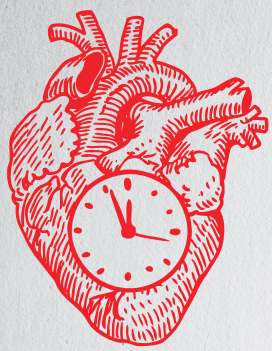


Re-imagining the 90-day high-risk period post-AMI: expert discussions on cholesterol efflux and apoA-I in plaque stabilization

This virtual symposium took place at ACC.21, the American College of Cardiology 2021 Congress, on Saturday May 15, 2021, 10:15–11:15 EST. The symposium was chaired by Prof. C. Michael Gibson and presented by Prof. Roxana Mehran and Prof. P. Gabriel Steg. This was a discussion-led session, which aimed to explore key topics and concepts regarding the 90-day high-risk period following an AMI, and also provide an explanation and insights into the role of cholesterol efflux and apolipoprotein A-I (ApoA-I) in plaque stabilization.

Prof. C. Michael Gibson
Interventional Cardiologist, Beth Israel Lahey Health, Boston, USA
CEO, Baim Institute for Clinical Research (FKA Harvard Clinical Research Institute) and PERFUSE, Boston USA
Professor of Medicine, Harvard Medical School, Boston, USA

Prof. Roxana Mehran
Director of Interventional Cardiovascular Research and Clinical Trials and Professor of Medicine, Mount Sinai School of Medicine, New York, USA

Prof. P. Gabriel Steg
Chief of the Cardiology Department, Hôpital Bichat-Claud Bernard, Paris, France
Professor of Cardiology, Université de Paris, France

Discussion Topic 1: Risk and Incidence of Recurrent CV Events Post-AMI

What do you consider to be the time period of highest modifiable risk for the incidence of "EARLY" recurrent CV events post-AMI?

A. 7 days
B. 30 days
C. 90 days
D. 1 year
E. >1 year

Responses were equally split between 30 days and 90 days

Box 1. Polling Question 1

The significance of recurrent risk up to 90-days post event

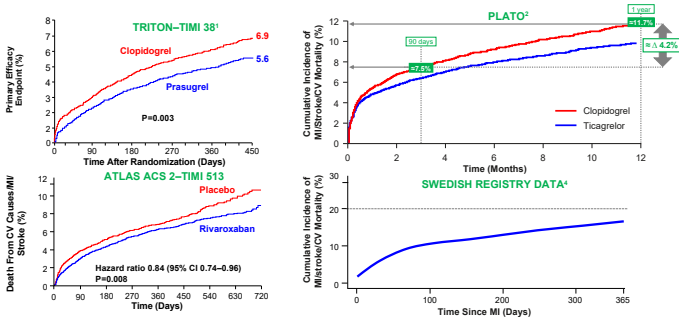
Prof. Gibson opened the session by polling the audience to find the time period of highest modifiable risk for the incidence of early recurrent events post-AMI (Box 1). The audience's opinions were equally split, with 50% apiece for 30 days and 90 days.

Prof. Mehran commented that PCI and AMI outcomes are usually discussed in terms of a 30-day endpoint, and that this is mirrored in clinical trial endpoints. This allows for rapid investigation of treatment efficacy and quick adjustment of treatment as needed.

Prof. Mehran added that the data from key studies, including those with clopidogrel and prasugrel (TRITON-TIMI), clopidogrel and ticagrelor (PLATO), and rivaroxaban and placebo (ATLAS ACS 2-TIMI 51), as well as Swedish Registry data[1–4] all show a very rich period of recurrent events during the first 90 days post-AMI or post-ACS (Figure 1). She emphasized this point with the PLATO study, which reported an overall 1-year event rate* of ~11.7%, of which the majority of events took place in the first 90 days (~7.5%).[2]

**Cumulative incidence of MI, stroke and CV mortality (%).*

Figure 1. The Time Period for Highest Modifiable Risk Post-ACS is the First 90 Days[1–4]



Prof. Steg added that the Swedish Registry data show high recurrent event rates from as early as the first week post-ACS, suggesting that despite intervention and the administration of medication, patients are still at very high risk following discharge and remain at high risk for up to 90 days.[4] Whilst antithrombotic treatment may act to reduce early risk, Prof. Gibson remarked that the Swedish Registry data show that there is still a substantial risk of almost 17–18% for recurrent events including death, MI and stroke occurring at up to 1 year in this real-world population.[4,5]

Risk factors for CV events

The panel subsequently looked at factors to help identify patients who are at increased risk of a recurrent event. They discussed the findings from a large international registry of stable patients with CAD, stratified according to risk factors for CVD, namely smoking status, diabetes status and vascular phenotype (CAD; CAD + CVD/PAD; CAD + CVD + PAD).[6] The study found a stepwise increase in risk of CVD in patients with diabetes and smokers, and reported a 5-year event rate of ~21% in patients with CAD + CVD + PAD who were also diabetic and smokers, compared to ~7% in patients with CAD + CVD + PAD who are neither diabetic nor smoke.[6]

MED-ALL-112-00325. Date of Preparation: July 2021

Prof. Gibson remarked that these risk factors are further amplified by the presence of multi-vessel and poly-vascular disease (not included in the study). Prof. Steg agreed, adding that many patients with 'single-vessel' disease (i.e., one focal stenosis) have non-significant disease in their entire vascular tree and will likely have different outcomes to those with a true discrete stenosis only. The panel agreed that is it important to look at the modifiable risk factors and see how these can be managed to reduce risk and the incidence of recurrent events.

The incidence of recurrent events with LDL-lowering therapies

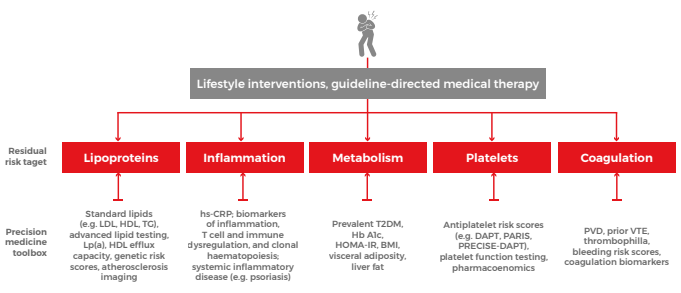
Results from the PROVE-IT and ODYSSEY OUTCOMES studies were highlighted by Prof. Steg. He noted that although an improvement in CV outcomes has been observed with improved LDL-lowering therapies, aggressive LDL-lowering strategies post-ACS do not completely abolish the risk of a recurrent event, even with a regimen based on PCSK9 inhibitors, which has the potential to achieve very low LDL levels.[7,8] Prof. Mehran drew attention to the curves and event rate† from the ODYSSEY OUTCOMES study, which are very similar between treatment arms (alirocumab vs. placebo) in the first 12 months post-ACS, suggesting that the role of LDL lowering is more influential in the long term.[8] She commented that during this 12 months of data convergence, modification of risk and therefore management of events may be required through a different pathophysiological pathway.

Exploring other pathways to modify risk of recurrent events in the first 90 days post-ACS

Prof. Gibson shared recent data presented at the ACC.21 virtual congress, which showed that the 90-day period yields the greatest statistical power for modifiable acute risk reduction. The panelists agreed that the extent of potential risk modification should be an important consideration when designing clinical trials rather than just focusing on accruing as many events as possible. In light of this, Prof. Gibson asked if there is a need to consider new targets for recurrent risk, in addition to the established therapies based on LDL, inflammation, metabolism, platelet and coagulation.

Regarding lipoproteins, Prof. Steg commented that lowering LDL with statins, ezetimibe and PCSK9 inhibitors has a proven clinical benefit. Reducing triglycerides also appears to yield a benefit, while approaches to increase HDL have so far been unsuccessful. He concluded that there may be more to lipid management than these approaches. He remarked that whilst plaques build up through the influx and accumulation of cholesterol, the process can be reversed through cholesterol efflux, which is an intriguing pathway in the 'lipoprotein toolbox' to explore (Figure 2).

Figure 2. Addressing the Risk of Recurrent CV Events in the Era of Precision Medicine[9]



Despite current SOC, there is a risk of recurrent CV events in patients post-AMI. The initial 90 days post-ACS represents the highest modifiable risk period.

Discussion Topic 2: Cholesterol Efflux and ApoA-I

On a scale of 1 to 5, how aware are you of the concept of cholesterol efflux and the role of ApoA-I?

1. ***Not aware***
2. *Fairly aware*
3. *Aware*
4. *Very aware*
5. *Extremely aware*

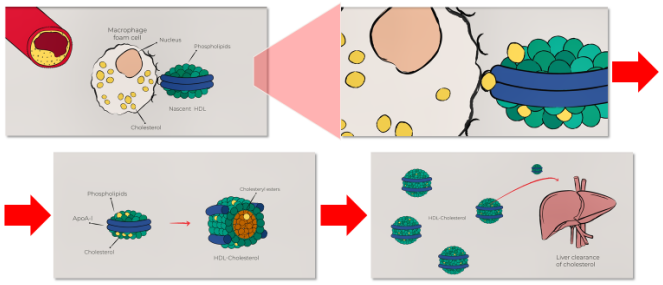
95% of responders were 'not aware'

Box 2. Polling Question 2

Mechanism of disease: Cholesterol efflux

Prof. Gibson opened this discussion around cholesterol efflux and ApoA-I with a second polling question (Box 2). Most respondents (95%) stated that they were not aware of cholesterol efflux and the role of ApoA-I.

Figure 3. The Mechanism of Cholesterol Efflux and the Role of ApoA-I[10-12]



Prof. Gibson provided a step-by-step explanation for the process of cholesterol efflux, beginning by debunking the common misconception that cholesterol is stored in the plaque; it is actually stored in macrophage foam cells. ApoA-I, a primary functional component of HDL, initiates cholesterol efflux by binding to transporters on the macrophage foam cells and promoting the movement (efflux) of free cholesterol onto the HDL particle. Cholesterol on the periphery of HDL is converted into cholesteryl esters by an enzyme called LCAT. Cholesteryl esters are internalized within the HDL core, thus freeing up space on the periphery of HDL for more cholesterol. Once lipid-depleted HDL ('nascent HDL') fills with cholesterol esters (becomes lipid-laden) it is transported to the liver for excretion (Figure 3).[10-12]

Clinical significance of cholesterol efflux capacity

Cholesterol Efflux Capacity:
A measure of HDL function. The ability of HDL to remove excess cholesterol from atherosclerotic plaques for transport to the liver.

Prof. Steg commented that studies aiming to increase HDL particle number or size have not reported any clinical benefit, indicating that these factors do not correlate directly with cholesterol efflux efficiency. Therefore, HDL function and its relationship to cholesterol efflux capacity and CV outcomes is rapidly becoming an area of interest,[11] with Prof. Mehran adding that significantly impaired cholesterol efflux capacity has been shown in ASCVD and ACS.[13]

Prof. Steg outlined the findings of a French study that investigated the association between serum cholesterol efflux capacity and mortality in a cohort of MI survivors (N=1609). The study reported a clear correlation in this group between increasing quartiles of cholesterol efflux capacity and survival rates at 6 years (Figure 4).[14]

For further information or to stay in contact, email us at CVM.medinfo@cslbehring.com

MED-ALL-112-00325. Date of Preparation: July 2021

Figure 4. Cholesterol Efflux Capacity Predicts Mortality in Patients with AMI[14]

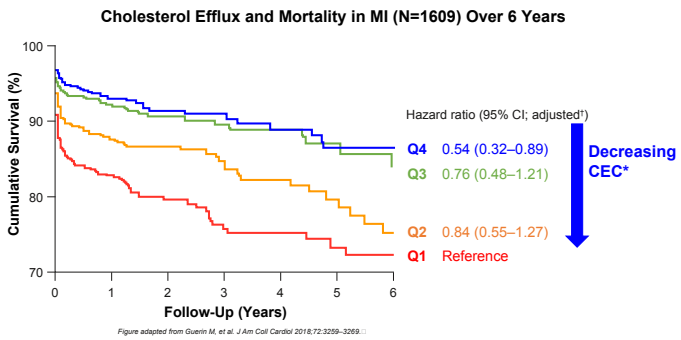


Figure adapted from Guerin M, et al. J Am Coll Cardiol 2018;72:3259–3269.

Prof. Mehran further observed that for patients with low cholesterol efflux capacity, the impact on survival is apparent within the first year post-AMI, with the biggest reduction seen within the first 90 days.[14] Prof. Steg remarked that similar results had also been observed in the population-based Dallas Heart Study , which reported a 67% reduction in CV risk in the highest quartile of cholesterol efflux capacity compared with the lowest quartile (HR: 0.33; 95% CI 0.19–0.55).[15] Furthermore, a meta-analysis presented at the ACC.21 virtual congress also showed that higher cholesterol efflux capacity is associated with fewer adverse CV outcomes.[16] It was agreed that at present, it is unclear whether cholesterol efflux is a potential treatment target, or a biomarker of CVD; however, current research is investigating the topic further.

The speakers concluded that there are factors outside of LDL control that can influence outcomes in patients following a CV event and the initial 90-day period post-ACS is a high-risk time period,[17] thus presenting an important window of opportunity for new treatment approaches. Correspondingly, cholesterol efflux capacity represents a fascinating new area to explore and warrants further research.

ApoA-I is a primary functional component of HDL and a key mediator of cholesterol efflux. Cholesterol efflux capacity is impaired in ASCVD and ACS and is inversely associated with the likelihood of adverse CV outcomes, leading to the question of whether improving cholesterol efflux capacity can reduce the risk of recurrent CV events.

Abbreviations: ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; AMI, acute myocardial infarction; ApoA-I, apolipoprotein A-I; ATLAS ACS 2-TIMI 51, Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome–Thrombolysis in Myocardial Infarction 51; CAD, coronary artery disease; CV, cardiovascular; CVD, cardiovascular disease; EPA, eicosapentaenoic acid; HDL, high-density lipoprotein; LCAT, lecithin–cholesterol acyltransferase; LDL, low-density lipoprotein; MACE, major adverse cardiovascular events; MI, myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; PCSK9, proprotein convertase subtilisin/kexin type 9; PLATO, Study of Platelet Inhibition and Patient Outcomes; REDUCE-IT, Reduction of Cardiovascular Events With Icosapent Ethyl–Intervention Trial; SOC, standard of care; SWEDEHEART, Swedish Web System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies; TRITON-TIMI, Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction.

References

1. Wiviott SD et al, *N Engl J Med* 2007;357:2001–2015.
2. Wallentin L et al, *N Engl J Med* 2009;361:1045–1057.
3. Mega JL et al, *N Engl J Med* 2012;366:9–19.
4. Jernberg T et al, *Eur Heart J* 2015;36:1163–1170.
5. Onwordi EN et al, *Interv Cardiol* 2018;13:87–92.
6. Gautier A et al, *Eur J Prev Cardiol* 2020; doi:10.1093/eurjpc/zwaa137. Online ahead of print.
7. Cannon CP et al, *N Engl J Med* 2004;350:1495–1504.
8. Schwartz GG et al, *N Engl J Med* 2018;379:2097–2107.
9. Patel KV et al, *Circulation* 2018;137:2551–2553.
10. Rader DJ et al, *J Lipid Res* 2009;50 Suppl:S189–S194.
11. Kingwell BA et al, *Circulation* 2013;128:1112–1121.
12. Kingwell BA et al, *Nat Rev Drug Discov* 2014;13:445–464.
13. Hafiane A et al, *Am J Cardiol* 2014;113:249–255.
14. Guerin M et al, *J Am Coll Cardiol* 2018;72:3259–3269.
15. Rohatgi A et al, *N Engl J Med* 2014;371:2383–2393.
16. Lee JJ et al. *J Am Coll Cardiol* 2021;77(18, Suppl 1):1486.
17. Varenhorst C et al. *J Am Heart Assoc*. 2018;7:e007174

CSL Behring
Biotherapies for Life™

MED-ALL-112-00325. Date of Preparation: July 2021

For further information or to stay in contact, email us at CVM.medinfo@cslbehring.com