Preventing Recurrent Cardiovascular Events through Plaque Stabilization:

A New Dimension in Cardiovascular Medicine

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Preventing Recurrent CV Events Supplement

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Preventing Recurrent Cardiovascular Events through Plaque Stabilization:

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Keith B. Allen, MD; James E. Alexander, MD

Summary

Enhancing cholesterol efflux from atherosclerotic plaques is an emerging novel therapeutic approach that may reduce the risk of recurrent cardiovascular (CV) events in the 90 days following an acute myocardial infarction (AMI). This high-risk period is not adequately addressed by the current standard of care. A new treatment approach could significantly improve clinical outcomes, reduce the quality of life burden to patients and costs for healthcare providers.

Key Points

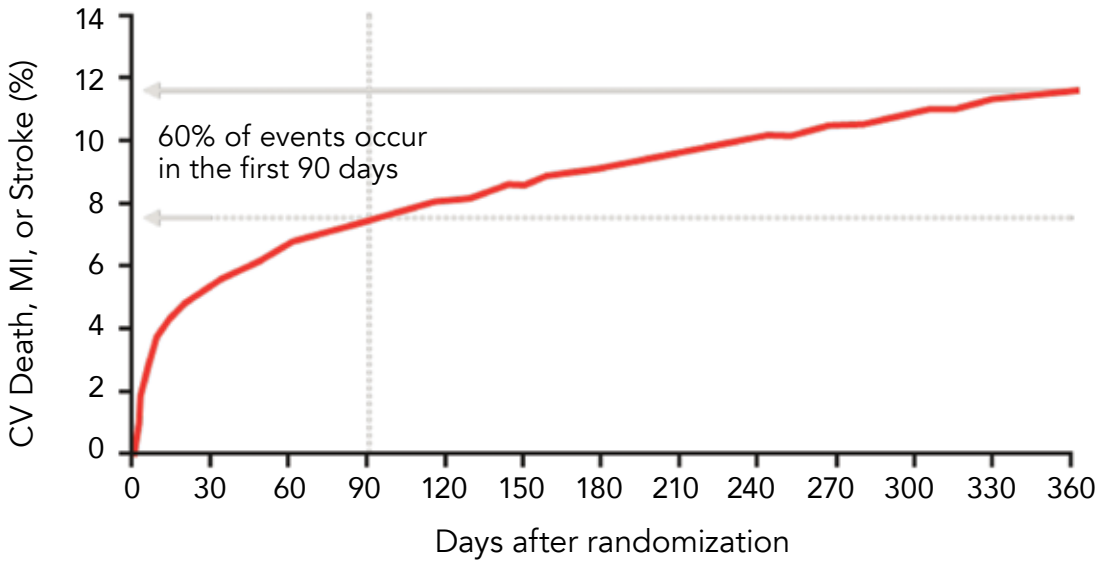
- Recurrent CV events in the high-risk 90-day period following an AMI represent a significant clinical and economic burden and the risk of recurrent CV events is particularly high for patients with additional risk factors, including multivessel disease.
- The current standard of care does not focus on the risk in the 90-day period after an AMI and most therapies, including statins, only become efficacious in reducing CV event rates after approximately four months.
- Recurrent CV events are equally as likely to arise from a culprit as they are a non-culprit-lesion and as such, AMI needs to be treated rapidly as a systemic disease.
- Considering the relationship between cholesterol efflux and CV risk, targeting high-density lipoprotein (HDL) function may prove more effective than previous therapies targeting increasing HDL number.
- Enhancing the efflux of cholesterol from lipid-rich plaques could stabilize lesions, reducing the risk of recurrent CV events and addressing the unmet clinical burden of the 90-day high-risk period after an AMI.

Recurrent Cardiovascular Events Following Acute Myocardial Infarction: An Unmet Clinical Need and Large Economic Burden

Recurrent cardiovascular (CV) event rates following acute myocardial infarction (AMI) present a significant clinical burden. There are an estimated 805,000 AMIs per year in the United States (U.S.), of which 200,000 are recurrent.[1] Those patients that survive an index AMI form the highest risk group for further coronary events.[2] Despite standard of care (SoC) treatment, the 90 days post-AMI is a high-risk period for recurrence (Exhibit 1).[3-5] In patients hospitalized for an acute coronary syndrome (ACS) who participated in the Platelet Inhibition and Patient Outcomes (PLATO) trial, recurrent CV events occurred in approximately 12 percent of patients within a year, and approximately 7 percent of patients within the first 90 days, indicating that around 60 percent of all one-year events (CV death, MI and stroke) occurred in the first 90 days.[3] Analysis of the Nationwide Readmissions Database found that 24 percent of the estimated 392,006 index AMI hospitalizations over a nine-month period resulted in readmission (all-cause) within 90 days.[4] According to an analysis of the Acute Coronary Treatment and Intervention Outcomes Network (ACTION) registry, of the AMI readmissions over a two-year period in older patients (≥65 years), one-third occurred within 90 days of discharge after the index event.[5]

Patients are at greater risk of mortality after recurrent AMI.[6-8] In the Osaka Acute Coronary Insufficiency Study (OACIS), recurrent AMI more than doubled the risk of all-cause mortality at five years,[6] while mortality rates in patients that experienced ST- or non-ST elevated myocardial infarction (STEMI or NSTEMI) in the Global Registry of Acute Coronary Events (GRACE) study were 19 percent and 22 percent at five-year follow-up, respectively.[8] In a study of 4,543 patients, mortality rates at one year were higher in patients with recurrent STEMI (18.9%) as compared to first STEMI (10.9%).[7] In a prospective cohort study

Exhibit 1: The Majority of Recurrent Cardiovascular Events Take Place in the High-Risk Ninety-Day Period Post-Myocardial Infarction[3]



CV = cardiovascular
MI = myocardial infarction

Figure adapted from N Engl J Med, Wallentin L, et al., Ticagrelor versus clopidogrel in patients with acute coronary syndromes, 361, 1045–57. Copyright © 2009 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society

of 146,743 Medicare beneficiaries hospitalized for AMI, life expectancy was roughly halved in post-AMI patients compared to those with no history of CV disease.[9] Those that survive to experience another CV event also have a significantly worse health-related quality of life than their previous trajectory, as demonstrated in the Valsartan in Acute Myocardial Infarction Trial.[10] Patients that experienced a second CV event within two years of an index AMI reported a 6.6 point decrease in their mean visual analog scale ($P < 0.001$), a 100 point scale that records the patient's own perspective of their current health, which was considered to represent significant deterioration.[10] Thus, avoiding recurrent events is crucial in maintaining long-term patient welfare.

The period following an AMI represents a significant economic burden to healthcare systems due to the high frequency of readmissions and their associated costs. A retrospective study of medical insurance claims over a five-year period showed that 30 percent of ACS patients were re-hospitalized with a new CV event within a year of the index hospitalization. The average expenditure per patient for rehospitalization was $9,510, equating to 22 percent of the $44,023 total healthcare expenditure per patient.[11] Costs increase with recurrent CV events compared to the index AMI.[12-15] In a study of the causes, timing, and cost of 30-day readmissions after STEMI, roughly 12 percent of AMI patients were readmitted to hospital within 30 days; around half of these readmissions were CV-related, and a quarter were secondary to chest pain, angina or ischemia.[13] The median cumulative cost (for index hospitalization and recurrent hospitalization) for those readmitted within 30 days was significantly higher than for those not readmitted ($31,072 versus $18,169, $P < 0.001$).[13] In an analysis of a U.S. claims database, rehospitalization costs accounted for 45 percent of total medical costs in the first year of follow-up after an AMI.[15]

The higher costs are not limited to inpatient expenditure alone. Higher post-discharge resource utilization leads to increased costs for patients with recurrent events.[12,14] In patients with hyperlipidemia, mean total incremental costs over a two-year period were $19,320 higher amongst patients with a historical CV event compared to a matched control cohort. Hospitalization costs in this cohort accounted for around 65 percent of the expenditure, with the remainder spent on visits (outpatient office, office and emergency room) and prescriptions. Costs in this study also increased with the number of additional CV events experienced. Mean total expenditure was 30 percent higher in patients with two CV events and 48 percent higher in patients with three CV events compared with patients with only one CV event.[14] Real-world clinical data from a study following 1,335 ACS patients undergoing percutaneous coronary

intervention (PCI) showed higher costs at one year in patients that had a new clinical event compared to those with no new events (£8,988 versus £5,809, respectively); and these costs were attributable to post-discharge resource use.[12] These sustained costs place considerable strain on healthcare systems.

Patients presenting with an AMI often have multiple atherothrombotic risk factors, including multivessel disease (MVD), diabetes, peripheral arterial disease, cerebrovascular disease, chronic renal dysfunction and hyperlipidemia.[14,16-18] These factors substantially increase the risk of recurrent events post-AMI. Registry data from 2010 to 2014 linked to claims data showed that three out of four patients had at least two risk factors, and that the probability of a recurrent CV event increases with the number of these risk factors. The risk of a composite event (defined as ischemic stroke, recurrent AMI or all-cause death) was as high as 25.5 percent for patients with more than three risk factors.[19] Patients with additional CV risk factors are associated with having a reduced quality of life and present a greater economic burden, particularly in the first year.[14,16-18] Data from the Reduction of Atherothrombosis for Continued Health (REACH) registry showed that outpatients with established atherosclerotic arterial disease experienced high annual CV event rates and the one-year risk of a CV event increased with the number of symptomatic arterial disease locations.[16] Event rates (CV death, AMI, stroke or hospitalization) increased five-fold, from 5.31 percent in patients with risk factors only (diabetes, diabetic nephropathy, low ankle brachial index, asymptomatic carotid stenosis, high carotid intima-media thickness, high systolic blood pressure, hypercholesterolemia, frequent smoking, or advanced age [≥65 years in men or ≥70 years in women]) to 26.27 percent in patients with three symptomatic atherothrombotic disease locations (coronary artery, peripheral artery and cerebrovascular disease; $P < 0.001$).[16] National Swedish Registry data show that the risk of CV events remains high even beyond the first year post-AMI, indicating the need for prolonged surveillance, particularly in patients with these additional risk factors.[17] One in five AMI patients had a recurrent CV event in the first year post-discharge. Beyond a year, this risk remained the same, with one in five patients suffering a subsequent event beyond one year.[17]

From an economic perspective, costs increase with an increasing number of risk factors. In a U.S. commercially insured population, annual CV-related and all-cause costs were around two times higher in patients with one or more risk factors compared to patients without risk factors during a five-year follow-up period.[18] In patients with hyperlipidemia, inpatient hospitalization costs were 10-fold higher in patients with a prior CV event over a two-year follow up compared to those with no prior CV event.[14] Patients with additional CV risk factors are, therefore, likely to present the greatest clinical and economic burden.

Limitations in the Current Standard of Care

Over the last two to three decades, the SoC for AMI has undergone myriad improvements.[20] Current U.S. guidelines are outlined by the American College of Cardiology/American Heart Association.[21-23] According to these guidelines, upon patient presentation, electrocardiogram monitoring should be initiated as soon as possible. Primary PCI, performed within 120 minutes of diagnosis, is the preferred reperfusion strategy if STEMI is diagnosed and coronary-stenting is the PCI of choice. If primary PCI is not possible within 120 minutes of presentation with STEMI, fibrinolysis is recommended. Where a large myocardial area is at risk or the patient is in cardiogenic shock, and primary PCI is not possible, coronary artery bypass graft surgery should be considered.[21-23] In patients with MVD (roughly 50 percent of patients with STEMI[24]), preventative revascularization of non-infarct related vessels should be considered at the time of primary PCI or as a planned staged procedure. Although complete revascularization shows long-term benefit, it does not improve outcomes at 90 days.[25] NSTEMI patients undergo separate risk stratification management, based predominantly on imaging and measured troponin level. Patients with suspected ACS or palpitations should be referred to the emergency department immediately, while patients exhibiting less severe symptoms may be referred to a chest pain unit or similar facility.[21]

In terms of periprocedural pharmacotherapy, dual anti-platelet therapy is recommended before and for the year following PCI. Once the patient is stable, chronic lipid-lowering therapy should be initiated or continued; this is primarily with high-intensity statins unless contraindicated.[21-23] In very high-risk patients with atherosclerotic CV disease, high-intensity statins are used in the first instance with the aim of reducing low-density lipoprotein (LDL) cholesterol (LDL-C) by 50 percent.[26] There is the option to introduce ezetimibe and/or proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i) if statins are ineffective.[26] After the initial intervention, inpatients are monitored,

with ongoing management based on risk factors such as prior cardiac health, comorbidities and available social support. There should be increased vigilance in high-risk groups (elderly patients, those with renal dysfunction, metabolic syndrome or diabetes for example). Long-term lifestyle interventions are recommended alongside optimization of therapies to address comorbidities, where appropriate. Cardiac rehabilitation programs are initiated after discharge, a combination of exercise, risk factor modification, education and psychosocial counselling.[21,23]

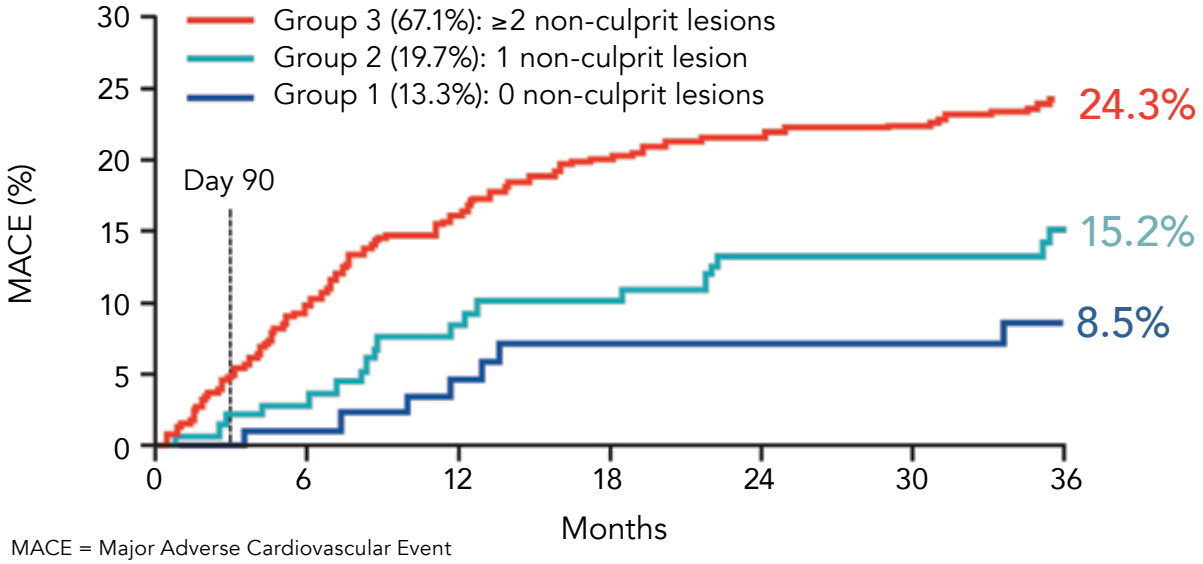
The changes in the management of AMI patients has led to consistent improvements over the last three decades, both in terms of long-term survival and reduced CV events.[2] Between 2006 and 2016, the annual mortality rate due to coronary artery disease (CAD) fell by 31.8 percent. However, the SoC still struggles to meet the needs of all patients, particularly those with additional risk factors, in the year following an AMI.[4,5,12] The current SoC in particular does not address the high-risk 90-day period post-AMI, due to the slow-acting nature of current treatments that fail to address this critical early post-discharge period.[27-30] Established pharmacotherapy for lowering LDL-C including statins,[27,29] ezetimibe,[28] and PCSK9i,[30] show benefit only in the longer term and initiation of statins post-ACS reduces unstable angina but is not associated with reduced mortality, AMI or stroke within the first four months.[27,29] The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering study found that early treatment with atorvastatin (80 mg/day) for 16 weeks reduced the primary combined endpoint (death, nonfatal AMI, cardiac arrest or rehospitalization) but not within the first 90 days.[29] A meta-analysis of randomized controlled trials concluded that statins (pravastatin, fluvastatin, atorvastatin and simvastatin) had not reduced death, MI, or stroke at either one or four month follow up post-onset of ACS.[27] Ezetimibe, when used as an adjunct therapy alongside statins, has also not shown a benefit on CV outcomes in the critical 90-day period after the event, but did incrementally improve outcomes from one year after initiating dosing.[28] Newer drugs such as PCSK9i are similarly only associated with reduced CV events in the longer term and a Kaplan-Meier probability estimate from the ODYSSEY OUTCOMES trial suggested that the benefits of PCSK9i drugs are apparent over the order of years.[30] As a result of this paucity of fast-acting therapies, recurrent CV event rates remain unacceptably high. In order to address the large residual risk of recurrent CV events, novel therapies that can rapidly stabilize plaque following an AMI are required and no existing therapies currently address this need in the short term.

Targeting High-Risk Patients with Multivessel Disease

Between 40 and 60 percent of patients presenting with STEMI are estimated to have additional stenoses caused by atherosclerosis in vessels unrelated to the initial infarct,[24,31-33] which is termed MVD. Post-AMI, patients with MVD have markedly worse clinical outcomes (reduced reperfusion success, higher early and late mortality, increased incidence of major adverse CV events [MACE] and recurrent AMI) than patients with single-vessel disease (SVD).[16,24,34] The risk of recurrent CV events is higher in MVD patients compared to SVD patients.[33,35,36] In a study of 68,000 stable post-AMI patients in Denmark, long-term risk of recurrent CV events (combined endpoint of AMI, stroke and CV mortality) was strongly associated with CAD severity (specifically the number of affected vessels), particularly in the first year after the index event.[33] In a sub-study of the patients enrolled in the Providing Regional Observations to Study Predictors of Events in the Coronary Tree trial, patients were divided into three groups, those with zero, one, or more than two non-culprit lesions (plaques that have not previously ruptured). Principal findings indicated that non-culprit lesions were evident in 87 percent of all patients with ACS, and that the risk of MACE was doubled in patients with one non-culprit lesion (15.2 percent) and tripled in those with two or more lesions (24.3 percent) compared to patients with no non-culprit lesions (8.5 percent) (Exhibit 2).[35]

In terms of economic burden, patients with MVD also use more services than those without MVD, amounting to a higher overall cost of care.[36,37] Analysis of baseline characteristics from patients that had suffered a previous STEMI registered in the National Inpatient Sample database showed that the cost of care in U.S. patients was greater in patients with MVD versus SVD ($24,953 versus $20,372, respectively, $P < 0.001$).[36] In an analysis of Medicare records, the costs of care for inpatients diagnosed with AMI were calculated in the 90 days following the index event. Of the 119,570 patients included, 26.8 percent of patients were found to have MVD.[37] Inpatient expenditure per stay was higher in patients with MVD compared to those with SVD ($12,732 versus $10,540, $P < 0.0001$), as was the total expenditure ($24,597 versus $23,319). Outpatient and emergency room service costs during the 90 days post-discharge

Exhibit 2: Patients with Multivessel Disease are at Increased Risk of a Recurrent Cardiovascular Event Compared to Patients with Single Vessel Disease[35]



MACE = Major Adverse Cardiovascular Event

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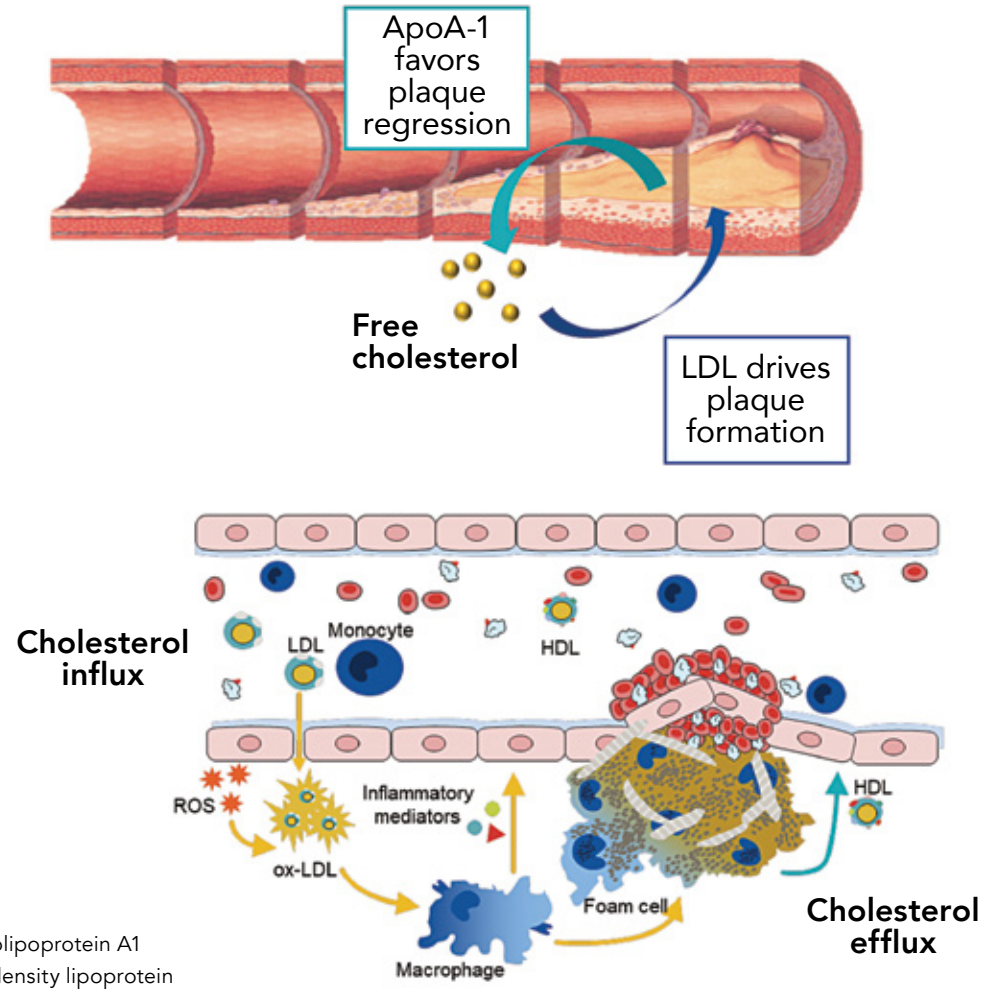
from hospital were also greater in MVD patients ($P < 0.0001$).[37] Given that MVD treatment costs are greater than SVD costs,[36] alternative treatment strategies to reduce overall expenditure have been investigated.[38,39] An economic evaluation of the Complete versus Lesion-only Primary PCI Trial suggested that complete revascularization at index AMI may be more cost-effective than culprit-lesion only treatment in patients with MVD undergoing PCI;[38] however, a similar investigation found no economic advantage in carrying out complete revascularization in patients presenting with index AMI.[39] The recently demonstrated improved clinical outcomes with complete revascularization versus culprit-lesion only treatment will likely add to this debate.[25] In summary, the increased risk and cost associated with MVD suggest that AMI should be treated as a systemic disease when developing strategies to reduce recurrent events in the critical 90-day period post-AMI.

Enhancing Cholesterol Efflux – A Novel Therapeutic Target

The key pathological factor in an AMI is the atherosclerotic plaque. Vulnerable plaques, so called due to their instability, are lipid-engorged and prone to rupture.[40-42] This rupture subsequently leads to a thrombus formation which can occlude a coronary vessel and trigger an AMI. It has been demonstrated that non-culprit lesions are equally as likely to cause recurrent CV events as the culprit lesion responsible for the initial AMI.[43,44] In patients that had undergone PCI for ACS, the cumulative rate of MACE during a three-year follow up was 20.4 percent; MACE was related to culprit lesions in 12.9 percent of events, and to non-culprit lesions in 11.6 percent of events.[43] In a real-world patient population, the risk attributed to non-culprit lesions was even greater; in a three-year follow-up of patients with index AMI, the risk of recurrent AMI (cumulative proportion) within eight years related to a non-culprit lesion was 0.06 compared with 0.03 for AMI related to the culprit lesion.[44] Thus, in combination with the greater risk associated with MVD, it becomes clear that a systemic medical treatment for AMI is required as opposed to stenting of the culprit lesion alone.[34,35,43-45] Statins have been shown to be effective in regressing plaque, but only in the longer term (> 6 months).[46] Daily rosuvastatin (10 mg) or atorvastatin (20 mg) were found to increase fibrous cap thickness ($P < 0.001$) and reduce the prevalence of thin-cap fibroatheroma ($P < 0.001$). Only rosuvastatin was seen to decrease macrophage density and total atheroma volume. All changes occurred over six months to one year.[46] The use of the PCKS9i, evolocumab, alongside statins also promotes plaque regression. The Global Assessment of Plaque Regression with a PCKS9 Antibody as Measured by Intravascular Ultrasound trial randomized patients (adults with a non-culprit coronary artery lesion and elevated cholesterol with additional CV risk factors, treated with statins for at

Exhibit 3: Cholesterol Transport in Atherosclerotic Plaques[40,64]



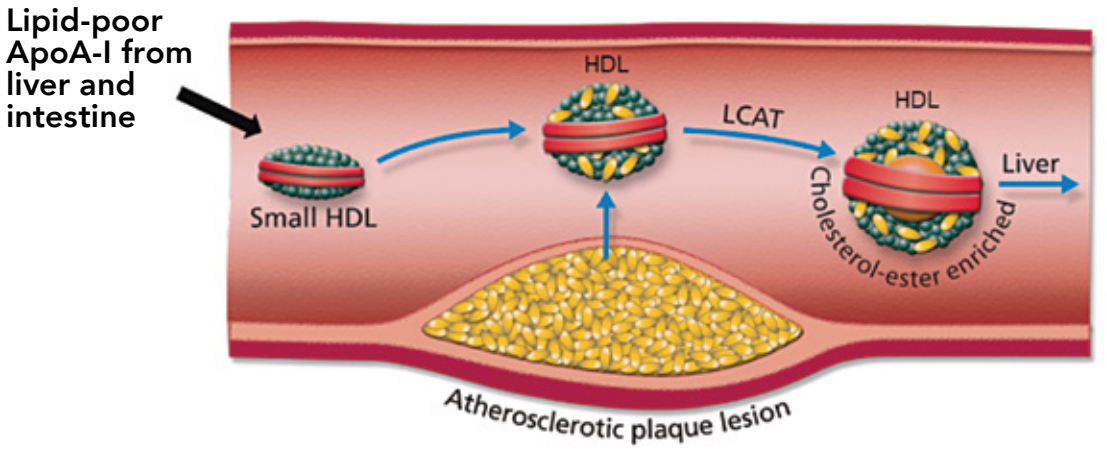
ApoA-I = apolipoprotein A1
HDL = high-density lipoprotein
LDL = low-density lipoprotein
ox-LDL = oxidized LDL
ROS = reactive oxygen species

Adapted from Am J Cardiol, 82(9), Pepine CJ, The effects of angiotensin-converting enzyme inhibition on endothelial dysfunction: potential role in myocardial ischemia, 23S–27S, Copyright (1998), with permission from Elsevier and Estrada-Luna, et al. Current therapies focused on high-density lipoproteins associated with cardiovascular disease. Molecules, 2018; 23:p.2730.

least four weeks) to receive placebo or evolocumab (420 mg) for 76 weeks. While evolocumab did significantly reduce percent atheroma volume versus placebo (–1.2% versus +0.17%, $P < 0.0001$) and total atheroma volume versus placebo (–3.6mm^3 versus –0.8mm^3, $P = 0.04$) after 78 weeks, it did not influence plaque composition.[47] Thus, it remains that there are no current SoC therapies that target plaque stabilization in the high-risk 90-day period post-AMI. This represents a novel therapeutic opportunity.

Atherosclerosis develops due to an imbalance between cholesterol influx and efflux[40,48,49] (Exhibit 3). Furthermore, a clinically strong association exists between reduced cholesterol efflux capacity (CEC) and increased risk for CV events.[50-52] In 2,924 adults free from CV disease participating in the Dallas Heart Study, an inverse association was found between increasing quartiles of CEC and atherosclerotic CV disease. There was a 67 percent reduction in the risk of incident CV disease in the highest versus the lowest quartile of CEC.[50] The same association was not apparent for high-density lipoprotein (HDL) cholesterol (HDL-C) levels after adjustment for CV risk factors and HDL particle concentration, suggesting a mechanism independent of HDL number.[50] CEC has also been shown to be a predictor of mortality in STEMI patients, independent of lipid levels and traditional CV risk factors.[53] A positive association has also been shown between increasing quartiles of CEC and cumulative survival in patients with CAD,[54] and serum CEC has been shown to be significantly lower in patients with ACS or stable

Exhibit 4: Mechanism of Cholesterol Efflux from Atherosclerotic Plaque Mediated by Apolipoprotein A-I



LCAT converts free cholesterol into cholesterol ester leading to formation of larger, mature HDL particles

ApoA-I = apolipoprotein A-I
HDL = high-density lipoprotein
LCAT = lecithin–cholesterol acyltransferase

angina than healthy patients ($P < 0.01$).[55] Crucially, this association between CEC and CV outcomes is independent of HDL-C,[50,53-55] thus generating increasing interest in the HDL function hypothesis – the notion that increasing HDL function, rather than number, may be therapeutically advantageous. HDL from patients with ACS has been shown to have a reduced CEC shortly after AMI.[56,57] The high-risk period post-AMI may be partly explained by this "cholesterol efflux" deficient state. The rapid efflux of cholesterol from lipid-rich plaque is hypothesized to stabilize the plaque, thus reducing the risk of rupture and so new therapies targeting this deficit could be beneficial in reducing the risk of early recurrent CV events.

Appreciating the potential benefits of targeting cholesterol efflux requires an appreciation of the process itself. A suitable candidate therapeutic target to directly address the acute cholesterol efflux impairment that occurs following an AMI is apolipoprotein A-I (apoA-I); a key functional component of HDL.[58-60] ApoA-I plays an important role in cholesterol efflux, itself the first critical step in reverse cholesterol transport (Exhibit 4). Reverse cholesterol transport describes the process by which cholesterol is removed from peripheral tissues and transferred to the liver for clearance. The process begins with the release of apoA-I into the circulation from the liver and the intestines. After apoA-I binds to ABCA1 transporters on cholesterol-containing macrophages resident in atherosclerotic plaques, the macrophages can then deposit their cholesterol onto apoA-I. Lecithin–cholesterol acyltransferase then converts this free cholesterol into its ester, forming mature HDL, which can then be cleared via the liver.[59]

It is important to delineate the concept of targeting reverse cholesterol transport from the HDL-C hypothesis, which has proven less successful than anticipated.[61-63] A Phase III trial of the cholesteryl ester transfer protein inhibitor dalcetrapib, which increases the HDL-C to LDL-C ratio, had to be terminated early due to lack of efficacy. Despite the expected changes in lipoprotein levels, there was no difference in the occurrence of the primary end-point (first occurrence of any component of the composite of death from coronary heart disease, nonfatal MI, ischemic stroke, unstable angina or cardiac arrest with resuscitation) between the treatment and placebo groups.[62] Results from the dal-ACUTE trial further support the concept that HDL-C levels and CEC are dissociated from one another and patients treated with dalcetrapib within one week of an ACS experienced 33.7 and 11.8 percent increases in HDL-C and apoA-I levels, respectively; however, total CEC only increased a small amount (9.5 percent) after four weeks.[63] These and other clinical trials have failed to demonstrate

that HDL is a consistent target for modifying CV risk, even though it remains a powerful predictor of risk.[61] The concept of targeting cholesterol efflux is based on the notion that improved HDL function may be more effective than increased HDL number.

Conclusions

Recurrent CV event rates in the high-risk 90-day period post-AMI represent a significant clinical and economic burden that is not adequately addressed by the current SoC. AMI is a systemic process, especially in high-risk patients with problematic vulnerable plaque in non-culprit vessels and there is a need to target more than just the culprit lesion to prevent recurrent events. Novel approaches to reducing recurrent CV events are required to address this substantial unmet clinical need. Enhancing cholesterol efflux with a view to increasing the stability of atherosclerotic plaques could form the next dimension in CV medicine to prevent recurrent events in the high-risk period post-AMI.

Author Bios

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Disclosure

Dr. Allen is a consultant to CSL Behring.

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