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REVIEW

Strategies to Overcome Residual Risk During Statins Era

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At present, atherosclerosis is one of the most important field in clinical and research medicine. Because it is closely related to cardiovascular (CV) and endocrine disorders such as coronary artery disease, cardiometabolic disorders, much research on how to manage atherosclerosis has been performed. The low-density lipoprotein cholesterol (LDL-C) concentration has been established as an independent risk factor for developing atherosclerosis, and considerable effort has been committed to educating both physicians and the general public on the importance of lowering LDL-C with statins. Although statins have already significantly improved CV outcomes, patients with LDL-C target levels achieved by intense statin therapy still have significant remaining CV risk. Statins already play a central role in managing hyperlipidemia; however, residual risk with statins is an important field of managing remaining CV risk. Recent studies have suggested residual cholesterol and inflammation risks in causing CV events. In the current review, we will discuss residual risk and suggest strategies to overcome it in the statins era.

Key Words: Cardiovascular diseases; Cholesterol; Inflammation; Residual risk; Statins

In developed countries, cardiovascular disease (CVD) causes significant morbidity and mortality. Despite significant advances in diagnosis and therapy of CVD, patients continue to experience myocardial infarction, stroke, peripheral arterial disease, and need for revascularization. Controlling risk factors is a cornerstone to decrease the burden of CVD. Managing the modifiable cardiovascular (CV) risk factors, including smoking, hypertension, dyslipidemia, diabetes mellitus, and obesity, has allowed the development of practice patterns and evidence-based guidelines in medical therapy and revascularization, which have contributed to the reduction in CVD mortality.[1–4] Statin therapy remarkably reduces CVD morbidity and mortality. However, despite these advances, up to 40% of statin-treated patients continue to suffer from life-threatening CV events even if the low-density lipoprotein cholesterol (LDL-C) target is achieved by intensive statin treatment. This is caused by unresolved 'residual risk'.[5] There has been a great effort to clarify and manage residual risk, but as yet no conclusive result. Managing residual risk is the ultimate purpose of treating atherosclerosis and eventually CVD.

Residual Cholesterol Risk

Total cholesterol (TC) is composed of high-density lipoproteins cholesterol (HDL-C) and atherogenic lipoproteins [LDL-C and triglyceride-rich lipoproteins cholesterol (TRL-C)], which contain apolipoprotein B (apoB) such as apoB-100, apoB-48 (**Figure 1**). In other words, apoB-containing atherogenic particles (non-HDL-C) can be calculated by subtracting HDL-C from TC.[5] Among LDL-C, small dense LDL is characterized as cholesterol-depleted LDL particles. Small dense LDL is known to have an association with CV events and more simplified methods of measuring small dense LDL are being developed.[6] Among the lipoproteins, lipoprotein (a) (Lp(a)) consists of LDL-like particle and the specific apolipoprotein (a), which is bound covalently to the apoB of the LDL-like particle.

Triglycerides (TRL-C, Non-HDL-C)

Therapies addressing residual cholesterol risk on the basis of high triglycerides (TG) or low HDL-C have not yet proved effective for event reduction in randomized clinical trials.[7] High TG and low HDL-C levels contribute strongly and synergistically to CVD even when LDL-C is well controlled. Thus, high TG might have greater importance in patients with optimal rather than in those with greater LDL-C concentrations.[8]

Because the level of TG is significantly correlated with the amount of remnant cholesterol in TRLs, the amount of TG may represent the level of remnant cholesterol. Therefore, the level of TG is a biomarker for circulating TRLs and their metabolic remnants.[5,9] Despite high-intensity statin therapy to lower LDL-C and more recently, statins with

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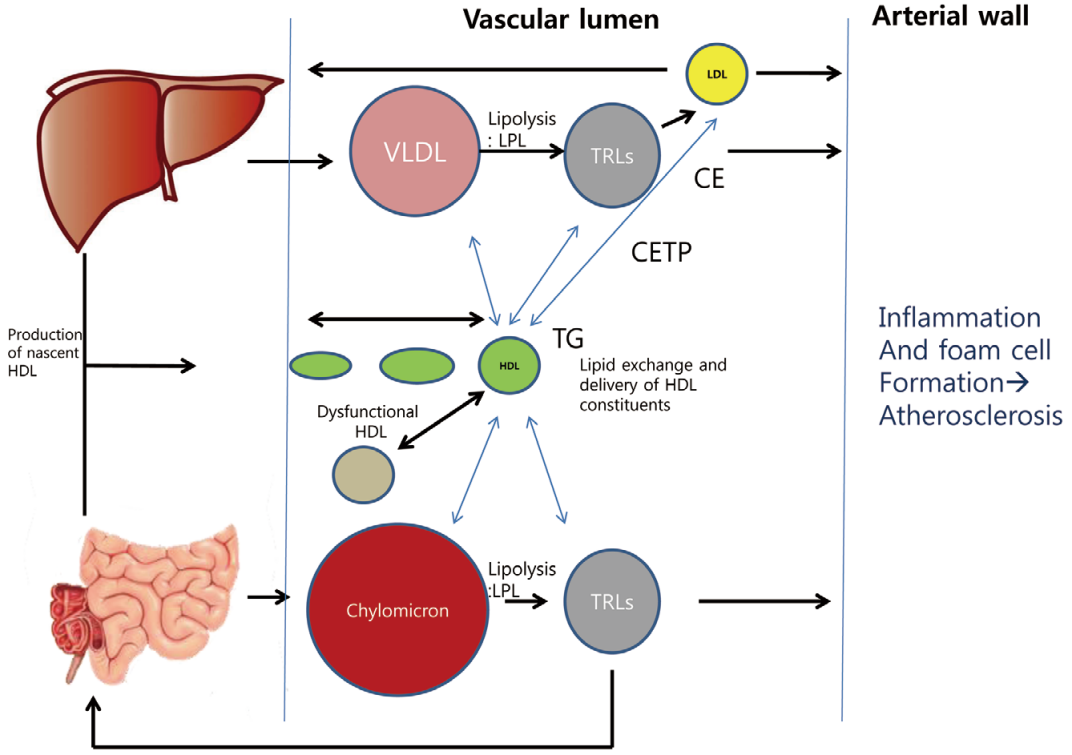

Figure 1. Production of triglyceride-rich lipoproteins (TRLs), remnant cholesterol that induces formation of atherosclerosis. Because triglyceride (TG) can be degraded by most cells, but cholesterol cannot be degraded by any cell, the cholesterol content of TRLs is more likely to be the cause of atherosclerosis and cardiovascular disease rather than raised TG per se. Indeed, cholesterol, rather than TG, accumulates in intimal foam cells and in atherosclerotic plaques, and remnant lipoproteins such as low-density lipoprotein (LDL) can enter the arterial intima. In contrast, chylomicrons are too large to enter. LPL activity on the surface of remnant particles, either on the surface of the vascular endothelium or within the intima, leads to liberation of free fatty acids, monoacylglycerols, and other molecules, each of which could cause local injury and inflammation. Although other possible mechanisms have been suggested, perhaps the simplest chain of events is that high TG concentrations are a marker for raised remnants rich in cholesterol, which, upon entering the intima, lead to low-grade inflammation, foam cell formation, atherosclerotic plaques, and ultimately cardiovascular disease and increased mortality. CE, cholesterol ester; CETP, cholesteryl ester transfer protein; HDL, high density lipoprotein; IDL, intermediate-density lipoprotein; LPL, lipoprotein lipase; VLDL, very low-density lipoprotein. Reprinted with permission from Han SH, et al.[5]

ezetimibe or proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors to further decrease LDL-C levels, a significant residual risk of CVD still persists. TRL-C may account, at least in part, for this residual risk. Recently, increased TRL-C levels were associated with increased CV risk. Lowering high TRL-C levels was effective in reducing CV events.[10] That study set angiopoietin-like 3 (ANGPTL3) or apolipoprotein C3 (APOC3) as a new target to improve TGs and TRL-C.[11] Drugs targeting ANGPTL3 (human monoclonal antibody against ANGPTL3, evinacumab, or antisense oligonucleotides against ANGPTL3 messenger-RNA) or APOC3 (antisense inhibitor of APOC3 synthesis) are under development.[12]

Of note, targeting TRL-C and non-HDL-C rather than lowering LDL-C down to very low concentrations to lower the residual CV risk are closely associated with cardiometabolic risk factors.[13] Although PCSK9 inhibitors reduce apoB levels meaningfully, it is not known if PCSK9 inhibitors are effective in lowering TRL-C and non-HDL-C. However, very recently, icosapent ethyl reduced CV events by reducing TG in patients who were already on statin treatment.[14]

Small Dense LDL

Small dense LDL is known as cholesterol-depleted LDL particles that are associated with increased serum concentrations of TG, reduced serum HDL-C levels, and an increased risk of coronary artery disease (CAD).[15] Small LDL particles trigger atherogenesis. The direct mechanisms include enhanced oxidative susceptibility, reduced clearance by LDL receptors in the liver with increased LDL receptor-independent binding in the arterial wall, and endothelial dysfunction that is independent of the concentrations of other lipids.[16]

Lipoprotein (a)

Lp(a) induces proinflammatory responses via accumulation of oxidized phospholipids and potentially exerts prothrombotic effects via the plasminogen-like apolipoprotein (a) moiety. It mediates atherogenicity via its LDL moiety, which has a similar proportion of cholesterol content as traditional LDL particles.[17]

Elevated baseline and on-statin Lp(a) show an independent approximately linear relation with CVD risk.[18] This suggests a rationale for testing a Lp(a)-lowering hypothesis

in CVD outcomes trials. Therefore, screening for elevated Lp(a) is recommended for those at intermediate or high CVD risk, with a desirable level <50 mg/dL as a function of global CV risk.

Lp(a) becomes a more potent predictor of residual risk especially when LDL-mediated risk is diminished with statins, because statin therapy only reduces LDL-C. In other words, statins do not reduce Lp(a)-mediated risk in patients with increased amounts of Lp(a).[18] Furthermore, the FOURIER and ODYSSEY OUTCOMES trials suggested that increased Lp(a) persists as a significant risk factor for atherosclerotic CV events.[19,20] These trials showed that elevated baseline Lp(a) remains a risk factor for CVD, even with on-treatment LDL-C <50 mg/dL in patients treated with statins and PCSK9 inhibitors. This observation is especially evident at Lp(a) concentrations >50 mg/dL. Nonetheless, PCSK9 inhibitors might reduce Lp(a) because evolocumab significantly reduced Lp(a) levels, and patients with higher baseline Lp(a) levels experience greater absolute reductions in Lp(a) and tend to derive greater coronary benefit from PCSK9 inhibition.[21] These findings provide a reason to evaluate drugs that can lower Lp(a) specifically, as they might have the potential to reduce residual CV risk after statin treatment.

Residual Inflammatory Risks

The revised ACC/AHA guideline 2018 recommends lipid management with statins as first-line therapy according to the serum LDL-C level, atherosclerotic CVD and diabetes.[22] However, many statin-treated patients continue to suffer from life-threatening vascular events despite reaching the target LDL-C level.[5,23] More intensive compared with less intensive LDL-C lowering has been associated with a greater reduction in risk of total and CV mortality in trials of patients with higher baseline LDL-C levels. This association is not present when the baseline LDL-C level is <100 mg/dL, suggesting that the greatest benefit from LDL-C-lowering therapy may occur for patients with higher baseline LDL-C levels.[24]

Recently, the hypothesis of residual inflammatory risk after statin treatment was confirmed. An early stage of atherosclerosis develops through accumulation of lipoproteins, but the late stage develops or is aggravated by inflammation that includes high-sensitivity C-reactive protein (hsCRP), interleukins (IL)-1β, and -6, etc.[25] When residual inflammatory risk in patients with both statin therapy and bococizumab or evolocumab was evaluated according to on-treatment levels of hsCRP and LDL-C, in the adjusted analyses of the association between LDL-C and hsCRP levels and CV risk both LDL-C and hsCRP were independently associated with the primary outcome.[26,27] Therefore, controlling residual inflammatory risks is mandatory in addition to controlling LDL-C and residual cholesterol risks.[28] More aggressive LDL-C reduction with ezetimibe or PCSK9 inhibitors proved its efficacy in reducing residual risk among those on statins, among those with statin intolerance, and among those with familial hyperlipidemia characterized by residual LDL receptor function. Achievement of dual LDL-C and hsCRP targets was more frequent with the addition of ezetimibe to simvastatin and associated with better outcomes.[29]

Residual inflammatory risk is the state of serum hsCRP >2 mg/L even though serum LDL-C is <70 mg/dL after statin therapy.[28] Unlike residual cholesterol risk, the method of treating residual inflammatory risk has not been verified, although numerous studies are in progress to find the proper management to decrease inflammatory risk. Although a high hsCRP level is related to adverse events, hsCRP is known as a relatively acute-phase substance and other substances that better reflect residual inflammation need to be elucidated.

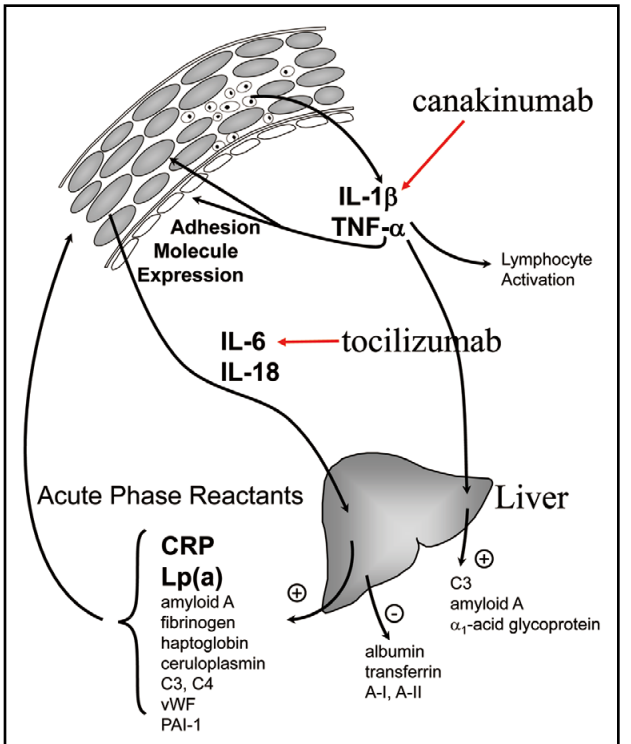

Figure 2. Proinflammatory cytokines such as interleukin (IL)-1β, IL-6, IL-18 and tumor necrosis factor (TNF)-α released from injured arteries initiate hepatic synthesis of acute-phase reactants. Some acute-phase reactants have effects on the arterial segment and contribute to the inflammatory response. Canakinumab specifically targets IL-1β, and tocilizumab directly targets IL-6 by blocking IL-6 binding. CRP, C-reactive protein; Lp(a), lipoprotein (a); PAI, plasminogen activator inhibitor; vWF, von Willebrand Factor.

Cytokines involved in human atherosclerosis can be broadly classified as proinflammatory and proatherogenic (e.g., IL-1, IL-6, and TNF [tumor necrosis factor]) or as anti-inflammatory and antiatherogenic (e.g., IL-10 and IL-1rA).[25] CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcomes Study) recently showed that specific targeting of IL-1β can significantly reduce CV event rates without lipid or blood pressure lowering. The magnitude of benefit of this cytokine-targeted approach to atherosclerosis treatment was associated with the magnitude of reduction in the central signaling cytokine IL-6 and the downstream clinical biomarker hsCRP.[30] By contrast, in CIRT (Cardiovascular Inflammation Reduction Trial), low-dose methotrexate neither reduced IL-1β, IL-6, or hsCRP nor lowered CV event rates.[31] Taken together, these 2 contemporary trials provide proof of principle that focused cytokine inhibition, not broad-spectrum anti-inflammatory therapy, is likely to be crucial for athero-protection. In addition, trials of colchicine, IL-1 inhibitors, and IL-6 inhibitors to target residual inflammatory risk rather than residual cholesterol risk are in progress (**Figure 2**).

Table. Observational and Causal (by Use of Genetics) Associations of Raised Remnant Cholesterol and TG With Risk of Ischemic Heart Disease, MI and All-Cause Death

		N total	N events	OR (95% CI)
Ischemic heart disease				
Remnant cholesterol increase of 39 mg/dL	Observational	56,667	2,874	1.4 (1.3–1.5)
	Causal using genetics	73,513	11,984	2.8 (1.9–4.2)
MI				
Remnant cholesterol doubling in concentration	Observational	10,394	1,098	1.7 (1.4–2.0)
	Causal using genetics	60,113	5,705	2.2 (1.5–3.4)
TG doubling in concentration	Observational	10,391	1,098	1.6 (1.3–1.9)
	Causal using genetics	60,113	5,705	1.9 (1.4–2.7)
All-cause death				
TG increase of 88.41 mg/dL	Observational	13,957	9,991	1.2 (1.1–1.2)
	Causal using genetics	10,208	4,005	2.0 (1.2–3.3)

Reprinted with permission from Han SH, et al[5] and modified from Nordestgaard BG, et al.[9] MI, myocardial infarction; OR, odds ratio; TG, triglycerides.

Frontline Management of Residual Risk

Ezetimibe

Lowering LDL-C levels to 58 mg/dL with ezetimibe on simvastatin 40 mg significantly reduced rates of major CV events without adverse effects, compared with simvastatin alone.[32] In addition to lowering LDL-C further, ezetimibe reduced visceral fat with beneficial effects on adiponectin and insulin resistance. Indeed, experimental studies have demonstrated that ezetimibe improves liver steatosis and insulin sensitivity in a rat model of metabolic syndrome.[33] Ezetimibe combined with simvastatin significantly decreased insulin levels and increased adiponectin levels and insulin sensitivity, and reduced visceral fat and blood pressure quite differently from simvastatin alone in patients with hypercholesterolemia.[34] These are the intriguing off-target effects of ezetimibe.[1,35] Indeed, simvastatin combined with ezetimibe therapy was more beneficial in patients with diabetes than in patients without diabetes.[36] Patients randomized to atorvastatin+ezetimibe therapy experienced a greater reduction in percent atheroma volume than those randomized to atorvastatin and it was not only because of the lower mean LDL-C level achieved.[37]

PSCK9 Monoclonal Antibodies and Therapeutic Oligonucleotides

Monoclonal antibodies to PCSK9 are subcutaneously administered (every 2 or 4 weeks) and they prevent PCSK9 from binding to LDL receptors while maintaining LDL receptors on hepatocytes with reducing plasma LDL level.[38,39] These antibodies only affect circulating PCSK9 without affecting intracellular pathways. Although it is known that PCSK9 is related to apoB synthesis, a recent study reported that PCSK9 monoclonal antibodies did not alter hepatic apoB production.[40]

Alirocumab and evolocumab, in addition to high-intensity statin, reduced recurrent ischemic CV events, non-fatal CV events and deaths in patient with acute coronary syndrome (ACS),[38,41] despite evolocumab with statin not changing plaque composition as measured by virtual histology imaging.[42] PCSK9 inhibitors achieve LDL-C reductions of ≥50–60% while also reducing total LDL particles, small and large LDL particles, and apoB levels. PCSK9 inhibitors also affect other aspects of lipoprotein metabolism, inflammation, thrombosis, and immune function. Monoclonal PCSK9 antibodies lower LDL-C and other atherogenic lipoproteins and favorably affect the complex inflammatory and thrombotic mechanisms related to atherosclerosis progression and acute events by intriguing off-target effects.[43–45] On the other hand, an oligonucleotide, inclisiran, a small interfering RNA (siRNA) targeting PCSK9 mRNA in hepatocytes, was recently developed. Interestingly, inclisiran lowered both apoB and non–HDL-C.[46] The advantage of inclisiran is sustained suppression of PCSK9 and LDL-C for at least 6 months, which allows for twice-yearly administration, which is promising as a cholesterol-lowering strategy. Inclisiran may be an alternative to statins and PCSK9 monoclonal antibodies because of its potency, relatively infrequent administration requirement, cost, etc.[47] However, recent clinical genetic studies reported that in subjects with glucose intolerance, genetic variants of PCSK9 or HMGCR have reduced LDL levels (presumably from loss of function) that were associated with similar independent and additive effects to increase the risk of diabetes per unit decrease in LDL-C.[48,49] PCSK9 inhibitors and statins use distinct mechanisms to lower LDL-C, the common downstream effect that is likely related to both protection against CVD and promotion of diabetes. This suggests that the effects of most statins in promoting diabetes is an on-target drug effect. Data caution that future outcome studies of PCSK9 inhibitors or oligonucleotide therapeutics, a new class of drugs that target RNA directly, should be designed for optimal detection of adverse metabolic actions.[47,50]

Targeting Hypertriglyceridemia (TG, TRL-C, Non-HDL-C)

Omega-3 Fatty Acids Epidemiological and clinical evidence suggests a significant inverse association between long-term intake of omega-3 fatty acids (n-3 FA) and death associated with CAD.[51] Meanwhile, consumption of n-3 FA causes improvement in many relevant CV biomarkers including those represented by hypertriglyceridemia,[52] vascular dysfunction and inflammation.[53]

By contrast, despite a significant reduction in TG and improvement of flow-mediated dilation, 2 g n-3 FA therapy did not significantly change insulin or plasma adiponectin levels, or insulin sensitivity relative to baseline measurements. Furthermore, n-3 FA therapy did not significantly improve acute-phase reactants or insulin sensitivity in patients with hypertriglyceridemia, regardless of dosage.[53] Recent studies report that low doses of n-3 FA failed to

reduce the rate of major CV events.[54,55]

By contrast, 4 g n-3 FA modified cardiac structures and tissue characteristics in patients receiving current guideline-based therapy.[56] Also, a different n-3 FA, icosapent ethyl (2 g twice daily), improved CV outcomes in patients with elevated TG despite statin therapy.[14]

How can we explain these different results? High dose or unique n-3 FA? Further investigation is needed. The role of n-3 FA, particularly high dose or unique n-3 FA, on CV events under modern guideline therapy should be further defined in the reduction of residual risk in the future.

Targeting Remnant Cholesterol Remnant cholesterol is causative for ischemic heart disease independent of HDL-C levels. Studies clearly demonstrate a role of non-fasting TG and remnant cholesterol levels on the predictions of CVD events in the general population.[57] Among patients receiving statin therapy after ACS, on-treatment TG ≤150 mg/dL was associated with a lower risk of recurrent CVD events independently of the level of LDL-C.[58] These data support the concept that achieving both low LDL-C and low TRLs may be important therapeutic goals in patients after ACS.

Recent Mendelian randomization studies with genetic variants reported several candidate genes that affect the concentrations of remnant cholesterol.[9] The relative risks of remnant cholesterol on ischemic heart disease and all-cause death according to causal genetic variants compared with corresponding observational results are shown in **Table**.

Fibric acid is a synthetic ligand of the nuclear receptor peroxisome proliferator-activated receptor α (PPARα), which is highly expressed in skeletal muscle and heart where it promotes β-oxidation of FA to mediate hypolipidemic actions. PPARα regulates the expressions of key proteins involved in atherogenesis, vascular inflammation, plaque stability, and thrombosis. Fibrate, a PPARα agonist, therapy significantly improves the lipoprotein profile and the flow-mediated dilator response to hyperemia, reduces levels of inflammatory markers, increases adiponectin levels, and improves insulin sensitivity.[59]

Fibrate therapy has improved clinical outcomes in primary and secondary prevention trials, especially in patients with low HDL-C and high TG, despite use of established therapy.[60] Fenofibrate did not reduce events overall in the trials, except in patients in the high TG and low HDL-C subgroups. However, the failure of fenofibrate in other patients has been blamed on several issues such as fairly low TG levels.[9] On the other hand, off-target effects of fibrates such as an anti-inflammatory effect have been discussed.[52,59] Indeed, although fibrates appear to work, their benefit is not associated with TG lowering. In other words, patients with high TG levels may be more likely to benefit, but not necessarily because of TG lowering itself.

Antisense inhibitor of APOC3 synthesis, a chemically-modified oligonucleotide, is delivered subcutaneously and internalized in the liver where it inhibits the translation of APOC3 mRNA and promotes mRNA degradation through activation of RNase H.[61] A phase 2 study resulted in dose-dependent and prolonged decreases in plasma APOC3 levels.[62] This study provided evidence for a causal relationship between APOC3 and TG metabolism.

Similar to APOC3, ANGPTL, ANGPTL3 and ANGPTL4 are thought to inhibit lipoprotein lipase activity, leading to elevated plasma TG levels. Pharmacological inhibition of these ANGPTLs could reduce plasma TG by a mechanism similar to that of anti-APOC3-focused therapies and result in reduced CVD risk. Genetic and therapeutic antagonism of ANGPTL3/4 in humans and of ANGPTL3 in mice is associated with decreased levels of all 3 major lipid fractions and decreased odds of atherosclerotic CVD.[63]

Targeting Residual Inflammatory Risk: hsCRP, IL-1β, IL-6 Statins have anti-inflammatory effects;[1,64] it has been demonstrated that statins reduced hsCRP and IL-6 levels in patients.[65] There is evidence of residual inflammatory risk persisting in patients treated with both statin therapy and PCSK9 inhibition.[26] A potent anti-inflammatory agent may control residual risk. Indeed, anti-inflammatory therapy targeting the IL-1β innate immunity pathway with canakinumab led to a significantly lower rate of recurrent CV events than placebo, independent of lipid-level lowering.[30] Unlike canakinumab, methotrexate failed to lower IL-1β, IL-6, or hsCRP levels and thus maybe did not result in fewer CV events. Even worse, methotrexate was associated with elevations in liver enzyme levels, reductions in leukocyte counts and hematocrit levels, and a higher incidence of non-basal-cell skin cancers than placebo.[31] Canakinumab was also associated with a higher incidence of fatal infections despite the reduction in CV events. To prove the hypothesis is intriguing, but it should be interpreted with caution because of serious adverse effects.

Conclusions

Although statins significantly decrease the risk of CVD, their effect is not enough to prevent or decrease the CV risk completely. Because of the complex etiology of atherosclerosis, residual risk such as cholesterol and inflammatory risk after statin treatment is present. Therefore, strategies to overcome residual risk during the statin era should be considered and investigated continuously.

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Disclosures

Dr. Koh holds a certificate of patent, 10-1579656 (pravastatin+valsartan).

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