Additional Lipid Targets to Modulate Atherosclerotic Plaques beyond LDL-C Lowering

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Residual cardiovascular risks under statin therapy suggest the need to develop additional therapeutic approach to further improve cardiovascular outcomes. Epidemiological and intravascular imaging studies have revealed the relationship of these lipid targets with atherosclerotic cardiovascular disease, indicating triglyceride and high-density lipoprotein cholesterol (HDL-C) as potential targets for achieving better clinical outcomes. However, clinical efficacy of lowering triglyceride and raising HDL-C level has not been established yet. Although findings from clinical trials testing novel agents targeting these lipid markers are disappointing, further search still continues to identify effective therapeutic approach due to their anti- or pro-atherogenic properties. Intravascular imaging modality has contributed to the elucidation of disease mechanism and the evaluation of novel drugs modulating triglyceride and HDL-C. In this review, anti- or pro-atherogenic properties of triglyceride and HDL-C, its association with clinical outcomes and atherosclerotic plaques will be summarized.

KEY WORDS: atherosclerosis, high-density lipoprotein cholesterol, imaging, triglyceride

I. Introduction

Lowering low-density lipoprotein cholesterol (LDL-C) is a cornerstone in the current therapeutic guideline to prevent atherosclerotic cardiovascular diseases1–7). This is because numerous large-scale randomized controlled trials have consistently demonstrated the beneficial effect of lowering LDL-C level with a statin for the primary and secondary prevention3–8). Furthermore, serial intravascular imaging studies have also supported its anti-atherosclerotic effects. Intensive lowering LDL-C has been shown to slow plaque progression and induce its regression if very low LDL-C level is achieved9–11). However, substantial amount of cardiovascular events still occurs even under intensive control of LDL-C level12, 13). The residual cardiovascular risks indicate the need to modulate additional therapeutic targets to further reduce atherosclerotic cardiovascular events.

The development and propagation of atherosclerosis is derived by the retention of cholesterol-rich lipoproteins within the subendothelial matrix of the arterial wall. While LDL has been considered as the main atherogenic cholesterol-rich particle, other apolipoprotein-B-containing lipoproteins also contribute to intimal cholesterol deposition. Triglyceride-rich lipoprotein is one of atherogenic particles potentially promoting formation and progression of atherosclerotic plaques14). In contrast to these lipoproteins, high-density lipoprotein harbours a variety of atheroprotective properties which may have the ability in halting atherosclerosis15). These properties suggest triglyceride-rich lipoprotein and high-density lipoprotein (HDL) as potential therapeutic targets for the prevention of atherosclerotic cardiovascular disease. However, controversies exist with regard to their associations with cardiovascular events and clinical efficacy of pharmacological modulation of triglyceride-rich lipoprotein and HDL.

Intravascular imaging modalities have contributed to the elucidation of atherosclerotic mechanisms and clinical efficacy of novel anti-atherosclerotic therapies5–8, 16–20). This review summarizes evidences from clinical and intravascular imaging studies to elucidate the contribution of triglyceride and HDL to atherosclerotic cardiovascular disease (ASCVD) and clinical impact of their modulation.

II. Triglyceride

Triglyceride exists in plasma as lipoprotein, pseudo lipid-protein complex. Apolipoprotein B is a component of triglyceride-rich lipoproteins including chylomicron, very-low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL) and LDL21, 22). Following the absorption of dietary lipids, chylomi-
cron is formulated and then hydrolyzed by lipoprotein lipase (LPL)\(^{21,22}\). This process leads to the development of chylomicron remnant, which is uptaken by liver through LDL receptor, hepatic triglyceride lipase and cell-surface proteoglycans\(^{23,24}\). Another triglyceride-rich lipoprotein, VLDL is assembled in the endoplasmic reticulum of hepatocytes. VLDL triglyceride is hydrolyzed by LPL, generating IDL and LDL. Partial hydrolysis causes VLDL remnants. Chylomicron and VLDL remnants are accumulated into vessel wall, leading to foam cell formation. In addition, these remnants have been shown to increase the expression of pro-inflammatory genes and induce apoptosis\(^{21,22}\). These atherogenic aspects of triglyceride suggest its potential contribution to atherosclerosis.

1. Epidemiological data (Table 1)

   a. Subjects who do not receive a statin

   Two observational studies (Copenhagen City Heart Study and Women’s Health Study) showed that elevated triglyceride level was associated with a higher risk of ASCVD including myocardial infarction, stroke and all-cause mortality\(^{23-25}\). One meta-analysis including 68 long-term prospective studies also reported that an increased level of triglyceride was associated with increased risk of ischemic heart disease and death in men and women.

   - **Table 1** The association of triglyceride level with cardiovascular events

     **Subjects without statin therapy**

     | Authors                  | Journal          | Subjects                                                                 | Outcomes                                                                 | Findings                                                                 |
     |--------------------------|------------------|-------------------------------------------------------------------------|--------------------------------------------------------------------------|--------------------------------------------------------------------------|
     | Nordestgaard BG, et al.  | JAMA 2007; 298: 299-308 | 13,981 subjects from the general population of Copenhagen, Denmark, aged 20 to 93 years | Incident myocardial infarction, ischemic heart disease and total death     | Elevated nonfasting triglyceride level was associated with increased risk of myocardial infarction, ischemic heart disease and death in men and women. |
     | Freiberg JJ, et al.      | JAMA 2008; 300: 2142-2152 | 13,956 men and women aged 20 through 93 years                           | Ischemic stroke                                                          | Nonfasting triglyceride level was associated with risk of ischemic stroke in both men and women. |
     | Bansal S, et al.         | JAMA 2007; 298: 309-316 | 26,509 healthy US women participating in the Women’s Health Study       | Non-fatal myocardial infarction, nonfatal ischemic stroke, coronary revascularization and cardiovascular death | Nonfasting triglyceride level was associated with incident cardiovascular events, independent of traditional cardiac risk factors, levels of other lipids, and markers of insulin resistance. |
     | Emerging Risk Factors Collaboration\(^{26}\) | JAMA 2009; 302: 1993-2000 | 302,430 people without vascular disease                                | Nonfatal myocardial infarction, coronary heart disease death, ischemic stroke, hemorrhagic stroke and unclassified stroke | Adjusted HR for coronary heart disease was 0.99 (95% CI 0.94-1.05) with triglyceride. |

   **Subjects with statin therapy**

   | Authors                  | Journal          | Subjects                                                                 | Outcomes                                                                 | Findings                                                                 |
     |--------------------------|------------------|-------------------------------------------------------------------------|--------------------------------------------------------------------------|--------------------------------------------------------------------------|
     | Miller M, et al.         | J Am Coll Cardiol 2008; 51: 724-730 | Atorvastatin 80 mg vs. pravastatin 40 mg (PROVEIT-TIMI22)               | Death, myocardial infarction, recurrent acute coronary syndrome          | Low on-treatment triglyceride (<150 mg/dl) was associated with reduced cardiovascular event risk (HR 0.80, 95% CI 0.66 to 0.97; p=0.025). Lower cardiovascular event risk was observed with triglyceride < 150 mg/dl and LDL-C < 70 mg/dl (HR 0.72, 95% CI 0.54 to 0.94; p=0.017) or low on-treatment triglyceride, LDL-C, and C-reactive protein (< 2 mg/l) (HR 0.59, 95% CI 0.41 to 0.83; p=0.002) compared with higher levels of these lipids markers. |
     | Faergeman O, et al.      | Am J Cardiol 2009; 104: 459-463 | TNT trial: atorvastatin 80 mg vs. atorvastatin 10 mg IDEAL: atorvastatin 80 mg vs. simvastatin 20 to 40 mg | Coronary death, non-fatal myocardial infarction, resuscitation after cardiac arrest, fatal or non-fatal stroke, coronary revascularization, hospitalization for unstable angina or heart failure, peripheral artery disease | Risk of cardiovascular events increased with increasing TGs (p < 0.001). |
not only triglyceride but also cholesterol content in remnant particles play a critical role in atheroma formation and progression.

b. Subjects receiving a statin

In recent clinical trials analyzing patients receiving a statin, the association of triglyceride with ASCVD was also observed. In the PROVEIT-TIMI (Pravastatin or Atorvastatin Evaluation and Infection Therapy – Thrombolysis in Myocardial Infarction) 22 trial, on-treatment triglyceride <150 mg/dl was independently associated with a lower risk of recurrent coronary events in patients with acute coronary syndrome (ACS) who achieved LDL-C below 70 mg/dl. Furthermore, pooled analysis of the TNT (Treating to New Targets) and IDEAL (Incremental Decrease in Clinical Endpoints Through Aggressive Lipid Lowering) trials demonstrated a trend for decreased cardiovascular event risks with lowering triglyceride levels. As such, while LDL-C lowering remains the first priority, additional therapies targeting an elevated triglyceride level may offer the possibility of incremental reduction in ASCVD risks in high-risk populations.

2. Intravascular imaging data

In vivo plaque imaging has enabled to identify the association of triglyceride level with atherosclerotic plaques. We retrospectively analyzed pooled intravascular ultrasound (IVUS) data from 9 clinical trials involving 4,957 patients with coronary artery disease. Over 95% of study population received a statin during the course of the study. On serial evaluation, progression rate increased when triglyceride level was above 110 mg/dl (Fig. 1). In addition, actual plaque progression occurred in association with triglyceride level above 200 mg/dl (Fig. 1). This relationship was further analyzed in subjects stratified into 4 groups according to LDL-C level and triglyceride levels. Achieving a lower level of triglyceride < 200 mg/dl was associated with more regression of coronary atherosclerosis regardless of on-treatment LDL-C levels (Fig. 2). Multivariate analysis demonstrated on-treatment triglyceride level as an independent predictor of atheroma progression. Furthermore, patients with achieved triglyceride level > 200 mg/dl exhibited a greater likelihood of experiencing a major cardiovascular event.

In diabetic patients, hypertriglyceridemia and low HDL-C level are characteristics of diabetic dyslipidemia. The association of this lipid feature with plaque instability was evaluated by using optical coherence tomography (OCT) imaging in diabetic subjects with coronary artery disease (CAD). This analysis included 128 patients with CAD who received percutaneous coronary intervention. On OCT imaging, high triglyceride/HDL-C ratio contributed to more vulnerable features such as a larger lipid arc and a higher frequency of cholesterol crystals. Even after adjusting differences in clinical demographics, triglyceride/HDL-C ratio was still related to lipidic materials within plaques.

3. Clinical efficacy of agents modifying triglyceride

Suggestive evidences from epidemiological studies have stimulated considerable interests to investigate efficacy of lowering triglyceride on cardiovascular outcomes. Fibrates, which are peroxisome proliferator-activated receptor α agonist, lowers triglyceride by 20–50% and raise HDL-C levels by 10%. Recent three large-scale clinical trials failed to prove its benefit for reduction of ASCVD. In the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study analyzing 5,518 type 2 diabetic subjects, despite a significant lowering of triglyceride...
levels with an increased level of HDL-C under fibrate therapy, additive cardiovascular risk reduction was not observed (p=0.32). Subgroup analyses identified diabetic patients with both high triglyceride and low HDL-C levels were less likely to develop cardiovascular events under fibrate use although this comparison did not meet statistical significance (p=0.06). Similar observation was identified by one recent meta-analysis including 45,058 patients. This analysis showed favourable benefit of fibrates in subjects with high triglyceride level with or without low HDL-C. These findings must be confirmed in a dedicated trial. Other new agents such as omega-3 fatty acids and selective peroxisome proliferator-activated receptor β modulators are expected to be efficacious for improvement of cardiovascular outcomes. Large clinical trials will be warranted to elucidate their clinical impact on ASCVD.

III. High-density lipoprotein

HDL particle is composed of triglyceride and cholesterol ester-rich hydrophobic core with an outer amphipathic layer of free cholesterol, phospholipid, and several apolipoproteins. The main protein component of HDL is apolipoprotein A-I (apoA-I) which plays a key role in the biogenesis and function of HDL. In addition, HDL particles carry a variety of enzymes, such as paraoxonase, platelet activating factor-acetyhylidrolase, lecithin cholesterol acyltransferase, and cholesteryl ester transfer protein (CETP). These components of HDL have been shown to contribute to its anti-atherosclerotic properties. One major atheroprotective ability of HDL is to promote cholesterol efflux from cells such as macrophages and the related complex physiological process of reverse cholesterol transport. This attractive process has been reported to occur through several mechanism: unidirectional ATP-dependent pathway mediated by ATP-binding cassette transporter A1 (ABCA1), a unidirectional ATP-dependent pathway mediated by the ATP-binding cassette G1 transporter (ABCG1), an ATP-independent, bidirectional pathway involving scavenger receptor class B type I (SR-BI), and receptor-independent passive diffusion according to cholesterol concentration gradient. Lipid-poor apoA-I promotes efflux of cholesterol via the transporter ABCA1 and that mature HDL contributes to cholesterol efflux via ABCG1, SR-BI and other mechanisms. Recently, one cross-sectional study have elucidated that HDL cholesterol efflux capacity is inversely associated with carotid intima-media thickness (β coefficient per 1-SD increase in efflux capacity; −0.03, 95% CI; −0.06 to −0.01, p=0.003) and the likelihood of angiographic CAD (odds ratio per 1-SD increase, 0.75; 95% CI, 0.63 to 0.90; p=0.002) even after adjusting HDL-C. This finding supports functionality but not quantity of HDL as an important factor associated with ASCVD.

HDL also harbours several properties which favourable modulate atherosclerosis such as anti-oxidative, anti-inflammatory and anti-thrombotic effects and vasodilatory ability. The association of these HDL-mediated functions with cardiovascular outcomes is not fully evaluated yet. However, modifying these properties also have great potential to halt atherosclerosis and prevent atherosclerotic cardiovascular events.

1. Diminished functionality of HDL and atherosclerosis

Recent investigations suggest that patients with cardiovascular disease have ‘dysfunctional’ HDL, which lacks typical atheroprotective properties and promotes pro-inflammatory effects. This observation was also identified in patients with ACS, type 2 diabetes or inflammatory diseases. Myeloperoxidase (MPO) is considered to cause functional impairment of HDL. This mechanistic link is supported by several studies, which elucidated HDL isolated from atherosclerotic lesions contain numerous MPO-derived peptides. In population studies, the direct association of serum MPO level with mortality or cardiovascular events in patients with or without CAD has been reported. IVUS imaging studies have elucidated that MPO level was associated with progression of coronary atherosclerosis in diabetic patients with CAD (Fig. 3). These observations might suggest MPO as another important therapeutic target for the prevention of cardiovascular events.

2. Epidemiological data (Table 2)

Many prospective studies from different racial and ethnic groups have confirmed that HDL-C is a strong, consistent, and independent predictor of incident cardiovascular events. An inverse association of triglyceride with risk of ischemic heart disease was identified in the Framingham Heart Study, Lipid Research Clinics Prevalence Mortality Follow-up Study, Coronary Primary Prevention Trial, Multiple Risk Factor Intervention trial.
Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) trial cohort, HDL-C level was inversely related to vascular risk in the placebo group, whereas there was no significant relationship between HDL-C level and cardiovascular events in patients given rosvastatin 20 mg. Similar observation was recognized by other statin trials including AFCAPS/TexCAPS (Air Force/Texas Coronary Atherosclerosis Prevention Study) and CARE (Cholesterol and Recurrent Events). However, in a large meta-analysis of eight statin trials, HDL-C level was strongly associated with a reduced cardiovascular risk, even

### Subjects without statin therapy

| Authors                | Journal                  | Subjects                                                                 | Outcomes                                                                 | Findings                                                                 |
|------------------------|--------------------------|-------------------------------------------------------------------------|--------------------------------------------------------------------------|--------------------------------------------------------------------------|
| Gordon T, et al.        | Am J Med 1977; 62: 707-714 | 2,815 men and women aged 49 to 82 years                                 | Coronary heart disease                                                  | HDL-C had an inverse association with the incidence of coronary heart disease (p<0.001) in either men or women. |
| Rhoads GG, et al.       | N Engl J Med 1976; 294: 293-298 | 1,859 Hawaii Japanese men 50 to 72 years old                            | Coronary heart disease                                                  | An inverse relationship between HDL-C and coronary heart disease existed. |
| Jacobs DR Jr, et al.    | Am J Epidemiol 1990; 131: 32-47 | 8,825 male and female participants                                       | Cardiovascular disease mortality                                         | Multivariate analysis demonstrated an inverse relationship between HDL-C and cardiovascular disease mortality. |

### Subjects with statin therapy

| Authors                | Journal                  | Subjects                                                                 | Outcomes                                                                 | Findings                                                                 |
|------------------------|--------------------------|-------------------------------------------------------------------------|--------------------------------------------------------------------------|--------------------------------------------------------------------------|
| Olsson AG, et al.      | Eur Heart J 2005; 26: 890-896 | 3,086 ACS patients, randomized to either atorvastatin 80 mg/day or placebo | Death, non-fatal myocardial infarction, cardiac arrest, worsening angina, repeat emergency hospitalization | Baseline HDL-C predicted outcome with a hazard ratio of 0.986 per mg/dl increment in HDL-C, p<0.001, indicating 1.4% reduction in risk for each 1 mg/dl increase in HDL-C. |
| Ray KK, et al.          | Arterioscler Thromb Vasc Biol 2009; 29: 424-430 | 4,162 patients with ACS who were randomized to atorvastatin 80 mg versus pravastatin 40 mg | Death and non-fatal acute coronary syndrome                              | apoB/AI (HR 1.10, 95% CI 1.01 to 1.20), TC/HDL (HR 1.12, 95% CI 1.01 to 1.24), and non–HDL-C (HR 1.20, 95% CI 1.07 to 1.35) predicted events, but HDL-C did not. |
| Ridker PM, et al.       | Lancet 2010; 376: 333-339 | 17,802 subjects with randomization to rosvastatin 20 mg or placebo      | Non-fatal myocardial infarction, stroke, hospitalization for unstable angina, revascularization, cardiovascular death | In the placebo group, HDL-C was inversely related to vascular risk both at baseline (top quartile vs bottom quartile HR 0.54, 95% CI 0.35-0.83, p=0.0039) and on-treatment (HR 0.55, 95% CI 0.35-0.87, p=0.0047). By contrast, in the rosvastatin 20 mg group, no significant relationships were noted between quartiles of HDL-C concentration and vascular risk either at baseline (HR 1.12, 95% CI 0.62-2.03, p=0.82) or on-treatment (HR 1.03, 95% CI 0.57-1.87, p=0.97). |
| Gotto AM Jr, et al.     | Circulation 2000; 101: 477-484 | 6,605 patients                                                          | Acute major coronary event                                               | Baseline HDL-C was a significant predictor of AMCE (p=0.01). However on-treatment HDL-C level was not. |
| Sacks FM, et al.        | Circulation 1998; 97: 1446-1452 | 4,159 patients randomized to pravastatin 40 mg or placebo               | Coronary death or non-fatal myocardial infarction                        | On multivariate analysis, on-treatment HDL-C level was weakly but significantly associated with the coronary event rate. |
| Boekholdt SM, et al.    | Circulation 2013; 128: 1504-1512 | 38,153 subjects from 8 statin trial                                     | Fatal or non-fatal myocardial infarction, fatal other coronary heart disease, hospitalization for unstable angina, fatal or nonfatal stroke | HDL-C levels were associated with a reduced risk of major cardiovascular events (adjusted HR 0.83; 95% CI 0.81-0.86 per 1 standard deviation increment). This association was also observed among patients achieving on-statin LDL-C < 50 mg/dl. |

Table 2  The association of HDL-C level with cardiovascular events

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and Honolulu Heart Study. By contrast, in patients treated with a statin, published studies showed inconsistent results. In the MIRACL (Myocardial Ischemia Reduction with Acute Cholesterol Lowering) study, HDL-C level predicted cardiovascular outcomes, indicating 1.4% reduction in risk for each 1mg/dl increase in HDL-C in ACS subjects receiving atorvastatin 80 mg. By contrast, post-hoc analysis from the PROVE IT-TIMI 22 has shown that on-treatment HDL-C did not provide prognostic information in ACS patients treated with either pravastatin 40 mg or atorvastatin 80 mg. In the JUPITER (Justification for the
among those achieving very low LDL-C level\textsuperscript{55}. Exact mechanism of these observations requires further investigation in the future.

3. Intravascular imaging data

The association of HDL-C level with atheroma progression was analyzed in 1,455 subjects with CAD receiving a statin\textsuperscript{56}. In this analysis, change in HDL-C level was inversely associated with atheroma progression on IVUS imaging. Multivariate analysis demonstrated that an increase in HDL-C level as well as on-treatment LDL-C level predicted atheroma regression. Furthermore, substantial atheroma regression was observed in subjects who achieved LDL-C level < 85 mg/dl and percent increase in HDL-C >8.5 % during the course of the study. Post-hoc analysis from the SATURN (the Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin Versus Atorvastatin) study elucidated that an increase in HDL-C under maximally intensive statin use induced plaque regression (p<0.001) and reduced necrotic core volume (p=0.03) on virtual-histology IVUS imaging\textsuperscript{57}.

OCT imaging elucidated the relationship of HDL-C level with plaque instability in 261 ACS subjects who received PCI\textsuperscript{58}. In this analysis, patients who exhibited thin-capped fibroatheroma at their culprit lesions were more likely to have lower HDL-C level, higher level of LDL-C and high sensitivity-CRP. In addition, HDL-C level was significantly associated with fibrous cap thickness\textsuperscript{59}. On multivariate analysis, HDL-C level was an independent predictors of thinner fibrous cap thickness and the presence of thin-capped fibroatheroma\textsuperscript{60}. These observations highlight more high-risk plaque phenotypes in CAD patients with low level of HDL-C.

4. Clinical efficacy of novel agents modulating HDL

a. Cholesteryl ester transfer protein (CETP) inhibitor

CETP is a hydrophobic glycoprotein which is synthesized by mainly liver\textsuperscript{61}. The main role of CETP is to transfer esterified cholesterol from HDL to VLDL and LDL particles accompanied by exchange for triglycerides\textsuperscript{62}. Its effect on atherogenesis is still controversial, but previous observational and animal studies have reported proatherogenic property of CETP. Subjects with CETP mutations have been shown to exhibit an increased level of HDL-C and lower incidence of CAD\textsuperscript{63,64}. In several animal studies using rodents without plasma CETP activity, an elevated HDL-C level and less atheroma formation were observed\textsuperscript{65}. Moreover, lower occurrence of cardiovascular events has been identified in patients with low CETP levels\textsuperscript{66}. Based on these observations, the efficacy of pharmacological CETP inhibition has been investigated in clinical trials. ILLUMINATE (Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events) study evaluated the clinical efficacy of torcetrapib, the first CETP inhibitor on clinical outcomes in 15,067 patients at high cardiovascular risk\textsuperscript{67}. Torcetrapib increased HDL-C by 72.1% as well as lowered LDL-C level by 24.9%. However, a significant increase in mortality and cardiovascular events was observed in patients receiving this agent, resulting in the early termination of the study. In this trial, off-target effects elevating blood pressure level was observed in the torcetrapib group. Additionally, basic studies have identified torcetrapib stimulated renin-angiotensin system\textsuperscript{68}. These negative effects of torcetrapib are considered to associate with worse clinical outcomes in torcetrapib group. The effect of torcetrapib on atheroma progression was evaluated by the ILLUSTRATE (Investigation of Lipid Level Management Using Coronary Ultrasound to Assess Reduction of Atherosclerosis by CETP Inhibition and HDL Elevation) study\textsuperscript{69}. This study compared progression of coronary atherosclerosis on IVUS imaging between torcetrapib versus placebo groups. While there was no significant difference in atheroma progression rate between two groups despite a significant increase in HDL-C level in patients treated with torcetrapib (change in percent atheroma volume, +0.19 vs. +0.12%, p=0.72), post-hoc analysis had demonstrated that the greatest increase in HDL-C with torcetrapib showed significant plaque regression (change in percent atheroma volume, −0.69% p=0.01 compared to baseline\textsuperscript{70}). This finding suggests the concept of intact HDL functionality in patients treated with torcetrapib.

Dalcetrapib is a less potent CETP inhibitor, which raises HDL-C levels by 25% to 35% but does not affect LDL cholesterol levels\textsuperscript{71}. The efficacy of this agent was tested in plaque imaging [The dal-PLAQUE study (Safety and efficacy of dalcetrapib on atherosclerotic study using novel non-invasive multimodality imaging)] and clinical outcome [Dal-OCTIMES study (A Study of Dalcetrapib in Patients with Stable Coronary Heart Disease, with Coronary Heart Disease Risk Equivalents or at Elevated Risk for Cardiovascular Disease)] studies\textsuperscript{69,70}. Similar to findings in trials using torcetrapib, favourable effect of dalcetrapib on atheroma burden, its inflammation and cardiovascular outcomes was not observed (least square mean ; 0.49 vs. 2.69 mm\textsuperscript{2}, p=0.12, cumulative event rate ; 8.3% vs. 8.0%, p=0.52)\textsuperscript{70,71}. In contrast to torcetrapib, any adverse effect on blood pressure was not identified under dalcetrapib for 24 months\textsuperscript{69,70}.

Anacetrapib is a more potent CETP inhibitor, with the ability to raise HDL-C by 138.1% and lower LDL cholesterol by 39.8%\textsuperscript{71}. The impact of anacetrapib on cardiovascular outcomes is currently being evaluated by REVEAL (Randomized Evaluation of the Effects of Anacetrapib through Lipid-modification) study\textsuperscript{72}.

Evacetrapib is the most recent CETP inhibitor which has the selective and potent ability in modulating CETP inhibitory activ-
ity \(^73\). In a phase 2 study, evacetrapib was associated with dose-dependent increase in HDL-C (from 53.6% to 128.8%) and decrease in LDL-C (13.6% to 35.9%) and triglyceride levels \(^74\). In addition, there was no adverse effect of evacetrapib on blood pressure or mineralocorticoid activity \(^76\). The clinical efficacy of evacetrapib has been investigated by the ACCELERATE (Assessment of Clinical Effects of Cholesteryl Ester Transfer Protein Inhibition with Evacetrapib in Patients at a High-Risk for Vascular Outcomes) study which enrolled 12,000 patients with atherosclerotic vascular disease who already received a statin. Despite favourable effect of evacetrapib on lipid profiles, any additive effect on cardiovascular outcomes was not observed.

b. Infusional agents of HDL

Infusional agent of HDL is another novel approach to raise this anti-atherosclerotic particle. It is generally composed of isolated, partially delipidated HDL proteins and native apoA-I or genetic variants such as apoA-I Milano complexed with phospholipids \(^75\). The advantage of this agent is to induce a rapid and time-dependent elevation in apoA-I and pre-βHDL particles \(^79\). Its clinical efficacy on coronary atherosclerosis has been investigated by using serial IVUS imaging. Nissen et al. tested intravenous infusions of reconstituted HDL containing recombinant human apoA-I Milano for 5 weeks in ACS subjects \(^80\). This study found out a significant reduction in atheroma burden under the therapies (change in percent atheroma volume, −1.29 and −0.73% in 15 and 45 mg/kg infusional HDL, respectively) \(^76\). Another IVUS clinical trial, ERASE (Evaluation the Effects of Reconstituted High-density Lipoprotein) trial, infusing HDL containing wild-type apoA-I for 4 weeks induces plaque regression in ACS patients \(^77\). However, the extent of plaque regression was comparable between reconstituted HDL infusion and placebo (change in percent atheroma volume, −3.4 vs. −1.6%, p=0.48, change in total atheroma volume, −5.3 vs. −2.3 mm\(^3\), p=0.39). Waksman et al. evaluated the effect of autologous infusion of delipidated HDL by using 2-D gel electrophoresis \(^78\). This system enabled to delipidate plasmas successfully converted from α HDL to preβ-like HDL. Serial evaluation on IVUS imaging showed a favourable trend toward regression of total atheroma volume (−12.18±36.75 mm\(^3\)) in patients receiving infusion of delipidated HDL compared to placebo (−2.8±21.25 mm\(^3\), p=0.26 between the groups) in 28 ACS patients \(^79\). The CHI-SQUARE (Can HDL Infusions Significantly QUicken Atherosclerosis Regression) study evaluated the efficacy of infusion of preβ HDL mimetic agent, CER-001 on atherosclerotic plaques in 417 ACS patients \(^80\). There were no significant differences in change in percent atheroma volume between placebo versus CER-001. However, favourable efficacy was observed in subjects with more extensive atheroma burden. In particular, the lowest dose of CER-001 significantly regressed atheroma compared to placebo (Fig. 4). This finding suggested ACS cases with extensive atheroma as important targets who benefit from infusional agent of HDL. The impact of HDL infusions on clinical outcomes will be warranted in dedicated studies in the future.

c. ApoA-I induction therapy

Enhancing apoA-I synthesis is another attractive strategy enabling to generate new HDL particles. The first oral agent to selectively induce hepatic synthesis of apoA-I is RVX-208 \(^82\). This agent has been shown to promote apoA-I transcription in hepatic cell lines \(^80\). In addition, a significant increase in apoA-I, HDL-C and large HDL particles were observed in subjects receiving RVX-208 \(^81\). The efficacy of RVX-208 on atheroma progression was investigated by the ASSURE (ApoA-I Synthesis Stimulation and Intravascular Ultrasound for Coronary Atheroma Regression Evaluation) study in 310 patients with ACS \(^82\). The use of RVX-208 for 6 months did not modulate change in atheroma volume compared to placebo. However, post-hoc analysis using virtual histology IVUS imaging has elucidated that RVX-208 was associated with a significant reduction of necrotic core and an increase in calcification. This observation suggests the ability of RVX-208 to stabilize atherosclerotic plaques in ACS cases. The impact of RVX-208 on cardiovascular outcome study is under investigation in on-going clinical trial.

IV. Conclusion

Continuing cardiovascular risk despite statin therapy indicates the on-going needs to establish additional novel therapeutic approaches. Epidemiological and intravascular imaging studies have provided insights into the potential benefit of modulating lipid targets including triglyceride and HDL-C. The clinical efficacy of novel agents modifying these targets is not established yet. However, due to complexity of mechanistic link between triglyceride, HDL-C and atherosclerosis, further extensive search
for effective therapeutic approach will continue.

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Abbreviations

ABCA1 = ATP-binding cassette transporter A1
ABCG1 = ATP-binding cassette G1 transporter
ACS = acute coronary syndrome
apoA-I = apolipoprotein A-I
ASCVD = atherosclerotic cardiovascular disease
CETP = cholesteryl ester transfer protein
IDL = intermediate-density lipoprotein cholesterol
IVUS = intravascular ultrasound
HDL-C = high-density lipoprotein cholesterol
LDL = low-density lipoprotein
LPL = lipoprotein lipase
MPO = myeloperoxidase
OCT = optical coherence tomography
PROVEIT-TIMI = Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction
SR-BI = scavenger receptor class B type I
VLDL = very-low-density lipoprotein

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