Lipids, Lipoproteins, and Cardiovascular Disease: Clinical Pharmacology Now and in the Future

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Context: While substantial benefit has accrued with respect to prevention and treatment of atherosclerotic cardiovascular disease (ASCVD) since the advent of statin therapy, much remains unknown and there is considerable need to address residual risk beyond statins. Moreover, many individuals are unable to tolerate statins.

Evidence Acquisition: As a result of several recent clinical trials and publications describing early Phase 1–3 clinical trials, the authors briefly discuss the current situation regarding pharmacological management for the prevention and treatment of individuals with disorders of lipid and lipoprotein metabolism, outline some of the unanswered questions, and speculate on where we might expect to be in 5–10 years.

Evidence Synthesis: Fortunately, recent developments in drug therapy hold considerable promise of additional benefits. In addition, new drugs in the pipeline, ongoing clinical trials, and new approaches to treatment hold promise for further improvements in therapy in the foreseeable future. During the next 5–10 years, we expect to know whether the PCSK9 inhibitors indeed live up to their promise and result in the hoped-for reduction in ASCVD events, whether triglyceride lowering indeed adds additional benefit, how best to approach HDL, and the importance of lipoprotein (a). Advances in the use of molecular biological approaches such as anti-sense oligonucleotides and RNA silencing, and the use of biological agents such as PSCK9 antibodies, is likely to play an important role in these advances.

Conclusions: The advent of PCSK9 inhibitors is likely to provide a major breakthrough in the management of individuals with heterozygous familial hypercholesterolemia, patients with established ASCVD who are unable to reach targets with other therapies, and high-risk individuals with statin intolerance. The next 5–10 years should also clarify uncertainties concerning the pharmacological management of individuals with low levels of HDL-cholesterol, hypertriglyceridemia, and elevated lipoprotein (a). **(*J Clin Endocrinol Metab* 101: 804–814, 2016)**

The relationship between lipids, lipoproteins, and atherosclerotic cardiovascular disease (ASCVD) has been known for more than a half a century. Tremendous progress in understanding the relationship between lipoproteins and cardiovascular disease (CVD) has occurred during the past 3 decades, including major advances in the prevention and treatment of CVD. By far the most successful of the therapeutic strategies has been the use of statins. However, despite

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Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CETP, cholesteryl ester transfer protein; CHD, coronary heart disease; CVD, cardiovascular disease; EPA, eicosapentaenoic acid; HDL, high-density lipoprotein: HDL-C, high-density lipoprotein-cholesterol; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein-cholesterol; LPL, lipoprotein lipase; TG, triglyceride; VLDL, very low-density lipoprotein.

their widespread use and current cost-effectiveness, CVD remains the leading cause of death in the United States, and considerable residual risk remains, much of which is attributable to lipids and lipoproteins. This article will focus on emerging therapeutics, and on unresolved issues that need to be addressed during the next 5–10 years, all of which are aimed at reducing the poststatin residual risk of CVD. To date, the greatest success has been achieved by a strategy that has focused on reduction of low-density lipoprotein (LDL) levels.

LDL

The robust relationship between plasma cholesterol and CVD has been appreciated for a very long time (1, 2). As research began to focus on plasma lipoproteins rather than lipids, it became clear that the relationship between cholesterol and CVD was primarily due to LDL cholesterol. Statins reduce LDL levels primarily by inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A-reductase, the rate-limiting enzyme in cholesterol synthesis. This leads to an upregulation of LDL receptors (3), but also is associated with a modest reduction in LDL production (4). Since the introduction of statins in the mid-1980s, their use has resulted in a remarkable reduction of coronary heart disease (CHD) events. Statins have proved to be of value in both primary and secondary prevention, and also have reduced cardiovascular mortality (5, 6). Moreover, they have also reduced the incidence of stroke (5, 7), despite stroke having a less robust relationship with LDL levels than CHD. Statins have proved to be beneficial in reducing CVD risk, whatever the nature of the risk. Thus, CVD risk is reduced by statins in women, men, (5, 6), Caucasians (6), blacks (8, 9), people with diabetes (8, 10, 11), smokers, hypertensives, and in individuals with other lipoprotein-related risk factors such as hypertriglyceridemia, low high-density lipoprotein (HDL)-cholesterol (HDL-C) levels (12), and high levels of lipoprotein (a) (13). Nonetheless, as noted earlier, despite the reduction in CVD events and mortality that started in the late 1960s (14, 15), considerable residual risk remains and CVD remains the major cause of death in the developed world.

What can be done about this residual risk? One possibility is that LDL-cholesterol (LDL-C) levels achievable by the use of statins alone may not be low enough. Strategies to achieve even lower LDL levels are now available, including the addition of cholesterol absorption inhibitors such as ezetimibe, and the recently available PCSK9 antibodies, the introduction of which will allow testing of whether achieving extremely low LDL levels will further reduce CVD events, and also safety of achieving very low levels of LDL-C. In addition, new LDL drugs in the pipeline offer promise for additional LDL lowering, particularly in those individuals who are unable to tolerate statins.

Combination therapy of statins and cholesterol absorption inhibitors

Considerable evidence suggests that "the lower the better" is a reasonable approach for reducing CVD by lowering LDL levels (16, 17). One way of achieving very low levels of LDL cholesterol is by the combined use of a statin and a cholesterol absorption inhibitor. Currently, the only approved drug in this class is ezetimibe, the target of which is the enzyme NPC1L1, the rate-limiting enzyme in the absorption of both exogenous and endogenous cholesterol in the intestine (18). The recently completed Examining Outcomes in Subjects With Acute Coronary Syndrome: Vytorin (Ezetimibe/Simvastatin) vs Simvastatin (IMPROVE-IT) trial showed that reducing LDL to very low levels by the addition of ezetimibe to a statin resulted in the expected additional lowering of CVD events predicted by the known regression relationship between on-trial LDL-C levels and clinical endpoints (19). Of interest, this additional lowering resulted in levels of LDL-C of 53 mg/dl in combined ezetimibe/simvastatin arm vs 69 mg/dl in the simvastatin/placebo arm with an overall risk reduction of 8%. These findings add credence to the notion that lowering LDL by any means would likely have a beneficial effect on clinical outcomes (20), and that lowering LDL by statins alone is not a magic bullet. Thus, the addition of a cholesterol absorption inhibitor to a statin may prove to be a good way of getting LDL to lower levels, especially when this agent becomes generic in the near future.

Cholesterol absorption inhibitors in 5–10 years

It would be informative to know the relative benefit of the addition of a cholesterol absorption inhibitor such as ezetimibe to a statin in subjects whose LDL levels were not as low as was observed in the IMPROVE-IT trial. However, to the best of our knowledge, there are no such clinical trials ongoing or planned at present, so no new data from randomized clinical trials are likely to be available in the next 5–10 years. Thus the physician will have to rely on clinical judgement in his or her quest to achieve LDL-C levels as low as possible in suitable very high risk patients.

PCSK9 inhibitors

Another way of getting LDL to very low levels is by using the new PCSK9 antibodies. Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a proprotein convertase originally identified at INSERM in Paris wherein mutations were associated with hypercholesterolemia (21, 22). The role of PCSK9 appears to direct LDL receptor toward lysosomal degradation rather than recycling to the plasma membrane, thereupon reducing the number and function of LDL receptors in mediating LDL clearance (23). Subsequently, both gain-of-function and loss-of-function mutations were identified that rapidly generated inter-

est in pharmacotherapeutics, specifically human monoclonal antibodies directed against PCSK9 (24). In the summer of 2015, phase 3 clinical trials were sufficient in demonstrating LDL-C lowering in addition to safety for approval of alirocumab and evolocumab for LDL-C lowering. In fact, the highest doses of these drugs exceeded the reduction of LDL-C of maximum dose statins (25, 26). Currently, PCSK9 inhibitors are indicated as adjuncts to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL-C. Although firm evidence from ongoing clinical trials is not yet available, a reduction in all-cause mortality, CVD mortality, and myocardial infarction has been reported from all the recent phase 2 and 3 randomized controlled trials (27).

PCSK9s and ASCVD in 5–10 years

For years now, LDL-C has been viewed by regulatory agencies as a surrogate for ASCVD. An unanswered question is whether this view holds at very low levels of LDL-C. The relationship between total cholesterol and CHD death is curvilinear, with less benefit with levels approaching 175 mg/dL (28). However, data from 27 randomized clinical trials suggest a linear relationship between the effect of LDL-C lowering with statins and reduced ASCVD events and related deaths from ASCVD (5). Data from IMPROVE-IT with ezetimibe + simvastatin (19) and post hoc data from Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER; rosuvastatin in patients with elevated highly sensitive C-reactive protein) (29) indicate that additional benefit ensues when LDL-C is reduced to less than 55 or 40 mg/dL, respectively. Presently, four large ASCVD outcome trials including an expected enrollment of more than 70,000 patients are ongoing, one each with alirocumab (ODYSSEY) and evolocumab (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk) and two with bococizumab (SPIRE-1, SPIRE-2). Considering the doses of the PCSK9 inhibitors used in these trials, many high-risk patients will have recurrent LDL-C levels below 40 mg/dL and a significant minority below 25 mg/dL (30, 31). Although the early data suggest an ASCVD benefit (30, 31), only after completion of the trials will we learn whether a threshold level of LDL-C achieves maximum benefit.

One clue to the potential safety of very low LDL-C levels comes from individuals with hypobetalipoproteinemia. These individuals have a mutation in the apoB gene, which results in very low lifelong LDL-C levels (32, 33). Despite these low levels, there is no evidence of adverse health effects, including cancer, Alzheimer's disease, or any other chronic disease, other than for an increase in fatty liver (34), likely because of impaired ability to secrete hepatic triglyceride [TG]) in the form of very low-density lipoprotein (VLDL). This side effect is unlikely to occur with the use of PCSK9 inhibitors because of their different mechanism of action. Nonetheless, individuals with hypobetalipoproteinemia are characterized by longevity and protection against CVD (33), suggesting that lowering LDL to very low levels by pharmacological means is not likely to have adverse effects. However, the extremely low LDL and TG levels associated with mutations in the microsomal TG transport gene, abetalipoproteinemia (35), is associated with severe neurological abnormalities because of the inability to transport fat soluble vitamins (32, 36). Therefore, fatty liver and fat-soluble vitamin deficiencies will need to be carefully looked for in ongoing PCSK9 clinical trials and in posttrial surveillance. Other approaches to inhibit PCSK9, such as the use of antisense oligonucleotides and RNA interference approaches might well be used in the future.

ATP citrate lyase inhibition

Inhibition of PCSK9 requires the use of injectable compounds. However, another orally administered LDL-lowering compound, ETC-1002, a once-daily small molecule designed to lower levels of LDL-C and to avoid side effects associated with existing LDL-C lowering therapies (37), is entering phase 3 clinical trials. ETC-1002 inhibits ATP citrate lyase, a key enzyme that supplies substrate for cholesterol and fatty acid synthesis in the liver (38). In phase 2 clinical trials, it has been reported to lower LDL-C levels by approximately 20–40% (37, 39, 40). Because its use has not been associated with some of the side effects that have been attributed to statins, it may be of particular use in individuals who are intolerant of statins (40). The drug also inhibits AMP kinase (41). This inhibitory property was associated with a lowering of blood glucose levels in an early clinical trial (39).

ApoB antisense oligonucleotides and microsomal TG transport inhibitors

Two other approaches have been used to lower LDL levels in individuals with very high levels. The first uses an antisense approach to inhibit the production of apoB-100, the major apolipoprotein of VLDL and LDL. Mipomersen, an injectable apoB antisense oligonucleotide (42), is approved in the United States for the treatment of homozygous familial hypercholesterolemia. However, the extremely high cost and the fatty liver that result from its use is likely to preclude its more widespread use in the foreseeable future.

Lomitapide is an inhibitor of microsomal TG transport protein, necessary for chylomicron absorption in the intestine and VLDL assembly and secretion in the liver (43, 44). It too has been approved in the United States as an orphan

drug for the treatment of homozygous familial hypercholesterolemia. Like mipomersen, it is extremely expensive and fatty liver results from it use. Also, steatorrhea can occur unless dietary fat is reduced to less than 20% of total caloric intake. These adverse effects also make it highly unlikely that this drug will enjoy more widespread use for the management of more common forms of hypercholesterolemia.

Role of HDL

Plasma levels of HDL-C are strongly and inversely related to the risk of CVD (45, 46). However, recent genetic studies that failed to show the expected benefit of polymorphisms that increase HDL-C levels (47) and some clinical trials that failed to show a benefit on CVD of raising HDL-C have cast doubt on the role of HDL as a cardioprotective lipoprotein. For example, elevation of HDL-C levels by cholesteryl ester transfer protein (CETP) inhibitors in the ILLUMINATE (Investigation of Lipid Level Management to Understand Its Impact in Atherosclerotic Events) trial failed to show the expected benefit on CVD end points, which in fact got worse with the use of torcetrapib. Torcetrapib, when added to atorvastatin, raised HDL-C levels by 72% and resulted in an additional 25% reduction in LDL-C levels compared to the group receiving atorvastatin alone, yet resulted in a significant excess in cardiovascular and noncardiovascular mortality (48). Although this worsening of CVD end points has been suggested to be due to an off target effect of the drug on increasing aldosterone levels and blood pressure (49), a clinical trial with dalcetrapib was discontinued because of futility (50), the development of evacetrapib has been halted, and only evacetrapib remains in an ongoing clinical trial. Moreover, two recent studies of the effect of the addition to statin therapy of niacin, which effectively raises HDL-C levels, have also been negative. In the Atherothrombosis Intervention in Metabolic Syndrome with low HDL/High Triglycerides: Impact on Global Health trial, the addition of extended release niacin to statin-treated subjects with very low baseline LDL-C levels on statins alone failed to show any additional benefit of niacin treatment (51). In the Treatment of HDL to Reduce the Incidence of Vascular Events trial, the addition to statin therapy of extended-release niacin in combination with laropiprant to inhibit flushing, also failed to confer clinical benefit beyond that observed in the statin-alone group (52). Moreover, the adverse effects of extended-release niacin were unacceptably high. These negative findings occurred despite niacin having been effective when used as monotherapy in the Coronary Drug Project in the prestatin era (53, 54). This raises the question of whether the benefit of niacin seen in that study was the result of niacin-induced LDL lowering.

Despite these negative genetic studies and clinical trials, studies in mice show a clear benefit on atherogenesis of increasing the level of HDL's major apolipoprotein, apoA-I (55, 56). Conversely, apoA-I deficiency confers increased risk of developing atherosclerosis in mice (57). Therefore, the relationship between HDL and ASCVD is more complex than hitherto appreciated. HDL is believed to protect against the development of atherosclerosis via it ability to stimulate reverse cholesterol transport from cells of the artery wall (58–60). Moreover, HDL has several other potentially antiatherogenic properties, including its ability to inhibit inflammation, oxidation, endothelial activation, and thrombogenesis.

This raises the question of whether HDL-C, rather than some other measurement of HDL function, is the appropriate metric for assessing the effect of interventions on HDL. It is therefore of considerable interest that measurement of cholesterol efflux capacity from macrophages, a metric of HDL function, showed a strong inverse association with both carotid intima-media thickness and the likelihood of angiographic coronary artery disease, independently of HDL-C levels (61). Similarly, in the Dallas Heart Study, cholesterol efflux capacity was inversely associated with the incidence of cardiovascular events in a population-based cohort (62). In the prospective nested case-control European Prospective Investigation of Cancer-Norfolk study of more than 25,000 individuals, cholesterol efflux capacity was significantly and inversely associated with incident CHD events, independent of age, sex, diabetes, hypertension, smoking and alcohol use, waist:hip ratio, body mass index, LDL-C concentration, log-triglycerides, HDL-C, and apoA-I concentration (63). Measurement of cholesterol efflux capacity depends on an ex vivo cellular assay which will be difficult to standardize, is time-consuming and expensive, and is unlikely to be available for widespread clinical use in the near future. Research techniques that have been used to measure reverse cholesterol transport in vivo in mice (64) are beginning to be applied to humans, but also are unlikely to be clinically applicable in the foreseeable future.

HDL and apoA-I infusions

Epidemiological studies that showed that a genetic variant of apoA-I, apoA-I Milano, was associated with a reduced incidence of CHD (65, 66), were supported by preclinical studies that also showed the ability of apoA-I infusion to halt the progression and cause regression of atherosclerosis (67). This resulted in the development of a recombinant apoA-I Milano phospholipid complex for testing in clinical trials. Although there was rapid regression by IV ultrasound in a small number of subjects with unstable angina, no wild-type apoA-I control was included

(67). However, progress in developing a product for clinical use appears to have stalled.

Several companies have been working on making apoA-I/phospholipid complexes for infusion in patients with acute coronary syndromes. The most promising is a product named CSL112 (68), which is being tested in ongoing clinical trials.

ApoA-I mimetics

Another approach to increase HDL levels and facilitate reverse cholesterol transport has been the use of apoA-I mimetics. Several apoA-I mimetic peptides, based on the helical structure of apoA-I, have been developed with the hope that they would mimic some of the antiatherogenic properties of HDL. To overcome the problem of intestinal digestion, some were synthesized with D amino acids, and recently they have been made by transgenic tomatoes (69). Several peptides have been shown to reduce atherosclerosis in animal models (70–73), although the mechanisms by which they do so is unclear and may relate more to their antioxidative properties than to their role in reverse cholesterol transport (74). To date, these apoA-1 mimetics have not been used in clinical trials.

HDL and ASCVD in 5–10 years

The role of altering HDL by lifestyle and pharmacological means has proved more difficult to sort out than originally imagined. Yet on the basis of emerging data, especially in animal models, there is hope that by focusing on measures of HDL functionality, rather than HDL-C levels, a better understanding of potentially beneficial modalities of therapy can be achieved. Therefore, in the next 5–10 years we are likely to see additional validation of measures of HDL functionality that predict CVD outcomes, and their incorporation into clinical trials and ultimately into clinical practice. Application of such techniques may confirm that HDL-C raising strategies such as CETP inhibitors and niacin may be of little value in CVD prevention. The jury is still out regarding fibrates (see the following section), which in addition to lowering TG levels, also modestly increase HDL-C.

As noted earlier, there has been considerable recent interest in HDL and apoA-I infusions, and the use of apoA-I mimetics, although mainly for use in the setting of acute coronary syndrome. A more rational approach to long term elevation of HDL that can facilitate reverse cholesterol transport has been strategies to increase apoA-I production. The most promising approach to date has been the use of apabetalone or RVX-208, a small-molecule drug that increases apoA-I production by an epigenetic mechanism as a result of it being a bromodomain extraterminal protein inhibitor (75). It increases the production of prebeta HDL, a particle that is believed to initiate reverse cholesterol transport. However, in small phase II intravascular ultrasound clinical trials in CVD patients (ApoA-1 Synthesis Stimulation and Intravascular Ultrasound for Coronary Atheroma Regression Evaluation), RVX-208 failed to reduce atheroma volume significantly; however, it also failed to raise HDL-C to a great extent (76, 77). Nonetheless, this compound will be entering phase 3 clinical trials in the near future. It is likely that we will see additional approaches along these lines during the next 5–10 years, and will hopefully, for once and for all, be able to answer the question of whether therapeutic approaches that target HDL and reverse cholesterol transport have merit.

Role of TG

TGs are mostly carried in chylomicrons, VLDL, and chylomicron and VLDL remnants. It has been well known for decades that hypertriglyceridemia is associated with increased CVD risk, specifically CHD in the early years (78, 79), but this risk is influenced in part by plasma levels of HDL that confer an independent and inverse relationship to CVD (80, 81). Although smaller TG-rich particles can cross the subintimal space and be found in atherosclerotic plaque (82), most plaque lipid is cholesteryl ester not TG. Moreover, still uncertain is whether the association of hypertriglyceridemia with CVD is causative or mediated indirectly by lipoprotein lipase (LPL)-mediated release of fatty acids or other toxins from TG-rich lipoproteins. Another mechanism is the adverse metabolic company that hypertriglyceridemia keeps with abdominal obesity, glucose intolerance, hypertension, and other components of the insulin resistant or metabolic syndrome (83, 84). In addition, increasing evidence suggests that nonfasting TG may be as if not more informative about CVD risk than fasting values (85, 86) and that higher levels of apoC-III, an apolipoprotein bound to TG-rich lipoproteins in addition to other particles, relates to atherogenesis (87). Proof of concept that hypertriglyceridemia is an independent predictor of CVD should be based on clinical trials. Pharmacological agents that work mostly on lowering fasting and nonfasting TG are the fibrates and omega-3 fatty acids.

Fibrates. Fibrates lower plasma TG by peroxisome proliferator-activated receptor-α–mediated effects on fatty acid oxidation diverting fatty acid incorporation away from VLDL-TG synthesis and secretion (88). Although the earliest fibrate trials were done with clofibrate, it was gemfibrozil that proved to reduce CVD events in the Helsinki Heart Study (89); however, this effect was mostly seen in patients who had very high levels of LDL and higher TG levels, a setting in which both TG and LDL-C were lowered (90). In the Veterans Administration HDL Intervention Trial (VA-HIT) gemfibrozil vs placebo was given to men with low levels

of HDL-C and existing CVD, and in this study events were reduced by 25% in the absence of changes in LDL-C (91). Of note, however, the amount of lowering of plasma TG with gemfibrozil did not correlate with reduction of risk (92). The Bezafibrate Infarction Prevention Study (93) and Fenofibrate Intervention on Endpoint Lowering in Diabetes Study (94) were both negative studies but in the latter, there was a substantial statin drop-in in the placebo group. When the data were examined post hoc, subgroups of patients with plasma TG higher than 200 mg/dL and TG at least 204 mg/dL plus HDL-C lower than 42 mg/dL, demonstrated benefit ($P < .02$) or borderline benefit ($P = .07$) respectively. In the Action to Control Cardiovascular Risk in Diabetes Lipid Study in which patients with type 2 diabetes were randomized to fenofibrate vs placebo on top of statin therapy, there was no benefit on the primary outcome but again, a subgroup analysis in patients with a fasting TG of at least 204 mg/dL and HDL-C lower than 34 mg/dL hinted at benefit, $P = .057$ (95).

Omega-3 fatty acids. Compared to fibrates, omega-3 fatty acids have been infrequently employed in ASCVD outcome trials, in part related to the current indications reserved for patients with TG at least 500 mg/dL. Although Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Prevenzione Trial was a low-dose eicosapentaenoic acid (EPA) (1.0 g) monotherapy trial in patients with a myocardial infarction that demonstrated a positive outcome on the primary CVD end point including all-cause mortality (96), the most frequently cited study is a trial done in Japan, the Jelis Study (97). This study enrolled more than 18 000 subjects (2/3 women) with a balance between those with and without existing ASCVD and baseline total cholesterol higher than 6.5 mmol/liter (575 mg/dl). Patients were all treated with low-dose statin ± 1.8 g of EPA, with a 4.6-year follow-up demonstrating a significant benefit in the total population, but only for secondary prevention. When a subgroup of patients with TG higher than 150 and HDL-C lower than 40 mg/dL was examined post hoc, a 53% reduction was seen (98). And from meta-analyses, other than a borderline benefit for cardiac death, there appears to be no benefit for omega-3 supplementation in patients with existing ASCVD (99).

Triglycerides and ASCVD in 5–10 years

At present, the optimal trial for TG lowering with a favorable CVD outcome awaits us. Such a trial would enroll patients with a previous CVD event or those at very high risk for such event, already treated with a statin (100) and with fasting TG between 200 and 500 mg/dl. For fibrates, the Veterans Administration Fenofibrate Intervention Trial has been planned and approved but not yet funded. Two such trials using omega-3 fatty acids are ongoing, the Reduction of Cardiovascular Events with EPA-Intervention Trial using ethyl-EPA (101) and STRENGTH (Statin Residual Risk Reduction with EpaNova in High Risk Patients with Hypertriglyceridemia) using omega-3 carboxylic acids. Because patients with increases in apoC-III are at increased risk of CVD and loss-of-function mutations of apoC-III are associated with a reduced risk of CVD (102, 103), new therapies directed at apoC-III may be another pathway to lower CVD risk related to hypertriglyceridemia. The relationship between apoC-III and hypertriglyceridemia has been attributed to inhibition of LPL-mediated lipolysis of circulating TG-rich lipoproteins (104); however, alternative mechanisms related to hepatic processing of chylomicron and VLDL remnants has also been raised (105). Antisense inhibition of apoC-III in hypertriglyceridemic patients with or without ongoing statin or fibrate therapy has been recently shown to reduce fasting TG by 40–80% in a dose-dependent manner (106). Another promising area for TG lowering is the relationship of angiopoietins to TG-rich lipoprotein metabolism. Angiopoietin-3 and angiopoietin-4 have been shown to inhibit LPL (107, 108). Yet to be replicated in humans are results from hypertriglyceridemic mice indicating that an antibody directed against angiopoietin-4 can lower fasting TG (109). Another consideration is either dual peroxisome proliferator-activated receptor-α/λ or peroxisome proliferator-activated receptor-α/δ agonists which result in moderate TG lowering (110); however, this class of agents has been delayed for approval based on adverse effects. Whichever novel therapy proves safe and effective in TG lowering and CVD outcomes to follow, there are a substantial number of patients with hypertriglyceridemia with or without statin therapy and with or without the metabolic syndrome who would benefit. The most recent National Health and Nutrition Examination Study data indicate that 31% of Americans have fasting TG higher than 150 mg/dL and 16% are above 200 mg/dL (111).

Lipoprotein (a)

Lipoprotein (a) is an apoB-containing lipoprotein that includes apolipoprotein (a) covalently bound to apoB, wherein plasma concentrations are determined mostly by genetics. The size of the apo (a) isoform is dependent on a variable number of kringle IV repeats with fewer repeats predicting a higher level of plasma lipoprotein (a) (112). Lipoprotein (a) concentrations vary substantially, with a several-fold higher level in populations of African and Asian descent (113). Increases in lipoprotein (a) and CVD have been repeatedly documented (114) and a threshold of plasma levels higher than 30–50 mg/dL indicates an increased risk of

Table 1. Predictions for 5–10 Years Hence

Lipoprotein	Prediction
LDL	1. PCSK9 trials will lower ASCVD events but no added effect will exist at LDL-C ≤40 mg/dl; the FDA may no longer consider LDL as a surrogate for ASCVD. 2. ETC-1002 will be approved but no outcome trials will be done. 3. ACC/AHA and other cholesterol guidelines will be updated. 4. Lomitapide will no longer be marketed.
HDL	1. CETP inhibitor outcome trials will be negative. 2. Measures of HDL function will be optimized and made clinically available. 3. ApoA-1 mimetics and drugs to increase apoA-1 synthesis will be further developed but not FDA approved.
TG-rich lipoproteins (VLDL, chylomicrons)	1. The optimal fibrate trial in patients with fasting TG ≥200 but ≤500 mg/dl will demonstrate a reduction in CVD events in high-risk patients on maximum tolerated statin therapy and a new FDA indication will follow. 2. The omega-3 fatty acids trial in patients with fasting TG ≥200 but ≤500 mg/dL in high-risk patients on maximum tolerated statin therapy will also demonstrate ASCVD risk reduction and a new FDA indication will follow. 3. Antisense ApoC-III in high risk patients on maximum tolerated statin therapy will also demonstrate ASCVD risk reduction and a new FDA indication will follow. 4. Antisense ApoC-III will also be approved for the reduction in pancreatitis incidence in patients with severe hypertriglyceridemia. 5. LPL gene therapy will be approved for the reduction in pancreatitis incidence in patients with severe hypertriglyceridemia. 6. Antibodies and antisense molecules that inhibit angiopoietin-4 will be further tested.
Lipoprotein (a)	1. Antisense lipoprotein (a) strategies to reduce ASCVD risk will be extended to phase 3 outcome trials and be FDA approved for this indication.

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; FDA, Food and Drug Administration.

CVD (115). Although this view of risk has been held for years, data from the Copenhagen Heart Study has suggested a gradient relationship between levels of lipoprotein (a) and CVD (116, 117). Moreover, in JUPITER, levels of lipoprotein (a) at baseline were not only associated with added CVD risk, in Caucasian statin-treated patients, higher levels predicted more events (13).

Lipoprotein (a) synthesis occurs mostly in the liver but some binding of the apo(a) protein to LDL apoB may occur in plasma (118). Elevation in lipoprotein (a) particles relate to CVD by their inability to be cleared by the LDL receptor, more atherogenic proinflammatory properties mediated by oxidized phospholipids, and antifibrinolytic activity secondary to structural homology to plasminogen (119).

Several approved drugs and one procedure lower lipoprotein (a): niacin, mipomersen, estrogens, and LDL apheresis (120); however, currently there are no data demonstrating independent effects of these interventions that reduce lipoprotein (a) results on CVD events. Of interest, in the Women's Health Initiative, estrogens may have conferred benefit on CVD events in postmenopausal women with the highest quintile of lipoprotein (a); and yet this outcome has been mostly ignored (121).

Lipoprotein (a) and CVD in 5–10 years

A promise for the future is antisense technology. phase 1 data have revealed a dose-dependent 40–80% reduction in lipoprotein (a) using ISIS-APO(a)RX (122).

When phase 2 antisense or alternative strategies for lipoprotein (a) lowering are completed, the definitive truth of the antiatherogenic effects of lipoprotein (a) lowering will require a long-term outcome study in patients with elevated lipoprotein (a) levels who are at high CVD risk and on statins and other evidence-based risk reduction therapies, a result that may be forthcoming by 10 years.

Table 1 provides some predictions of where the science of each of these four lipoprotein classes will be in 5–10 years.

Gene therapy

This use of this approach is likely to be limited to genetic conditions in which a mutation in a single gene results in a difficult to treat form of hyperlipidemia. Gene therapy for LPL deficiency, using an adeno-associated viral vector (123), is currently approved for this rare condition in Europe, but not yet in the United States. Replacement of the LDL receptor gene for homozygous familial hypercholesterolemia was attempted several years ago, but failed as a result of problems with the viral vector used. Conceivably, gene therapy for this condition might be tried again in the next several years, now that better viral vectors are available (124). Gene therapy with apoA-I, especially with apoA-I Milano, has also been suggested as a possible way of increasing functional HDL and facilitating reverse cholesterol transport. However, this ap-

proach awaits much more information regarding the role of HDL in atherosclerosis prevention.

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