Abstract: The introduction of statins ≈30 years ago ushered in the era of lipid lowering as the most effective way to reduce risk of atherosclerotic cardiovascular disease. Nonetheless, residual risk remains high, and statin intolerance is frequently encountered in clinical practice. After a long dry period, the field of therapeutics targeted to lipids and atherosclerosis has entered a renaissance. Moreover, the demonstration of clinical benefits from the addition of ezetimibe to statin therapy in subjects with acute coronary syndromes has renewed the enthusiasm for the cholesterol hypothesis and the hope that additional agents that lower low-density lipoprotein will decrease risk of atherosclerotic cardiovascular disease. Drugs in the orphan disease category are now available for patients with the most extreme hypercholesterolemia. Furthermore, discovery and rapid translation of a novel biological pathway has given rise to a new class of cholesterol-lowering drugs, the proprotein convertase subtilisin kexin-9 inhibitors. Trials of niacin added to statin have failed to demonstrate cardiac benefits, and 3 cholesterol ester transfer protein inhibitors have also failed to reduce atherosclerotic cardiovascular disease risk, despite producing substantial increases in HDL levels. Although the utility of triglyceride-lowering therapies remains uncertain, 2 large clinical trials are testing the influence of omega-3 polyunsaturated fatty acids on atherosclerotic events in hypertriglyceridemia. Novel antisense therapies targeting apolipoprotein C-III (for triglyceride reduction) and apo(a) (for lipoprotein(a) reduction) are showing a promising trajectory. Finally, 2 large clinical trials are formally putting the inflammatory hypothesis of atherosclerosis to the test and may open a new avenue for cardiovascular disease risk reduction. 

Key Words: cardiovascular diseases ■ cholesterol ■ high density lipoprotein cholesterol ■ low density lipoprotein cholesterol ■ triglycerides
Despite the great progress made over the past 4 decades, atherosclerotic cardiovascular disease (ASCVD) still remains the leading cause of death worldwide. Multiple lines of evidence, from genetic, experimental, epidemiological, and clinical studies, have converged on plasma cholesterol, particularly low-density lipoprotein cholesterol (LDL-C), as the principal driver of the initiation and progression of the atherosclerotic plaque. One of the most significant scientific achievements over this time has been the discovery and development of the statin drugs, which effectively lower LDL-C and the rate of morbidity and mortality caused by ASCVD. For >25 years, the statins have been the cornerstone of therapy, with only modest incremental additions to the therapeutic armamentarium. Fortunately, the field of lipid therapeutics has recently entered a renaissance. This review will examine the history and therapeutic development of the statins and provide a reasoned approach that ultimately leads to clinical ischemia.

### Role of Lipoproteins and Inflammation in Atherosclerosis

Atherosclerosis is a complex process involving many steps and the interplay of systemic and local factors. Chief among them are the apolipoprotein B-containing lipoproteins (apoB LPs). ApoB, the primary protein constituent of all atherogenic lipoproteins, provides structural integrity to the particle and serves as a ligand for receptor-mediated clearance. ApoB LPs, particularly low-density lipoprotein (LDL), drive the atherogenic process. Specifically, plasma LDL penetrate the arterial endothelial cell lining in susceptible regions of nonlaminar flow (bends, branch points) and enter the subendothelial space.

The mechanism by which apoB LPs traverse the endothelial layer and navigate the artery wall is incompletely understood and remains an obstacle to the development of therapeutic and preventive strategies. Intimal apoB LPs are retained in the extracellular matrix by binding to subendothelial proteoglycans, whose negatively charged sulfate groups interact with positively charged residues (arginine and lysine) on apoB.

The ensuing response to the subendothelial retention of apoB LPs leads to the evolution and propagation of the atheroma, as aggregation, oxidation, and other modifications of LDL make them suitable substrates for intracellular accumulation via scavenger receptors on macrophages and other arterial phagocytes. Because scavenger receptors are not subject to feedback regulation by cellular cholesterol levels, macrophages internalize excessive quantities of cholesterol ester and eventually transform into foam cells. Additional mechanisms of foam cell formation have been recently elucidated. Oxidized LDLs mimic damage-associated molecular patterns (DAMPs), oxidized molecular complexes that are cleared by pattern recognition (Toll-like) receptors on macrophages. When these receptors are ligated, signal transduction initiates a gene expression program that leads to production of costimulatory molecules (CD80, CD86, and CD40) that activate other immune cells and induces production of reactive oxygen and nitrogen species, proteases (eg, collagenases, elastases, and cathepsins), pro-inflammatory eicosanoids (eg, leukotriene B4 and prostaglandin E), chemokines (eg, monocyte chemotactant protein-1), and proinflammatory cytokines (eg, interleukin [IL]-1, tumor necrosis factor, and IL-6). Cumulatively, this has the effect of recruiting more monocytes into the coronary intima and of attracting smooth muscle cells from the media. Although there has been an emphasis on the critical role of LDL modification before uptake by macrophages, alternative pathways for foam cell formation that do not depend on LDL modification have been described, including uptake of aggregated LDL and fluid phase pinocytosis.

Although the initial inflammatory response is inherently appropriate, it is ultimately maladaptive in advanced atherosclerosis largely caused by defective inflammation resolution, with persistent recruitment of monocytes that differentiate into proinflammatory macrophages (M1), rather than into alternatively activated macrophages (M2), which promote inflammation resolution. In addition, defects in macrophage egress from advanced lesions coupled with defects in clearance of apoptotic macrophages (effeocytosis) lead to an expanded necrotic core. In summary, retention of apoB LPs initiates and then sustains this continuous, nonresolving inflammatory response that ultimately leads to clinical ischemia.

Given the underlying biology of atherosclerosis, current and future treatment strategies focus on lowering plasma apoB LPs and attenuating inflammation. A variety of other approaches have been attempted in the past, and new treatment strategies are in development.

### Current Evidence-Based Treatment for Lipid Management to Reduce ASCVD Risk

#### Statins

The cholesterol hypothesis positions this essential molecule as the central actor in the development of ASCVD when delivered as cargo by apoB LPs. The therapeutic culmination...
of this well-proven hypothesis has been the development and widespread utilization of statin drugs, the most useful class of medications for the prevention and treatment of ASCVD. The statin story represents one of the great triumphs in clinical science. Several seminal events led to the birth of this class of medications, which are reviewed in Table 1.

After the discovery and scientific validation of the statins, numerous clinical trials ensued. The 4S (Scandinavian Simvastatin Survival Study) trial was the first to show the astonishing power of LDL reduction in secondary prevention. Soon after, the CARE (Cholesterol and Recurrent Events) study, AFCAPS/TexCAPS (Air Force Coronary Atherosclerosis Prevention Study/Texas Coronary Atherosclerosis Prevention Study), and LIPID (Long-Term Intervention with Pravastatin in Ischaemic Disease) study demonstrated the same findings—statins reduce LDL-C and ASCVD events in both primary and secondary prevention settings. Relative risk reductions were strikingly similar with a 1% reduction in LDL-C, yielding a 1% reduction in ASCVD events. The larger trials also demonstrated significant reductions in total mortality. Subgroup analyses from these trials also suggested that all major subgroups (eg, women, diabetics, elderly, primary prevention, and secondary prevention) enjoyed the same benefit from therapy. The Heart Protection Study (HPS), which randomized ≈20000 subjects with ASCVD or diabetes mellitus, demonstrated that simvastatin (versus placebo) significantly reduced the incidence of myocardial infarction and stroke irrespective of baseline LDL-C, thus introducing a challenge to lower on-treatment LDL as the most logical guideline goal.

Although statins emerged as the most effective drugs for LDL-C lowering, ASCVD risk reduction was far from satisfactory, with the majority of statin-treated patients remaining at substantial risk in each trial. This observation motivated the next phase of statin studies (comparing high- versus low-dose statin). The PROVE-IT/TIMI-22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy/Thrombolysis in Myocardial Infarction-22) study enrolled subjects after recent acute coronary syndrome and randomized them to either atorvastatin 80 mg daily or pravastatin 40 mg daily. Subjects randomized to atorvastatin achieved a median LDL-C of 62 mg/dL and those randomized to pravastatin achieved a median LDL-C of 95 mg/dL. Atorvastatin proved superior in reducing major adverse cardiovascular events but not total mortality in this short 2-year study. Interestingly, the event curves separated early (at 30 days), suggesting rapid effects of the high-dose, high-potency statin on plaque stabilization. Subsequent trials in other acute coronary syndrome (ACS) populations and in those with stable coronary artery disease (CAD) have also compared intensive versus conventional statin therapy and have yielded similar results. These data have informed the most recent national guidelines on cholesterol management. The value of the statin mega-trials has been enhanced by the sharing of patient-level data among different studies by the Cholesterol Treatment Trialists’ Collaborators to produce an authoritative meta-analysis that has included >170000 participants in 26 randomized trials of statins. The major finding of this analysis is that a reduction of 39 mg/dL in LDL-C levels yields a consistent 22% reduction in the risk of major vascular events and 10% reduction in all-cause mortality >5 years, independent of baseline LDL-C.

Despite the remarkable achievements with the statin trials, approximately two thirds of the expected CVD events in statin-treated patients continue to occur. In addition, many patients cannot tolerate statin or reach acceptable LDL-C levels on treatment. Thus, the need for additional therapies remains paramount.

**Ezetimibe**

There are numerous nonstatin LDL-C–lowering therapies that are considered in light of their ability to mitigate ASCVD risk in this review. Ezetimibe inhibits cholesterol absorption at the jejunal brush border by binding to the Niemann-Pick C1-like-1 receptor, resulting in moderate reduction in LDL-C (16%–24%). As statins reduce cholesterol synthesis in the liver, counter-regulatory measures increase cholesterol absorption in the gut. The Food and Drug Administration approval of ezetimibe was based only on its ability to lower LDL-C. Initial clinical trials of ezetimibe did not demonstrate vascular benefits in combination with a statin. The ENHANCE study (Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression) randomized 720 subjects with heterozygous familial hypercholesterolemia to simvastatin or ezetimibe plus simvastatin. The combination reduced LDL-C by an additional 17% but did not affect carotid intima-media thickness (CIMT). ARBITER 6-HALTS (Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6 - HDL and LDL Treatment Strategies) randomized patients to simvastatin plus either extended release niacin (ERN) or ezetimibe. At 14 months, there was a statistically significant reduction in CIMT in the ERN group not seen in the ezetimibe group. The authors speculated that raising high-density lipoprotein cholesterol (HDL-C) improves risk reduction from statin therapy more than further lowering LDL-C. Newer data now call into question the value of CIMT as a surrogate marker for predicting ASCVD events. The Simvastatin...
Evidence-Based Treatment Failures

HDL Therapies

The inverse relationship between HDL-C levels and risk of ASCVD is among the most reproducible observations in clinical epidemiology. Inverse finding has been the impetus for developing therapies to raise HDL-C. Indeed, animal studies suggest that increasing HDL-C attenuates atherosclerosis. Pharmacological doses of nicotinic acid (niacin and vitamin B3) have numerous effects on lipid metabolism, including increasing HDL-C by 30%. Early clinical trials (Coronary Drug Project) and more recent imaging studies (HDL Atherosclerosis Treatment Study [HATS] and ARBITER 6-HALTS) suggested benefit from the use of niacin. The AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides: Impact on Global Health) study was the first of 2 large prospective randomized controlled trials that put niacin to the test in the statin era. In patients with low HDL-C and stable CAD, ERN was added to statin therapy and incidence of ASCVD events was assessed. Despite the fact that ERN increased HDL by 15%, the trial was terminated prematurely because of futility (no benefit, no harm). Possible explanations for the lack of benefit included (1) low baseline LDL-C (71 mg/dL), (2) too small an HDL-C difference between groups, and (3) the short period of observation (2½ years).

A larger and more definitive outcome trial with niacin is the HPS-2, which randomized 25,673 adults with ASCVD to simvastatin and either ERN plus laropiprant (an inhibitor of the niacin-induced flush) or placebo. Baseline LDL-C was low (63 mg/dL), and HDL-C and triglyceride levels were close to normal. During a median follow-up period of 3.9 years, ERN increased HDL but failed to reduce events when compared with statin alone. Since the publication of these 2 landmark trials, the use of niacin has been relegated to niche applications including the treatment of elevated lipoprotein (a) [Lp(a)] and the use in statin-intolerant patients.

Cholesterol ester transfer protein inhibitors (CETPi) can raise HDL-C by 40% to 120%. In the phase III trial ILLUMINATE (Investigation of Lipid Level Management to Understand Its Impact in Atherosclerotic Events), 15,067 subjects at high cardiovascular risk received the CETPi torcetrapib or placebo on top of atorvastatin. Torcetrapib increased HDL-C by 72%, reduced LDL-C by 25%, and was surprisingly associated with worse cardiovascular outcomes in only 10 months, leading to early termination of the trial and discontinuation of the research program. Further analyses pointed to off-target effects specific to this molecule as possible culprit, and thus additional CETPi were pursued. The dal-OUTCOMES (Randomized, Double-Blind, Placebo Controlled Study Assessing the Effect of RO4607381 on Cardiovascular Mortality and Morbidity in Clinically Stable Patients With a Recent Acute Coronary Syndrome) trial tested the CETPi dalteparin. Although there was no toxicity associated with the drug, dalteparin failed to lower ASCVD events despite increasing HDL-C by 31%, and the development of this agent was terminated. Two more potent CETPi are discussed below. However, the phase III CVD outcome trial of 1 of these 2 drugs, evacetrapib, was terminated in October 2015 because of futility.

RVX-208 is a novel agent that selectively stimulates production of apolipoprotein A1 (apoA1; the major protein constituent of HDL). In addition, serum from subjects taking RVX-208 exhibit increased cholesterol efflux capacity, suggesting increased HDL functionality. In the ASSURE (Efficacy and Safety of a Novel Oral Inducer of Apolipoprotein A-I Synthesis in Statin-Treated Patients With Stable Coronary Artery Disease) trial, 299 subjects with CAD on baseline statin therapy received RVX-208 or placebo. The drug only caused a modest increase in HDL-C (3.2%–8.3%), and transient transaminisits was noted in some subjects. The ASSURE (ApoAI Synthesis Stimulation and Intravascular Ultrasound for Coronary Atheroma Regression Evaluation) trial examined the effect of 26 weeks of treatment with RVX-208 on the progression of coronary atherosclerosis as assessed by intravascular ultrasound (IVUS) in 323 subjects with symptomatic CAD and low HDL-C levels. No significant change in plaque regression was observed between placebo and the RVX-208 group. Furthermore, the drug did not increase apoAI or HDL-C levels, but it induced transaminase elevations.

In support of the validity of these negative pharmacotherapeutic trials, a recent Mendelian randomization study also failed to validate the relationship between HDL-C levels and
ASCVD risk seen in classic epidemiology work. A single nucleotide polymorphism in the endothelial lipase gene, which increased HDL-C levels by 5.5 mg/dL (=12%) in carriers, was not associated with lower rates of myocardial infarction. Furthermore, polymorphisms in 14 other genes linked to lifetime HDL-C increases also failed to show association with myocardial infarction rates.

These high-profile failures have called into question the validity of the HDL hypothesis. A plausible explanation for these findings is that cholesterol content of HDL does not always reflect its protective effects. Measures of HDL particle concentration (HDL-P) may be more closely linked to HDL function than is HDL-C. An interesting analysis from MESA (Multiethnic Study of Atherosclerosis) demonstrated that HDL-P and HDL-C are both inversely associated with CIMT and incident CHD, but the relationship with HDL-C was weakened after adjusting for HDL-P and LDL-P (LDL particle concentration), whereas adjustment for HDL-C and LDL-P did not affect the predictive value of HDL-P.

Although several static measures of HDL composition predict ASCVD, a dynamic measure of HDL function may improve its predictive ability. A study by Khera et al strengthened the case that HDL-C and triglycerides predict risk even after LDL-C.

The Helsinki Heart Study assessed the efficacy of gemfibrozil as a primary prevention strategy in 4081 subjects. It demonstrated a 22% reduction in cardiovascular events in patients with non–HDL-C ≥200 mg/dL. The VA-HIT (Veterans Affairs Cooperative Studies Program High-Density Lipoprotein Cholesterol Intervention Trial) enrolled 2531 men with CHD and low HDL-C (<40 mg/dL) and randomized them to gemfibrozil or placebo. Gemfibrozil was associated with a 22% decrease in the rate of death from CHD or nonfatal myocardial infarction. The BIP (Bezafibrate Infarction Prevention) trial evaluated the effect of bezafibrate (n=1548) versus placebo (n=1542) on major coronary events and mortality in patients with CHD with elevated LDL. The study did not produce evidence of clinical benefits from the fibrate.

The FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) study evaluated the effect of fibrate therapy on ASCVD events in patients with type 2 diabetes mellitus. A total of 9795 subjects with diabetes mellitus not on statin therapy at study entry were randomized to fenofibrate (200 mg daily) or placebo for 5 years. There was no statistically significant difference in the primary outcome (CHD death and nonfatal myocardial infarction) although those on fenofibrate had a significant 24% reduction in nonfatal myocardial infarction. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial enrolled 5518 diabetic patients on baseline statin therapy and randomized them to fenofibrate or placebo. The addition of fenofibrate to statin therapy yielded no significant ASCVD risk reduction.

One of the ironic aspects of these 5 large trials of fibrates is the fact that most subjects had triglyceride levels <200 mg/dL. With this in mind, the negative trial results are not surprising, but they may not be definitive. In fact, subgroup analyses across all of these trials demonstrated that fibrate treatment benefited the dyslipidemic population (triglycerides ≥204 mg/dL and HDL-C ≤34 mg/dL) but not those without dyslipidemia (35% reduction in CHD events).

Within this context, it is conceptually attractive to consider dual PPAR (α and γ) agonists. These agents not only agonize PPAR-α (like the fibrates) but also PPAR-γ (like the thiazolidinediones used to treat diabetes mellitus) and thus impact gene regulation in multiple metabolic pathways. Nonetheless, the path to the development of dual PPAR agonists is littered with molecular corpses, as 2 agents, muraglitazar and tesaglitazar, were associated with adverse events (myocardial ischemia and nephotoxicity, respectively), and their programs were terminated.

Aleglitazar was the first dual PPAR agent studied in a large cardiovascular outcomes trial. AleCardio (Effect of Aleglitazar on Cardiovascular Outcomes After Acute Coronary Syndrome in Patients With Type 2 Diabetes Mellitus) tested aleglitazar versus placebo on top of standard of care in patients with diabetes mellitus after recent ACS. Aleglitazar improved lipid parameters and reduced hemoglobin A1c levels, but did not affect rates of cardiovascular outcomes. There was excess toxicity associated with treatment, including increased incidence of heart failure, renal dysfunction, bone fractures, gastrointestinal hemorrhage, and hypoglycemia. The possibility that other, unmeasured adverse consequences of PPAR activation contributed to the neutrality of the primary results cannot be excluded, given the multiplicity of genes regulated by PPARs. More recently, selective PPAR modulators have been developed in an attempt to maximize the favorable metabolic effects of PPAR activation, while minimizing the adverse effects. Phase I and II clinical trials with selective PPAR modulator-α and selective PPAR modulator-γ have demonstrated significant reductions in triglyceride levels among other favorable metabolic changes.

The preceding summary highlights the challenges that scientists and the pharmaceutical industry have faced when trying to reduce ASCVD risk above and beyond statin therapy. Clearly, the most successful strategy for primary and secondary prevention of ASCVD has been targeting LDL-C. Despite the residual risk that remains after reducing LDL-C and evidence that HDL-C and triglycerides predict risk even after LDL-C
has been successfully treated, approaches to modulate these targets have to date not yielded benefit. The following section highlights new and emerging lipid-modifying therapies.

New/Emerging Therapies

Therapies Targeting LDL

An increasingly common approach to drug target discovery is the characterization of patients with extreme phenotypes. Inherited hypolipidemias include familial hypobetalipoproteinemia (caused by mutations in apoB), abetalipoproteinemia (caused by mutations in microsomal triglyceride transfer protein [MTP]), familial combined hypolipopidemia (caused by mutations in angiopoietin-like 3 [ANGPTL3]), and low cholesterol caused by mutations in proprotein convertase subtilisin/kexin type-9 (PCSK9).

Mipomersen

Targeting apoB for lipid lowering attempts to mimic familial hypobetalipoproteinemia, a rare condition caused by mutations in the gene coding for apoB, leading to reduced expression or protein truncation. Mipomersen is a synthetic single-strand apoB antisense oligonucleotide (ASO). Hybridization of the ASO to the cognate apoB mRNA leads to degradation via RNase H. The details of antisense technology and pharmacology are beyond the scope of this review, and readers are directed to comprehensive examinations of this general topic.

Mipomersen was specifically developed for patients with homozygous familial hypercholesterolemia (HoFH). In a phase III clinical trial testing mipomersen in 51 subjects with HoFH, weekly subcutaneous injections reduced LDL-C by 25% and Lp(a) by 32%. Mipomersen has been studied in 3 additional phase III trials. In aggregate, LDL-C reduction ranged from 28% to 36%, apoB from 25% to 34%, and Lp(a) from 21% to 33%. An open-label extension study demonstrated sustained reductions in all atherogenic lipoproteins for ≤2 years. Mipomersen’s side effects include skin reactions at the site of injection, hepatic steatosis, and flu-like symptoms.

Lomitapide

Similar to mipomersen, lomitapide’s development was informed by a rare genetic disorder, abetalipoproteinemia, which is caused by mutations in the gene that codes for MTP, the protein that adds the lipid droplet to apoB in the endoplasmic reticulum to produce very low density lipoprotein and HDL particles. Lomitapide is a small molecule inhibitor of MTP. In a phase III dose titration trial of lomitapide in 29 subjects with HoFH, full-dose lomitapide reduced LDL-C by 50% from baseline to week 26. ApoB and Lp(a) levels were reduced by 49% and 13%, respectively. Side effects associated with lomitapide treatment are dominated by gastrointestinal complaints caused by increased triglyceride content of enterocytes. This mandates adherence to a low-fat diet with a gradual increase in dose over time. Similar to mipomersen, elevated transaminases caused by increased hepatic triglycerides are seen in a significant number of patients.

ANGPTL3 Inhibition

ANGPTL3 is a circulatory protein, which inhibits lipoprotein lipase (LPL) and endothelial lipase. Loss-of-function (LOF) mutations in this gene result in more efficient metabolism of very low density lipoprotein and HDL particles. This manifests clinically as low levels of triglycerides, HDL, and LDL. Because LOF mutations in ANGPTL3 are not associated with comorbidities, therapeutic strategies are being developed against this target. A phase I blinded, placebo-controlled, dose-escalation study with an ASO demonstrated mean reductions in ANGPTL3 levels of ≤82% with concomitant reductions in triglycerides and total cholesterol of 49% and 28%, respectively.

PCSK9 Inhibition

In 2003, Abifadel et al. reported PCSK9 as an additional gene causing autosomal dominant hypercholesterolemia via a gain-of-function mutation. This finding launched a remarkable series of investigations that placed PCSK9 squarely in control of plasma LDL trafficking. PCSK9 binds to the LDL receptor (LDLR) and targets it for destruction in the lysosome. PCSK9 action reduces LDLR and causes hypercholesterolemia, whereas loss of function increases LDLR, reduces LDL-C levels, and markedly reduces rates of ASCVD. Remarkably, few individuals with no circulating PCSK9 have been described, who show extremely low levels of LDL-C (≈15 mg/dL), normal health and reproductive capacity, and no evidence of neurological or cognitive dysfunction. Collectively, these observations provided the basis for the development of therapeutic antagonism of PCSK9.

Approaches to inhibiting PCSK9 include monoclonal antibodies (mAbs), adnectins (targeted biologics derived from a member of the immunoglobulin superfamily), ASOs, small interfering RNAs, and mimetic peptides. Small molecule inhibitors have been difficult to develop given the flat–surface interaction between PCSK9 and LDLR. To date, approaches using mAbs are the farthest along in clinical development. Clinical trials of mAbs targeted to PCSK9 have been tested in subjects with different levels of CVD risk, as monotherapy or combination therapy (statin+ezetimibe), in statin-intolerant patients, and in both heterozygous familial hypercholesterolemia and HoFH. The mAbs have consistently demonstrated remarkable efficacy in reducing LDL-C (≈50% as monotherapy and ≈70% reduction in combination with a statin) with an outstanding short-term safety and tolerability profile. Furthermore, in pooled analyses of randomized controlled trials with PCSK9 inhibitors, Lp(a) was also lowered by 25% to 30% (Figure 1). A recent systematic review and meta-analysis of 24 phase II and III randomized controlled trials testing PCSK9 mAbs in 10159 subjects demonstrated a highly significant 47.5% reduction in LDL-C with no difference in the rate of adverse events. None of the completed randomized controlled trials has been powered to evaluate cardiovascular events and mortality, but this large meta-analysis suggests extraordinarily large benefits (myocardial infarction [odds ratio, 0.49], all-cause mortality [odds ratio, 0.45], and cardiovascular mortality [odds ratio, 0.50]).

Currently, there are 4 large prospective randomized controlled outcome trials examining the impact of 3 PCSK9

ew approaches to reducing atherosclerotic risk

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inhibitors on ASCVD in >70,000 subjects (Table 2). The completion of the first of these 4 trials is projected for late 2017. Even in advance of these outcome trials results, the Food and Drug Administration approved alirocumab and evolocumab in the summer of 2015 as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (also HoFH for evolocumab) or patients with clinical ASCVD who require additional lowering of LDL-C.

Administration of mAbs to PCSK9 is associated with a rapid decline in plasma LDL-C, especially when compared with other drugs that influence LDLR expression (eg, statins, cholesterol absorption inhibitors, and bile acid sequestrants). This observation is fully accounted for by examining the mechanism of action of these various agents. The drugs that decrease hepatic cholesterol stores promote counterregulatory measures that culminate in increased expression and density of the LDLR at the hepatocyte surface. The synthesis of new translation of PCSK9 protein (G). Administration of mAbs blocks PCSK9 binding to the LDLR on the cell surface (H). These therapeutic approaches seem to have similar LDL-cholesterol-lowering efficacy, as they both impede the biological effect of PCSK9 and cause unchecked LDLR recycling (Illustration credit: Ben Smith).
LDLR protein takes time, and thus peak efficacy of these drugs occurs at $\approx 2$ weeks. Because the PCSK9 inhibitors act on the LDLR recycling pathway (each receptor normally recycles $\approx 150x$), the increase in hepatocyte surface LDLR density occurs quickly, as no new protein needs to be synthesized.\textsuperscript{96}

Most recently, a phase I trial evaluating RNA interference (ALN-PCSsc) to PCSK9 demonstrated essentially equivalent LDL-C–lowering efficacy when compared with PCSK9 mAbs with a more durable effect\textsuperscript{97} (Figure 2). Preliminary data demonstrated a mean 64% decrease in LDL-C with duration of effect that exceeded 4 months. This prolonged LDL-C reduction suggests that this therapy could potentially be administered subcutaneously quarterly and possibly biannually.

Inhibition of PCSK9 holds tremendous promise. Although mAbs targeting PCSK9 are already in the market, the results of the large clinical outcomes trials will determine the fate of this new pharmacological approach. However, as the physiological role of PCSK9 is not fully understood, the implications of long-term antagonism of this protein remain to be determined.

**ETC-1002**

Although statins as a class are well tolerated, 2 adverse effects have been emphasized—myalgia and myopathy in as many as 15% of users—and increased incidence of diabetes mellitus in patients with cardiometabolic risk factors. ETC-1002 is an investigational small molecule with a reported dual mechanism of action: inhibition of the ATP-citrate lyase and activation of AMP-activated protein kinase.\textsuperscript{98} ATP-citrate lyase is an enzyme in the cholesterol biosynthetic pathway, upstream of 3-hydroxy-3-methylglutaryl reductase, which catalyzes the conversion of citrate to acetyl-CoA, the precursor for fatty acid and cholesterol synthesis. On the basis of metabolic pathway, blocking ATP-citrate lyase should theoretically reduce hepatic cholesterol stores, increase LDLR expression, and decrease very low density lipoprotein production. Indeed, detailed pharmacological studies demonstrate that inhibiting ATP-citrate lyase results in reduction of both plasma cholesterol and triglycerides.\textsuperscript{99} Activation of AMP-activated protein kinase, a key signaling protein that facilitates the transfer of energy substrates to tissues in need, increases gluconeogenesis, $\beta$-oxidation of fatty acids, and mitochondrial density.\textsuperscript{100} This produces favorable effects on lipid and carbohydrate metabolism and attenuation of inflammation.\textsuperscript{101}

Across the clinical trial program, ETC-1002 was associated with reductions in LDL-C and high-sensitivity C-reactive protein (hs-CRP) of $\leq 40\%$. In a phase II study in subjects with statin intolerance, ETC-1002 was associated with significantly greater reductions in LDL-C (29%) than in placebo.\textsuperscript{102} There was no increase in muscle-related adverse events with ETC-1002 when compared with placebo. A phase III program is anticipated to launch at the end of 2015, which will include a cardiovascular outcomes trial.

**Therapies Targeting HDL**

Although targeting LDL-C has had stunning results, it is disconcerting to note that targeting HDL-C has not yielded benefit, given that the epidemiological association of HDL-C and ASCVD is at least as strong as that of LDL-C. HDL is a far more complex particle than LDL, with a myriad of non-redundant functions that extend beyond lipid metabolism. Besides its prominent role in reverse cholesterol transport, HDL exhibits antioxidative, antiplatelet, anti-inflammatory, and antiapoptotic properties.\textsuperscript{103} It is also a key participant in the innate immune system and favorably modulates glucose metabolism.\textsuperscript{104–107} The HDL spectrum encompasses particles that differ in composition, size, and function.\textsuperscript{108} Much of the functional heterogeneity is presumably related to differences in its proteome and lipidome.\textsuperscript{109,110} Although there is intense interest in this area, structure–function relationships are not clearly defined. Despite the many setbacks, the scientific community remains engaged and committed to this field with several emerging agents in development.

**CETPi**

As noted earlier, CETP inhibition dramatically raises HDL-C levels by blocking the exchange of cholesteryl ester from HDL to apoB LPs. Near-total CETP inhibition also reduces LDL-C

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**Table 2. Anticipated Large Phase III Cardiovascular Outcomes Trials With Proprotein Convertase Subtilisin/Kexin Type (PCSK)-9 Monoclonal Antibodies**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Setting</th>
<th>Study Drug</th>
<th>No. of Subjects</th>
<th>Primary End Point</th>
<th>Duration</th>
<th>Estimated Study Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>ODYSSEY OUTCOMES</td>
<td>Post ACS</td>
<td>Alirocumab</td>
<td>18 000</td>
<td>Time to CHD death, any nonfatal MI, fatal and nonfatal ischemic stroke, or unstable angina requiring hospitalization</td>
<td>64 mo</td>
<td>December 2017</td>
</tr>
<tr>
<td>FOURIER</td>
<td>High ASCVD risk; LDL-C ≥70 mg/dL</td>
<td>Evolocumab</td>
<td>27 654</td>
<td>Time to cardiovascular death, MI, stroke, coronary revascularization, or hospitalization for unstable angina</td>
<td>5 y</td>
<td>February 2018</td>
</tr>
<tr>
<td>SPIRE-1</td>
<td>High ASCVD risk; LDL-C ≥70 mg/dL</td>
<td>Bococizumab</td>
<td>17 000</td>
<td>Time to cardiovascular death, nonfatal MI, nonfatal stroke, and hospitalization for unstable angina requiring urgent revascularization</td>
<td>5 y</td>
<td>June 2018</td>
</tr>
<tr>
<td>SPIRE-2</td>
<td>High ASCVD risk; LDL-C ≥100 mg/dL</td>
<td>Bococizumab</td>
<td>9000</td>
<td>Time to cardiovascular death, nonfatal MI, nonfatal stroke, and hospitalization for unstable angina requiring urgent revascularization</td>
<td>5 y</td>
<td>March 2018</td>
</tr>
</tbody>
</table>

ACS indicates acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; FOURIER, Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; ODYSSEY Outcomes, Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab; SPIRE-1, The Evaluation of Bococizumab in Reducing the Occurrence of Major Cardiovascular Events in High Risk Subjects; and SPIRE-2, The Evaluation of Bococizumab in Reducing the Occurrence of Major Cardiovascular Events in High Risk Subjects.
levels in the range of the statin effect. CETP inhibitors cause accumulation of the largest subpopulation of HDL, while reducing the number of small pre-β-HDLS, which may be more efficient cholesterol acceptors.\textsuperscript{111} For HDL-raising agents to be effective, they must increase HDL-P, enhance HDL function, or both. Torcetrapib was not associated with an increase in HDL-P, and dalcetrapib was associated with only a 9% increase in HDL-P.\textsuperscript{112} Preclinical work with anacetrapib and evacetrapib suggests that they enhance HDL function, at least as measured by in vitro cholesterol efflux and anti-inflammatory assays.\textsuperscript{113} Of note, the phase II DEFINE (Determining the Efficacy and Tolerability of CETP Inhibition With Anacetrapib) study demonstrated the safety of anacetrapib in 1623 subjects with an increase in HDL-C of 138% and decrease of LDL-C by 40%, relative to statin only.\textsuperscript{114} Of concern, however, is a follow-up study that demonstrated detectable levels of plasma concentrations of anacetrapib ≤4 years after the last treatment dose.\textsuperscript{115} The REALIZE study (Randomized Evaluation of Anacetrapib Lipid-Modifying Therapy in Patients with Heterozygous Familial Hypercholesterolemia) enrolled 306 subjects with FH and randomized them to treatment with anacetrapib 100 mg daily on top of background statin therapy.\textsuperscript{116} Lipid and lipoprotein changes were consistent with other trials of anacetrapib, but a nonsignificant increase in CVD events was noted. On October 12, 2015, the phase III CVD outcome trial of evacetrapib (Assessment of Clinical Effects of Cholesteryl Ester Transfer Protein Inhibition With Evacetrapib in Patients at a High Risk for Vascular Outcomes [ACCELERATE]) was terminated after the data monitoring committee determined that there was a low probability that the study would achieve its primary endpoint. The results of the ongoing phase III CVD outcome trial of anacetrapib (Randomized Evaluation of the Effects of Anacetrapib Through Lipid-Modification [REVEAL]) should become available in 2017 if the study runs to completion.

Another CETPi in development, TA-8895, has been tested in a phase IIb trial with 364 dyslipidemia patients and demonstrated LDL-C lowering of ≤68% in combination with a statin, whereas raising HDL-C ≤179% and decreasing Lp(a) ≤37%. It also increases cholesterol efflux capacity by ≥40%.\textsuperscript{117} The phase III program is ongoing.

**HDL Infusion Agents**

HDL infusion agents encompass a broad class of HDL therapeutic potentials with the potential to increase HDL-P and enhance HDL function. This therapeutic modality is currently targeted for patients with ACS to stabilize the ruptured plaque(s).

HDL infusion formulations are produced by mixing recombinant apoA-I with phospholipids to mimic a pre-β-like HDL particle. ApoAI interacts with ABCA1 to facilitate mobilization of cellular cholesterol.\textsuperscript{118,119} Although normal apoAI may be used, there has been special interest in the mutant ApoAI\textsubscript{Milano} as this variant is associated with increased cholesterol efflux and antioxidant properties and associated with longevity in human carriers.\textsuperscript{120} Five weekly infusions of recombinant ApoAI\textsubscript{Milano} reduced mean plaque atheroma volume by 1.6% in ACS subjects as assessed by IVUS.\textsuperscript{121} Native apoAI was tested in the ERASE (Effect of HDL on Atherosclerosis - Safety and Efficacy) trial.\textsuperscript{122} It demonstrated favorable effects on plaque morphology in patients with ACS, but the development has been discontinued because of liver toxicity. Further refinements in this formulation (CSL112) were tested in a phase IIa trial that demonstrated enhanced cholesterol efflux (measured using a permanent cell line) without major adverse effects after a single infusion in patients with stable ASCVD. CSL122 is currently being tested in a phase 2b randomized, placebo-controlled trial (A Phase 2b Study of CSL112 in Subjects With Acute Myocardial Infarction [AEGIS-I]), investigating its safety and tolerability in 1200 patients with post-myocardial infarction.

CER-001 contains human recombinant apoA-I reconstituted with a variety of phospholipids including sphingomyelin, which may increase HDL-stimulated cholesterol efflux.\textsuperscript{123} CHI-SQUARE (Effect of CER-001 on Atherosclerosis in Acute Coronary Syndrome Patients - Efficacy and Safety) enrolled 507 subjects with ACS and randomized them to 6 infusions >5 weeks with CER-001 or placebo.\textsuperscript{124} Plaque volume assessed by IVUS did not differ 3 weeks after the last infusion. A second trial, MODE (Modifying Orphan Disease Evaluation), tested CER-001 in patients with HoFH.\textsuperscript{125} Twenty-three subjects received 12 biweekly infusion of CER-001 with carotid MRI performed at baseline and at 6 months.\textsuperscript{126} One hour after the infusion, there were no significant changes in HDL-C or LDL-C. CER-001 therapy was associated with a statistically significant reduction in carotid vessel wall area and volume (~2.53% change for both).

**Other Emerging HDL Therapies**

There are a number of additional promising HDL therapies in early development, including recombinant lecithin–cholesterol acyltransferase, HDL mimetic peptides (D4F, L4F, 5A, ATI-5261), P2Y13 receptor agonists (CER-209), selective liver X receptor agonists, and ASOs targeted to several nodes in the HDL pathway. Besides infusion therapy, acute HDL delipidation is a novel intervention that involves preparation of delipidated HDL for autologous reinfusion as a means to increase pre-β-HDL.\textsuperscript{127} One such plasma delipidation system has been studied in a trial, LS-001 (Lipid Sciences Selective Delipidation Trial), which randomized 26 subjects post-ACS.\textsuperscript{128} The infusions were associated with a 28-fold increase in pre-β-like HDL particles in plasma compared to baseline. However, atheroma volume assayed by IVUS showed only a nonsignificant effect of treatment.

**Therapies Targeting Triglycerides**

The modest interest in triglyceride management for ASCVD prevention has traditionally stemmed from confusing epidemiology and equivocal clinical trial results with triglyceride-lowering therapies.\textsuperscript{51–53,55} However, renewed interest in triglycerides is building as randomized controlled trials with HDL-C–raising therapies have failed and genetic studies suggest that triglycerides, not HDL, are causative in ASCVD.\textsuperscript{26,27} Mendelian randomization and genome-wide association studies have consistently demonstrated increased risk of ASCVD with increased levels of triglycerides, independent of HDL-C.\textsuperscript{129} In fact, a recent genetic analysis evaluated 44 single nucleotide polymorphisms that primarily impact triglyceride levels (with minimal effects on LDL-C) in >86000
subjects and demonstrated that the influence of these single nucleotide polymorphisms on triglycerides was associated to the degree of ASCVD risk.\textsuperscript{130}

Because triglycerides do not accumulate in foam cells, the association of plasma triglycerides with ASCVD may be because of its relationship with remnant lipoproteins (rich in both cholesterol and triglycerides) or to effects of triglycerides on the inflammatory response. Remnants may, in fact, have greater atherogenic potential because they do not require modification before engulfment by subendothelial macrophages and are taken up in an unregulated manner. Furthermore, hydrolysis of remnant triglycerides by LPL at the endothelial surface or within the subendothelial space generates a host of proinflammatory mediators, including free fatty acids and monoacylglycerols.\textsuperscript{131} Indeed, a multidirectional Mendelian randomization demonstrated that genetically raised remnant cholesterol, but not LDL-C, levels cause low-grade inflammation.\textsuperscript{132} Targeting remnant lipoproteins represents a new frontier for modulating ASCVD risk.

\textbf{\(\omega-3\) Polyunsaturated Fatty Acids}

The marine \(\omega-3\) polysaturated fatty acids (PUFAs), eicosapentaenoic acid (EPA), and docosahexaenoic acid at therapeutic doses of 2 to 4 g per day are effective triglyceride-lowering agents.\textsuperscript{133} Beyond triglyceride lowering, marine-derived \(\omega-3\) PUFAs have additional putative benefits including enhanced endothelial function, vasodilation, decreased platelet aggregability, and decreased myocyte excitability.\textsuperscript{134} Nonetheless, the application of \(\omega-3\) PUFAs to reduce CVD risk has had mixed results. Early studies with either EPA/docosahexaenoic acid or EPA alone suggested cardiovascular benefit.\textsuperscript{135-137} Recent trials and meta-analyses have called these initial studies into question. To some extent, it is difficult to come to firm conclusions because these agents have been studied in diverse populations with different doses, formulations, and concentrations of EPA and docosahexaenoic acid.\textsuperscript{138} In addition, recent trials have been performed in cohorts on contemporary background medical and interventional therapies, including aspirin, statins, \(\beta\)-blockers, angiotensin-converting enzyme inhibitors, and coronary stents, making it more difficult for any investigational therapy to demonstrate incremental value.

Prescription fish oil is usually formulated as ethyl ester, but a new formulation containing \(\omega-3\) carboxylic acids has been introduced.\textsuperscript{139} The EPA-only product apparently does not cause the LDL-C rise often seen when triglycerides decrease. The carboxylic acid formulation has better absorption and greater bioavailability than ethyl ester formulations.\textsuperscript{140-142} The clinical value of these properties is currently being evaluated in 2 large prospective randomized controlled outcomes trials—The Reduction of Cardiovascular Events With EPA-Intervention Trial (REDUCE-IT) and The Statin Residual Risk Reduction With Epanova in High CV Risk Patients With Hypertriglyceridemia study (STRENGTH). Importantly, both of these trials are enrolling subjects with triglyceride levels between 200 and 500 mg/dL. These studies will ultimately answer the question as to whether \(\omega-3\) PUFA reduce ASCVD outcomes.

Icosabutate is a synthetic EPA derivative in early clinical development. In mice, this agent lowered triglycerides by 68\%, primarily by increasing hepatic LDLR expression without impacting the LPL pathway.\textsuperscript{143} In a clinical study, icosabutate 600 mg versus placebo for 12 weeks in 87 subjects with median triglyceride levels of 650 mg/dL reduced triglycerides by 51\% versus baseline (33\% versus placebo).\textsuperscript{144} It also raised HDL-C and LDL-C (by 18\% and 28\%, respectively) without a significant change in apoB.

\textbf{ApoC-III Inhibition}

Several recent high profile studies have identified many genetic variants affecting metabolism of triglyceride-rich lipoproteins. Specifically, LOF mutations (resulting in reduced protein function) in \textit{APOC3} and gain-of-function mutations in \textit{APOA5} protect against atherosclerosis. Two recent studies demonstrated that LOF mutations in \textit{APOC3} are associated with reduced triglycerides (39\%–44\%) and risk of ASCVD (40\%–41\%).\textsuperscript{145,146} An earlier study linked LOF mutations in \textit{APOC3} to decreased burden of subclinical atherosclerosis.\textsuperscript{147} ApoC-III is an antagonist of LPL action, but its impact on triglyceride metabolism reaches beyond this canonical pathway, as it also reduces hepatic very low-density lipoprotein secretion and decreases uptake of apoB LPs by the liver.\textsuperscript{148} Consistent with this latter point, a recent study demonstrated the efficacy of antagonizing apo-CIII in patients with familial chylomicronemia (including subjects without functional LPL).\textsuperscript{149}

Recently, a second-generation ASO complementary to \textit{APOC3} mRNA has been developed and evaluated in a phase 2 randomized trial of 57 subjects with triglycerides 350 to 2000 mg/dL (mean, 581 mg/dL) administered once weekly as monotherapy.\textsuperscript{150} After 13 weeks, apoC-III inhibition caused 80\% reduction in plasma apoC-III levels, 71\% reduction in triglycerides (versus 20\% in the placebo group), and a 46\% increase in HDL-C. Similar findings were reported in a second cohort on stable background fibrate therapy. This compound is now being studied in a phase III trial (A Randomized, Double-Blind, Placebo-Controlled Phase 3 Study of ISIS 304801 Administered Subcutaneously to Patients With Hypertriglyceridemia [COMPASS]) enrolling participants with triglyceride levels >500 mg/dL.

\textbf{Therapies for Familial Chylomicronemia}

Lomitapide was developed and is approved for treatment of HoFH. In addition, the Food and Drug Administration granted lomitapide orphan drug designation for treatment of familial chylomicronemia. Recently, gene replacement therapy has become a treatment option for individuals with LPL deficiency.\textsuperscript{151} It is approved in Europe for adults with documented LPL deficiency and recurrent or severe pancreatitis despite conventional therapy. Diaicylglycerol acyltransferase 1 is an enzyme highly expressed in the small intestine that catalyzes the final committed step in triglyceride synthesis.\textsuperscript{152} Pradigastat is a selective inhibitor of diaicylglycerol acyltransferase 1 and as such decreases plasma triglycerides by reducing chylomicron secretion. It is being developed for the treatment of familial chylomicronemia.\textsuperscript{153} Its main side effect is diarrhea, which is dependent on both dose of drug and amount of fat in diet.

\textbf{Therapies Targeting Lp(a)}

Lipoprotein (a) (Lp(a)) is an enigmatic particle that consists of a molecule of apolipoprotein(a) (apo(a)), a nonfunctional
mimic of plasminogen, covalently bound to apoB on the LDL particle.\textsuperscript{154} Epidemiological and genetic data consistently suggest that Lp(a) is an independent risk factor for ASCVD.\textsuperscript{155–159} A Mendelian randomization analysis established that apo(a) is in the causal pathway of ASCVD.\textsuperscript{155} The atherogenicity of Lp(a) is likely multifactorial and related to both its LDL and apo(a) moieties and to its enriched concentration of oxidized phospholipids. Furthermore, given its similarity with a portion of plasminogen, Lp(a) may interfere with the fibrinolytic system and thereby facilitate atherothrombosis.\textsuperscript{160} Two recent trials, JUPITER (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin) and AIM-HIGH, demonstrated residual high risk associated with elevated Lp(a) despite achievement of target LDL-C during treatment.\textsuperscript{161,162}

Currently, there is no drug that selectively decrease Lp(a) and no evidence that lowering Lp(a) results in ASCVD risk reduction. In fact, no end point study has ever been performed in patients recruited on the basis of elevated Lp(a). Niacin, estrogens, mipomersen, lomitapide, PCSK9 inhibitors, and CETP inhibitors not only reduce Lp(a) levels but also modify other lipid and lipoprotein levels. Apheresis is used in high-risk individuals with very high levels of Lp(a), despite aggressive medical therapy. A recent prospective observational study of 170 subjects with elevated Lp(a) found that apheresis effectively lowers the incidence of ASCVD.\textsuperscript{163} The National Lipid Association and the European Atherosclerosis Society have issued guidelines that suggest statins to lower LDL-C and niacin to lower Lp(a) for patients with elevated Lp(a).\textsuperscript{164,165}

An ASO against apo(a) has recently been developed as a tool to reduce Lp(a) levels. In a recent double-blind phase I trial, 47 subjects with elevated Lp(a) (≥100 mg/L) were randomized to the ASO or placebo (3:1). In 31 participants who received 6 total injections over 4 weeks, there was a dose-related reduction in Lp(a) of ≤78% at the highest dose (300 mg) without changes in other lipoproteins.\textsuperscript{166} Efforts to enhance target delivery of ASOs have led to new technologies that facilitate conjugation of triantennary N-acetyl galactosamine to the ASO. Triantennary N-acetyl galactosamine binds to the asialo-glycoprotein receptor with high affinity. Asialoglycoprotein receptor is highly expressed on hepatocytes and allows for more efficient delivery of drug. A recent study demonstrated a near-10-fold increase in potency and increased duration of the pharmacological effect by leveraging this technology.\textsuperscript{167} The triantennary N-acetyl galactosamine–modified ASO targeted to Lp(a) is currently being examined in a phase I trial.

**Therapies Targeting Inflammation**

The majority of this review has focused on therapeutic targeting of lipids. This approach has seen tremendous successes and spectacular failures over the past decades, and as pointed out, new developments are poised to transform lipid management in the future. However, it is important to note that a substantial proportion of ASCVD events occur in individuals without overt hyperlipidemia. As such, attention has turned to other pathophysiological drivers of atherosclerosis beyond lipids. Because inflammation is intimately involved in all stages of atherosclerosis, interventions modulating systemic or local inflammatory responses have become attractive means to alter CVD risk.

Several lines of evidence ranging from experimental models to population studies support the notion that inflammation is a driver of atherosclerosis. From the epidemiological perspective, hs-CRP, a marker of subclinical inflammation, has repeatedly demonstrated its association with ASCVD outcomes, independent of traditional risk factors. More than 50 prospective primary prevention cohort studies have consistently demonstrated the risk associated with elevations in hs-CRP.\textsuperscript{168} In fact, hs-CRP predicts future ASCVD risk and do total cholesterol and HDL-C levels.\textsuperscript{169} Initial observations demonstrated that statin therapy is associated with a reduction in hs-CRP.\textsuperscript{170} Later studies extended this finding and established that in primary and secondary prevention trials with statins those that achieved both low LDL-C and low hs-CRP fared the best.\textsuperscript{171} In an intriguing post hoc analysis of AFCAPS/TexCAPS, investigators observed that statin therapy remained effective at mitigating risk in subjects with elevated hs-CRP but low LDL-C.\textsuperscript{172} This finding, in part, led to the development of a landmark study in primary prevention, the JUPITER trial.\textsuperscript{173} Subjects were enrolled on the basis of low LDL-C (below the median, <130 mg/dL) and elevated hs-CRP (above the median, ≥2 mg/dL) and did not qualify for statin therapy by guideline eligibility criteria. Individuals were randomized to either rosuvastatin 20 mg daily or placebo. The trial was terminated prematurely because of remarkable benefit (44% relative risk reduction in the composite outcome) in the rosvuastatin arm.\textsuperscript{174} Whether the benefit observed in JUPITER was because of lipid lowering, attenuation of inflammation or both processes is not known.

On the basis of data presented above, there has been intense interest in exploring specific anti-inflammatory therapies as a means to reduce residual vascular risk and offer an opportunity to directly test the inflammatory hypothesis of ASCVD. Anti-inflammatory therapies for ASCVD are conceived broadly in 2 categories: (1) those that target the central inflammatory signaling (IL-1–tumor necrosis factor–α–IL-6) pathway; and (2) those that target other pathways (eg, 5-lipoxygenase, phospholipase A\textsubscript{2}, and adhesion molecules). These agents have to date not proven to reduce ASCVD risk, but interest persists in anti-inflammatory therapies outside of the central pathway. P-selectin, found on endothelial cells and activated platelets, is instrumental in recruiting leukocytes into the subendothelial space. The SELECT-ACS (Effects of the P-Selectin Antagonist Inclacumab on Myocardial Damage after Percutaneous Coronary Intervention for Non-ST-Elevation Myocardial Infarction) phase II trial investigated the effects of an antibody to P-selectin (inclacumab) in 544 subjects presenting with non–ST-segment–elevation myocardial infarction.\textsuperscript{174} Participants who received the highest dose of inclacumab had reduced myocardial necrosis as demonstrated by a statistically significant 24% reduction in peak troponin. About the central pathway, observational and genetic epidemiology studies have consistently linked its biomarkers to ASCVD risk. Studies enrolling subjects with rheumatoid and psoriatic arthritis showed reduced vascular risk in participants who received therapies...
(methotrexate, etanercept, infliximab, and tocilizumab) targeted at the IL-1–tumor necrosis factor–α–IL-6 pathway. An additional pathway to enhanced local inflammation is present in atherosclerosis. Plaque cholesterol can crystallize and activate a multimolecular signaling complex known as nucleotide-binding leucine-rich repeat-containing pyrin receptor 3 inflammasome. Activation of the nucleotide-binding leucine-rich repeat-containing pyrin receptor inflammasome results in caspase-1–mediated production of IL-1β and ultimately IL6, which amplify the inflammatory cascade (Figure 3). The significance of this finding needs to be emphasized as it offers a mechanistic link between hypercholesterolemia and vascular inflammation. The importance of cholesterol crystals within foam cells extends beyond its ability to enhance inflammation. Crystalline cholesterol is also thought to induce plaque rupture by physical disruption of the fibrous cap as well.

Two cardiovascular outcomes trials are putting the inflammatory hypothesis of ASCVD to the test. The CANTOS (The Canakinumab Anti-Inflammatory Thrombosis Outcomes Study) trial has enrolled 10,200 participants with stable CAD with history of myocardial infarction and hs-CRP >2 mg/L. The subjects have been randomized to the standard of care with or without canakinumab, a human mAb targeted to IL-1β and shown to reduce measures of inflammation (hs-CRP, IL-6, and fibrinogen) without influencing lipids. The other trial, CIRT (Cardiovascular Inflammation Reduction Trial), is enrolling 7000 subjects with CAD and metabolic syndrome or diabetes mellitus to the standard of care with or without low-dose methotrexate. Both CANTOS and CIRT are designed as event-driven trials with the primary end point defined as the rate of major cardiovascular events. The results of these trials are anticipated in 2017 and 2018, respectively. Given the nature of the therapies being examined, careful attention must be paid to the competing risks associated with immunomodulation. Nonetheless, the results of these trials hold the potential to add a profoundly different and orthogonal dimension to ASCVD risk management in the future.

Conclusion
When the results of the 4S study ushered in the statin era, many prophesized the end of ASCVD as the most prominent killer of mankind. Although the statins have significantly reduced morbidity and mortality, CVD remains the leading cause of death worldwide. However, recent efforts have provided renewed optimism. Now there is evidence that nonstatin agents reduce event rates. In addition, Mendelian randomization data suggest that lower LDL caused by PCSK9 polymorphisms is associated with lower rates of ASCVD, and thus therapeutic gains are expected from the use of PCSK9 inhibitors. These findings significantly challenge the statin exceptionalism hypothesis and offer a realistic prospect for the development of novel-targeted pharmacotherapeutics to reduce ASCVD. Linking genetic insights to molecular pathways and mechanisms of drug action holds the potential to fulfill the promise of precision medicine for ASCVD risk reduction. We are at the dawn of a new era and the future is bright!

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