Nonstatin Low-Density Lipoprotein–Lowering Therapy and Cardiovascular Risk Reduction—Statement From ATVB Council


Abstract—Pharmacological reduction of low-density lipoprotein (LDL) cholesterol using statin drugs is foundational therapy to reduce cardiovascular disease (CVD) risk. Here, we consider the place of nonstatin therapies that also reduce LDL cholesterol in prevention of CVD. Among conventional nonstatins, placebo-controlled randomized clinical trials showed that bile acid sequestrants, niacin, and fibrates given as monotherapy each reduce CVD end points, whereas adding a fibrate or niacin showed no incremental benefit. From trials in which patients’ LDL cholesterol was already well controlled on a statin, adding ezetimibe incrementally reduced CVD end points, whereas adding a fibrate or niacin showed no incremental benefit. Among emerging nonstatins, monoclonal antibodies against proprotein convertase subtilisin kexin type 9 added to a statin and given for ≤78 weeks showed preliminary evidence of reductions in CVD outcomes. Although these promising early findings contributed to the recent approval of these agents in Europe and in North America, much larger and longer duration outcomes studies are ongoing for definitive proof of CVD benefits. Other nonstatin agents recently approved in the United States include lomitapide and mipomersen, which both act via distinctive LDL receptor independent mechanisms to substantially reduce LDL cholesterol in homozygous familial hypercholesterolemia. We also address some unanswered questions, including measuring alternative biochemical variables to LDL cholesterol, evidence for treating children with monitoring of subclinical atherosclerosis, and potential risks of extremely low LDL cholesterol. As evidence for benefit in CVD prevention accumulates, we anticipate that clinical practice will shift toward more assertive LDL-lowering treatment, using both statins and nonstatins initiated earlier in appropriately selected patients. (Arterioscler Thromb Vasc Biol. 2015;35:2269-2280. DOI: 10.1161/ATVBAHA.115.306442.)

Key Words: atherosclerosis ■ cardiovascular diseases ■ cholesterol, LDL ■ guideline ■ lipids ■ lipoproteins ■ therapeutics

Statins disrupt the atherosclerotic process and have made regression of atherosclerosis possible for many. Akira Endo’s painstaking pharmacological screening of compounds that interfered with cholesterol biosynthesis led to isolation of compactin in 1973 from the rice mold Penicillium citrinum Pen-51.1 Compactin’s descendants—lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, and pitavastatin—are used by tens of millions of patients to reduce death and disability from cardiovascular disease (CVD), following from irrefutable randomized clinical trial (RCT) evidence of their benefits.2 Statins’ benefits are inextricably linked to low-density lipoprotein (LDL) cholesterol lowering: for each 1.0 mmol/L (=40 mg/dL) reduction in LDL cholesterol, major vascular events and all-cause mortality are reduced by 22% and 10%, respectively, across all patient subgroups.2 Statins’ other putative biological effects include improving endothelial dysfunction; antioxidant, antiinflammatory effects; inhibiting cell proliferation; anticarcinogenic actions; atherosclerotic plaque stabilization; and inhibiting graft rejection after organ transplantation.3 Elevated LDL cholesterol per se influences these processes adversely; it remains controversial whether proposed LDL-independent effects of statins could result from putative pleiotropic direct effects of statin molecules and their metabolites on non-LDL–related pathways or simply from their LDL-lowering effects.3,4

If LDL lowering by statins is integral to their ability to reduce CVD events, then nonstatin-based LDL cholesterol reductions should also be beneficial in the absence of unrelated
detrimental effects. With the recent approval of inhibitors of proprotein convertase subtilisin kexin 9 (PCSK9), a review of all nonstatin LDL cholesterol—lowering therapies was timely. Mechanistic understanding is important: if statins’ benefits are in part LDL-independent, then drug development programs should pursue these alternate pathways as well. This review will define the known benefits of lower LDL cholesterol concentrations from favorable genetic endowment and various clinical interventions.

**LDL as a Causal Factor in Atherosclerosis**

**Epidemiology, Pathology, and Molecular Biology**

It is beyond the scope here to recapitulate the non-RCT evidence supporting LDL’s causal role in atherosclerosis. Guideline writers have aggregated much of this evidence already. The centrality of LDL cholesterol in predicting CVD risk has been confirmed repeatedly in classic epidemiological and observational studies. Furthermore, thousands of pathology and cell and molecular biology experiments implicate perturbed lipid metabolism, particularly quantitative and qualitative abnormalities of LDL, as drivers of dysfunctional immune and inflammatory responses in atherogenesis. Even as new proinflammatory and anti-inflammatory pathways are being discovered, the foundational role of LDL in atherogenesis remains axiomatic.

**Atherosclerosis Development Early in Life**

Atherosclerosis begins early in life, with higher levels of LDL cholesterol contributing to early atherogenesis. The Pathobiological Determinants of Atherosclerosis in Youth Study (PDAY) and the Bogalusa Heart Study showed that every 0.26 to 0.39 mmol/L (10–15 mg/dL) increase of non–high-density lipoprotein (HDL) cholesterol is associated with an additional year of vascular aging. Thus, a 15-year-old with heterozygous familial hypercholesterolemia (FH) has essentially the same amount of atherosclerosis as a 20- to 35-year-old with an average lipid profile, depending on the presence of additional risk factors. Four longitudinal studies confirm that lipids measured in youth better predict subclinical atherosclerosis measured in middle age than do risk factors measured in middle age concurrently with arterial imaging. This implies that when atherosclerosis prevention is started later in life, not only must risk factors be lowered but also existing advanced disease must be regressed to be completely effective.

**Importance of LDL Cholesterol From Human Genetics**

Two types of human genetic evidence support LDL’s role in atherosclerosis. First, in the rare single-gene disorder FH, lifelong elevations of plasma LDL cholesterol lead to early atherosclerosis. Second, Mendelian randomization studies of common DNA polymorphisms with modest effects on LDL cholesterol suggest a causative role in CVD. Within the Mendelian randomization framework, if a biomarker is causally associated with a disease, its genetic determinants are also associated with disease risk. Mendelian randomization avoids confounding and reverse causation and assumes that the culprit genetic variants influence only the biomarker of interest. This is not always the case for plasma lipid traits, where multiple lipid effects are evident for several gene loci, including CETP, LPL, and APOA5. However, genetic variants at the PCSK9, HMGCR, and NPC1L1 loci associate specifically with LDL cholesterol; these variants also predict coronary heart disease (CHD) risk.

For instance, Cohen et al showed that loss-of-function mutations in PCSK9 were associated with reduced LDL cholesterol and substantial reductions in CHD risk. Similarly, the Myocardial Infarction Genetics Consortium Investigators resequenced the NPC1L1 gene and showed that the p.Arg406X loss-of-function mutation was associated with 10% lower LDL cholesterol and 50% decreased CHD risk in a large replication sample. Ference et al studied 108 376 subjects from 14 RCTs and reported that genetic variants at NPC1L1 and HMGCR loci were associated with reductions in LDL cholesterol of 0.06 and 0.07 mmol/L (2.4 and 2.9 mg/dL) and in lifetime CHD risk of 4.8 and 5.3%, respectively. Because PCSK9, NPC1L1, and HMGCR genes have minimal effects on other variables, these studies support the direct causal relationship between LDL cholesterol and CHD. Furthermore, reductions in CHD risk in these studies for this degree of LDL reduction are at least twice as large as would be predicted from short-term statin RCTs, presumably because genetic influences are present from birth.

**Importance of LDL Cholesterol From RCTs**

Early RCTs of LDL lowering studied diet, ideal bypass, and various nonstatin drugs. Of the latter, estrogen and dextrothyroxine had undesirable physiological effects and failed to reduce CVD despite cholesterol reduction. Fibrates and niacin have shown some benefit when used as monotherapy, but no incremental protection when added to a statin in patients who had achieved low LDL cholesterol levels. All other LDL-reducing interventions have benefits, including reduced saturated fat and increased polyunsaturated fat intake, interrupting enterohpatic circulation by a bile acid sequestrant or surgical intervention, blocking intestinal cholesterol absorption by ezetimibe, inhibiting cholesterol biosynthesis by statins, and removing LDL cholesterol by repeated LDL apheresis. Early statin RCTs, such as the Scandinavian Simvastatin Survival Study (4S) and West of Scotland Coronary Prevention Study (WOSCOPS), used less potent statins, that is, simvastatin and pravastatin, respectively, and achieved 30% to 36% reductions in major coronary events. Stronger statins, such as rosuvastatin, lower risk by 45. The Lipid Research Clinics (LRC) and Cholesterol Treatment Trialsist Collaboration (CTTC) each concurred that lower is better, whether achieved with a statin or nonstatin mechanism.

**Conventional Nonstatins and CVD Risk**

**Ezetimibe**

Ezetimibe blocks intestinal sterol absorption by interfering with Niemann Pick C1–like receptor 1, with LDL cholesterol reduction of ≈20%. Convincing evidence of reduced CVD events with ezetimibe has been slow to emerge. In 2011, the Study of Heart and Renal Protection (SHARP) showed ezetimibe plus simvastatin versus double placebo...
reduced CVD events in patients with renal impairment. In 2015, the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) showed that, compared with simvastatin alone, ezetimibe plus simvastatin significantly reduced major cardiovascular events by ≈7% when started within 10 days of an acute coronary syndrome, which was commensurate with its incremental LDL cholesterol-lowering effect of ≈0.4 mmol/L (16 mg/dL). A subgroup analysis showed proportionally greater benefit in diabetic patients. A study using intravascular ultrasound showed that ezetimibe plus atorvastatin induced significantly greater regression of coronary artery plaque volume than atorvastatin alone. Collectively, these results support LDL cholesterol reduction by ezetimibe as having beneficial effects on atherosclerotic CVD.

Bile Acid Sequestrants
Bile acid sequestrants bind bile acids in the intestinal lumen, diverting them from the enterohepatic circulation, depleting the liver of bile, which upregulates bile synthesis from cholesterol by 7-α-hydroxylase. This depletes the intrahepatic cholesterol pool, upregulating LDL receptor activity, which reduces LDL cholesterol levels. Increased 7-α-hydroxylase activity raises triglyceride. At daily doses of 24 g cholestyramine, 20 g colestipol, or 4.5 g colesvelam, LDL cholesterol is reduced 18% to 25%. Bile acid sequestrants also augment the LDL-lowering effects of other drugs, notably statins. Colesevelam improves glycemic control modestly in patients with type 2 diabetes mellitus. Gastrointestinal side effects and drug interactions (perhaps somewhat lower with colesvelam) limit the use of these agents. In the LRC Coronary Primary Prevention Trial (CPPT), bile acid sequestrants reduced CHD events in treated hypercholesterolemic subjects, with benefit proportional to the degree of LDL cholesterol lowering.

Niacin
Pharmacological doses of niacin (nicotinic acid), through incompletely defined mechanisms, lower LDL cholesterol and triglyceride by ≈25% and ≈50%, respectively, and raise HDL cholesterol by ≈30%. At high doses, niacin also lowers Lp(a) by ≈30%. As monotherapy, niacin administered to hypercholesterolemic men reduced the risk of recurrent myocardial infarction in the Coronary Drug Project and also reduced total mortality in a 15-year follow-up. Decreased atherosclerosis progression has also been observed in imaging studies of niacin’s effects.

More recently, the Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides and Impact on Global Health Outcomes (AIM-HIGH) study and Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) showed no reductions in CVD events or mortality when niacin was added to statin therapy in patients with pre-existing CVD and well-controlled LDL cholesterol. These results undermined the hypothesis that HDL directly protects from atherosclerosis, and when considered together with niacin’s side effects (skin flushing, hepatotoxicity, hyperuricemia, and hyperglycemia), have stifled enthusiasm for its use, although it may still have use in severe FH until newer agents become widely available.

Fibrates
Individuals with the metabolic syndrome, with or without type 2 diabetes mellitus, are at higher risk for CVD events and mortality. Lowering LDL cholesterol with statins in this group is associated with expected reductions in CVD risk, although absolute on-treatment CVD event rates are higher than in people free of metabolic syndrome or type 2 diabetes mellitus. The dyslipidemia characterized by high triglyceride and reduced HDL cholesterol increases CVD risk, with both on-treatment triglyceride and HDL cholesterol levels predicting CVD events in statin RCTs. Fibrates lower triglyceride and raise HDL cholesterol via moderate agonism of peroxisome proliferator–activated receptor-α; however, results of CVD outcome trials with fibrate monotherapy have been mixed. Two studies (1 each in primary and secondary prevention) were positive, but 3 (2 in primary and 1 in secondary prevention) were negative. In monotherapy studies, post hoc subgroup analyses suggested a benefit of fibrates in subjects with high triglyceride with or without low HDL cholesterol.

In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial of 5518 individuals with type 2 diabetes mellitus, adding fenofibrate on top of background simvastatin therapy (LDL cholesterol, 2.1 mmol/L [80 mg/dL]) reduced triglyceride and increased HDL cholesterol by ≈16% and ≈2.4%, respectively, compared with placebo, but had no effect on CVD end points (risk reduction 8%, P=0.32). Subgroup analyses showed that women did significantly worse than men and (2) 17% of the cohort, with a prespecified group with both upper tertile of triglyceride (>2.3 mmol/L or 204 mg/dL) and lower tertile of HDL cholesterol (<0.9 mmol/L or 34 mg/dL), trended toward greater CVD event reduction (P=0.06). Adverse musculoskeletal events were not increased with fenofibrate plus simvastatin, whereas raised serum creatinine on fenofibrate returned to baseline levels with cessation of treatment. There is no evidence supporting the use of fenofibrate in nondyslipidemic people and in women without dyslipidemia, fenofibrate may increase risk of CVD events. Subgroup analyses suggesting benefit in individuals with higher triglyceride and HDL cholesterol must be confirmed in a dedicated trial.

Nonstats in Children
Limited RCT data support ezetimibe use in children and adolescents. As monotherapy, after 12 weeks of treatment, ezetimibe lowered LDL cholesterol by 27% in 6- to 10-year-old children with FH. In adolescents, in combination with simvastatin, ezetimibe lowered LDL cholesterol by an additional 10% to 15%. Although colesvelam modestly lowered LDL cholesterol (6%–12%) irrespective of background statin use, children on statins at trial entry sometimes discontinued this treatment during the open label phase, and LDL cholesterol actually increased on colesvelam alone. This highlights the
importance of compliance to achieve therapeutic goals and also the need for additional RCT evidence in this group.

**Newer Nonstatin Agents**

**PCSK9 Inhibitors**

PCSK9 interrupts the recycling of the LDL receptor by diverting it toward lysosomal degradation after receptor-mediated endocytosis of LDL particles. Gain-of-function mutations in the PCSK9 gene cause autosomal-dominant hypercholesterolemia, whereas loss-of-function mutations are associated with lower LDL cholesterol and reduced CVD risk. Monoclonal antibodies (mAbs) against PCSK9 were recently approved in Europe and North America. Alirocumab and evolocumab, both fully human mAbs, have completed the majority of their phase 3 efficacy and safety trials, whereas these have not yet been completed for bococizumab, a humanized mAb. Large RCTs of CVD outcomes are under way for all 3 PCSK9 mAbs.

LDL cholesterol–lowering efficacy varies from 40% to 65% for PCSK9 mAbs (Table). LDL-lowering efficacy is comparable for alirocumab 150 mg biweekly, evolocumab 140 mg biweekly, and 420 mg every 4 weeks. On maximal statin therapy, mean LDL cholesterol levels of ≈0.9 mmol/L (35 mg/dL) are achievable with PCSK9 mAbs, and many patients achieve LDL cholesterol <0.64 mmol/L (25 mg/dL). Efficacy appears similar across most patient subgroups, including heterozygous FH patients. PCSK9 mAbs allowed a substantial proportion of FH patients to achieve LDL cholesterol <1.8 mmol/L (<70 mg/dL) for the first time. In patients with homozygous FH on maximal lipid-lowering therapy, evolocumab 420 mg every 4 weeks reduced LDL cholesterol by ≈30%, with efficacy related to the degree of residual LDL receptor activity. In addition to robust LDL cholesterol lowering, evolocumab and alirocumab improve other lipid parameters, for example, Lp(a) reduced ≈25%. Evolocumab and alirocumab seem well tolerated in trials ≤78 weeks in duration. Injection site reactions are relatively infrequent and mild. Myalgia was slightly more frequent with alirocumab compared with placebo. A small, nonsignificant increase in neurocognitive events was reported for alirocumab and evolocumab, as well as a small nonsignificant increase in ophthalmologic events for alirocumab. No excess of adverse events has emerged in patients with LDL cholesterol <0.65 mmol/L (<25 mg/dL) or 0.39 mmol/L (<15 mg/dL) on >2 occasions over 78 weeks of treatment. Both evolocumab and alirocumab are well accepted by statin-intolerant patients, with muscle-related adverse event comparable with those seen with ezetimibe.

Preliminary data suggest that PCSK9 mAbs reduce CVD events over 1 to 1.5 years. A meta-analysis of phase 2 and 3 trials found reduced total mortality with alirocumab and evolocumab, in trials ranging from 12 to 78 weeks. Four large, ongoing trials of CVD events and safety are evaluating alirocumab, evolocumab, and bococizumab in high risk patient populations. Patients with FH and high risk patients unable to tolerate high-intensity statin therapy, or unable to achieve >50% LDL cholesterol reduction on statin therapy, will likely benefit from PCSK9 mAbs. Although long-term CVD outcomes data are pending, PCSK9 mAbs represent an option for patients who might benefit from an additional 50% to 60% reduction in LDL cholesterol, such as those with severe heterozygous FH and evidence of atherosclerosis or individuals with recurrent CVD events despite maximally tolerated doses of oral therapies. The availability of PCSK9 inhibitors might stimulate reconsideration of the concept of LDL cholesterol targets as part of lipid management guidelines.

**ApoB Antisense Therapy**

Mipomersen is a second generation antisense oligonucleotide that concentrates in the liver and specifically binds to human apoB mRNA. The bound mRNA is degraded by hepatic RNAse, preventing the translation of apoB and synthesis of apoB-containing lipoproteins. Mipomersen 200 mg administered subcutaneously once weekly reduces LDL cholesterol, apoB and Lp(a) by ≈30%. Because mipomersen does not require functional LDL receptors, equivalent responsiveness is seen in LDL receptor negative homozygous FH patients. Side effects include injection site reactions and influenza-like symptoms; discontinuation rates in RCTs have been high. Increases in transaminase levels and hepatic steatosis are also of concern. Longer term, larger studies are needed to evaluate its efficacy and potential hepatotoxicity. Mipomersen is approved in the United States only for use in homozygous FH.

**Lomitapide**

Microsomal triglyceride transfer protein is essential for assembly and secretion of hepatic and intestinal lipoproteins. Microsomal triglyceride transfer protein facilitates the incorporation of cholesteryl ester and triglyceride into very low-density lipoprotein (VLDL) in hepatocytes and chylomicrons in enterocytes by interacting with hepatic apoB-100 or intestinal apoB-48, respectively. Inhibiting microsomal triglyceride transfer protein targets synthesis of apoB-containing lipoproteins independent of the LDL receptor. Thus, lomitapide, an oral microsomal triglyceride transfer protein inhibitor, reduces LDL cholesterol by 35 to 50% in subjects with homozygous FH. Lomitapide has Food and Drug Administration (FDA) and European Medicines Agency (EMA) approval for the treatment of homozygous FH as an adjunct to diet and drug therapy, with concerns over long-term effects, that is, elevated liver enzymes and hepatic steatosis.

**Cholesteryl Ester Transfer Protein Inhibition**

Cholesteryl ester transfer protein (CETP) mediates neutral lipid transfer between lipoproteins, with net reduction in HDL cholesterol and cholesterol enrichment of apoB-containing lipoproteins. Thus, CETP has received considerable attention as a drug target, although 2 CETP inhibitors have failed in large CVD outcome trial. Torcetrapib-treated individuals experienced increased CV events and mortality despite substantial reductions in LDL cholesterol, putatively because of off-target increases in blood pressure. An outcomes trial using dalcetrapib, an agent with modest HDL-raising effects and essentially no effect on LDL cholesterol, was stopped for futility. Two other compounds, anacetrapib and evacetrapib, remain under active investigation; both have substantial
HDL-raising and LDL-lowering effects\textsuperscript{86,87} without apparent off-target effects.\textsuperscript{105} Ongoing RCTs will determine whether additional beneficial effects of CETP inhibition translate into improved outcomes.\textsuperscript{106,107}

**Table. Nonstatins and Their Effects on LDL Cholesterol and Cardiovascular Disease End Points**

<table>
<thead>
<tr>
<th>Class</th>
<th>Examples</th>
<th>Typical % LDL Cholesterol Reduction</th>
<th>Evidence for Clinical CVD End Point Reduction</th>
<th>Key Reference(s)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Statins</strong></td>
<td>Lovastatin, simvastatin, pravastatin, atorvastatin, rosvastatin, pitavastatin</td>
<td>35%–55%</td>
<td>Incontrovertible: 22% CVD risk reduction for 1 mmol/L (≈40 mg/dL) LDL cholesterol reduction, plus =10% reduced all-cause mortality</td>
<td>2</td>
<td>Reference comparator for nonstatin agents in this table</td>
</tr>
<tr>
<td><strong>Cholesterol absorption inhibitor</strong></td>
<td>Ezetimibe</td>
<td>18%–25%</td>
<td>Strong: modest incremental =7% reduction when added to statin therapy in acute coronary syndrome patients</td>
<td>32</td>
<td>No studies with ezetimibe as monotherapy</td>
</tr>
<tr>
<td><strong>Bile acid sequestrants</strong></td>
<td>Colestyramine, colestipol, colesvelam</td>
<td>18%–25%</td>
<td>Good evidence vs placebo: =20% CVD risk reduction in events in primary prevention</td>
<td>30,37</td>
<td>No studies with resins added to statins</td>
</tr>
<tr>
<td><strong>Niacin-based preparations</strong></td>
<td>Crystalline niacin (short acting), extended release niacin</td>
<td>20%–25%</td>
<td>Good evidence vs placebo: =20% CVD risk reduction in events, with reductions in mortality over longer term; no incremental CVD risk reduction when added to statin therapy in patients with well-treated LDL cholesterol</td>
<td>49–51</td>
<td>Multiple effects on lipid profile; neutral outcomes when given to patients well-treated on statin</td>
</tr>
<tr>
<td><strong>Fibrates</strong></td>
<td>Gemfibrozil, fenofibrate, bezafibrate</td>
<td>5%–15%, varies depending on baseline triglyceride levels</td>
<td>Good evidence vs placebo: =20% CVD risk reduction in events; no incremental CVD risk reduction when added to statin therapy in patients with well-treated LDL cholesterol</td>
<td>64,66–68</td>
<td>Multiple effects on lipid profile; subgroup analyses suggest benefit in men with high TG, low HDL cholesterol</td>
</tr>
<tr>
<td><strong>PCSK9 inhibitors</strong></td>
<td>Evolocumab, alirocumab, bococizumab</td>
<td>40%–65%</td>
<td>Promising evidence: ≈50% reduction in CVD events when added to statin therapy in aggregated small early phase study results</td>
<td>78,89</td>
<td>Possible new standard of therapy; long-term outcomes data pending</td>
</tr>
<tr>
<td><strong>APOB antisense oligonucleotide</strong></td>
<td>Mipomersen</td>
<td>30%–45%</td>
<td>No evidence: good efficacy for LDL cholesterol reduction in homozygous familial hypercholesterolemia</td>
<td>83</td>
<td>Also lowers Lp(a); injection site reactions, flu-like symptoms</td>
</tr>
<tr>
<td><strong>MTP inhibitor</strong></td>
<td>Lomitapide</td>
<td>35%–50%</td>
<td>No evidence: good efficacy for LDL cholesterol reduction in homozygous familial hypercholesterolemia</td>
<td>84, 85</td>
<td>GI symptoms, fatty liver</td>
</tr>
<tr>
<td><strong>CETP inhibitors</strong></td>
<td>Anacetrapib, evacetrapib</td>
<td>20%–35%</td>
<td>No evidence: awaiting large-scale outcomes studies</td>
<td>86, 87</td>
<td>Also raise HDL cholesterol by 80%–100%</td>
</tr>
<tr>
<td><strong>ATP citrate lyase inhibitor</strong></td>
<td>Bempedoic acid</td>
<td>20%–28%</td>
<td>No evidence: early in development</td>
<td>88</td>
<td>No long-term data; apparently well tolerated</td>
</tr>
</tbody>
</table>

CETP indicates cholesteryl ester transfer protein; CVD, cardiovascular disease; GI, gastrointestinal; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MTP, microsomal triglyceride transfer protein; PCSK9, proprotein convertase subtilisin kexin 9; and TG, triglyceride.

**Bempedoic Acid**

Bempedoic acid (previously known as ETC-1002) is a small molecule inhibitor of ATP citrate lyase, a cytoplasmic enzyme that generates acetyl coenzyme A for de novo synthesis of fatty acids and cholesterol.\textsuperscript{88} Phase 2 trials in patients with hypercholesterolemia\textsuperscript{108} and type 2 diabetes mellitus\textsuperscript{109} show that bempedoic acid 80 and 120 mg daily reduced LDL cholesterol by 25% and 43%, respectively, over a short term. Bempedoic acid may also result in incremental reductions in LDL cholesterol when coadministered with a statin or ezetimibe. Larger and longer phase 3 trials are needed to assess the durability and safety of this drug’s novel mechanism of action.

**Remaining Unanswered Questions**

**Are There Better Alternatives to LDL Cholesterol as Measures of Atherogenicity?**

Although the concept of LDL cholesterol as agent provocateur, chief epidemiological analyte and target for treatment is embedded in the cardiovascular field, LDL as a tangible clinical entity has its limitations.\textsuperscript{110} For instance, methods to directly measure LDL are either labor intensive or incompletely validated. LDL cholesterol in the real world is often indirectly calculated from other lipid and lipoprotein fractions and requires a relatively long period of fasting. Furthermore, its measurement incompletely captures the total burden of atherogenic particles, and accuracy of its determination is affected when LDL levels are low or triglycerides are high.\textsuperscript{110} Thus, pursuit of alternatives to LDL cholesterol has been a focus of epidemiological and mechanistic research.
Atherosclerosis was long recognized as more closely related to the total number of apoB-containing particles rather than LDL cholesterol concentration. One apoB molecule is present on the surface of chylomicrons, VLDL, intermediate density lipoprotein, LDL, and Lp(a). Thus, apoB may more directly measure circulating atherogenic lipoproteins than LDL cholesterol. ApoB has analytic and biological stability and is valid in nonfasting samples, which is useful for epidemiological studies. Non-HDL cholesterol is the sum of VLDL, intermediate density lipoprotein, and LDL cholesterol and is calculated by subtracting HDL cholesterol from total cholesterol. Non-HDL cholesterol quantifies cholesterol content of all atherogenic apoB-containing lipoproteins and is highly correlated with apoB levels. The superiority of non-HDL cholesterol to LDL cholesterol in CHD prediction was shown in the Health Professionals Follow-up Study, the Framingham Heart Study and Framingham Offspring Study, and the Women’s Health Study. Non-HDL cholesterol and apoB had equivalent predictive value and were both superior to LDL cholesterol in the Emerging Risk Factors Collaboration. Although RCTs have predominantly used LDL cholesterol reduction as a primary biochemical end point, many also measured non-HDL cholesterol and apoB and found these to also be excellent markers of CHD risk reduction. For instance, the Treating to New Targets (TNT) and Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) showed that on-treatment apoB and non-HDL cholesterol were better predictors of reduced CVD events than levels of LDL cholesterol. In the Collaborative Atorvastatin Diabetes Study (CARDS) trial, both apoB and non-HDL cholesterol predicted CHD better than LDL cholesterol. Meta-analyses show apoB and non-HDL cholesterol as being superior to LDL cholesterol in predicting CHD events. Because non-HDL cholesterol and apoB can be determined from nonfasting samples and better predict atherogenicity than LDL cholesterol, several guidelines recommend including these measurements as adjuncts or alternatives to LDL cholesterol for risk assessment and monitoring treatment. What Is the Role of LDL Treatment in Children? Current recommended lipid-lowering therapy in childhood is directed toward those with either FH (LDL cholesterol >4.9 mmol/L [>190 mg/dL] or > 4.1 mmol/L [>160 mg/dL] after diet management) or those with elevated LDL cholesterol in association with diabetes mellitus or multiple other known major risk factors. Because outcomes-linked RCTs initiated in youth are logistically challenging, treatment goals attempt to balance the value of LDL cholesterol lowering against risk of long-term side effects. Statins are first choice treatments with a goal of achieving LDL cholesterol reduction of >50% or achieving a goal of LDL cholesterol <3.36 mmol/L (130 mg/dL). Treatment is generally initiated at ages 8 to 10 with FDA-approved medications at doses used in pediatric RCTs conducted in FH patients. Trials of newer agents, including rosuvastatin and pitavastatin, may extend indications to lower ages. Few LDL cholesterol-lowering RCTs in contexts other than FH have been performed in children; these have been of short duration in children with type 1 diabetes mellitus, lupus, or Kawasaki disease. Carotid intima-media thickness assessment in children affected with heterozygous FH compared with their siblings suggest that accelerated atherosclerosis can be appreciated early in the second decade, perhaps treatment below this age is not beneficial. Conversely, initiating statin treatment in the third to fourth decade may be insufficient to reverse advanced atherosclerosis that developed in adolescence or young adulthood. Optimal benefit may require initiation of lipid-lowering treatment at the age at which plaque development is most likely to commence; regression of early atherosclerosis may restore vessels to optimum health. Conversely, a small subgroup of children will not achieve satisfactory LDL cholesterol lowering with statins, particularly those with homozygous or severe heterozygous FH. LDL apheresis is an adjunct to pharmacological treatment in homozygous FH, in particular requiring treatment at diagnosis and regardless of age because of risk of adverse events in childhood; LDL cholesterol reduction is greater with the addition of ezetimibe or colesevale. Clinical trials using newer agents discussed above are desperately needed to determine pediatric safety and efficacy in children with FH. What Is the Role of Monitoring Subclinical Atherosclerosis? Subclinical atherosclerosis assessment has convincingly shown that populations with higher LDL cholesterol have more atherosclerosis and that the presence of subclinical atherosclerosis, particularly coronary artery calcium, improves risk classification. Nonetheless, the role of monitoring subclinical markers in clinical practice is not established, and a full discussion is beyond the scope of this article. In FH or other conditions with elevated lifetime risk, noninvasive subclinical atherosclerosis assessment can be taken into account when determining baseline risk and could be monitored serially as a surrogate for response to treatment, which in turn might affect treatment decisions. If changes in subclinical disease markers could be shown to predict outcomes independently of LDL cholesterol lowering, use of such tests could one day be justified in clinical practice. However, current use is limited by logistical issues, such as cost and invasiveness, as well as lack of evidence. Can LDL Cholesterol Be Too Low? There are some signals of adverse effects of VLDL cholesterol that should be monitored now that we have therapies capable of driving levels to such depths. For instance, fatty liver disease leading to hepatic fibrosis in children and cirrhosis and hepatocellular carcinoma in adults have been seen in heterozygous familial hypobetalipoproteinemia, where patients have lifetime LDL cholesterol <0.78 mmol/L (<30 mg/dL). Severe fatty liver has also been described in patients with ANGPTL3 mutations with similarly low LDL cholesterol levels. In the Open-Label Study of Long-Term Evaluation Against LDL Cholesterol (OSLER) study, among those on evolocumab, 3 patients (1%) reported amnesia and 5 (1%) reported either memory or mental impairment.
(unrelated to achieved LDL cholesterol), whereas no cases were reported in controls. The FDA issued a directive for neurocognitive assessment in ongoing PCSK9 mAb RCTs. Also, subjects randomized to rosuvastatin who achieved LDL cholesterol <0.78 mmol/L (<30 mg/dL) had higher rates of diabetes mellitus, hematuria, hepatobiliary disorders, and insomnia. Long-term follow-up is needed to better define the risk profile when LDL cholesterol is reduced to <0.78 mmol/L (<30 mg/dL).

**Does Diabetes Mellitus Risk With Statins Extend to Nonstatins?**

Statins effectively reduce CVD in people with diabetes mellitus who have a 2-fold long-term increase in CVD morbidity and mortality. However, several studies suggest that statins increase risk of developing type 2 diabetes mellitus in prediabetic individuals. A meta-analysis of 13 statin trials reported that standard dose statin therapy was associated with 9% higher type 2 diabetes mellitus risk over 4 years, with greater risk associated with intensive statin therapy and pre-existing risk factors for diabetes mellitus. No compelling evidence indicates differences in the risk of incident diabetes mellitus between statins. There is intense interest in identifying underlying mechanisms, with no definitive results to date. Recent genetic data from carriers of variants that reduce the activity of 3-hydroxy-3-methyl-glutaryl-CoA reductase or cause FH have raised the question as to whether statins per se, cholesterol synthesis, or LDL receptor function is actually causative. However, 1 CVD event is prevented for each 100 to persistently reduced CVD risk in statin-treated patients. Long-term follow-up of statin trials demonstrate persistently reduced CVD risk in statin-treated patients from the trial over the next decade or 2. Long-term follow-up of the ongoing CVD outcomes trials of new agents will also help characterize the legacy effect of plaque stabilization and regression in high-risk patients. It may be that aggressive LDL cholesterol lowering for 3 to 4 years may stabilize plaque in most patients, and subsequent maintenance on maximal statin therapy could be adequate to suppress new plaque formation. Thus, the cost of expensive new drugs could amortized over a longer period.

Animal data suggest dramatic LDL cholesterol reduction early in the course of atherosclerosis can completely regress atherosclerosis and normalize arterial function. Together, these data suggest that early, aggressive LDL cholesterol lowering can reset the vascular aging clock, and intermittent retreatment every decade or so might, in essence, cure atherosclerosis.

**Targets or No Targets?**

Reopening the debate on the role of target lipid levels in treatment guidelines is beyond the scope of this review. Using an evidence base that relied on drugs and doses from RCTs, the 2013 AHA/ACC guidelines eliminated lipid targets, instead advising treatment decisions based on CVD risk. Other jurisdictions have retained targets for now, in part because of local values and preferences among community practitioners in favor of targets. Validity of targets versus no targets was evaluated in the offspring and third generation cohorts of the Framingham Heart Study based on Framingham risk factors, LDL thresholds based on the updated ATP III guidelines and the 2013 ACC/AHA pooled cohort calculator. Incident CVD was determined at a median 9.4-year follow-up. Statin-eligible participants by the 2013 ACC/AHA guidelines had increased hazard ratios for incident CVD compared with those eligible by ATP III guidelines: 6.8 (95% confidence interval, 3.8–11.9) versus 3.1 (95% confidence interval, 1.9–5.0), respectively ($P<0.001$). Thus, compared with LDL cholesterol thresholds in ATP III, the ACC/AHA guidelines seemed to more accurately identify increased risk of incident CVD and subclinical CHD, particularly in intermediate-risk subjects. However, the availability PCSK9 inhibitors and pending results of large CVD outcomes studies using those drugs will likely initiate reevaluation of the concept of LDL cholesterol targets in clinical practice.

**Conclusions**

The biological, genetic, epidemiological, and clinical trial evidence supporting a direct causal role of LDL cholesterol in atherogenesis and resulting major cardiovascular events is compelling. In the clinic, whether the physician or patient thinks that statin benefits derive primarily from LDL cholesterol reduction or from other pleiotropic effects is practically irrelevant. Committing to treatment is based on evidence of CVD risk reduction from RCTs. Statins have the greatest body of RCT evidence supporting benefit in CVD risk reduction, but until recently, the relative importance of LDL cholesterol versus other pleiotropic effects of statins in driving these benefits has been disputed. The issue is important because nonstatin therapies lower LDL cholesterol without statins’ other effects, and these agents may play an increasingly important role in CVD prevention. Recent RCT evidence, specifically significant CVD end point reductions seen with ezetimibe in IMPROVE-IT in patients with acute coronary syndromes and with both evolocumab and alirocumb over 52 to 78 weeks complement earlier RCT evidence of CVD event reduction with such nonstatin therapies, such as diet, intestinal bypass, and monotherapy with cholestyramine, niacin, and fibrates. The common link between the CVD benefits of statins and the large number of nonstatin agents is LDL cholesterol reduction, often via upregulation of the LDL receptor.
At some point, it becomes unwieldy for even the most passionate LDL skeptic to invoke individual non-LDL–related pleiotropic effects, given the wide range of different mechanisms of action of nonstatins. Nonstatins have a place for patients who are absolutely statin intolerant whose dyslipidemia requires management. In the near future, larger, longer term RCT results of PCSK9 mAbs may provide definitive support to this growing body of evidence. Although diet and statins represent the cornerstones of management of dyslipidemia, our review suggests that nonstatin treatments will play an increasingly important role. Rather than stoking the debate over LDL cholesterol targets, going forward we now have data from IMPROVE-IT on when to add ezetimibe to a statin. Moreover, algorithms for clinical action with PCSK9 inhibitors used either as monotherapy or added to statin drugs to reduce CVD will soon be clear. In the future, we anticipate that there will be an increasing focus on the optimal timing of initiating treatment, so that event rate reductions predicted from Mendelian randomization studies can be achieved for the general population.

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References


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**ATV Council Statement: Nonstatin Therapy**


Nonstatin Low-Density Lipoprotein–Lowering Therapy and Cardiovascular Risk Reduction—Statement From ATVB Council
Robert A. Hegele, Samuel S. Gidding, Henry N. Ginsberg, Ruth McPherson, Frederick J. Raal, Daniel J. Rader, Jennifer G. Robinson and Francine K. Welty

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