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Treating Coronary Artery Disease: Beyond Statins, Ezetimibe, and PCSK9 Inhibition

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Abstract

Statins, ezetimibe, and PCSK9 inhibitors are currently the standard of care for the prevention and treatment of coronary artery disease. Despite their widespread use, coronary artery disease remains the leading cause of death worldwide, a fact that pleads for the development of new protective therapies. In no small part due to advances in the field of human genetics, many new therapies targeting various lipid traits or inflammation have recently received approval from regulatory agencies such as the US Food and Drug Administration or fared favorably in clinical trials. This wave of new therapies promises to transform the care of patients at risk for life-threatening coronary events.

INTRODUCTION

Coronary artery disease (CAD) is the leading cause of death worldwide. No ethnicity, nation, or community is spared. After the age of 40, one in two men and one in three women suffer coronary events during their lifetimes (1)—even though millions of people take medications that have been established to prevent coronary events, namely statins, ezetimibe, and PCSK9 inhibitors. Indeed, in the United States, mortality from cardiovascular disease has begun to rise after decades of decline (2). Preventing even a fraction of the unaddressed events globally would reduce healthcare spending by the equivalent of billions of US dollars each year, and it would improve quality of life for many individuals who would otherwise suffer sequelae of CAD, such as heart failure and arrhythmias. New preventive agents will be indispensable in light of CAD emerging as the preeminent global health threat of the twenty-first century.

Encouragingly, in just the past couple of years, a variety of new therapies outnumbering the previous mainstays of preventive cardiology either have received strong validation in clinical trials or are undergoing trials that will read out in the near future. A common thread among many of these medications is that their success has been augured by human genetics—by the recognition that naturally occurring variants in key genes and pathways are linked to protection against CAD in the individuals fortunate enough to have inherited the variants.

STANDARD THERAPIES

Statins, the medications most commonly used to reduce low-density lipoprotein (LDL) cholesterol, are the recommended first-line therapy for CAD prevention in patients deemed to be at sufficiently high risk to warrant pharmacotherapy (3). In diverse randomized clinical trials with different statins at different dosages in patients with differing levels of CAD risk, statins have proven to substantially reduce the risk of cardiovascular events and, particularly in secondary prevention patients, cardiovascular mortality. All statins act as inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR), a key enzyme in the synthesis of cholesterol. Although statins were clinically validated and widely adopted before the modern era of human genetic research, it is noteworthy that naturally occurring human genetic variants in *HMGCR* that are associated with decreased LDL cholesterol are also associated with decreased CAD risk (4). This relationship provides a post hoc rationale for the use of statins in patients (not that cardiovascular practitioners would find any rationalization necessary in light of the ample preexisting clinical trial evidence). Notably, there is a genetic association between the same *HMGCR* variants and mildly increased risk of type 2 diabetes mellitus (4)—lending support to the equivocal clinical evidence that statins can increase the risk of diabetes. Thus, statins have proven to be a useful test case for the proposition that human genetics can predict the clinical efficacy and safety of medications targeting specific gene targets.

Ezetimibe provided an even more remarkable test case. Ezetimibe inhibits the Niemann-Pick C1-like 1 (NPC1L1) protein in the gastrointestinal tract, thereby reducing cholesterol absorption via the diet and modestly reducing blood LDL cholesterol levels. After its regulatory approval for patient use on the basis of its ability to reduce LDL cholesterol, ezetimibe incited controversy after early randomized clinical trials using CAD surrogates (rather than cardiovascular events) as endpoints suggested a lack of clinical efficacy. Years later, a large randomized controlled trial, IMPROVE-IT, finally unequivocally established ezetimibe's ability to reduce CAD risk (5). Mere days before the public announcement of the results of IMPROVE-IT, a human genetic study establishing an association between naturally occurring inactivating variants in *NPC1L1* and protection from CAD was published (6). Ezetimibe is now the widely accepted, recommended second-line therapy for CAD prevention after statins (3).

In contrast to the statins and ezetimibe, the inhibitors of PCSK9 (proprotein convertase subtilisin/kexin type 9) owe their existence to human genetic studies. Activating mutations in *PCSK9* were discovered in 2003 to be a cause of familial hypercholesterolemia (7); the PCSK9 protein was found to be preferentially produced in the liver and secreted into the bloodstream, where it antagonizes cellular LDL receptors. Soon thereafter, inactivating mutations in *PCSK9* were observed to have the effect of reducing blood LDL cholesterol levels (8). These same inactivating mutations were established to be highly protective against CAD, reducing the risk by up to 88% (9). Of note, the individuals who enjoyed this reduced CAD risk were carriers of just one inactivating mutation (in the two copies of *PCSK9*). The discovery of healthy individuals with two inactivating mutations—full knockout of PCSK9 function—with no serious adverse consequences argued for the safety of PCSK9 inhibition (10, 11). This observation energized a number of drug development programs with PCSK9 as the intended target. In 2015, only 12 years after the discovery of the gene, the first two PCSK9 inhibitors—the monoclonal antibodies evolocumab and alirocumab, which are administered via injections every few weeks—received regulatory approval for patient use (12). Each of the antibodies has proven to reduce cardiovascular events in randomized controlled trials—FOURIER and ODYSSEY OUTCOMES, respectively (13, 14)—and for that reason, both are now included in guidelines as third-line agents after statins and ezetimibe (3). Inclisiran, a small interfering RNA (siRNA) therapy that with a single administration can knock down hepatic *PCSK9* expression for at least six months, has proven its mettle in clinical trials as an LDL cholesterol–lowering agent (15, 16). Contingent on regulatory approval of the drug, it is anticipated that high-risk patients will receive inclisiran just two times per year.

ADDITIONAL LDL CHOLESTEROL–LOWERING DRUGS

Elevated LDL cholesterol is unequivocally a causal risk factor for CAD. Mutations in LDL cholesterol–related genes—*LDLR* (LDL receptor), *APOB* (apolipoprotein B), and *PCSK9*—that cause familial hypercholesterolemia also result in premature CAD, as early as childhood (7, 17, 18). Just as tellingly, common genetic variants that are associated with mildly altered blood LDL cholesterol levels are also associated with modified CAD risk. In a study with a cohort of more than 50,000 individuals with or without CAD, a genetic score incorporating 13 common variants associated with LDL cholesterol was calculated for all participants (19). Observational epidemiological studies predict that a one-standard-deviation increase in LDL cholesterol (≈35 mg/dL increase) should be associated with a 54% increase in CAD risk. A one-standard-deviation increase in LDL cholesterol caused by variance in the genetic score was actually associated with a 113% increase in CAD risk ($p = 2 \times 10^{-10}$).

Two LDL cholesterol–lowering medications, lomitapide and mipomersen, are intended for use in extreme cases, namely patients with homozygous familial hypercholesterolemia who have not adequately responded to standard therapies. Lomitapide is an inhibitor of microsomal triglyceride transfer protein (expressed by *MTTP*), which is involved in the assembly of nascent lipoproteins in hepatocytes. Lomitapide therefore reduces hepatic lipoprotein secretion and, in turn, blood LDL cholesterol levels (20). Naturally occurring inhibitory mutations in *MTTP* cause the recessive condition abetalipoproteinemia, which is marked not only by very low LDL cholesterol but also by a host of other problems including hepatosteatosis and steatorrhea (21). Not surprisingly, lomitapide can cause the same issues in patients, which limits its use to extreme cases. Mipomersen is an antisense oligonucleotide (ASO) drug that binds the *APOB* messenger RNA and thereby reduces expression of apolipoprotein B, the core protein of LDL particles. Like lomitapide, mipomersen interferes with the assembly and secretion of lipoproteins from hepatocytes and thereby reduces

LDL cholesterol (22). Inhibitory mutations in *APOB* cause familial hypobetalipoproteinemia (23), which in severe cases can present similarly to abetalipoproteinemia. Mipomersen, like lomitapide, must be used cautiously because of the risk of hepatosteatosis. Although neither drug has been proven formally to reduce the risk of CAD in patients with homozygous familial hypercholesterolemia, each drug received regulatory approval for use based on the logical premise that reduction of the very high LDL cholesterol levels in these patients should be of clinical benefit.

Bempedoic acid, another LDL cholesterol–lowering drug, recently received regulatory approval for clinical use in patients with familial hypercholesterolemia or established CAD who are already on maximally tolerated statin therapy and require additional LDL cholesterol reduction. It acts by inhibiting ATP citrate lyase (expressed by *ACLY*), which, like HMGCR, is a key enzyme in the synthesis of cholesterol; it catalyzes a reaction upstream of the one catalyzed by HMGCR. Bempedoic acid received regulatory approval on the basis of its ability to reduce LDL cholesterol in two clinical trials (24, 25), although the effect was modest compared to that of statins and there was increased risk of gout and tendon rupture. A human genetic study found that common variants surrounding *ACLY*, when aggregated, were associated with CAD risk (26), suggesting that pharmacological inhibition of ATP citrate lyase by bempedoic acid should reduce cardiovascular events. This hypothesis will be formally tested by an ongoing randomized controlled study, CLEAR Outcomes, that is expected to be completed in 2022.

MODIFYING LIPIDS BESIDES LDL CHOLESTEROL

Epidemiological analyses of other blood lipids besides LDL cholesterol—namely high-density lipoprotein (HDL) cholesterol, lipoprotein(a) [Lp(a)], and triglycerides—suggest some degree of association with CAD. The magnitude of the inverse association between HDL cholesterol and CAD risk is comparable to that of the direct association between LDL cholesterol and CAD risk (27). Nonetheless, human genetics suggests that the link between HDL cholesterol and CAD is not a causal one. In a study with a cohort of more than 50,000 individuals with or without CAD, a genetic score incorporating 14 common variants associated with HDL cholesterol was calculated for all participants (19). Observational epidemiological studies predict that a one-standard-deviation increase in HDL cholesterol (≈15 mg/dL increase) should be associated with a 38% decrease in CAD risk. Yet a one-standard-deviation increase in HDL cholesterol caused by variance in the genetic score was not significantly associated with a change in CAD risk (7% decrease, $p = 0.63$). This observation suggests that most if not all interventions that specifically increase HDL cholesterol alone would not favorably modify CAD risk. Consistent with this conclusion, the best-studied HDL cholesterol–raising medications have largely proved futile in reducing cardiovascular events in randomized controlled trials.

The AIM-HIGH and HPS2-THRIVE trials showed no benefit for extended-release niacin or for a combination of extended-release niacin and laropiprant (the latter agent added to mitigate side effects of high-dose niacin), respectively (28, 29). Three inhibitors of cholesteryl ester transfer protein (CETP)—torcetrapib, dalcetrapib, and evacetrapib—all raise HDL cholesterol substantially, in some patients more than doubling the blood levels, but their respective trials—ILLUMINATE, dal-OUTCOMES, and ACCELERATE (30–32)—all were stopped early for futility. A fourth CETP inhibitor, anacetrapib, did show a small (9%) reduction of coronary events in the HPS3/TIMI55–REVEAL trial (33), but anacetrapib is distinct from the other CETP inhibitors in that along with its HDL cholesterol–raising effect, it also modestly reduces blood LDL cholesterol levels. Accordingly, the observed protective effect of anacetrapib has been attributed to altered levels of LDL cholesterol, not HDL cholesterol. These results (28–33) have effectively ruled out CETP inhibitors as a practical means for CAD risk reduction in patients.

Lp(a) is an LDL-like particle that is covalently linked to the protein apolipoprotein(a), expressed by *LPA*. The blood Lp(a) level is notable in that it varies up to 1,000-fold among individuals, with most of the variability due to genetic variation in *LPA*, in particular a highly variable number of kringle IV domains (ranging from 3 to >40) encoded in the gene (34). Observational epidemiological studies have shown blood Lp(a) levels to be directly associated with CAD risk, with disproportionate risk arising at the high extreme of Lp(a) levels (35). Genetic studies with variants in *LPA* have established that genetically elevated Lp(a) results in increased risk of CAD (36, 37), arguing for Lp(a) being a causal risk factor independently of LDL cholesterol. This observation has motivated the development of an ASO drug to bind the *LPA* messenger RNA and reduce expression of apolipoprotein(a), thereby knocking down the blood Lp(a) level. In randomized controlled studies, the drug has proven to be effective at reducing Lp(a) in healthy volunteers and in CAD patients with elevated Lp(a) levels, with up to 80% reduction observed with weekly injections (38, 39). Whether the drug will prove effective at reducing CAD risk in patients remains to be seen; the placebo-controlled Lp(a)HORIZON trial has begun enrolling CAD patients with elevated Lp(a) levels and is expected to reach completion with an assessment of cardiovascular events in 2024.

Triglycerides appear to have a more complicated relationship with CAD. Human genetic studies to assess for a causal link between blood triglyceride levels and CAD risk are confounded by pleiotropy, i.e., most common variants that are associated with triglycerides are also associated with other traits such as HDL cholesterol level. One study attempted to rigorously address this issue by employing a genetic score arrived at by a statistical framework in which the triglyceride-associated effects of variants on CAD risk were separated from the LDL and HDL cholesterol–associated effects of the variants (40). A one-standard-deviation increase in triglycerides caused by variance in genetic score was associated with a 54% increase in CAD risk ($p = 1 \times 10^{-8}$). This finding suggests that there are at least some mechanisms of triglyceride reduction that would protect against CAD. The results of randomized controlled studies of triglyceride-lowering agents have been mixed. As already noted, the AIM-HIGH and HPS2-THRIVE trials with niacin—which not only increases HDL cholesterol levels but also reduces triglyceride levels—were negative (28, 29). So too was the ACCORD-Lipid trial, which tested the clinical efficacy of fenofibrate, a fibrate drug commonly used to treat hypertriglyceridemia (41).

Purified fish oil preparations, i.e., omega-3 fatty acids, are also used for the reduction of high triglyceride levels. Most randomized controlled studies of omega-3 fatty acids, including the recent large trials ASCEND, VITAL, and STRENGTH (42–44), found no reduction of CAD risk (STRENGTH was stopped early for futility). These three trials evaluated a combination of eicosapentaenoic acid (EPA) and docosahexaenoic acid. In contrast, the REDUCE-IT trial tested a high-dose preparation of EPA only (2 g twice daily) and had a remarkably positive result—a 25% reduction of cardiovascular events in CAD patients with elevated triglycerides as well as a commensurate reduction of cardiovascular mortality, albeit with increased risk of atrial fibrillation or flutter requiring hospitalization and increased risk of bleeding (45). The mechanism(s) by which EPA produced the clinical benefit is unclear. Although the patients receiving EPA did have reduced blood triglyceride levels compared to the control group, the magnitude of the change was relatively small (14%). Extrapolating from observational epidemiological studies, that level of triglyceride reduction should not have singlehandedly produced the large reduction of cardiovascular events observed with EPA. Moreover, patients experienced the clinical benefit regardless of the triglyceride level achieved. These observations suggest that EPA might work through pleiotropic mechanisms that remain to be defined. As such, it is difficult to regard REDUCE-IT as a strong endorsement of the virtue of pharmacologically reducing triglyceride levels. Nonetheless, the efficacy of the tested high-dose preparation of EPA has resulted in the drug being incorporated into

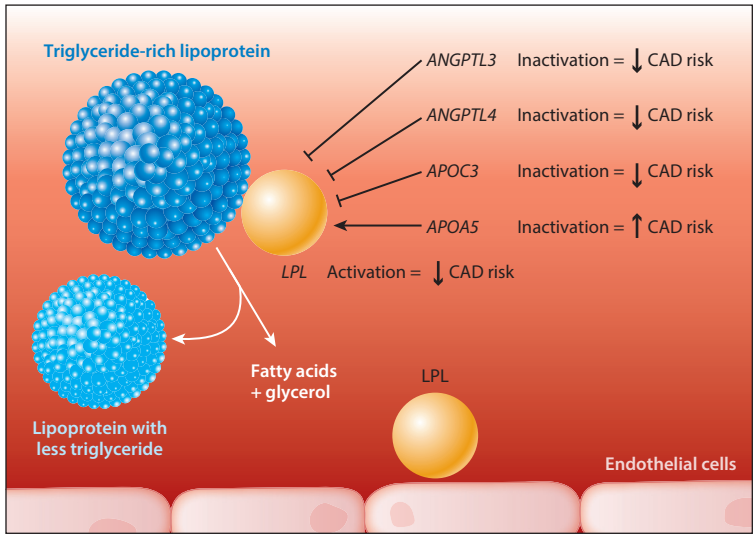

Figure 1

The lipoprotein lipase (LPL) pathway. LPL proteins tethered to endothelial cells in blood vessels engage with triglyceride-rich lipoproteins in the bloodstream, where they catalyze triglycerides within the particles and mobilize the breakdown products into the blood. Naturally occurring mutations in various genes with protein products in this pathway modify the risk of coronary artery disease (CAD), highlighting the importance of triglyceride-rich lipoproteins for the pathogenesis of disease.

the latest clinical guidelines as an option for CAD risk reduction in high-risk patients who are already on maximally tolerated statin therapy and have elevated triglycerides (46, 47).

Human genetic studies of individual genes have suggested that it is triglyceride-rich lipoproteins (TRLs), rather than the triglycerides carried by the particles in the blood, that are causally linked to CAD risk. Genetic association analyses have convincingly linked variants in at least seven genes that regulate blood triglyceride levels to CAD risk—*LPL* (lipoprotein lipase), *APOA5* (apolipoprotein A-V), *APOA4* (apolipoprotein A-IV), *APOC3* (apolipoprotein C-III), *ANGPTL4* (angiopoietin-like 4), *ANGPTL3* (angiopoietin-like 3), and *TRIB1* (tribbles-1) (19, 48–57). Five of the genes in this list are part of the same pathway, either encoding LPL or encoding direct regulators of LPL, a key enzyme that hydrolyzes triglycerides in various TRLs (**Figure 1**). Inactivating mutations in *LPL* increase both blood triglyceride levels and CAD risk, whereas activating mutations in *LPL* have the opposite effects (48). Inactivating mutations in *APOA5*, which encodes an activator of *LPL*, increase triglycerides and CAD risk (49–51). Conversely, as described in more detail below, inactivating mutations in *APOC3*, *ANGPTL4*, or *ANGPTL3*, which all encode inhibitors of LPL, decrease triglycerides and CAD risk. These genetic observations represent strong evidence that therapies that act upon any of these members of the LPL pathway should modify CAD risk. As such, all five genes represent potential targets for CAD prevention. Of note, neither niacin nor fibrates specifically target the LPL pathway, possibly accounting for the lack of clinical efficacy of these triglyceride-lowering agents in clinical trials.

APOC3 is a gene specific in its expression to the liver and small intestine. Its protein product, apolipoprotein C-III, is carried by TRLs and serves to inhibit hydrolysis of the particles' triglycerides by LPL, thereby boosting blood triglyceride levels. A human genetic study in an Old Order Amish cohort identified an inhibitory mutation as being linked to decreased triglycerides as well as decreased coronary artery calcification (52). Subsequent studies found that individuals with a

single inhibitory mutation in *APOC3* had a 35–40% reduction in CAD risk (53, 54). Remarkably, an entire Pakistani family (two parents, nine children) with homozygosity for a nonsense mutation in *APOC3* was identified; the family members were healthy, had reduced triglycerides and increased HDL cholesterol, on physiological testing displayed marked blunting of the rise in triglyceride levels normally experienced after an oral fat load, and had no apparent adverse effects (58). The favorable phenotypes of the family members recommended *APOC3* as a target for novel therapies.

Volanesorsen, an ASO drug that silences *APOC3* in its primary site of expression, hepatocytes, was observed in clinical trials to substantially reduce blood triglyceride levels in patients with hypertriglyceridemia (59, 60). A substantial proportion of the study participants also displayed thrombocytopenia, halting the drug's further development as a therapeutic for CAD prevention, although it is approved in Europe for use in patients with familial chylomicronemia syndrome. A more potent next-generation ASO drug that inhibits *APOC3* is now undergoing assessment in clinical trials and, if its safety is established, may ultimately prove to have value for patients at high risk for CAD. An siRNA drug against hepatic *APOC3* and a monoclonal antibody against apolipoprotein C-III are also in development.

ANGPTL4 is highly expressed in the liver and is also expressed in a variety of other tissues, including adipose, pancreas, intestine, and brain. The ANGPTL4 protein is secreted into the bloodstream, where it inhibits LPL and increases triglyceride levels. Human genetic studies have shown that inhibitory mutations in *ANGPTL4* protect against CAD as well as type 2 diabetes mellitus, suggesting it as a therapeutic target (48, 55). A monoclonal antibody against ANGPTL4 substantially reduced blood triglyceride levels in mice and monkeys (55); however, abdominal lymphadenopathy from lipid accumulation was observed in both animal models, militating against further development of the antibody or other ANGPTL4 inhibitors as human therapeutics.

Of the three aforementioned genes encoding LPL inhibitors, it is perhaps *ANGPTL3* that holds the most therapeutic potential for the prevention of CAD. Although it shares structural and functional features with *ANGPTL4*, *ANGPTL3* has distinctive properties that make its inhibition an attractive alternative to *PCSK9* inhibition. *ANGPTL3* originally was discovered as a liver-specific gene that, when mutated, was responsible for the hypolipidemic phenotype of a mouse strain with abnormally low triglyceride and total cholesterol levels (61). Independently, *ANGPTL3* was discovered to be the cause of a recessive condition in humans called familial combined hypolipidemia, marked by very low levels of LDL cholesterol, HDL cholesterol, and triglycerides (62). The first individuals recognized to have this condition were four siblings of a single family who each harbored two different nonsense mutations in the first exon of *ANGPTL3*, effectively making them natural knockouts for the gene—notable because the siblings were free of CAD, had no apparent adverse consequences of gene knockout, and had healthy children (56, 62). Subsequent work showed that individuals carrying just one inhibitory *ANGPTL3* mutation enjoyed a 35–40% reduction of CAD risk (56, 57).

The ANGPTL3 protein is expressed in hepatocytes and secreted into the bloodstream, where it inhibits LPL and thereby increases triglycerides. The mechanism(s) by which ANGPTL3 increases blood LDL cholesterol levels remains unclear but appears to be independent of the LDL receptor. The unique potential of ANGPTL3 inhibitors to safely block two orthogonal axes of CAD risk—LDL cholesterol and TRLs—has stimulated intensive efforts to develop such inhibitors. A monoclonal antibody, evinacumab, has proven effective in reducing both LDL cholesterol and triglycerides in healthy volunteers as well as patients with familial hypercholesterolemia (57, 63). Indeed, unlike PCSK9 inhibitors—which have limited LDL cholesterol–lowering effects in homozygous familial hypercholesterolemia patients, especially those who lack LDL receptor altogether (PCSK9 being an antagonist of LDL receptor)—evinacumab is just as potent at LDL

cholesterol reduction in homozygous familial hypercholesterolemia patients as in other individuals (63). The fact that *ANGPTL3* is predominantly expressed in hepatocytes makes it amenable to therapeutic approaches that preferentially target the liver. An ASO drug targeting the *ANGPTL3* messenger RNA in hepatocytes has been demonstrated to reduce LDL cholesterol and triglycerides in healthy volunteers (64). An siRNA targeting *ANGPTL3* in hepatocytes appears to have similar effects. Thus, three distinct drugs that inhibit *ANGPTL3* function might eventually be available as options for CAD risk reduction, either as therapy that is additive to standard therapies for high-risk patients or as primary therapy for severe familial hypercholesterolemia patients who poorly respond to PCSK9 inhibitors.

MODIFYING INFLAMMATORY PATHWAYS

Besides blood lipids, the other axis of CAD risk that has been explored extensively for therapeutic potential is inflammation. Observational epidemiological studies have established markers of inflammation, most notably C-reactive protein (CRP), as being associated with CAD risk. Indeed, the strength of association of the blood CRP level, measured by a high-sensitivity CRP assay, with CAD rivals that of LDL cholesterol with CAD (65). Nonetheless, multiple well-powered human genetic studies have found that genetic variants in the *CRP* locus are not associated with CAD risk (66, 67). These results indicate that CRP itself is not a causal risk factor for CAD, paralleling findings with HDL cholesterol. These observations suggest that not all interventions that decrease inflammation would favorably modify CAD risk, but they do not rule out that certain specific inflammatory pathways are causal for CAD.

A host of randomized controlled studies assessing whether anti-inflammatory agents can reduce cardiovascular events were negative. Most notably, the CIRT trial tested low-dose methotrexate for general suppression of inflammation in high-risk patients with stable CAD and found no difference in cardiovascular outcomes (68). The SOLID-TIMI 52 trial assessed darapladib, an inhibitor of lipoprotein-associated phospholipase A2 (Lp-PLA2), in patients following acute coronary syndromes and found no reduction in coronary events (69). The LATITUDE-TIMI 60 trial evaluated losmapimod, an inhibitor of p38 mitogen-activated protein kinase (MAPK)-stimulated inflammation, and found no change in cardiovascular risk (70).

In contrast, a randomized controlled study testing the effect of inhibition of the interleukin-1β/interleukin-6 (IL-1β/IL-6) inflammatory pathway was positive. Unlike other inflammatory mechanisms, there is genetic evidence for this pathway being causal for CAD; multiple human genetic studies have demonstrated variants in the IL-6 receptor locus, *IL6R*, to be associated with CAD risk (71, 72). In the CANTOS trial, patients with stable CAD and elevated high-sensitivity CRP levels were randomized to various doses of canakinumab, a monoclonal antibody targeting IL-1β, or placebo (73). With canakinumab, there was a dose-dependent reduction of high-sensitivity CRP levels without any significant change in various blood lipid levels. At the highest doses of canakinumab, there were 14–15% reductions in incident cardiovascular events. There was higher incidence of fatal infection with canakinumab, but there was also lower cancer mortality, balancing out to no difference in all-cause mortality. While it is unclear whether canakinumab will ever be promoted as an agent for CAD risk reduction, due to the expense of the medication, the CANTOS trial did provide a strong validation for the concept that non-lipid-based interventions can be beneficial for patients, as can judiciously targeted anti-inflammatory interventions.

More recently, the randomized controlled trial COLCOT tested the anti-inflammatory drug colchicine, commonly used for the treatment of pericarditis and gout, in patients after myocardial infarction (74). Colchicine conferred a 23% reduction in cardiovascular events, although there were no significant reductions in individual endpoints such as recurrent myocardial infarction or

cardiovascular mortality. Because colchicine is an old drug that is inexpensive in many countries, the potential for its adoption as a secondary prevention drug is intriguing. Additional trials showing a clear CAD benefit will likely be required before colchicine is included as a recommended CAD therapy in clinical guidelines.

OUTLOOK

After years during which statins, ezetimibe, and PCSK9 inhibitors were the only available proven effective therapies for the prevention and treatment of CAD, we are now witnessing progress on a number of fronts—additional LDL cholesterol–lowering drugs, drugs that modify other causal lipid traits, and anti-inflammatory drugs. A common theme undergirding many of the new drugs is strong support from human genetics, with genetic studies nominating or validating target genes and pathways. An important consequence is that therapies can now be tailored specifically to those genes and pathways, in contrast to the traditional approach of screening large libraries of small molecules for therapeutic activity. Many of the new drugs are biologics, whether monoclonal antibodies, ASOs, or siRNAs. While these drugs have advantages with respect to efficacy, safety, and specificity, they all have limited half-lives and require frequent injections for the remainder of the patient's lifetime. The future will undoubtedly see the development of gene therapies and genome-editing therapies that with a single administration can protect patients from CAD in perpetuity—one-and-done preventives, conceptually akin to vaccinations (75). Such options will be invaluable in tackling the preeminent global health threat of the twenty-first century.

DISCLOSURE STATEMENT

The author is a cofounder and advisor of Verve Therapeutics and an advisor of Variant Bio and currently holds equity in both companies.

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