Lipoproteins as Biomarkers and Therapeutic Targets in the Setting of Acute Coronary Syndrome

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Abstract: The period following an acute coronary syndrome (ACS) represents a critical time frame with a high risk for recurrent events and death. The pathogenesis of this increase in clinical cardiovascular disease events after ACS is complex, with molecular mechanisms including increased thrombosis and inflammation. Dyslipoproteinemia is common in patients with ACS and predictive of recurrent cardiovascular disease events after presentation with an ACS event. Although randomized clinical trials have provided fairly convincing evidence that high-dose statins reduce the risk of recurrent cardiovascular events after ACS, there remain questions about how aggressively to reduce low-density lipoprotein cholesterol levels in ACS. Furthermore, no other lipid-related interventions have yet been proven to be effective in reducing major cardiovascular events after ACS. Here, we review the relationship of lipoproteins as biomarkers to cardiovascular risk after ACS, the evidence for lipid-targeted interventions, and the potential for novel therapeutic approaches in this arena. (Circ Res. 2014;114:1880-1889.)

Key Words: cholesterol ▪ coronary artery disease ▪ lipids

Lipoproteins represent major risk factors, both positive and negative, for atherosclerotic cardiovascular disease. The major plasma lipid traits, low-density lipoprotein cholesterol (LDL-C), triglycerides, and high-density lipoprotein cholesterol (HDL-C) are all predictive of cardiovascular risk and have been considered targets for therapeutic intervention. Here, we specifically consider the role of these lipids and lipoproteins in the setting of acute coronary syndrome (ACS) and review their changes in ACS, their predictive ability for recurrent events, and their status as therapeutic targets in patients with ACS.

LDL as a Biomarker and Therapeutic Target in ACS
LDL-C is a negative acute phase reactant that was shown to fall by a maximum of 50% at 7 days after an acute myocardial infarction (MI) in an era before therapies that limit infarct size were known or widely used. The magnitude of reduction in LDL-C was in proportion to the myocardial injury and inflammatory response after an acute coronary syndrome (ACS). Similar observations were seen in the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering...
primary outcome (first occurrence of death from any cause, MI, documented unstable angina requiring hospitalization, revascularization with either percutaneous coronary intervention or coronary artery bypass surgery performed 30 days after randomization, and stroke) and secondary outcome (composite of death from coronary heart disease [CHD], nonfatal MI, or revascularization after 30 days). When baseline LDL-C was examined as a continuous variable, LDL-C levels >66 mg/dL were significant predictors of the primary end point and secondary end point in multivariate models that were adjusted for predictors of the primary outcome and secondary outcome, respectively. In PROVE-IT-TIMI 22, ratios of total cholesterol/HDL-C and apolipoprotein B/A-I and non–HDL-C provided similar information on 2-year event rates as LDL-C.6

Several statin trials have enrolled patients within a window after presentation with ACS. A meta-analysis of 18 randomized placebo-controlled clinical trials involving 14 303 patients with statin therapy initiated within 14 days of an ACS event8 revealed a favorable trend (risk ratio, 0.93) but not a statistically significant reduction in hard end points of death, MI, and stroke at 1 or 4 months with early statin therapy compared with placebo on top of standard of care. However, at 4 months after ACS, there was a significant reduction in the occurrence of unstable angina and rehospitalization in patients receiving early statin therapy. The PROVE-IT-TIMI 22 trial was designed to evaluate the efficacy of high-versus moderate-dose statin therapy in reducing clinical events in patients with ACS.8 Patients presenting with ACS were randomized to atorvastatin 80 mg or pravastatin 40 mg and followed for a mean of 2 years. High-dose atorvastatin therapy significantly reduced primary end point events (death, MI, unstable angina requiring rehospitalization, stroke, or revascularization) by 16% when compared with 40 mg pravastatin. Atorvastatin 80 mg daily was superior to pravastatin 40 mg daily across LDL-C quartiles when the baseline LDL-C was >66 mg/dL. In this trial, both LDL-C and C-reactive protein (CRP) were reduced to a significantly greater extent in the atorvastatin 80 mg group compared with the pravastatin 40 mg group. This study raised the possibility that the effects of high-dose statins in ACS may be attributable to statin pleiotropic effects in modulation of inflammation, endothelial dysfunction, and thrombosis.9 Overall, the statin ACS trials have resulted in the incorporation of high-dose statin therapy as standard of care in the patient with ACS (Table).

No trials with LDL-lowering therapies other than statins have been reported in the setting of ACS. However, the IMProved Reduction of Outcomes: VYtorin Efficacy International Trial (IMPROVE-IT) with ezetimibe was designed as an ACS trial, in which the patients with more severe initial non–ST-segment-elevation MIs as stratified by troponin levels had the lowest levels of LDL-C and the highest levels of inflammatory markers.2 After 6 weeks, the LDL-C levels in the placebo group increased by 12% from baseline values. In contrast, in the Limiting UNdertreatment of lipids in ACS (LUNAR) trial that included patients with ST-segment-elevation MI, non–ST-segment-elevation MI, and unstable angina, patients reported an initial reduction in LDL-C that increased at 4 days.3 Thus, more recent trials indicate that early measurements of LDL-C levels are reliable even when measured within several days after an ACS.

In patients with ACS enrolled in clinical trials with high-intensity statin therapy, the use of baseline and on-trial LDL-C in the prediction of cardiovascular events has been inconsistent. In the MIRACL trial, neither baseline nor on-trial LDL-C predicted ischemic cardiac events or death at 16 weeks.4 In contrast, the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22 (PROVE-IT-TIMI 22) trial reported that in statin-naive patients with ACS, baseline LDL-C was a predictor of both
Figure 1. Anti-atherothrombotic properties of statins and potential relevance in patients with acute coronary syndrome. LDL indicates low-density lipoprotein; Lp-PLA, lipoprotein-associated phospholipase A; M-CSF, monocyte colony stimulating factor; MCP-1, monocyte chemotactant protein-1; MM-LDL, minimally modified LDL; Ox-LDL, oxidized LDL; PAI-1, plasminogen activator inhibitor-1; PGI2, prostacyclin; and VLDL, very-low-density lipoprotein. (Illustration credit: Ben Smith.)

Figure 2. Anti-atherothrombotic properties of high-density lipoprotein (HDL) and potential relevance in patients with acute coronary syndrome. ABCA1 indicates ATP binding cassette protein A1; ICAM1, intercellular adhesion molecule-1; HDL-M, medium HDL particles; HDL-S, small HDL particles; HDL-VS, very-small HDL particles; LDL, low-density lipoprotein; and VCAM-1, vascular cell adhesion protein-1. (Illustration credit: Ben Smith.)
Whether additional LDL-C reduction beyond what is achieved causality. Furthermore, no randomized clinical trials have the observational data and making it impossible to attribute strongly inversely associated with HDL-C levels, confounding causes of new CVD events at 16 weeks. In contrast, in the PROVE-IT-TIMI 22 trial, within subjects randomized to atorvastatin 80 mg daily, LDL-C levels were not predictive of recurrent cardiovascular events during a longer follow-up period. Thus, it remains uncertain whether LDL-C levels per se are predictive of events post-ACS in patients treated with high-dose statin therapy.
atorvastatin 80 mg daily had fewer outcomes than those individu-
als treated with atorvastatin 10 mg daily.22 Low HDL-C levels (
<43 mg/dL) were associated with an increased risk of CVD in
patients randomized to treatment with atorvastatin 10 mg daily,
but there was no association in patients randomized to atorvast-
in 80 mg daily.23 However, lower levels of HDL-C in TNT par-
ticipants were inversely associated with higher levels of apoB,
which raises the issue of HDL-C as a biomarker of atherogenic
lipoproteins. In a prospective cohort study of 6111 patients with
stable vascular disease (CAD, cerebrovascular disease, peripheral
artery disease, or aneurysm of the abdominal aorta), low HDL-C
levels were associated with increased CVD events in patients pre-
scribed statin therapy with an expected LDL-C lowering <40% (pravastatin, fluvastatin, atorvastatin 10 mg, simvastatin <40 mg),
whereas no association was observed in patients prescribed in-
tensive LDL-C lowering ≥40% (low-dose atorvastatin or simvas-
tatin in combination with ezetimibe 10 mg, atorvastatin ≥20 mg,
simvastatin ≥40 mg, rosuvastatin at all dosages).24 In the Clinical
Outcomes Utilizing Revascularization and Aggressive Drug
Evaluation (COURAGE) trial, on-trial HDL-C levels at 6 months
were associated with increased CVD risk after 4 years in the sub-
group of 2193 patients who achieved LDL-C levels ≤70 mg/dL.25
In these patients, low levels of HDL-C were associated with fea-
tures of the metabolic syndrome (higher body mass index, higher
glycerol, more hypertension and diabetes mellitus) that in
other studies is associated with higher concentrations of athero-
genic lipoproteins.26

In contrast, in a primary prevention setting, HDL-C levels in
patients on high-dose statin therapy may not be as predic-
tive of cardiovascular events. In the Justification for the Use of
Statins in Primary Prevention: An Intervention Trial Evaluating
Rosuvastatin (JUPITER) trial, on-trial levels of HDL-C in ro-
svastatin-treated participants were not predictive of incident
CVD events, whereas in the placebo group, HDL-C levels
were strongly predictive of events.27 Interestingly, in prospec-
tive population studies28 and randomized clinical trials of
lipid-modifying therapy,29,30 the concentration of HDL par-
ticles may be a more accurate biomarker of cardiovascular risk
than HDL-C. In the rosuvastatin-treated subjects in JUPITER,
low HDL particles were a significant predictor of CVD events
even though HDL-C was not.26 Relatively little data exist with
regard to the relationship of HDL particles in the setting of ACS
to recurrent cardiovascular events.

HDL and apoA-I have been shown to have several antiather-
genic properties; the most extensively studied has been their
ability to promote cholesterol efflux from macrophages and
mediate the process of reverse cholesterol transport from the
periphery to the intestinal lumen.31 The concept of the chole-
terol efflux capacity of human HDL and methods for measuring
it were developed by Rothblat and colleagues.32,33 The method
generally involves the quantification of the ability of human
HDL (often as serum from which apoB lipoproteins have been
precipitated) to promote cholesterol efflux from macrophages
in cell culture. The cholesterol efflux capacity of HDL was
shown to be significantly inversely associated with carotid
intimal–medial thickness,34 atherosclerotic carotid stenosis,35
prevalent angiographic coronary disease,34,36 and prevalent
clinical CAD in an outpatient preventive cardiology clinic.36 On
the contrary, an analysis of incident cardiovascular events in a
cohort ascertained based on having coronary angiography sug-
gested that cholesterol efflux capacity was positively associated
with incident cardiovascular events within 3 years of angiog-
raphy.36 The overall number of events was small, and the de-
finite answer to the relationship of cholesterol efflux capacity
to incident CVD events awaits much larger prospective cohort
analyses.37 Recently, the functionality of HDL in patients with
ACS was evaluated; compared with healthy controls, HDL cho-
lesterol efflux capacity was reduced in patients with ACS within
3 days of onset of symptoms and remained low 3 months later.38
The relationship of cholesterol efflux capacity in the setting of ACS
to recurrent CVD events has yet to be established.

HDL has been shown to have a variety of additional prop-
erties39 including antioxidant effects,40 anti-inflammatory
effects with reduction of endothelial adhesion molecules41
and induction of the macrophage activating transcription fac-
tor 3,42 stimulation of endothelial nitric oxide (NO) synthase
and production of NO,43 reduction of endothelial apoptosis,44
antithrombotic effects by reducing platelet reactivity,45 and
serving as a transport vehicle in plasma for several proteins
involved in innate immunity and other pathways.46 The anti-
oxidant capacity of HDL is reduced in the setting of ACS,47
and both the cholesterol efflux and antioxidant functions of
HDL are impaired in ischemic cardiomyopathy.48 The ability
of HDL from patients with ACS or stable CAD to inhibit
apoptosis is impaired as well.44 In addition, in patients with a
recent MI, the HDL proteome is enriched in inflammatory
proteins.49,50 The HDL proteome and lipidome have a crucial
influence of many aspects of HDL functionality.20,25 Under
proinflammatory conditions, the HDL proteome and lipidome
are altered such that the antiatherosclerotic functional char-
acteristics of HDL are impaired resulting in either a nonfunc-
tional or dysfunctional HDL particle. The details of how the
HDL proteome and lipidome change in the setting of ACS and
the relationship of these changes to HDL function and cardio-
vascular outcomes post-ACS have yet to be fully elucidated.

The increased risk associated with ACS and the residual
risk even in statin-treated patients have provided a stimulus
for developing new approaches to treat patients with ACS. In
theory, interventions that improve HDL function might induce
regression or stabilization of unstable atherosclerotic coronary
lesions and thereby improve cardiovascular outcomes after
an ACS event. Research in preclinical models has focused on
molecular mechanisms of HDL-based interventions that are
proven to regress or stabilize atherosclerotic plaques. Perhaps
the best-studied HDL-based intervention that favorably influ-
ences atherosclerosis in preclinical models is apoA-I infusion
and overexpression. Abundant data indicate that apoA-I infu-
sion51 and somatic viral-mediated overexpression53 can result
in regression of pre-existing atherosclerosis and changes in
plaque composition consistent with stabilization. A variety of
studies in animal models have confirmed that apoA-I infusion
or somatic overexpression results in improvement in a variety
of HDL-based functional measures. Increasing plasma apoA-I
increases the cholesterol efflux capacity of HDL and promotes
macrophage reverse cholesterol transport in vivo54 through di-
rect promotion of cholesterol efflux via the ATP binding cas-
sette protein A1 (ABCA1) pathway. Although promotion of the
reverse cholesterol transport pathway is likely to be one
important way in which HDL and apoA-I regress and stabilize plaques, it is almost certainly not the only operative mechanism in vivo. Indeed, promotion of cholesterol efflux itself can have other beneficial effects that could impact plaque stabilization and events post-ACS. Recently, it was reported that hematopoietic stem and progenitor cells are substantially mobilized after experimental MI, resulting in the production of excess monocytes and neutrophils that promote the formation of atherosclerosis and could contribute to recurrent cardiovascular events after ACS. Interestingly, cholesterol efflux pathways are linked to the hematopoietic generation of proatherogenic inflammatory cells; molecules responsible for cholesterol efflux such as ABCA1 and ATP binding cassette protein G1 (ABCG1) are highly expressed in hematopoietic stem and progenitor cells. Mice deficient in these pathways have increased atherosclerosis in part attributable to increased production of monocytes and neutrophils, an effect that is suppressed by the administration of apo-A-I. Thus, promotion of macrophage reverse cholesterol transport as well as suppression of hematopoietic generation of monocytes and neutrophils might be efflux-related mechanisms by which HDL and apoA-I exert plaque regressing and stabilizing effects.

HDL and apoA-I exert additional anti-inflammatory effects that have been conclusively demonstrated in vivo. When murine atherosclerotic aorta was transplanted into mice overexpressing apoA-I, the lesions regressed quickly and macrophages from the plaques had substantially decreased expression of proinflammatory genes and enrichment of M2 (tissue repair) macrophage markers. Furthermore, CD68+ cells in the plaques demonstrated induction of the chemokine receptor type 7, and there was evidence of substantial emigration of these cells from the plaques in response to the apoA-I overexpression. Recently, HDL was reported to inhibit the macrophage production of cytokines in response to toll-like receptor activation and that this required the HDL/apoA-I-induced upregulation of the transcription factor activating transcription factor 3. Importantly, treatment of mice with either HDL or apoA-I in vivo markedly reduced macrophage cytokine release and downstream tissue damage in response to toll-like receptor ligands, and this effect was dependent on activating transcription factor 3. Of note, apoA-I infusion therapy also significantly reduces the cytokine-induced endothelial adhesion molecule expression, providing a potential link between its anti-inflammatory effects on macrophages and endothelial cells. This effect of apoA-I and HDL on inhibiting endothelial inflammation is through induction of the expression of the endothelial enzyme 3F-hydroxysteroid-Δ24 reductase expression, which results in the activation of phosphatidylinositol 3-kinase/Akt with subsequent induction of heme oxygenase 1. Thus, anti-inflammatory effects on both macrophages and endothelial cells may contribute to the plaque-stabilizing effects of apoA-I in model systems.

Under certain circumstances, HDL particles and apoA-I may become dysfunctional. In patients with ACS, the HDL proteome is characterized by increased abundance of serum amyloid A, complement C3, and other inflammatory proteins; however, these changes in HDL composition did not impair macrophage cholesterol efflux through ABCA1, ABCG1, or scavenger receptor BI-mediated pathways. In contrast, myeloperoxidase-mediated oxidation of specific residues on apoA-I has been shown to inhibit ABCA1 macrophage cholesterol efflux. Although oxidation of apoA-I by the myeloperoxidase–H2O2–Cl− system occurs mainly within the subendothelial compartment, detection of multiple oxidation residues has been detected in apoA-I of circulating HDL and lipid-poor apoA-I in the atherosclerotic lesions. Specifically, HDL isolated from coronary atherosclerotic lesions has higher concentrations of 3-chlorotyrosine and 3-nitrotyrosine than plasma HDL.

Stable CAD patients and ACS patients have higher levels of chlorinated tyrosine-192 and oxidized methionine-148 than control subjects. Higher concentrations of both chlorinated tyrosine-192 and oxidized methionine-148 were associated with reduced ABCA1-mediated macrophage cholesterol efflux and CAD status. In contrast with circulating HDL, the majority of apoA-I in atheroma is not associated with the HDL particle. Lipid-poor apoA-I in atheroma is cross-linked and oxidized, resulting in impaired ABCA1 interaction that impairs ABCA1-mediated macrophage cholesterol efflux. Oxidation of Try72 on apoA-I is a site-specific target for myeloperoxidase-dependent oxidation that results in the formation of oxindole alanine (2-hydroxy l-tryptophan) moiety that was detected in 20% of apoA-I recovered from human atherosclerotic lesions.

In addition to reduced ABCA1 macrophage cholesterol efflux, anti-inflammatory and antioxidative activities of HDL can be impaired as a result of the accumulation in HDL of oxidized phospholipids, which possess potent proinflammatory and pro-oxidative properties. Myeloperoxidase-dependent oxidation of Try72 on lipid-poor apoA-I results in the formation of oxindolyl alanine (2-hydroxy l-tryptophan) moiety that augments nuclear factor-κB activation and vascular cell adhesion protein-1 expression. Endothelial dysfunction is common in patients with ACS, and recurrent events are sometimes attributed in part to this phenomenon. NO is critical for normal endothelial function, and reduced bioavailability of NO is widely considered the pathophysiological basis for endothelial dysfunction. ApoA-I overexpression results in increased NO generation, increased endothelial function, and improved endothelial healing after injury in vivo. The molecular mechanism requires scavenger receptor BI as a plasma membrane cholesterol sensor and seems to involve the promotion of cholesterol efflux from endothelial cells resulting in intracellular signaling leading to activation of endothelial NO synthase. Whether promotion of NO in vivo is a key mechanism of plaque stabilization and occurs in humans with apoA-I infusion remains to be determined. In any case, there are a variety of plausible molecular mechanisms that have been proven in vivo in animal models that could contribute to plaque stabilization by HDL-based therapies in humans.

Niacin is an HDL-raising drug, and within the past several years, 2 randomized trials of extended release niacin in stable CAD patients on statin therapy failed to meet their primary end points and showed no significant reduction in major CVD events. Niacin has never been studied in the setting of ACS and has effects on lipids beyond HDL-C alone. Few clinical trials in patients with ACS have used specific therapies that selectively target HDL. The only such trial to date is the Dal-Outcomes trial with the cholesteryl ester transfer protein (CETP) inhibitor dalcetrapib. A total of 15,871 patients...
with ACS were randomized to dalcetrapib 60 mg or placebo on top of standard of care including high-dose statin. At randomization, LDL-C was 76 mg/dL and HDL was 42 mg/dL. LDL-C increased 4% to 11% in the placebo group and 30% to 40% in the dalcetrapib group. At the second interim analysis, the trial was stopped because there was no difference in the occurrence of major acute cardiovascular events (the primary end point) with 8.3% in the dalcetrapib group and 8.0% in the placebo group. There are several reasons why this trial may have failed, but it does suggest that modest HDL-C increases in the post-ACS setting are not themselves sufficient to reduce CVD events. Development of dalcetrapib has been discontinued. However, other potent CETP inhibitors such as anacetrapib and evacetrapib are still in late-stage clinical development. At the doses being used in the hard end point clinical trials, they produce a 120% to 130% increase in HDL-C along with a 30% to 40% reduction in LDL-C. The clinical phase 3 CETP inhibitor trials currently underway include Randomized Evaluation of the Effects of Anacetrapib Through Lipid-modification (REVEAL) with anacetrapib (NCT00685776) in patients with stable CHD and Assessment of Clinical Effects of Cholesteryl Ester Transfer Protein Inhibition with Evacetrapib (ACCELERATE) with evacetrapib (NCT01687998) in patients with high-risk vascular disease, including those 30 to 365 days from an ACS event. These trials will determine whether potent CETP inhibition producing a substantial increase in HDL-C, accompanied by a reduction in LDL-C, will provide important reductions in clinical events on top of high-dose statin therapy.

There remains substantial interest in the concept of HDL infusion therapy, particularly in the setting of ACS. A reduction in coronary plaques quantified by intravascular ultrasound has been reported after HDL infusions in patients with ACS. In small proof-of-concept studies, intravenous infusion of apoA-I/phospholipid complexes or autologous preβ-HDL reducted total atheroma volume in 5 to 7 weeks compared with baseline. Another study in patients with peripheral arterial disease scheduled for atherectomy showed that a single infusion of recombinant HDL led to acute changes in plaque lipid content and inflammation. Larger studies of recombinant HDL infusions with hard clinical end points are required. HDL infusion therapy will hopefully eventually provide definitive data on the potential role of HDL as a therapeutic target to reduce clinical events in high-risk ACS patients.

In summary, in post-ACS patients treated with a high-dose statin, on-treatment HDL-C levels have an inconsistent association with recurrent CVD events. The only clinical trials of an HDL-raising drug (dalcetrapib) performed post-ACS failed to show clinical benefit. Although there is no current evidence base for attempting to raise HDL-C with pharmacological therapy post-ACS, additional HDL-targeted therapies are in clinical development, including in the post-ACS setting.

Additional Lipoprotein-Related Biomarkers and Therapeutic Targets in ACS

ACS is an inflammatory condition in which multiple inflammation-related biomarkers are elevated. CRP is known to increase in ACS and has been shown to be a marker of recurrent CVD events, even on high-dose statin therapy. Indeed, statins reduce CRP levels in ACS, and robust reductions in both LDL-C and CRP are the best predictors of reduced risk of CVD events post-ACS in statin-treated patients. These combined results provide support for the concept that there may be a dual mechanism of benefit, lipid lowering, and reduction in inflammation, in the ACS patient treated with high-dose statin.

Secretory phospholipases hydrolyze fatty acids at the sn2 position of phospholipids, including those in lipoproteins such as LDL and HDL, and generate multiple bioactive lipids, several of which are proinflammatory. In particular, secretory phospholipase A2 groups IIA (sPLA2-IIA) and V (sPLA2-V) have been suggested to be proatherogenic. sPLA2-IIA is a positive acute reactant that increases with inflammation, including MI. Plasma levels of sPLA2-IIA mass and total sPLA2 activity are predictive of cardiovascular events in patients with ACS. In the MIRACL trial, baseline sPLA2-IIA mass was not associated with the primary efficacy measure of death, MI, or unstable angina. However, sPLA2-IIA mass was associated with an increased risk of death in placebo-treated participants after multivariate models that included major risk factors, previous MI, LDL-C, troponin T levels, and high-sensitivity CRP levels. When the treatments groups were analyzed separately, this association remained significant in the placebo group but not in the atorvastatin group. When compared with placebo, atorvastatin 80 mg daily significantly reduced sPLA2-IIA mass and sPLA2 activity. These data suggest that atorvastatin reduces the risk of sPLA2-IIA–associated inflammation in patients with ACS. In patients with ACS, treatment with the pan-sPLA2 inhibitor, varespladib methyl, plus atorvastatin 80 mg daily reduced LDL-C and sPLA2-IIA mass, but these changes in biomarkers were confined to patients with diabetes mellitus. In a short-term clinical outcomes trial of patients with ACS treated with atorvastatin, varespladib methyl increased acute MIs resulting in early termination of this trial.

Holmes et al investigated the validity of sPLA2-IIA as a therapeutic target, and colleagues who conducted a Mendelian randomization meta-analysis that included 10 ACS cohorts (2520 recurrent major vascular events in 18355 individuals) investigated observational studies between the PLA2G2A rs11573156 variant that encodes the sPLA2-IIA isoenzyme and cardiovascular events. In the ACS cohorts, the PLA2G2A rs11573156 C allele was associated with 44% lower circulating sPLA2-IIA mass and 3% sPLA2 enzyme activity per C allele. The odds ratio for major vascular events per rs11573156 C allele was 0.96 (95% confidence interval, 0.90–1.03) in ACS cohorts. In the ACS cohorts, both the genetic instrumental variable and observational odds ratios showed no association with major vascular events. Several unresolved issues concerning this analysis include the nonreporting of values for sPLA2-IIA levels and activity, which is important because of marked differences in sPLA2 levels that results from the acute phase reaction in patients with ACS, use of different analytical methods, and reliance on total sPLA2 activity as a surrogate for sPLA2-IIA activity. Interestingly, a recent report indicated that group X sPLA2 is atheroprotective.

In another analysis of stable CHD patients, Holmes et al reported no association between the PLA2G5 variant rs525380, the major single-nucleotide polymorphism for PLAG5 expression, a surrogate for sPLA2-V levels, and CHD events.
Lipoprotein-associated phospholipase A₂ (Lp-PLA₂) is an LDL-associated enzyme that cleaves oxidized fatty acids from the sn2 position of oxidized phospholipids and results in the elaboration of multiple proinflammatory mediators that include lysophosphatidylcholine and oxidized nonesterified fatty acids. Lp-PLA₂ mass and activity are associated with increased CVD risk in stable CHD patients, but the association in ACS is inconsistent.79 Because Lp-PLA₂ is bound to apoB, reductions in apoB-containing lipoproteins in the acute phase response result in fewer carriers of this proatherogenic enzyme. In MIRACL trial, Lp-PLA₂ mass and activity were not associated with the primary or secondary outcome measures.80 In this trial, atorvastatin significantly reduced Lp-PLA₂ mass and activity concordant with reductions in LDL-C and apoB. In PROVE-IT, similar reductions in Lp-PLA₂ mass and activity were seen in atorvastatin 80 mg–treated participants, whereas pravastatin 40 mg–treated participants had a substantially lesser reduction in Lp-PLA₂ mass and a modest increase in Lp-PLA₂ activity. Similar to MIRACL trial, there were no associations between Lp-PLA₂ mass or activity with clinical events in PROVE-IT. Selective inhibition of Lp-PLA₂ activity with darapladib in stable CHD patients did not reduce the primary outcome measure of time to cardiovascular death, MI, or stroke.89 However, the secondary end points of major coronary events (0.90 [0.82–1.00]; P=0.05) and total coronary events (0.91 [0.84–0.98]; P=0.02) were significantly lower in darapladib–versus placebo-treated participants. Importantly, however, the effect of darapladib on recurrent CVD events after ACS is being evaluated in the ongoing Stabilization Of pLaques uSing Darapladib-Thrombolysis In Myocardial Infarction 52 (SOLID-TIMI-52) trial (NCT01000727).

Conclusions

The substantially increased risk of cardiovascular events post-ACS represents a significant unmet medical need and opportunity for novel therapeutic approaches. Elevated levels of atherogenic lipoproteins (LDL and triglyceride-rich lipoproteins) and reduced levels of HDL are predictive of cardiovascular events post-ACS. Lipoprotein levels change acutely after an ACS event (LDL-C and HDL-C levels fall and triglyceride levels rise). High-dose statin therapy significantly reduces cardiovascular events post-ACS, possibly through a dual mechanism of reduced LDL-C and reduced inflammation. Trials with the new class of LDL-lowering proprotein convertase subtilisin/kexin type 9 inhibitors in ACS are awaited. No trials have been performed in ACS with triglyceride-lowering agents, representing a major gap in reverse cholesterol transports in ACS. The only ACS trial with an HDL-raising agent was with the CETP inhibitor dalcetrapib and was a negative trial; there are other more potent CETP inhibitors that are in late-stage clinical development. However, many patients with ACS have HDL with reduced functionality and thus may not be the correct population to evaluate therapies directed at simply increasing HDL-C concentration. There remains interest in the potential of HDL infusion therapies as treatments for reducing CVD events, including in the setting of ACS. In summary, existing drugs and novel therapies in development focused on lipoproteins have the potential to substantially reduce the incidence of CVD events after ACS.

Disclosures

R.S. Rosenson serves on the advisory board of Aegerion, Amgen, Astra Zeneca, Eli Lilly, GSK, Jansen, LipScience, Novartis, Regeneron, and Sanofi; serves as a consultant for Novartis and Sanofi; and receives honorarium from Kowa. Stock holdings: LipScience, Medicines Company, Mesoblast, and Teva. Research support to institution was provided by Amgen, Astra Zeneca, Hoffman LaRoche, Sanofi. H.B. Brewer serves as a consultant/speaker for Merck, Pfizer, Roche, Eli Lilly, Amgen, CSL, Cerenis, and Medicines Company. D.J. Rader serves on the advisory board of Aegerion, Alnylam, Eli Lilly, Merck, Novartis, and Sanofi and has stock holdings in Aegerion.

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