the Determining the efficacy and Tolerability of CETP Inhibition with Anacetrapib (DEFINE) study, which involved randomization of 1623 subjects with known CHD or with high risk for CHD to receive 100 mg of anacetrapib or placebo daily for 18 months. Eligible subjects were on a statin and had LDL-C levels consistent with recommended guidelines. Patients were followed for 76 weeks and results yielded a 39.8% reduction of LDL-C and a 138.1% increase in HDL-C in the anacetrapib-treated group compared with placebo ($P < .001$). In addition, anacetrapib treatment had an acceptable side-effect profile, with neither any adverse effects on blood pressure, serum aldosterone, or serum electrolytes (as is seen with torcetrapib), nor any increase in liver enzymes or myalgia (as is seen with statin use). Adverse outcomes (death from cardiovascular causes, MI, hospitalization for unstable angina, or stroke) occurred in 2% of patients in the anacetrapib group as compared with 2.6% in the placebo group (hazard ratio, 0.76, 95% confidence interval [CI], 0.39-1.45; $P = .40$). Figures 3 and 4 show the effects of anacetrapib and placebo on study subjects.[43,44]

Bile Acid Sequestrants

Bile acid sequestrant agents bind to bile acids; they increase fecal excretion and disrupt enterohepatic

circulation, which in turn leads to increased hepatic consumption of cholesterol to produce bile acids and increased LDL-C clearance from the circulation.[45] However, these agents have a modest dose-dependent LDL-C–lowering effect, usually in the range of 10% to 20%, which limits their use as monotherapy. Another impediment is patient tolerance of side effects, which include constipation, flatulence, and diarrhea.[46] They may also bind to drugs and fat-soluble vitamins and impair their absorption. Some of the newer agents in this class, such as colesevelam, have shown anti-inflammatory effects, in addition to lowering total cholesterol and LDL-C and increasing HDL-C and Apo A-I. Another advantage of colesevelam is the lack of gastrointestinal side effects seen with other bile acid sequestrants, leading to better patient compliance.[33,47,48]

Peroxisome Proliferator-Activated Receptors

Peroxisome proliferator-activated receptor (PPAR)α, PPARδ, and PPARϒ are the three identified nuclear receptors that control lipid metabolism. Fibrates target PPARα and thiazolidinediones activate PPARϒ.[49-50]

Fibrates substantially increase HDL-C and decrease triglycerides, in addition to slightly decreasing LDL-C. They are as effective as monotherapy in combination with statins.[51] Fibrates, especially gemfibrozil, can increase risk of myopathy when used in combination with statins. This stems from inhibition of statin metabolism and subsequent increase in plasma concentration of statins.[52,53] Fenofibrate is a safer alternative, with no significant effect on statin metabolism and plasma levels.[54]

Thiazolidinediones, in addition to their adjunctive role in management of type 2 diabetes, have a beneficial effect in dyslipidemia by selective activation of PPARϒ receptors. The effect relates to a decrease in serum triglycerides, total cholesterol, and LDL-C, and an increase in HDL-C levels in patients with dyslipidemia. Pioglitazone has been shown to have superior beneficial effects on lipid profile compared with rosiglitazone. However, this class of drugs falls short of being a first choice in management of dyslipidemias.[55-57] A science advisory from the American Heart Association and American College of Cardiology Foundation suggests that thiazolidinediones should not be used with an expectation of benefit with respect to ischemic heart disease events. The advisory also suggests that thiazolidinediones increase the risk of heart failure and should not be initiated in patients with class III/IV heart failure.[58]

Other Novel Compounds on the Horizon

Squalene Synthase Inhibitors

Squalene synthase inhibitors represent a novel class of hypolipidemic agents that impact enzymes involved in the late part of cholesterol synthesis. Several drugs in this class were studied and some, such as lapaquistat, came close to clinical application by virtue of inhibition of cholesterol biosynthesis and inhibition of hepatic triglyceride synthesis. However, their clinical development was discontinued due to hepatotoxicity observed at low doses.[59]

Squalene Epoxidase Inhibitors

Green tea polyphenols and resveratrol demonstrate a cholesterol-lowering effect due to squalene epoxidase (SQLE) inhibition. Synthetic products such as NB-598 and Tu 2208 have been studied. NB-598 has potent SQLE activity but causes skin side effects.[60] Tu 2208 has been shown to decrease hepatic cholesterol concentration and reduce gallstone formation. Some other compounds deserve mention, including lanosterol synthase inhibitors such as Ro 48-8071, which has similar activity as Tu 2208.[61] Lanosterol 14α-demethylase inhibitors and emopamil-binding protein inhibitors are two other classes of potentially hypolipidemic drugs that are under investigation.[62,63]

Current Studies

The Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health (AIM-HIGH) study has enrolled 3414 patients ≥ 45 years with established vascular disease and atherogenic dyslipidemia. The study is designed to test whether the combination of extended-release niacin and simvastatin is superior to simvastatin therapy alone at comparable levels of LDL-C over a period of 4 years.[64] The other clinical trial is the Heart Protection Study 2 Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE), which has recruited 25,673 patients with a previous history of MI, cerebrovascular atherosclerotic disease, peripheral arterial disease, or diabetes mellitus. The primary aim of the study is to assess the effects of raising HDL-C with extended-release niacin + laropiprant, 2 g, compared with placebo on the risk of heart attack, coronary death, or stroke, or need for revascularization. The study results are expected in 2013.[65]

Another current study that merits mention is the dal-OUTCOMES

trial, which is a multicenter, randomized, double-blind, placebo-controlled trial to study the efficacy and safety of dalcetrapib in patients with a recent acute coronary event. The study will enroll approximately 15,600 patients who will receive either 600 mg/d of dalcetrapib or placebo, starting 4 to 12 weeks after an index acute coronary event. The primary efficacy measure of the study is time to first occurrence of CHD death, major nonfatal coronary event, or stroke. The trial is expected to culminate in 2013.[66]

Conclusions

This article identifies a need for the development of alternative therapeutic agents with efficacy comparable to that of statins, but without the corresponding side effects. The development of some of these compounds was discontinued due to undesired side effects. Continued efforts are required in the research and development of statin alternatives as management of hyperlipidemia takes a center stage in arresting the process of atherosclerosis. Another important point to consider is that LDL-C may not be the best benchmark for evaluation of antihyperlipidemic therapy. LDL-P or its more widely available surrogate measure, Apo B, serves as a better predictor of cardiovascular events in high-risk patients. This stand was endorsed by the American Association for Clinical Chemistry in 2009 and by a consensus statement by the American Diabetes Association and the American College of Cardiology.[67,68] Patients with LDL-C within treatment guidelines but with elevated LDL-P should be treated more aggressively with a combination of statins such as ezetimibe, bile acid sequestrants, niacin, fibrates, and/or omega-3 fatty acids.[9] Current management for patients with low HDL-C should start with diet, exercise, and cessation of tobacco use, followed by lowering LDL-C often using statin therapy, and, in selected patients, safe drug therapy to increase HDL-C. ■

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MAIN POINTS

- Studies underscore the need to address abnormalities in lipid fractions other than low-density lipoprotein cholesterol (LDL-C). Up to 50% of patients treated with statins continue to have cardiovascular disease (CVD) events.
- A residual risk of CVD events has been observed when LDL-C is used alone as a benchmark for evaluation of antihyperlipidemic therapy.
- LDL particle and apolipoprotein measurement have been shown to be more predictive of cardiovascular events compared with LDL-C alone.
- Current management for patients with low high-density lipoprotein cholesterol (HDL-C) should start with diet, exercise, and cessation of tobacco use, followed by lowering LDL-C (often using statin therapy), and, in selected patients, safe drug therapy to increase HDL-C.