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ATVB Council Statement: Non-statin LDL-lowering Therapy and Cardiovascular Risk Reduction

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Abstract

Pharmacologic 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 non-statin therapies that also reduce LDL cholesterol in prevention of CVD. Among conventional non-statins, placebo-controlled randomized clinical trials showed that bile acid sequestrants, niacin and fibrates given as monotherapy each reduce CVD end points. From trials in which patients' LDL cholesterol was already well-controlled on a statin, adding ezetimibe incrementally reduced CVD end points, while adding a fibrate or niacin showed no incremental benefit. Among emerging non-statins, monoclonal antibodies against proprotein convertase subtilisin kexin type 9 (PCSK9) added to a statin and given for up to 78 weeks showed preliminary evidence of reductions in CVD outcomes. While these promising early findings contributed to the recent approval of these agents in Europe and the US, much larger and longer duration outcomes studies are ongoing for definitive proof of CVD benefits. Other non-statin agents recently approved in the US include lomitapide and mipomersen, which both act via distinctive LDL-receptor independent mechanisms to substantially reduce LDL cholesterol in homozygous familial

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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 towards more assertive LDL-lowering treatment, using both statins and non-statins initiated earlier in appropriately selected patients.

Introduction

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 *P. 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, anticoagulant and anti-inflammatory effects; inhibiting cell proliferation; anti-carcinogenic 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 upon 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 non-statin-based LDL cholesterol reductions should also be beneficial in the absence of unrelated detrimental effects (4). With the recent approval of inhibitors of proprotein convertase subtilisin kexin 9 (PCSK9), a review of all non-statin 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 (5). The centrality of LDL cholesterol in predicting CVD risk has been confirmed repeatedly in classic epidemiological (6–8) and observational (9) 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 (10–12). Even as new pro- and anti-inflammatory pathways are being discovered, the foundational role of LDL in atherogenesis remains axiomatic (12).

Atherosclerosis development early in life

Atherosclerosis begins early in life, with higher levels of LDL cholesterol contributing to early atherogenesis (13). The Pathobiological Determinants of Atherosclerosis in Youth Study (PDAY) and the Bogalusa Heart Study showed that every 0.26–0.39 mmol/L (10–15 mg/dL) increase of non-HDL cholesterol is associated with an additional year of vascular aging (14,15). Thus, a 15 year old with heterozygous familial hypercholesterolemia (FH) has essentially the same amount of atherosclerosis as a 20–35 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 (14, 16–18). 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 (19). 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 (20). Mendelian randomization avoids confounding and reverse causation (20), 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 loss of function (LOF) mutations in *PCSK9* were associated with reduced LDL cholesterol and substantial reductions in CHD risk (21). Similarly, the Myocardial Infarction Genetics Consortium Investigators re-sequenced the *NPC1L1* gene and showed that the p.Arg406X LOF mutation was associated with 10% lower LDL cholesterol and 50% decreased CHD risk in a large replication sample (22). 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 (23). Since *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 randomized clinical trials

Early RCTs of LDL lowering studied diet, ileal bypass and various non-statin drugs. Of the latter, estrogen and dextrothyroxine had undesirable physiological effects and failed to reduce CVD despite cholesterol reduction (24). Fibrates and niacin have shown some benefit when used as monotherapy (25,26), but no incremental protection when added to a statin in patients who had achieved low LDL cholesterol levels (27,28). All other LDL-reducing interventions have benefits, including reduced saturated fat and increased polyunsaturated fat intake (29), interrupting enterohepatic circulation by a bile acid sequestrant (30) or surgical intervention (31), blocking intestinal cholesterol absorption by ezetimibe (32), inhibiting cholesterol biosynthesis by statins (2) and removing LDL-cholesterol by repeated LDL-apheresis (33). Early statin RCTs such as the Scandinavian Simvastatin Survival Study (4S) (34) and West of Scotland Coronary Prevention Study (WOSCOPS) (35) used less potent statins, i.e. simvastatin and pravastatin, respectively, and achieved 30 – 36 % reductions in major coronary events. Stronger statins, such as rosuvastatin, lower risk by 45% (36). The Lipid Research Clinics (LRC) (30,37) and Cholesterol Treatment Trialists Collaboration (CTTC) each concurred that “lower is better”, whether achieved with a statin or non-statin mechanism (2,38).

Conventional non-statins and CVD risk

Ezetimibe

Ezetimibe blocks intestinal sterol absorption by interfering with Niemann Pick C1 like receptor 1 (NPC1L1), with LDL cholesterol reduction of ~20%. Convincing evidence of reduced CVD events with ezetimibe has been slow to emerge (39). In 2011, the Study of Heart and Renal Protection (SHARP) showed ezetimibe plus simvastatin vs double placebo reduced CVD events in patients with renal impairment (40). 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) (32). A subgroup analysis showed proportionally greater benefit in diabetic patients (32). A study employing intravascular ultrasound showed that ezetimibe plus atorvastatin induced significantly greater regression of coronary artery plaque volume than atorvastatin alone (41). 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 (42), depleting the liver of bile, which upregulates bile synthesis from cholesterol by 7-alpha-hydroxylase. This depletes the intra-hepatic cholesterol pool, upregulating LDL receptor activity, which reduces LDL cholesterol levels. Increased 7-alpha-hydoxylase activity raises triglyceride (TG) (43). At daily doses of 24 g cholestyramine, 20 g colestipol or 4.5 g colesevelam, LDL cholesterol is reduced 18–25% (44). Bile acid sequestrants also augment the LDL-lowering effects of other drugs, notably statins (45). Colesevelam improves glycemic control modestly in patients with type 2

diabetes (46). Gastro-intestinal side effects and drug interactions (perhaps somewhat lower with colesevelam) limit the use of these agents (47). 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 (30,37).

Niacin

Pharmacologic doses of niacin (nicotinic acid), through incompletely defined mechanisms, lower LDL cholesterol and TG by up to 25% and 50% respectively, and raise HDL cholesterol by up to 30% (48). At high doses, niacin also lowers Lp(a) by up to 30% (49). As monotherapy, niacin administered to hypercholesterolemic men reduced the risk of recurrent myocardial infarction in the Coronary Drug Project (50), and also reduced total mortality in a 15-year follow-up (26). Decreased atherosclerosis progression has also been observed in imaging studies of niacin's effects (51).

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-C (28,52). These results undermined the hypothesis that HDL directly protects from atherosclerosis (53), and when considered together with niacin's side effects (skin flushing, hepatotoxicity, hyperuricemia and hyperglycemia), have stifled enthusiasm for its use (54), although it may still have utility in severe FH until newer agents become widely available.

Fibrates

Individuals with the metabolic syndrome, with or without type 2 diabetes, are at higher risk for CVD events and mortality (55,56). 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 (55,57–59). The dyslipidemia characterized by high TG and reduced HDL cholesterol increases CVD risk (60), with both on-treatment TG and HDL cholesterol levels predicting CVD events in statin RCTs (61–63). Fibrates lower TG and raise HDL cholesterol via moderate agonism of peroxisome proliferator activated receptor-alpha; however results of CVD outcome trials with fibrate monotherapy have been mixed (64–67). Two studies (one each in primary and secondary prevention) were positive (25,64), but three (two in primary and one in secondary prevention) were negative (65–67). In monotherapy studies, post hoc subgroup analyses suggested a benefit of fibrates in subjects with high TG with or without low HDL cholesterol (68).

In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial (27) of 5518 individuals with type 2 diabetes, adding fenofibrate on top of stable background simvastatin therapy (LDL cholesterol 2.1 mmol/L [80 mg/dL]) reduced TG and increased HDL cholesterol by ~16% and ~2.4%, respectively, compared to placebo, but had no effect on CVD end points (risk reduction 8%, P=0.32). Subgroup analyses showed: 1) women did

significantly worse than men; and 2) 17% of the cohort, with a pre-specified group with both upper tertile of TG (>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, while raised serum creatinine on fenofibrate returned to baseline levels with cessation of treatment (69). There is no evidence supporting the use of fenofibrate in non-dyslipidemic people and in women without dyslipidemia, fenofibrate may increase risk of CVD events. Subgroup analyses suggesting benefit in individuals with higher TG and HDL cholesterol (68) must be confirmed in a dedicated trial.

Non-statins in children

Limited RCT data support ezetimibe use in children and adolescents (70). As monotherapy, after 12 weeks of treatment, ezetimibe lowered LDL cholesterol by 27% in 6 – 10 year old children with FH. In adolescents, in combination with simvastatin, ezetimibe lowered LDL cholesterol by an additional 10–15% (71). While colesevelam 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 colesevelam alone (72). This highlights the importance of compliance to achieve therapeutic goals, and also the need for additional RCT evidence in this group.

Newer non-statin agents

PCSK9 inhibitors

PCSK9 interrupts the recycling of the LDL receptor by diverting it towards lysosomal degradation after receptor-mediated endocytosis of LDL particles. Gain-of-function mutations in the *PCSK9* gene cause autosomal dominant hypercholesterolemia (73), while loss-of-function mutations are associated with lower LDL cholesterol and reduced CVD risk (21,74). Monoclonal antibodies (mAbs) against PCSK9 were recently approved in Europe and the US (75). Alirocumab and evolocumab, both fully human mAbs, have completed the majority of their Phase 3 efficacy and safety trials, while these have not yet been completed for bococizumab, a humanized mAb (76). Large RCTs of CVD outcomes are under way for all three PCSK9 mAbs.

LDL cholesterol lowering efficacy varies from 50–65% for PCSK9 mAbs (Table 1). LDL-lowering efficacy is comparable for alirocumab 150 mg biweekly and 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) (77,78). Efficacy appears similar across most patient subgroups, including heterozygous FH patients (78,79). PCSK9 mAbs allowed a substantial proportion of FH patients to achieve LDL cholesterol <1.8 mmol/L (<70 mg/dL) for the first time (80,81). 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 (82). In addition to robust LDL cholesterol lowering, evolocumab and alirocumab improve other lipid parameters, e.g. Lp(a) is reduced up to 25% (78,79).

Evolocumab and alirocumab appear well tolerated in trials up to 78 weeks in duration (78, 79, 83). Injection site reactions are relatively infrequent and mild. Myalgia was slightly more frequent with alirocumab compared to 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 to those seen with ezetimibe (84, 85).

Preliminary data suggest that PCSK9 mAbs reduce CVD events over 1 to 1.5 years (78,83). 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 (86). Four large, ongoing trials of CVD events and safety are evaluating alirocumab, evolocumab, and bococizumab in high risk patient populations (87–90). 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 (91). While long-term CVD outcomes data are pending, PCSK9 mAbs represent an option for patients who might benefit from an additional 50–60% 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.

Apolipoprotein B antisense therapy

Mipomersen is a second-generation antisense oligonucleotide that concentrates in the liver and specifically binds to human apolipoprotein (apo) B mRNA (92). The bound mRNA is degraded by hepatic RNAse, preventing the translation of apo B and synthesis of apo B-containing lipoproteins. Mipomersen 200 mg administered subcutaneously once weekly reduces LDL cholesterol, apo B and Lp(a) by ~30% (93). Since mipomersen does not require functional LDL receptors, equivalent responsiveness is seen in LDL receptor negative HoFH patients (94). 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 US only for use in homozygous FH (95).

Lomitapide

Microsomal triglyceride transfer protein (MTP) is essential for assembly and secretion of hepatic and intestinal lipoproteins (96). MTP facilitates the incorporation of cholesteryl ester and triglyceride into VLDL in hepatocytes and chylomicrons in enterocytes by interacting with hepatic apo B-100 or intestinal apo B-48, respectively. Inhibiting MTP targets synthesis of apo B-containing lipoproteins (93) independent of the LDL receptor. Thus, lomitapide, an oral MTP inhibitor, reduces LDL cholesterol by up to 50% in subjects with homozygous FH (97,98). Lomitapide has 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, i.e. elevated liver enzymes and hepatic steatosis (99).

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 apo B-containing lipoproteins. Thus CETP has received considerable attention as a drug target, although two CETP inhibitors have failed in large CVD outcome trial (100,101). Torcetrapib-treated individuals experienced increased CV events and mortality despite substantial reductions in LDL cholesterol (100), putatively due to 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 (101). Two other compounds, anacetrapib and evacetrapib, remain under active investigation; both have substantial HDL-raising and LDL-lowering effects (102,103) without apparent off-target effects (104). Ongoing RCTs will determine whether additional beneficial effects of CETP inhibition translate into improved outcomes (105,106).

Bempedoic acid

Bempedoic acid (previously known as ETC-1002) is a small molecule inhibitor of ATP citrate lyase (ACL), a cytoplasmic enzyme that generates acetyl coenzyme A for de novo synthesis of fatty acids and cholesterol (107). Phase 2 trials in patients with hypercholesterolemia (108) and type 2 diabetes (109) show that bempedoic acid 80 and 120 mg daily reduced LDL cholesterol by 25% and 43%, respectively, over a very short term. Bempedoic acid may also result in incremental reductions in LDL cholesterol when co-administered 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?

While 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 (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 very low or triglycerides are high (110). Thus, pursuit of alternatives to LDL cholesterol has been a focus of epidemiologic and mechanistic research.

Atherosclerosis was long recognized as more closely related to the total number of apo B–containing particles rather than LDL cholesterol concentration (111). One apo B molecule is present on the surface of chylomicrons (CMs), very low-density lipoprotein (VLDL), intermediate density lipoprotein (IDL), LDL and Lp(a) (112). Thus, apo B may more directly measure circulating atherogenic lipoproteins than LDL cholesterol (110, 113). Apo

B has analytic and biological stability and is valid in non-fasting samples, which is useful for epidemiological studies (114).

Non-HDL cholesterol is the sum of VLDL-, IDL- and LDL cholesterol, and is calculated by subtracting HDL cholesterol from total cholesterol. Non-HDL cholesterol quantifies cholesterol content of all atherogenic apo B-containing lipoproteins and is highly correlated with apo B levels (112). The superiority of non-HDL cholesterol to LDL cholesterol in CHD prediction was shown in the Health Professionals Follow-up Study (115), the Framingham Heart Study (116) and Framingham Offspring Study (117), and the Women's Health Study (118). Non-HDL cholesterol and apo B had equivalent predictive value and were both superior to LDL cholesterol in the Emerging Risk Factors Collaboration (119).

While RCTs have predominantly used LDL cholesterol reduction as a primary biochemical end point, many also measured non-HDL cholesterol and apo B, 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 apo B and non-HDL cholesterol were better predictors of reduced CVD events than levels of LDL cholesterol (120). In the Collaborative Atorvastatin Diabetes Study (CARDS) trial, both apo B and non-HDL cholesterol predicted CHD better than LDL cholesterol (121). Meta-analyses show apo B and non-HDL cholesterol as being superior to LDL cholesterol in predicting CHD events (122–124). Because non-HDL cholesterol and apo B can be determined from non-fasting 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 (13, 125, 126).

What is the role of LDL treatment in children?

Current recommended lipid lowering therapy in childhood is directed towards 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 or multiple other known major risk factors (127). 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 – 10 with FDA approved medications at doses utilized 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, lupus, or Kawasaki disease (128–130).

Carotid intima media thickness measures in children affected with heterozygous FH compared to their siblings suggests accelerated atherosclerosis can be appreciated early in the second decade (131); 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 (132). 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 (133). LDL apheresis is an adjunct to pharmacologic treatment in homozygous FH (33,133). FH homozygotes in particular require 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 colesevelam (71,72,134,135). Clinical trials utilizing 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 presence of subclinical atherosclerosis, particularly coronary artery calcium, improves risk classification. Nonetheless, the role of monitoring subclinical markers in clinical practice is not established (136, 137), and a full discussion is beyond the scope of this paper. In FH or other conditions with elevated lifetime risk, noninvasive subclinical atherosclerosis assessment can be taken into account when determining baseline risk (138), 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 (139,140), as well as lack of evidence.

Can LDL cholesterol be too low?

There are some signals of adverse effects of very low LDL 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 (141) and cirrhosis and hepatocellular carcinoma in adults (142–145) 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 (146). In the OSLER study, among those on evolocumab, three patients (1%) reported amnesia and five (1%) reported either memory or mental impairment (unrelated to achieved LDL cholesterol), whereas no cases were reported in controls (147). The FDA issued a directive for neurocognitive assessment in ongoing PCSK9 mAb RCTs (147). Also, subjects randomized to rosuvastatin who achieved LDL cholesterol <0.78 mmol/L (<30 mg/dL) had higher rates of diabetes, hematuria, hepatobiliary disorders and insomnia (148). Longer 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 risk with statins extend to non-statins?

Statins effectively reduce CVD in people with diabetes (2,59), who have a two-fold long-term increase in CVD morbidity and mortality. However, several studies suggest that statins increase risk of developing type 2 diabetes in pre-diabetic individuals (148–151). A meta-

analysis of 13 statin trials (150) reported that standard-dose statin therapy was associated with 9% higher type 2 diabetes risk over four years, with greater risk associated with intensive statin therapy (151) and pre-existing risk factors for diabetes (152). No compelling evidence indicates differences in the risk of incident diabetes between statins. There is intense interest in identifying underlying mechanisms (153), with no definitive results to date. Recent genetic data from carriers of variants that reduce the activity of 3-hydroxy-3-methyl-glutaryl-CoA (HMGCoA) reductase (154) or cause FH (155), have raised the question as to whether statins *per se*, cholesterol synthesis, or LDL receptor function is actually causative. However, one CVD event is prevented for each 100–150 people treated with a statin while 500 people must be treated to cause one new case of type 2 diabetes, emphasizing risk-benefit considerations of statin therapy (150,151). So far, similar risks have not been observed with non-statins, except for niacin (28,52). Finally, the incidence of type 2 diabetes in IMPROVE-IT (32) and the ongoing trials of CETP inhibitors and PCSK9 inhibitors will provide important mechanistic clues.

Can newer non-statins regress lesions?

In the statin RCTs, greater relative CVD risk reductions occurred with progressively lower achieved LDL cholesterol levels; atherosclerosis regression continues as LDL cholesterol levels reach 0.39 mmol/L (15 mg/dL) (156,157). This suggests that combinations of maximally tolerated statins, ezetimibe, and new drugs such as PCSK9 or CETP inhibitors to dramatically reduce LDL cholesterol may have profound effects on atherosclerosis stabilization and regression. The opportunity exists to explore two new approaches to cardiovascular prevention. First, long-term follow-up of statin trials demonstrates persistently reduced CVD risk in statin-treated patients from the trial over the next decade or two (158,159). 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 very aggressive LDL cholesterol lowering for three to four 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 time period

Animal data suggest dramatic LDL cholesterol reduction early in the course of atherosclerosis can completely regress atherosclerosis and normalize arterial function (160). 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 (132).

Targets or no targets?

Re-opening the debate on the role of target lipid levels in treatment guidelines is beyond the scope of this review. Employing 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 (91). Other jurisdictions have retained targets for now, in part due to local values and preferences among community practitioners in favor of targets (125,126). Validity of targets versus no targets was evaluated in the offspring and third-generation cohorts of the FHS based on Framingham risk factors, LDL thresholds based on the updated

ATP III guidelines (5) and the 2013 ACC/AHA pooled cohort calculator (91,161). Incident CVD was determined at a median 9.4 year follow-up (162). 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%CI, 3.8–11.9) vs 3.1 (95%CI, 1.9–5.0), respectively (P<0.001). Thus, compared to 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 re-evaluation of the concept of LDL cholesterol targets in clinical practice.

Conclusion

The biological, genetic, epidemiological and clinical trial evidence supporting a direct causal role for LDL cholesterol in atherogenesis and resulting major cardiovascular events is compelling. In the clinic, whether the physician or patient believes 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 non-statin 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 alirocumab over 52–78 weeks complement earlier RCT evidence of CVD event reduction with such non-statin 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 non-statin 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 non-statins. Non-statins 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. While diet and statins represent the cornerstones of management of dyslipidemia, our review suggests that non-statin 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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Table 1

Non-statins and their effects on low-density lipoprotein cholesterol and cardiovascular disease end points

class	examples	typical % LDL cholesterol reduction	evidence for clinical CVD end point reduction	key reference(s)	comments
statins	lovastatin, simvastatin, pravastatin, fluvastatin atorvastatin, rosuvastatin, pitavastatin	35–55%	incontrovertible: 22% CVD risk reduction for 1 mmol/L (~40 mg/dL) LDL cholesterol reduction, plus ~10% reduced all-cause mortality	2	reference comparator for non-statin agents in this table
cholesterol absorption inhibitor	ezetimibe	18–25%	strong: modest incremental ~7% reduction when added to statin therapy in acute coronary syndrome patients	32	no studies with ezetimibe as monotherapy
bile acid sequestrants	cholestyramine, colestipol, colesevelam	18–25%	good evidence vs placebo: ~20% CVD risk reduction in events in primary prevention	30,37	no studies with resins added to statins
niacin-based preparations	crystalline niacin (short acting), extended release niacin	20–25%	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	49–51	multiple effects on lipid profile; neutral outcomes when given to patients well-treated on statin
fibrates	gemfibrozil, fenofibrate, bezafibrate	5–15%, varies depending on baseline triglyceride levels	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	64,66–68	multiple effects on lipid profile; subgroup analyses suggest benefit in men with high TG, low HDL cholesterol
PCSK9 inhibitors	evolocumab, alirocumab, bococizumab	40–65%	promising evidence: ~50% reduction in CVD events when added to statin therapy in aggregated small early phase study results	78,81	possible new standard of therapy; long term outcomes data pending
APOB antisense oligonucleotide	mipomersen	30–45%	no evidence: good efficacy for LDL cholesterol reduction in homozygous familial hypercholesterolemia	94	also lowers Lp(a); injection site reactions, flu-like symptoms
MTP inhibitor	lomitapide	35–50%	no evidence: good efficacy for LDL cholesterol reduction in homozygous familial hypercholesterolemia	97, 98	GI symptoms, fatty liver
CETP inhibitors	anacetrapib, evacetrapib	20–30%	no evidence: awaiting large scale outcomes studies	102, 103	also raise HDL cholesterol by 80–100%
ATP citrate lysase inhibitor	bempedoic acid	20–28%	no evidence: early in development	107	no long term data; apparently well tolerated

abbreviations: APOB, apolipoprotein B; ATP, adenosine triphosphate; CETP, 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; TG, triglyceride.