Highlighting Residual Atherosclerotic Cardiovascular Disease Risk

Yunosuke Matsuura, Jenny E. Kanter, Karin E. Bornfeldt

Precision medicine is increasingly moving health care from a conventional one-size-fits-all approach toward a personalized medicine strategy. For example, patients with certain types of cancer can now make treatment choices based not only on the tumor's histological type but also on tissue expression of targeted proteins and specific gene mutations. Precision medicine has made less progress in atherosclerotic cardiovascular disease (ASCVD). What will be necessary for us to achieve effective precision medicine in patients with ASCVD? Since the landmark Scandinavian Simvastatin Survival Study demonstrated a beneficial effect of statin treatment on recurrent cardiovascular events in patients with overt hyperlipidemia,[1] many subsequent studies on primary and secondary prevention have demonstrated favorable effects of LDL (low-density lipoprotein) cholesterol (LDL-C)–lowering therapies on ASCVD outcomes.[2–5] These beneficial effects of statins are now known to extend to patients without clear dyslipidemia or preexisting cardiovascular disease. However, many statin-treated patients remain at a significantly elevated risk of having a major cardiovascular event that is unresolved, despite statin treatment. This is commonly referred to as residual risk.

The American College of Cardiology and American Heart Association recently published the 2018 clinical practice guidelines for management of blood cholesterol.[6] The guidelines suggest that the more LDL-C is reduced, the greater will be the ASCVD risk reduction. The guidelines stratify patients based on LDL-C levels, history of ASCVD events, conventional risk factors (such as diabetes mellitus) and risk-enhancing factors (such as metabolic syndrome or chronic inflammatory conditions) and recommend treatment options/intensity of treatment based on each stratum for primary and secondary ASCVD prevention. Even with more stringent treatment strategies going forward, there are several important questions to be addressed, including (1) whether optimal LDL-C control varies from person to person rather than according to overall clinical subgroup; (2) whether residual ASCVD risk could be prevented by even more aggressive LDL-C lowering using more stringent statin regimens or additional LDL-C–lowering strategies, such as inhibitors of PCSK9 (proprotein convertase subtilisin/kexin type 9),[7] which has some effects distinct from those of statins on non–LDL-C risk factors[8,9]; and (3) to what extent non–LDL-C risk factors explain the residual risk.

Type 2 diabetes mellitus is associated with dyslipidemia characterized by a number of abnormalities that have collectively been referred to as the atherogenic dyslipidemia complex[10] and are believed to contribute to residual risk in these patients. Thus, high prevalence of ASCVD can be observed in type 2 diabetic patients with elevated levels of plasma triglycerides and low levels of HDL (high-density lipoprotein) cholesterol (HDL-C) and levels of glycated hemoglobin outside the target range of 7%.[11,12] A large study on >270 000 patients with type 2 diabetes mellitus included in the Swedish National Diabetes Register indicated that when glycated hemoglobin, LDL-C, albuminuria, blood pressure, and smoking are all within the target range, these patients have no residual risk of myocardial infarction (MI), as compared with the general population.[12] This suggests that well-controlled diabetes mellitus per se does not increase residual risk as long as LDL-C and the other assessed risk factors are well controlled.

Conversely, genome-wide association studies, Mendelian randomization studies, and studies on humans with loss-of-function mutations in identified genes have made it abundantly clear that variations in genes not only related to LDL-C (eg, *PCSK9*, *SORT1*, and *APOB*) but also related to triglycerides (eg, *APOC3*, *LPL*, and *ANGPTL3*) and inflammation (eg, *CXCL12* and *IL6R*) associate with ASCVD risk.[13,14] Residual risk is, therefore, likely to be higher in certain populations of patients with genetic risk and patients who for other reasons have elevated triglycerides, low HDL-C, or increased inflammation.

In this *ATVB* highlights article, we will review recent articles published in *ATVB* related to residual risk in cardiovascular disease and put this research into a wider context. We will focus primarily on TRLs (triglyceride-rich lipoproteins) and their remnants, HDL, Lp(a) (lipoprotein[a]), and inflammation as residual risk factors. Increased understanding of the contributions of those residual risk factors in different patient populations will move the field closer toward more effective precision medicine approaches to prevent ASCVD events.

TRLs and Their Remnants

Treatment strategies to improve triglyceride clearance or reduce triglyceride production, especially in patients with type 2 diabetes mellitus, have become a central topic in the debate over residual risk of ASCVD. Blood concentrations of triglycerides are generally considered to reflect atherogenic lipoproteins, such as TRLs and their remnants. TRLs are converted into their remnants primarily by LPL, and subsequently, these smaller apoB (apolipoprotein B)-containing

From the Department of Medicine (Y.M., J.E.K., K.E.B.) and Department of Pathology (K.E.B.), University of Washington Medicine Diabetes Institute, University of Washington School of Medicine, Seattle.

Correspondence to Karin Bornfeldt, PhD, University of Washington Medicine Diabetes Institute, University of Washington School of Medicine, 750 Republican St, Seattle, WA 98109. Email bornf@uw.edu

(*Arterioscler Thromb Vasc Biol*. 2019;39:e1-e9.
DOI: 10.1161/ATVBAHA.118.311999.)

© 2018 American Heart Association, Inc.

Arterioscler Thromb Vasc Biol is available at https://www.ahajournals.org/journal/atvb

DOI: 10.1161/ATVBAHA.118.311999

Downloaded from http://ahajournals.org by on February 20, 2019

lipoprotein remnant particles can penetrate and accumulate in the subendothelial arterial space and induce local and systemic atherogenic responses. Thus, patients with familial dysbetalipoproteinemia (also known as type III hyperlipoproteinemia or remnant removal disease) exhibit markedly accelerated atherosclerosis, despite LDL-C levels being in the normal range.[15] These patients exhibit elevated remnants primarily because of mutations in the *APOE* (apolipoprotein E) gene, which prevent effective hepatic clearance of the apoE-containing TRLs. Furthermore, increased arterial inflammation, measured as increased arterial 18F-fluorodeoxyglucose uptake, can be seen in patients with familial dysbetalipoproteinemia.[16] Increased 18F-fluorodeoxyglucose uptake is closely associated with inflammatory activation of macrophages,[17] suggesting that remnants cause increased activation of lesional macrophages. The elevated remnant levels result in increased lipid accumulation in circulating monocytes and increased expression of adhesion molecules in these cells, as well as monocytosis,[15] which would all be predicted to increase macrophage accumulation in lesions of atherosclerosis. Thus, a marked increase in remnants results in atherogenic effects both systemically and locally.

In patients without known genetic conditions affecting TRL remnant clearance, the role of remnants in ASCVD is more difficult to assess, in part, because remnants are poorly defined and are difficult to measure. One common method of assessing remnant levels is to subtract LDL-C and HDL-C from total cholesterol levels. This method is inexact, especially at high triglyceride levels. Measurements of plasma triglyceride levels, often used as a surrogate of TRLs and remnants, are also an approximation because fasting concentrations of plasma triglycerides correspond to the sum of triglyceride content in nascent VLDL (very low-density lipoprotein) and remnants. Nevertheless, fasting triglyceride levels can predict long-term and short-term cardiovascular risk in patients with acute coronary syndrome who are treated effectively with statins,[18] suggesting that elevated fasting triglycerides, directly or indirectly, contribute to residual risk. Triglyceride content in plasma increases in the postprandial state because of the presence of triglyceride-rich chylomicrons and their remnants.[19] Nonfasting triglycerides are also associated with increased risk of ischemic heart disease and MI[20] and with a stepwise higher risk of heart failure.[21] Therefore, in some patients, it is recommended to assess both nonfasting and fasting lipid profiles.[22]

A recent article in *ATVB* highlights the importance of postprandial triglyceride clearance in atherosclerosis in humans. Kurihara et al[23] used optical coherence tomography to visualize high-risk atherosclerotic lesions, defined as thin-cap fibroatheroma, and the association with postprandial dyslipidemia after a meal tolerance test in 30 patients with stable coronary artery disease. They demonstrated that thin-cap fibroatheromas are associated with increased levels of remnants after the meal tolerance test, and with elevated baseline apoC-III (apolipoprotein C-III) levels, suggesting baseline abnormalities in TRL clearance in patients with high-risk lesions. In another *ATVB* article, insulin treatment of diabetic mice was shown to reduce plasma triglycerides and cholesterol and to increase LPL (lipoprotein lipase) activity concomitant with a reduction in atherosclerosis.[24] LPL hydrolyzes triglycerides and promotes uptake of fatty acids into tissues, thereby lowering plasma triglyceride levels. Interestingly, blood glucose lowering by an SGLT2 (sodium-glucose cotransporter-2) inhibitor had no such effects, suggesting that in diabetes mellitus, lipids are more important than glucose in promoting atherosclerosis,[25] at least in this mouse model.

Do abnormalities in triglyceride metabolism causally associate with ASCVD? A number of clinical trials evaluating the effect of triglyceride-lowering therapies on ASCVD have yielded variable results.[26–28] The conflicting results between trials can be interpreted in several ways: (1) niacin, fish oils, and fibrates tested have multiple effects, including effects unrelated to triglyceride-lowering; (2) the dose setting or formulations of triglyceride-lowering drugs might have been insufficient to show a beneficial effect on ASCVD; (3) the most relevant patient populations might not have been targeted by these clinical trials; and (4) plasma triglycerides are regulated by a number of different genes and mechanisms. The recently published REDUCE-IT trial (Reduction of Cardiovascular Events With Icosapent Ethyl-Intervention Trial) tested the effect of icosapent ethyl (a pure and stable eicosapentaenoic acid ethyl ester; 4 g daily dose) in statin-treated high-risk ASCVD patients with baseline fasting plasma triglyceride levels ranging from 135 to 499 mg/dL. After a median study period of 5 years, the results showed a 25% reduction in the primary composite end points, including coronary revascularization or unstable angina, and a 26% reduction in the secondary end points composed of cardiovascular death, MI, and stroke.[29] The icosapent ethyl treatment resulted in an 18% reduction in plasma triglycerides during the first year of the study. These results are similar to those of JELIS (Japan Eicosapentaenoic Acid Lipid Intervention Study), which also demonstrated a beneficial effect of eicosapentaenoic acid on ASCVD events in statin-treated subjects.[30] To what extent the beneficial effects of eicosapentaenoic acid ethyl ester on ASCVD are because of triglyceride lowering needs further study. Thus, it remains unclear whether triglyceride lowering is effective in preventing ASCVD in patients with residual risk. Several additional trials are under way that will aid our understanding of the roles of TRLs in ASCVD risk.[28]

On the contrary, recent Mendelian randomization studies strongly support the causal relationship between genes involved in triglyceride metabolism and coronary heart disease.[31] Genetic and genomic studies have revealed that genes involved in triglyceride clearance, including *APOC3*,[32–34] *APOA5*,[35] *ANGPTL3*,[36] and *LPL*,[37] strongly associate with cardiovascular disease risk. Indeed, plasma apoC-III levels associate with high-risk coronary plaques[23] and the risk of ASCVD.[38] Consistently, the low risk of cardiovascular disease in patients with *APOC3* loss-of-function mutations is considered to be mainly mediated by the associated low remnant cholesterol and not by the low level of LDL-C.[34] Also, apoC-III is involved in the formation of small dense LDL[39,40]—another cardiovascular risk factor; therefore, its inhibition can potentially modify the proatherogenic properties of LDL in addition to increasing triglyceride clearance. New strategies, such as inhibition of APOC3 or ANGPTL3 (angiopoietin-like 3; which inhibits LPL), might prove to be effective therapeutic options to increase triglyceride clearance and reduce residual risk of ASCVD.[28]

Downloaded from http://ahajournals.org by on February 20, 2019

Mechanisms whereby TRL remnants or genes that impair remnant removal promote major ASCVD events are still poorly understood but are believed to include increased trapping of remnants in the artery wall, increased remnant uptake by lesional macrophages, inflammatory and proapoptotic effects on lesional cells, and procoagulant effects.[41]

HDL

Low levels of HDL-C are often associated with elevated triglycerides and are a clinical hallmark in patients with metabolic syndrome or type 2 diabetes mellitus. Reduced levels of HDL-C can also be observed in other populations. For example, a recent publication in *ATVB* demonstrated that HDL-C levels are reduced by environmental factors, such as traffic-related pollution.[42] A large number of epidemiological studies have consistently shown a strong inverse correlation between HDL-C and the incidence of cardiovascular events; therefore, therapies to increase the level of HDL-C have been extensively tested as a strategy to reduce cardiovascular events, particularly in patients with type 2 diabetes mellitus.[43]

HDL is a heterogeneous population of particles with sizes ranging from 7 to 14 nm that collectively contain >80 different proteins and can be divided into partly distinct subpopulations characterized by different protein composition, which may have different functions.[44] We know now that small HDL particles are the most effective in removing cholesterol from cells through the cholesterol transport protein ABCA1 (ATP-binding cassette transporter A1),[45] whereas large HDL contains the most cholesterol.[43] A recent article published in *ATVB* demonstrated that the function of both small HDL (preβ-1 HDL) and large HDL (α-1+α-2 HDL) is altered in patients with coronary artery disease.[46] Therefore, treatment strategies that increase levels of HDL-C would not necessarily be predicted to increase the atheroprotective cholesterol efflux capacity of HDL. Strategies to boost the atheroprotective function of HDL particles might prove to be more effective.

To date, the main strategy for increasing HDL has focused on increasing HDL-C levels by inhibition of CETP (cholesteryl ester transfer protein). Because CETP transfers triglycerides from VLDL and other lipoproteins to HDL in exchange for cholesteryl esters, its inhibition results in increased levels of cholesteryl esters in HDL in humans.[47] Consistently, a recent study published in *ATVB* used a new rabbit CETP knockout model to demonstrate that CETP deficiency results in elevated HDL-C levels, increased cholesterol efflux capacity of apoB-depleted plasma, markedly reduced levels of VLDL, and protection against cholesterol diet-induced atherosclerosis.[48] Another study found that pharmacological inhibition of CETP activity reduces in-stent restenosis via inhibition of vascular smooth muscle cell proliferation,[49] suggesting that CETP inhibition may be a potential strategy to protect against ASCVD and related vascular damage. Whereas these animal models show beneficial effects of loss of CETP, human studies are less conclusive. Three clinical trials using different types of CETP inhibitors failed to demonstrate a beneficial effect on cardiovascular outcomes, despite showing increased HDL-C levels.[50] A recent Mendelian randomization study[51] found that a common variation in the *CETP* gene reduced the risk of MI; however, this gene variant was also associated with a decreased level of LDL-C coupled with the increased level of HDL-C. Recently, the REVEAL trial (Randomized Evaluation of the Effects of Anacetrapib Through Lipid Modification) demonstrated that CETP inhibition by anacetrapib reduced coronary artery disease events; however, this agent not only increased the HDL-C level but also reduced the LDL-C level,[52] similar to the findings observed in the above Mendelian randomization study. Taking these results together, we still cannot conclude that a low level of HDL-C is a causal risk factor of ASCVD because we are unable to exclude the effect of LDL-C lowering by CETP inhibition on the positive results.

Another approach to raise HDL-C is to increase levels of apoA-I (apolipoprotein A-I)—the main structural protein of HDL.[53] To date, several interventional approaches targeting apoA-I have been developed,[54,55] and a few of them revealed beneficial effects against atherosclerosis in humans,[56] but none of these strategies have resulted in clinical use. A recent article published in *ATVB* demonstrated that apoA-I vascular gene therapy targeting endothelial cells shows a protective effect against atherosclerosis in hyperlipidemic rabbits,[57] suggesting that increased apoA-I expression in the endothelium is atheroprotective. In addition, apoA-I mimetic peptides have been continuously developed in parallel with the investigation of its functionality in vivo.[58]

EL (endothelial lipase; gene name, *LIPG*) determines HDL-C levels by hydrolyzing HDL phospholipids, and mice deficient in EL exhibit a marked increase in fasting HDL-C and increased numbers of HDL particles.[59] Consistently, *LIPG* gene variants have been shown to be associated with increased plasma HDL-C in humans.[60,61] However, the effect of EL on atherogenesis is controversial.[62,63] Recent studies published in *ATVB* examined rabbit and mice overexpressing human EL in the liver. In the rabbit model, HDL-C levels and atherosclerotic lesions were reduced by EL overexpression.[64] In the mouse model, HDL levels were similarly reduced, but reverse cholesterol transport was not dampened unless hepatic scavenger receptor class B type I was inhibited.[65] Furthermore, a Mendelian randomization study found that carriers of the *LIPG* 396Ser allele had higher HDL-C but similar levels of other lipid and nonlipid risk factors for MI compared with noncarriers; yet this allele was not associated with reduced risk of MI.[51]

Moreover, a recent *ATVB* article on the relationship between HDL-C and mortality has shown a U-shaped curve, suggesting that an extremely high level of HDL-C is not related to a favorable outcome, in contrast, showing increased mortality.[66] These results suggest that a strategy simply aimed at quantitatively increasing HDL-C levels does not improve cardiovascular outcomes. Taken together, the dogma that HDL-C is atheroprotective is not uniformly supported by human data.

In this context, there is a growing debate on HDL's functionality, rather than cholesterol content, in mediating HDL's atheroprotective effect.[43] Higher cholesterol efflux capacity of plasma HDL, measured as cholesterol mass efflux, was recently shown to be associated with lower risk of incident coronary heart disease events.[67] The correlation between plasma HDL cholesterol mass efflux capacity and HDL-C in this study was modest. Furthermore, studies on the effect of exercise and weight loss have demonstrated that some measures of

Downloaded from http://ahajournals.org by on February 20, 2019

HDL function can be improved at least partly independently of HDL-C levels.[68,69] The search for mechanisms that improve HDL function is, therefore, an intense topic of study. One such mechanism is related to sphingosine-1-phosphate (S1P), which seems to mediate some of the atheroprotective functions of HDL. Thus, Denimal et al[70] demonstrated that blunted activation of eNOS (endothelial NO synthase) by HDL in patients with metabolic syndrome was mainly because of reduced levels of S1P in HDL. Apolipoprotein M is the main carrier of S1P in plasma, and a subpopulation of HDL carries apoM and binds S1P. The relative level of S1P in HDL versus apoB-containing lipoproteins is modulated by CETP.[71] It has been shown that apoM-bound S1P is responsible for HDL's ability to suppress adhesion molecule expression in the endothelium.[72] These findings suggest that S1P is a mediator of at least some of the atheroprotective effects of HDL. Further studies on the functionality of HDL and regulators of its functionality will be needed.

Furthermore, a series of studies have supported the idea that the concentration of HDL particles is a superior marker of ASCVD risk over HDL-C and of residual risk after statin treatment.[73,74] Consistently, niacin and CETP inhibitors that raised HDL-C but did not show a beneficial effect on cardiovascular disease[50,75] had only weak effects on increasing the number of HDL particles.[76] Therapeutic strategies to increase HDL particle concentrations might be able to reduce the residual risk. Further investigation of the clinical significance of various HDL metrics and their effectiveness in preventing ASCVD risk is needed.

Lp(a)

Lp(a) (gene name, *LPA*) is an apo-B100–containing LDL particle covalently attached to the protein apo(a) (apolipoprotein[a]). Lp(a) levels are not generally lowered by statins, which makes Lp(a) a strong residual risk factor candidate. However, increased Lp(a) does not seem to explain the residual risk associated with diabetes mellitus.[10] Instead, a series of genetic studies, including meta-analysis and Mendelian randomization studies, have suggested that genetically elevated levels of Lp(a) causally associate with cardiovascular disease risk.[77] Plasma levels of Lp(a) vary >1000-fold between individuals and partly reflect acute or chronic inflammation; however, they are primarily determined by polymorphisms in the *LPA* gene. *LPA* variants associate with cardiovascular events in patients receiving statin therapy.[78] Moreover, progression of carotid atherosclerosis positively associates with the level of Lp(a) in patients treated with intensive lipid-lowering medication with the goal of LDL-C <70 mg/dL.[79] These findings support the notion that Lp(a) is a candidate component of residual ASCVD risk in some patients. In addition to apo(a) synthesis in hepatocytes, catabolic pathways impact plasma levels of Lp(a). A large-scale genetic study in humans found that differences in plasma Lp(a) levels are associated with *APOE* genotypes, suggesting that apoE can affect the catabolism of Lp(a), perhaps through competition for the hepatic clearance receptors LDLR (LDL receptor) and LRP1 (LDL receptor–related protein 1).[80]

Given that Lp(a) might be a promising therapeutic target in some patients with increased residual risk, we need to define its therapeutic threshold value. There have been continuous efforts to determine the therapeutic cutoff value for Lp(a).[81] A recent analysis estimating population impact of lowering the plasma Lp(a) level to <50 mg/dL, based on data from a large prospective cohort study, suggested that reducing Lp(a) is expected to have a significant beneficial impact on cardiovascular disease.[82] Niacin,[83–85] PCSK9 inhibition,[9,86] apo(a) antisense oligonucleotides,[87] CETP inhibition by anacetrapib,[88] and the removal of Lp(a) by lipoprotein apheresis[89] might be candidates for therapeutic strategies to reduce Lp(a) levels. A recent chronic renal insufficiency cohort study showed that elevated Lp(a) is independently associated with MI and death among patients with chronic kidney disease[90]; therefore, therapeutic intervention to lower Lp(a) might provide benefits especially in high-risk populations with prevalent chronic kidney disease.

The mechanisms whereby Lp(a) promotes atherothrombotic disease are not well understood, in part, because rodents and rabbits, which are commonly used for mechanistic studies on atherogenesis, do not normally express Lp(a). Animals transgenic for Lp(a) suggest that Lp(a) promotes fatty streak formation and atherosclerotic lesion calcification, but better models are needed to understand the mechanisms.[91]

Inflammation

It is now well recognized that inflammation, orchestrated by various types of immune cells,[92] their subpopulations,[93] and cytokines[94,95] in circulation or in the local milieu, associates with and participates in the development and progression of atherosclerosis. Moreover, interest in the relationships among inflammatory processes and ASCVD extends to the involvement of humoral immunity,[96] such as the classic pathway of complement activation,[97] IgM,[98] and IgE.[99] Conditions associated with an increased ASCVD risk, such as diabetes mellitus, are characterized by increased low-grade inflammation. In addition, it is interesting to note that ambient air pollution is associated with systemic inflammation,[100] which in turn might contribute to incident cardiovascular events.[101]

Although we have known for decades from mechanistic animal models that inflammatory processes are critically involved in atherosclerosis, whether inflammation itself can be a therapeutic target in prevention of ASCVD in humans has been a longstanding clinical question. The CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcome Study) recently offered an answer to this question by demonstrating that inhibition of the cytokine IL (interleukin)-1β can prevent ASCVD events in subjects with a prior MI and elevated hs-CRP (high-sensitivity C-reactive protein) highlighting inflammation as a nonlipid residual risk factor in these patients.[102] The results of this trial showed that targeting the IL-1β innate immunity pathway with canakinumab (a human IL-1β neutralizing monoclonal antibody) at a dose of 150 mg every 3 months led to a lower rate of recurrent cardiovascular events than did placebo treatment, independent of lipid lowering.[102] It is noteworthy that a majority of subjects included in the CANTOS trial were on statin therapy. Also, it is worth mentioning that this study proposed the concept of residual inflammatory risk[103,104] and suggested that inflammation is a major residual risk factor

Downloaded from http://ahajournals.org by on February 20, 2019

of ASCVD. The CANTOS trial concurrently demonstrated that IL-1β can contribute to cardiovascular events in humans. However, it is unknown whether blocking IL-1β would be effective in the general population of patients with elevated ASCVD risk, including those who do not have increased CRP (C-reactive protein). The recent CIRT (Cardiovascular Inflammation Reduction Trial) failed to demonstrate a beneficial effect of low-dose methotrexate as an anti-inflammatory agent in ASCVD patients with a median level of hs-CRP at randomization at 1.5 mg/L (compared with >4 mg/L in CANTOS).[102,105] However, methotrexate did not reduce circulating levels of IL-1β, IL-6, or hs-CRP, suggesting that the treatment did not alter the key inflammatory pathway(s).

Many lines of evidence evoke IL-1β as especially important in ASCVD. Chai et al[106] identified *Il1b* as one of the upstream regulators of enriched gene sets when comparing the transcriptome of macrophages from symptomatic atherosclerotic lesions with that of macrophages from asymptomatic lesions. Inflammasomes are essential for IL-1β secretion via activation of caspase-1.[107] Thus, the inactivation of inflammasomes might be a therapeutic option to prevent cardiovascular event.[108] Indeed, a recent study using apoE-deficient mice treated with a specific inhibitor of the most studied inflammasome component, NLRP3 (nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing-3), showed attenuation of atherosclerosis development.[109] Conversely, physiological activators of inflammasomes include saturated fatty acids,[110] ceramide,[111] oxidized LDL,[112] and cholesterol crystals,[113,114] which are present in atherosclerotic lesions. These lipids or other inflammasome activators are, therefore, likely to accelerate inflammation and lesion progression.

Recently, clonal hematopoiesis of indeterminate potential has emerged as another nonlipid residual risk factor related to inflammation in older patients.[115] Deficiency of one of the most common genes responsible for clonal hematopoiesis of indeterminate potential in humans, TET2 (tet methylcytosine dioxygenase 2), was shown to promote atherogenesis in mouse models through an IL-1β–dependent and NLRP3 inflammasome- dependent mechanism.[115] Taken together, activation of the NLRP3 inflammasome—a mediator associated with both cell death and inflammation—can be a potential mechanism underlying the formation of the large necrotic cores and accumulation of inflammatory cells, which characterize the high-risk plaque.

Defective efferocytosis—the process by which dying cells are removed by phagocytes—also contributes to the expansion of necrotic cores in lesions of atherosclerosis. However, the mechanisms that determine the efficiency of efferocytosis have only partly been worked out. In an interesting study, Wang et al[116] recently demonstrated that mitochondrial fission in response to the initial uptake of apoptotic or dying cells is essential for continued efferocytosis. This finding suggests that defective efferocytosis might be partly because of the failure of mitochondrial remodeling after uptake of a first round of apoptotic cells. In agreement, Yu et al[117] demonstrated that human atherosclerotic plaques exhibit marked mitochondrial dysfunction, defined by increased mitochondrial DNA damage and reduced mitochondrial respiration, and that reducing mitochondrial DNA damage and increasing mitochondrial respiration led to attenuated necrotic core formation in mice. Rinne et al offered a solution to limit expansion of necrotic cores. By treating *Apoe*$^{-/-}$ mice with palmitoylethanolamide—an endogenous fatty acid mediator, they generated a proresolving environment, which reduced inflammation and enhanced efferocytosis, thus resulting in smaller necrotic cores.[118] These findings support the notion that inflammation and associated cell death and impaired efferocytosis in response to the lesion environment concertedly shape pathological traits of high-risk atherosclerotic plaques. However, inflammation cannot be characterized by the dualism of good or bad in the process of atherogenesis. Therefore, the development of additional strategies to target specific inflammatory processes relevant to ASCVD demands further research.

Summary

We are now in an era where it is becoming possible to integrate individual large-scale data on disease, genomics, and artificial intelligence,[119] which will likely allow us to redefine the meaning of residual risk factor for ASCVD to go beyond LDL-C control and statin treatment. That is, if more detailed understanding of residual risk factors of ASCVD could be achieved in parallel with mechanistic insights, we would be able to fine-tune treatment and prevention strategies. In this article, we focused on TRLs and their remnants, HDL, Lp(a), and inflammation as candidates of residual risk factors of ASCVD. Full understanding of residual risk in ASCVD might be a difficult task; however, with continuous research efforts in clinical and basic studies relevant to residual risk, it might not be long before precision medicine can be more efficiently applied in this area.

Sources of Funding

Research in the authors' laboratories is supported by grants from the National Institutes of Health (P01HL092969, P30DK017047, R01HL126028, DP3DK108209, R01HL127694, and R21AI135447) and the American Diabetes Association (1-16-IBS-153).

Disclosures

None.

References

1. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the scandinavian simvastatin survival study (4s). *Lancet*. 1994;344:1383–1389.
2. Mills EJ, Rachlis B, Wu P, Devereaux PJ, Arora P, Perri D. Primary prevention of cardiovascular mortality and events with statin treatments: a network meta-analysis involving more than 65,000 patients. *J Am Coll Cardiol*. 2008;52:1769–1781. doi: 10.1016/j.jacc.2008.08.039
3. Ridker PM, Pradhan A, MacFadyen JG, Libby P, Glynn RJ. Cardiovascular benefits and diabetes risks of statin therapy in primary prevention: an analysis from the JUPITER trial. *Lancet*. 2012;380:565–571. doi: 10.1016/S0140-6736(12)61190-8
4. Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, Brown L, Warnica JW, Arnold JM, Wun CC, Davis BR, Braunwald E. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and recurrent events trial investigators. *N Engl J Med*. 1996;335:1001–1009. doi: 10.1056/NEJM199610033351401
5. Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, Joyal SV, Hill KA, Pfeffer MA, Skene AM; Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 Investigators. Intensive versus moderate lipid lowering with statins

Downloaded from http://ahajournals.org by on February 20, 2019

after acute coronary syndromes. *N Engl J Med*. 2004;350:1495–1504. doi: 10.1056/NEJMoa040583
6. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APHA/ASPC/NLA/PCNA guideline on the management of blood cholesterol [published online November 10, 2018]. *Circulation*. doi: 10.1161/CIR.0000000000000625. https://www.ahajournals.org/doi/10.1161/CIR.0000000000000625.
7. Giugliano RP, Pedersen TR, Park JG, et al; FOURIER Investigators. Clinical efficacy and safety of achieving very low LDL-cholesterol concentrations with the PCSK9 inhibitor evolocumab: a prespecified secondary analysis of the FOURIER trial. *Lancet*. 2017;390:1962–1971. doi: 10.1016/S0140-6736(17)32290-0
8. Chan DC, Watts GF, Somaratne R, Wasserman SM, Scott R, Barrett PHR. Comparative effects of PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibition and statins on postprandial triglyceride-rich lipoprotein metabolism. *Arterioscler Thromb Vasc Biol*. 2018;38:1644–1655. doi: 10.1161/ATVBAHA.118.310882
9. Raal FJ, Giugliano RP, Sabatine MS, Koren MJ, Langslet G, Bays H, Blom D, Eriksson M, Dent R, Wasserman SM, Huang F, Xue A, Albizem M, Scott R, Stein EA. Reduction in lipoprotein(a) with PCSK9 monoclonal antibody evolocumab (AMG 145): a pooled analysis of more than 1,300 patients in 4 phase II trials. *J Am Coll Cardiol*. 2014;63:1278–1288. doi: 10.1016/j.jacc.2014.01.006
10. Stahel P, Xiao C, Hegele RA, Lewis GF. The atherogenic dyslipidemia complex and novel approaches to cardiovascular disease prevention in diabetes. *Can J Cardiol*. 2018;34:595–604. doi: 10.1016/j.cjca.2017.12.007
11. Jeppesen J, Hein HO, Suadicani P, Gyntelberg F. Low triglycerides-high high-density lipoprotein cholesterol and risk of ischemic heart disease. *Arch Intern Med*. 2001;161:361–366.
12. Rawshani A, Rawshani A, Franzén S, Sattar N, Eliasson B, Svensson AM, Zethelius B, Miftaraj M, McGuire DK, Rosengren A, Gudbjörnsdottir S. Risk factors, mortality, and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2018;379:633–644. doi: 10.1056/NEJMoa1800256
13. Assimes TL, Roberts R. Genetics: implications for prevention and management of coronary artery disease. *J Am Coll Cardiol*. 2016;68:2797–2818. doi: 10.1016/j.jacc.2016.10.039
14. Benn M, Nordestgaard BG. From genome-wide association studies to Mendelian randomization: novel opportunities for understanding cardiovascular disease causality, pathogenesis, prevention, and treatment. *Cardiovasc Res*. 2018;114:1192–1208. doi: 10.1093/cvr/cvy045
15. Mahley RW, Weisgraber KH, Innerarity TL, Rall SC Jr. Genetic defects in lipoprotein metabolism. Elevation of atherogenic lipoproteins caused by impaired catabolism. *JAMA*. 1991;265:78–83.
16. Bernelot Moens SJ, Verweij SL, Schnitzler JG, Stiekema LCA, Bos M, Langsted A, Kuijk C, Bekkering S, Voermans C, Verberne HJ, Nordestgaard BG, Stroes ESG, Kroon J. Remnant cholesterol elicits arterial wall inflammation and a multilevel cellular immune response in humans. *Arterioscler Thromb Vasc Biol*. 2017;37:969–975. doi: 10.1161/ATVBAHA.116.308834
17. Tavakoli S, Downs K, Short JD, Nguyen HN, Lai Y, Jerabek PA, Goins B, Toczek J, Sadeghi MM, Asmis R. Characterization of macrophage polarization states using combined measurement of 2-deoxyglucose and glutamine accumulation: implications for imaging of atherosclerosis. *Arterioscler Thromb Vasc Biol*. 2017;37:1840–1848. doi: 10.1161/ATVBAHA.117.308848
18. Schwartz GG, Abt M, Bao W, DeMicco D, Kallend D, Miller M, Mundl H, Olsson AG. Fasting triglycerides predict recurrent ischemic events in patients with acute coronary syndrome treated with statins. *J Am Coll Cardiol*. 2015;65:2267–2275. doi: 10.1016/j.jacc.2015.03.544
19. Chapman MJ, Ginsberg HN, Amarenco P, et al; European Atherosclerosis Society Consensus Panel. Triglyceride-rich lipoproteins and high-density lipoprotein cholesterol in patients at high risk of cardiovascular disease: evidence and guidance for management. *Eur Heart J*. 2011;32:1345–1361. doi: 10.1093/eurheartj/ehr112
20. Nordestgaard BG, Benn M, Schnohr P, Tybjaerg-Hansen A. Nonfasting triglycerides and risk of myocardial infarction, ischemic heart disease, and death in men and women. *JAMA*. 2007;298:299–308. doi: 10.1001/jama.298.3.299
21. Varbo A, Nordestgaard BG. Nonfasting triglycerides, low-density lipoprotein cholesterol, and heart failure risk: two cohort studies of 113 554 individuals. *Arterioscler Thromb Vasc Biol*. 2018;38:464–472. doi: 10.1161/ATVBAHA.117.310269
22. Nordestgaard BG, Langsted A, Mora S, et al; European Atherosclerosis Society (EAS) and the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) Joint Consensus Initiative. Fasting is not routinely required for determination of a lipid profile: clinical and laboratory implications including flagging at desirable concentration cut-points-a joint consensus statement from the European Atherosclerosis Society and European Federation of Clinical Chemistry and Laboratory Medicine. *Eur Heart J*. 2016;37:1944–1958. doi: 10.1093/eurheartj/ehw152
23. Kurihara O, Okajima F, Takano M, Kato K, Munakata R, Murakami D, Miyauchi Y, Emoto N, Sugihara H, Seino Y, Shimizu W. Postprandial hyperchylomicronemia and thin-cap fibroatheroma in nonculprit lesions. *Arterioscler Thromb Vasc Biol*. 2018;38:1940–1947. doi: 10.1161/ATVBAHA.118.311245
24. Park K, Li Q, Evcimen ND, Rask-Madsen C, Maeda Y, Maddaloni E, Yokomizo H, Shinjo T, St-Louis R, Fu J, Gordin D, Khamaisi M, Pober D, Keenan H, King GL. Exogenous insulin infusion can decrease atherosclerosis in diabetic rodents by improving lipids, inflammation, and endothelial function. *Arterioscler Thromb Vasc Biol*. 2018;38:92–101. doi: 10.1161/ATVBAHA.117.310291
25. Bornfeldt KE. Does elevated glucose promote atherosclerosis? Pros and cons. *Circ Res*. 2016;119:190–193. doi: 10.1161/CIRCRESAHA.116.308873
26. Nordestgaard BG, Varbo A. Triglycerides and cardiovascular disease. *Lancet*. 2014;384:626–635. doi: 10.1016/S0140-6736(14)61177-6
27. Ginsberg HN, Elam MB, Lovato LC, et al; ACCORD Study Group. Effects of combination lipid therapy in type 2 diabetes mellitus. *N Engl J Med*. 2010;362:1563–1574. doi: 10.1056/NEJMoa1001282
28. Sandesara PB, Virani SS, Fazio S, Shapiro MD. The forgotten lipids: triglycerides, remnant cholesterol, and atherosclerotic cardiovascular disease risk [published online October 11, 2018]. *Endocr Rev*. doi: 10.1210/er.2018-00184. https://academic.oup.com/edrv/advance-article/doi/10.1210/er.2018-00184/5126386.
29. Bhatt DL, Steg PG, Miller M, Brinton EA, Jacobson TA, Ketchum SB, Doyle RT Jr, Juliano RA, Jiao L, Granowitz C, Tardif JC, Ballantyne CM; REDUCE-IT Investigators. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia [published online November 17, 2018]. *N Engl J Med*. doi: 10.1056/NEJMoa1812792. https://www.nejm.org/doi/full/10.1056/NEJMoa1812792.
30. Yokoyama M, Origasa H, Matsuzaki M, et al; Japan EPA Lipid Intervention Study (JELIS) Investigators. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. *Lancet*. 2007;369:1090–1098. doi: 10.1016/S0140-6736(07)60527-3
31. Holmes MV, Asselbergs FW, Palmer TM, et al; UCLEB Consortium. Mendelian randomization of blood lipids for coronary heart disease. *Eur Heart J*. 2015;36:539–550. doi: 10.1093/eurheartj/eht571
32. Pollin TI, Damcott CM, Shen H, Ott SH, Shelton J, Horenstein RB, Post W, McLenithan JC, Bielak LF, Peyser PA, Mitchell BD, Miller M, O'Connell JR, Shuldiner AR. A null mutation in human APOC3 confers a favorable plasma lipid profile and apparent cardioprotection. *Science*. 2008;322:1702–1705. doi: 10.1126/science.1161524
33. Crosby J, Peloso GM, Auer PL, et al; TG and HDL Working Group of the Exome Sequencing Project; National Heart, Lung, and Blood Institute. Loss-of-function mutations in apoc3, triglycerides, and coronary disease. *N Engl J Med*. 2014;371:22–31.
34. Wulff AB, Nordestgaard BG, Tybjærg-Hansen A. APOC3 loss-of-function mutations, remnant cholesterol, low-density lipoprotein cholesterol, and cardiovascular risk: mediation- and meta-analyses of 137 895 individuals. *Arterioscler Thromb Vasc Biol*. 2018;38:660–668. doi: 10.1161/ATVBAHA.117.310473
35. Do R, Stitziel NO, Won HH, et al; NHLBI Exome Sequencing Project. Exome sequencing identifies rare LDLR and APOA5 alleles conferring risk for myocardial infarction. *Nature*. 2015;518:102–106. doi: 10.1038/nature13917
36. Stitziel NO, Khera AV, Wang X, et al; PROMIS and Myocardial Infarction Genetics Consortium Investigators. ANGPTL3 deficiency and protection against coronary artery disease. *J Am Coll Cardiol*. 2017;69:2054–2063. doi: 10.1016/j.jacc.2017.02.030
37. Boer JM, Kuivenhoven JA, Feskens EJ, Schouten EG, Havekes LM, Seidell JC, Kastelein JJ, Kromhout D. Physical activity modulates the effect of a lipoprotein lipase mutation (D9N) on plasma lipids and lipoproteins. *Clin Genet*. 1999;56:158–163.
38. van Capelleveen JC, Bernelot Moens SJ, Yang X, Kastelein JJP, Wareham NJ, Zwinderman AH, Stroes ESG, Witztum JL, Hovingh GK, Khaw KT, Boekholdt SM, Tsimikas S. Apolipoprotein C-III levels and incident coronary artery disease risk: the EPIC-Norfolk prospective population study. *Arterioscler Thromb Vasc Biol*. 2017;37:1206–1212. doi: 10.1161/ATVBAHA.117.309007

Downloaded from http://ahajournals.org by on February 20, 2019

39. Mendoza S, Trenchevska O, King SM, Nelson RW, Nedelkov D, Krauss RM, Yassine HN. Changes in low-density lipoprotein size phenotypes associate with changes in apolipoprotein C-III glycoforms after dietary interventions. *J Clin Lipidol*. 2017;11:224–233.e2. doi: 10.1016/j.jacl.2016.12.009
40. Zheng C, Khoo C, Furtado J, Sacks FM. Apolipoprotein C-III and the metabolic basis for hypertriglyceridemia and the dense low-density lipoprotein phenotype. *Circulation*. 2010;121:1722–1734. doi: 10.1161/CIRCULATIONAHA.109.875807
41. Toth PP. Triglyceride-rich lipoproteins as a causal factor for cardiovascular disease. *Vasc Health Risk Manag*. 2016;12:171–183. doi: 10.2147/VHRM.S104369
42. Bell G, Mora S, Greenland P, Tsai M, Gill E, Kaufman JD. Association of air pollution exposures with high-density lipoprotein cholesterol and particle number: the multi-ethnic study of atherosclerosis. *Arterioscler Thromb Vasc Biol*. 2017;37:976–982. doi: 10.1161/ATVBAHA.116.308193
43. He Y, Kothari V, Bornfeldt KE. High-density lipoprotein function in cardiovascular disease and diabetes mellitus. *Arterioscler Thromb Vasc Biol*. 2018;38:e10–e16. doi: 10.1161/ATVBAHA.117.310222
44. Furtado JD, Yamamoto R, Melchior JT, Andraski AB, Gamez-Guerrero M, Mulcahy P, He Z, Cai T, Davidson WS, Sacks FM. Distinct proteomic signatures in 16 HDL (high-density lipoprotein) subspecies. *Arterioscler Thromb Vasc Biol*. 2018;38:2827–2842. doi: 10.1161/ATVBAHA.118.311607
45. Du XM, Kim MJ, Hou L, Le Goff W, Chapman MJ, Van Eck M, Curtiss LK, Burnett JR, Cartland SP, Quinn CM, Kockx M, Kontush A, Rye KA, Kritharides L, Jessup W. HDL particle size is a critical determinant of ABCA1-mediated macrophage cellular cholesterol export. *Circ Res*. 2015;116:1133–1142. doi: 10.1161/CIRCRESAHA.116.305485
46. Asztalos BF, Horvath KV, Schaefer EJ. High-density lipoprotein particles, cell-cholesterol efflux, and coronary heart disease risk. *Arterioscler Thromb Vasc Biol*. 2018;38:2007–2015. doi: 10.1161/ATVBAHA.118.311117
47. Reyes-Soffer G, Millar JS, Ngai C, et al. Cholesteryl ester transfer protein inhibition with anacetrapib decreases fractional clearance rates of high-density lipoprotein apolipoprotein A-I and plasma cholesteryl ester transfer protein. *Arterioscler Thromb Vasc Biol*. 2016;36:994–1002. doi: 10.1161/ATVBAHA.115.306680
48. Zhang J, Niimi M, Yang D, et al. Deficiency of cholesteryl ester transfer protein protects against atherosclerosis in rabbits. *Arterioscler Thromb Vasc Biol*. 2017;37:1068–1075. doi: 10.1161/ATVBAHA.117.309114
49. Wu BJ, Li Y, Ong KL, Sun Y, Shrestha S, Hou L, Johns D, Barter PJ, Rye KA. Reduction of in-stent restenosis by cholesteryl ester transfer protein inhibition. *Arterioscler Thromb Vasc Biol*. 2017;37:2333–2341. doi: 10.1161/ATVBAHA.117.310051
50. Tall AR, Rader DJ. Trials and tribulations of CETP inhibitors. *Circ Res*. 2018;122:106–112. doi: 10.1161/CIRCRESAHA.117.311978
51. Voight BF, Peloso GM, Orho-Melander M, et al. Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomisation study. *Lancet*. 2012;380:572–580. doi: 10.1016/S0140-6736(12)60312-2
52. Bowman L, Hopewell JC, Chen F, Wallendszus K, Stevens W, Collins R, Wiviott SD, Cannon CP, Braunwald E, Sammons E, Landray MJ; HPS3/TIMI55–REVEAL Collaborative Group. Effects of anacetrapib in patients with atherosclerotic vascular disease. *N Engl J Med*. 2017;377:1217–1227. doi: 10.1056/NEJMoa1706444
53. Di Bartolo BA, Scherer DJ, Nicholls SJ. Inducing apolipoprotein A-I synthesis to reduce cardiovascular risk: from ASSERT to SUSTAIN and beyond. *Arch Med Sci*. 2016;12:1302–1307. doi: 10.5114/aoms.2016.62906
54. Shah PK, Yano J, Reyes O, Chyu KY, Kaul S, Bisgaier CL, Drake S, Cercek B. High-dose recombinant apolipoprotein A-I(milano) mobilizes tissue cholesterol and rapidly reduces plaque lipid and macrophage content in apolipoprotein e-deficient mice. Potential implications for acute plaque stabilization. *Circulation*. 2001;103:3047–3050.
55. Nicholls SJ, Gordon A, Johansson J, Wolski K, Ballantyne CM, Kastelein JJ, Taylor A, Borgman M, Nissen SE. Efficacy and safety of a novel oral inducer of apolipoprotein A-I synthesis in statin-treated patients with stable coronary artery disease a randomized controlled trial. *J Am Coll Cardiol*. 2011;57:1111–1119. doi: 10.1016/j.jacc.2010.11.015
56. Nissen SE, Tsunoda T, Tuzcu EM, Schoenhagen P, Cooper CJ, Yasin M, Eaton GM, Lauer MA, Sheldon WS, Grines CL, Halpern S, Crowe T, Blankenship JC, Kerensky R. Effect of recombinant ApoA-I Milano on coronary atherosclerosis in patients with acute coronary syndromes: a randomized controlled trial. *JAMA*. 2003;290:2292–2300. doi: 10.1001/jama.290.17.2292
57. Wacker BK, Dronadula N, Bi L, Stamatikos A, Dichek DA. Apo A-I (apolipoprotein A-I) vascular gene therapy provides durable protection against atherosclerosis in hyperlipidemic rabbits. *Arterioscler Thromb Vasc Biol*. 2018;38:206–217. doi: 10.1161/ATVBAHA.117.309565
58. Ditiatkovski M, Palsson J, Chin-Dusting J, Remaley AT, Sviridov D. Apolipoprotein A-I mimetic peptides: discordance between in vitro and in vivo properties-brief report. *Arterioscler Thromb Vasc Biol*. 2017;37:1301–1306. doi: 10.1161/ATVBAHA.117.309523
59. Ishida T, Choi S, Kundu RK, Hirata K, Rubin EM, Cooper AD, Quertermous T. Endothelial lipase is a major determinant of HDL level. *J Clin Invest*. 2003;111:347–355. doi: 10.1172/JCI16306
60. Brown RJ, Edmondson AC, Griffon N, Hill TB, Fuki IV, Badellino KO, Li M, Wolfe ML, Reilly MP, Rader DJ. A naturally occurring variant of endothelial lipase associated with elevated HDL exhibits impaired synthesis. *J Lipid Res*. 2009;50:1910–1916. doi: 10.1194/jlr.P900020-JLR200
61. Singaraja RR, Sivapalaratnam S, Hovingh K, et al. The impact of partial and complete loss-of-function mutations in endothelial lipase on high-density lipoprotein levels and functionality in humans. *Circ Cardiovasc Genet*. 2013;6:54–62. doi: 10.1161/CIRCGENETICS.111.962613
62. Ishida T, Choi SY, Kundu RK, Spin J, Yamashita T, Hirata K, Kojima Y, Yokoyama M, Cooper AD, Quertermous T. Endothelial lipase modulates susceptibility to atherosclerosis in apolipoprotein-E-deficient mice. *J Biol Chem*. 2004;279:45085–45092. doi: 10.1074/jbc.M406360200
63. Ko KW, Paul A, Ma K, Li L, Chan L. Endothelial lipase modulates HDL but has no effect on atherosclerosis development in apoE-/- and LDLR-/- mice. *J Lipid Res*. 2005;46:2586–2594. doi: 10.1194/jlr.M500366-JLR200
64. Wang C, Nishijima K, Kitajima S, Niimi M, Yan H, Chen Y, Ning B, Matsuhisa F, Liu E, Zhang J, Chen YE, Fan J. Increased hepatic expression of endothelial lipase inhibits cholesterol diet-induced hypercholesterolemia and atherosclerosis in transgenic rabbits. *Arterioscler Thromb Vasc Biol*. 2017;37:1282–1289. doi: 10.1161/ATVBAHA.117.309139
65. Takiguchi S, Ayaori M, Yakushiji E, Nishida T, Nakaya K, Sasaki M, Iizuka M, Uto-Kondo H, Terao Y, Yogo M, Komatsu T, Ogura M, Ikewaki K. Hepatic overexpression of endothelial lipase lowers high-density lipoprotein but maintains reverse cholesterol transport in mice: role of scavenger receptor class B type I/ATP-binding cassette transporter A1-dependent pathways. *Arterioscler Thromb Vasc Biol*. 2018;38:1454–1467. doi: 10.1161/ATVBAHA.118.311056
66. Hamer M, O'Donovan G, Stamatakis E. High-density lipoprotein cholesterol and mortality: too much of a good thing? *Arterioscler Thromb Vasc Biol*. 2018;38:669–672. doi: 10.1161/ATVBAHA.117.310587
67. Shea S, Stein JH, Jorgenson NW, McClelland RL, Tascau L, Shrager S, Heinecke JW, Yvan-Charvet L, Tall AR. Cholesterol mass efflux capacity, incident cardiovascular disease, and progression of carotid plaque: the Multi-Ethnic Study of Atherosclerosis. *Arterioscler Thromb Vasc Biol*. 2019;39:89–96. doi: 10.1161/ATVBAHA.118.311366
68. Sarzynski MA, Ruiz-Ramie JJ, Barber JL, Slentz CA, Apolzan JW, McGarrah RW, Harris MN, Church TS, Borja MS, He Y, Oda MN, Martin CK, Kraus WE, Rohatgi A. Effects of increasing exercise intensity and dose on multiple measures of HDL (high-density lipoprotein) function. *Arterioscler Thromb Vasc Biol*. 2018;38:943–952. doi: 10.1161/ATVBAHA.117.310307
69. Khan AA, Mundra PA, Straznicky NE, Nestel PJ, Wong G, Tan R, Huynh K, Ng TW, Mellett NA, Weir JM, Barlow CK, Alshehry ZH, Lambert GW, Kingwell BA, Meikle PJ. Weight loss and exercise alter the high-density lipoprotein lipidome and improve high-density lipoprotein functionality in metabolic syndrome. *Arterioscler Thromb Vasc Biol*. 2018;38:438–447. doi: 10.1161/ATVBAHA.117.310212
70. Denimal D, Monier S, Brindisi MC, Petit JM, Bouillet B, Nguyen A, Demizieux L, Simoneau I, Pais de Barros JP, Vergès B, Duvillard L. Impairment of the ability of HDL from patients with metabolic syndrome but without diabetes mellitus to activate eNOS: correction by S1P enrichment. *Arterioscler Thromb Vasc Biol*. 2017;37:804–811. doi: 10.1161/ATVBAHA.117.309287
71. Kurano M, Hara M, Ikeda H, Tsukamoto K, Yatomi Y. Involvement of CETP (cholesteryl ester transfer protein) in the shift of sphingosine-1-phosphate among lipoproteins and in the modulation of its functions. *Arterioscler Thromb Vasc Biol*. 2017;37:506–514. doi: 10.1161/ATVBAHA.116.308692
72. Ruiz M, Frej C, Holmér A, Guo LJ, Tran S, Dahlbäck B. High-density lipoprotein-associated apolipoprotein m limits endothelial inflammation by delivering sphingosine-1-phosphate to the sphingosine-1-phosphate receptor 1. *Arterioscler Thromb Vasc Biol*. 2017;37:118–129. doi: 10.1161/ATVBAHA.116.308435
73. Mora S, Glynn RJ, Ridker PM. High-density lipoprotein cholesterol, size, particle number, and residual vascular risk after potent statin therapy. *Circulation*. 2013;128:1189–1197. doi: 10.1161/CIRCULATIONAHA.113.002671

Downloaded from http://ahajournals.org by on February 20, 2019

74. Khera AV, Demler OV, Adelman SJ, Collins HL, Glynn RJ, Ridker PM, Rader DJ, Mora S. Cholesterol efflux capacity, high-density lipoprotein particle number, and incident cardiovascular events: an analysis from the JUPITER trial (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin). *Circulation*. 2017;135:2494–2504. doi: 10.1161/CIRCULATIONAHA.116.025678
75. Boden WE, Probstfield JL, Anderson T, Chaitman BR, Desvignes-Nickens P, Koprowicz K, McBride R, Teo K, Weintraub W; AIM-HIGH Investigators. Niacin in patients with low hdl cholesterol levels receiving intensive statin therapy. *New Engl J Med*. 2011;365:2255–2267.
76. Kontush A. HDL particle number and size as predictors of cardiovascular disease. *Front Pharmacol*. 2015;6:218. doi: 10.3389/fphar.2015.00218
77. Tsimikas S. A test in context: lipoprotein(a): diagnosis, prognosis, controversies, and emerging therapies. *J Am Coll Cardiol*. 2017;69:692–711. doi: 10.1016/j.jacc.2016.11.042
78. Wei WQ, Li X, Feng Q, et al. LPA variants are associated with residual cardiovascular risk in patients receiving statins. *Circulation*. 2018;138:1839–1849. doi: 10.1161/CIRCULATIONAHA.117.031356
79. Hippe DS, Phan BAP, Sun J, Isquith DA, O'Brien KD, Crouse JR, Anderson T, Huston J, Marcovina SM, Hatsukami TS, Yuan C, Zhao XQ. Lp(a) (lipoprotein(a)) levels predict progression of carotid atherosclerosis in subjects with atherosclerotic cardiovascular disease on intensive lipid therapy: an analysis of the AIM-HIGH (atherothrombosis intervention in metabolic syndrome with low HDL/high triglycerides: impact on global health outcomes) carotid magnetic resonance imaging substudy-brief report. *Arterioscler Thromb Vasc Biol*. 2018;38:673–678. doi: 10.1161/ATVBAHA.117.310368
80. Moriarty PM, Varvel SA, Gordts PL, McConnell JP, Tsimikas S. Lipoprotein(a) mass levels increase significantly according to APOE genotype: an analysis of 431 239 patients. *Arterioscler Thromb Vasc Biol*. 2017;37:580–588. doi: 10.1161/ATVBAHA.116.308704
81. Varvel S, McConnell JP, Tsimikas S. Prevalence of elevated Lp(a) mass levels and patient thresholds in 532 359 patients in the United States. *Arterioscler Thromb Vasc Biol*. 2016;36:2239–2245. doi: 10.1161/ATVBAHA.116.308011
82. Afshar M, Kamstrup PR, Williams K, Sniderman AD, Nordestgaard BG, Thanassoulis G. Estimating the population impact of Lp(a) lowering on the incidence of myocardial infarction and aortic stenosis-brief report. *Arterioscler Thromb Vasc Biol*. 2016;36:2421–2423. doi: 10.1161/ATVBAHA.116.308271
83. Croyal M, Ouguerram K, Passard M, Ferchaud-Roucher V, Chétiveaux M, Billon-Crossouard S, de Gouville AC, Lambert G, Krempf M, Nobécourt E. Effects of extended-release nicotinic acid on apolipoprotein (a) kinetics in hypertriglyceridemic patients. *Arterioscler Thromb Vasc Biol*. 2015;35:2042–2047. doi: 10.1161/ATVBAHA.115.305835
84. Ooi EM, Watts GF, Chan DC, Pang J, Tenneti VS, Hamilton SJ, McCormick SP, Marcovina SM, Barrett PH. Effects of extended-release niacin on the postprandial metabolism of Lp(a) and ApoB-100-containing lipoproteins in statin-treated men with type 2 diabetes mellitus. *Arterioscler Thromb Vasc Biol*. 2015;35:2686–2693. doi: 10.1161/ATVBAHA.115.306136
85. van Capelleveen JC, van der Valk FM, Stroes ES. Current therapies for lowering lipoprotein (a). *J Lipid Res*. 2016;57:1612–1618. doi: 10.1194/jlr.R053066
86. O'Donoghue ML, Fazio S, Giugliano RP, et al: Lipoprotein(a), PCSK9 inhibition and cardiovascular risk: insights from the FOURIER trial [published online November 30, 2018]. *Circulation*. doi: 10.1161/CIRCULATIONAHA.118.037184
87. Tsimikas S, Viney NJ, Hughes SG, Singleton W, Graham MJ, Baker BF, Burkey JL, Yang Q, Marcovina SM, Geary RS, Crooke RM, Witztum JL. Antisense therapy targeting apolipoprotein(a): a randomised, double-blind, placebo-controlled phase 1 study. *Lancet*. 2015;386:1472–1483. doi: 10.1016/S0140-6736(15)61252-1
88. Thomas T, Zhou H, Karmally W, et al. CETP (cholesteryl ester transfer protein) inhibition with anacetrapib decreases production of lipoprotein(a) in mildly hypercholesterolemic subjects. *Arterioscler Thromb Vasc Biol*. 2017;37:1770–1775. doi: 10.1161/ATVBAHA.117.309549
89. Roeseler E, Julius U, Heigl F, et al; Pro(a)LiFe-Study Group. Lipoprotein apheresis for lipoprotein(a)-associated cardiovascular disease: prospective 5 years of follow-up and apolipoprotein(a) characterization. *Arterioscler Thromb Vasc Biol*. 2016;36:2019–2027. doi: 10.1161/ATVBAHA.116.307983
90. Bajaj A, Damrauer SM, Anderson AH, et al; Chronic Renal Insufficiency Cohort (CRIC) Study Investigators*. Lipoprotein(a) and risk of myocardial infarction and death in chronic kidney disease: findings from the CRIC study (Chronic Renal Insufficiency Cohort). *Arterioscler Thromb Vasc Biol*. 2017;37:1971–1978. doi: 10.1161/ATVBAHA.117.309920
91. Yeang C, Cotter B, Tsimikas S. Experimental animal models evaluating the causal role of lipoprotein(a) in atherosclerosis and aortic stenosis. *Cardiovasc Drugs Ther*. 2016;30:75–85. doi: 10.1007/s10557-015-6634-1
92. Welsh C, Welsh P, Mark PB, Celis-Morales CA, Lewsey J, Gray SR, Lyall DM, Iliodromiti S, Gill JMR, Pell J, Jhund PS, Sattar N. Association of total and differential leukocyte counts with cardiovascular disease and mortality in the UK biobank. *Arterioscler Thromb Vasc Biol*. 2018;38:1415–1423. doi: 10.1161/ATVBAHA.118.310945
93. Thomas GD, Hamers AAJ, Nakao C, Marcovecchio P, Taylor AM, McSkimming C, Nguyen AT, McNamara CA, Hedrick CC. Human blood monocyte subsets: a new gating strategy defined using cell surface markers identified by mass cytometry. *Arterioscler Thromb Vasc Biol*. 2017;37:1548–1558. doi: 10.1161/ATVBAHA.117.309145
94. Herder C, de Las Heras Gala T, Carstensen-Kirberg M, et al. Circulating levels of interleukin 1-receptor antagonist and risk of cardiovascular disease: meta-analysis of six population-based cohorts. *Arterioscler Thromb Vasc Biol*. 2017;37:1222–1227. doi: 10.1161/ATVBAHA.117.309307
95. Schnabel RB, Yin X, Larson MG, Yamamoto JF, Fontes JD, Kathiresan S, Rong J, Levy D, Keaney JF Jr, Wang TJ, Murabito JM, Vasan RS, Benjamin EJ. Multiple inflammatory biomarkers in relation to cardiovascular events and mortality in the community. *Arterioscler Thromb Vasc Biol*. 2013;33:1728–1733. doi: 10.1161/ATVBAHA.112.301174
96. Tsiantoulas D, Diehl CJ, Witztum JL, Binder CJ. B cells and humoral immunity in atherosclerosis. *Circ Res*. 2014;114:1743–1756. doi: 10.1161/CIRCRESAHA.113.301145
97. Hertle E, Arts ICW, van der Kallen CJH, Feskens EJM, Schalkwijk CG, Stehouwer CDA, van Greevenbroek MMJ. Classical pathway of complement activation: longitudinal associations of C1q and C1-INH with cardiovascular outcomes: the CODAM study (Cohort on Diabetes and Atherosclerosis Maastricht)-brief report. *Arterioscler Thromb Vasc Biol*. 2018;38:1242–1244. doi: 10.1161/ATVBAHA.118.310806
98. Lewis MJ, Malik TH, Ehrenstein MR, Boyle JJ, Botto M, Haskard DO. Immunoglobulin M is required for protection against atherosclerosis in low-density lipoprotein receptor-deficient mice. *Circulation*. 2009;120:417–426. doi: 10.1161/CIRCULATIONAHA.109.868158
99. Wilson JM, Nguyen AT, Schuyler AJ, Commins SP, Taylor AM, Platts-Mills TAE, McNamara CA. IgE to the mammalian oligosaccharide galactose-α-1,3-galactose is associated with increased atheroma volume and plaques with unstable characteristics-brief report. *Arterioscler Thromb Vasc Biol*. 2018;38:1665–1669. doi: 10.1161/ATVBAHA.118.311222
100. Li W, Dorans KS, Wilker EH, Rice MB, Ljungman PL, Schwartz JD, Coull BA, Koutrakis P, Gold DR, Keaney JF Jr, Vasan RS, Benjamin EJ, Mittleman MA. Short-term exposure to ambient air pollution and biomarkers of systemic inflammation: the Framingham Heart Study. *Arterioscler Thromb Vasc Biol*. 2017;37:1793–1800. doi: 10.1161/ATVBAHA.117.309799
101. Erqou S, Clougherty JE, Olafiranye O, Magnani JW, Aiyer A, Tripathy S, Kinnee E, Kip KE, Reis SE. Particulate matter air pollution and racial differences in cardiovascular disease risk. *Arterioscler Thromb Vasc Biol*. 2018;38:935–942. doi: 10.1161/ATVBAHA.117.310305
102. Ridker PM, Everett BM, Thuren T, et al; CANTOS Trial Group. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med*. 2017;377:1119–1131. doi: 10.1056/NEJMoa1707914
103. Ridker PM. How common is residual inflammatory risk? *Circ Res*. 2017;120:617–619. doi: 10.1161/CIRCRESAHA.116.310527
104. Ridker PM. Residual inflammatory risk: addressing the obverse side of the atherosclerosis prevention coin. *Eur Heart J*. 2016;37:1720–1722. doi: 10.1093/eurheartj/ehw024
105. Ridker PM, Everett BM, Pradhan A, et al. Low-dose methotrexate for the prevention of atherosclerotic events. *N Engl J Med*. 2018. doi: 10.1056/NEJMoa1809798. https://www.nejm.org/doi/full/10.1056/NEJMoa1809798.
106. Chai JT, Ruparelia N, Goel A, Kyriakou T, Biasiolli L, Edgar L, Handa A, Farrall M, Watkins H, Choudhury RP. Differential gene expression in macrophages from human atherosclerotic plaques shows convergence on pathways implicated by genome-wide association study risk variants. *Arterioscler Thromb Vasc Biol*. 2018;38:2718–2730. doi: 10.1161/ATVBAHA.118.311209
107. Wang Z, Hu W, Lu C, Ma Z, Jiang S, Gu C, Acuña-Castroviejo D, Yang Y. Targeting NLRP3 (nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing-3) inflammasome in cardiovascular disorders. *Arterioscler Thromb Vasc Biol*. 2018;38:2765–2779. doi: 10.1161/ATVBAHA.118.311916

Downloaded from http://ahajournals.org by on February 20, 2019

108. Guo H, Callaway JB, Ting JP. Inflammasomes: mechanism of action, role in disease, and therapeutics. *Nat Med*. 2015;21:677–687. doi: 10.1038/nm.3893
109. van der Heijden T, Kritikou E, Venema W, van Duijn J, van Santbrink PJ, Slütter B, Foks AC, Bot I, Kuiper J. NLRP3 inflammasome inhibition by MCC950 reduces atherosclerotic lesion development in apolipoprotein E-deficient mice-brief report. *Arterioscler Thromb Vasc Biol*. 2017;37:1457–1461. doi: 10.1161/ATVBAHA.117.309575
110. Karasawa T, Kawashima A, Usui-Kawanishi F, et al. Saturated fatty acids undergo intracellular crystallization and activate the NLRP3 inflammasome in macrophages. *Arterioscler Thromb Vasc Biol*. 2018;38:744–756. doi: 10.1161/ATVBAHA.117.310581
111. Vandanmagsar B, Youm YH, Ravussin A, Galgani JE, Stadler K, Mynatt RL, Ravussin E, Stephens JM, Dixit VD. The NLRP3 inflammasome instigates obesity-induced inflammation and insulin resistance. *Nat Med*. 2011;17:179–188. doi: 10.1038/nm.2279
112. Liu W, Yin Y, Zhou Z, He M, Dai Y. OxLDL-induced IL-1 beta secretion promoting foam cells formation was mainly via CD36 mediated ROS production leading to NLRP3 inflammasome activation. *Inflamm Res*. 2014;63:33–43. doi: 10.1007/s00011-013-0667-3
113. Duewell P, Kono H, Rayner KJ, et al. NLRP3 inflammasomes are required for atherogenesis and activated by cholesterol crystals. *Nature*. 2010;464:1357–1361. doi: 10.1038/nature08938
114. Rajamäki K, Lappalainen J, Oörni K, Välimäki E, Matikainen S, Kovanen PT, Eklund KK. Cholesterol crystals activate the NLRP3 inflammasome in human macrophages: a novel link between cholesterol metabolism and inflammation. *PLoS One*. 2010;5:e11765. doi: 10.1371/journal.pone.0011765
115. Sano S, Wang Y, Walsh K. Clonal hematopoiesis and its impact on cardiovascular disease. *Circ J*. 2018. doi: 10.1253/circj.CJ-18-0871
116. Wang Y, Subramanian M, Yurdagul A Jr, Barbosa-Lorenzi VC, Cai B, de Juan-Sanz J, Ryan TA, Nomura M, Maxfield FR, Tabas I. Mitochondrial fission promotes the continued clearance of apoptotic cells by macrophages. *Cell*. 2017;171:331–345.e22. doi: 10.1016/j.cell.2017.08.041
117. Yu EPK, Reinhold J, Yu H, Starks L, Uryga AK, Foote K, Finigan A, Figg N, Pung YF, Logan A, Murphy MP, Bennett M. Mitochondrial respiration is reduced in atherosclerosis, promoting necrotic core formation and reducing relative fibrous cap thickness. *Arterioscler Thromb Vasc Biol*. 2017;37:2322–2332. doi: 10.1161/ATVBAHA.117.310042
118. Rinne P, Guillamat-Prats R, Rami M, Bindila L, Ring L, Lyytikäinen LP, Raitoharju E, Oksala N, Lehtimäki T, Weber C, van der Vorst EPC, Steffens S. Palmitoylethanolamide promotes a proresolving macrophage phenotype and attenuates atherosclerotic plaque formation. *Arterioscler Thromb Vasc Biol*. 2018;38:2562–2575. doi: 10.1161/ATVBAHA.118.311185
119. Krittanawong C, Zhang H, Wang Z, Aydar M, Kitai T. Artificial intelligence in precision cardiovascular medicine. *J Am Coll Cardiol*. 2017;69:2657–2664. doi: 10.1016/j.jacc.2017.03.571

KEY WORDS: diabetes mellitus ■ inflammation ■ lipoproteins ■ simvastatin ■ statin ■ triglycerides

Downloaded from http://ahajournals.org by on February 20, 2019