Title: Novel Therapies to Achieve the Recommended Low-density Lipoprotein Cholesterol Concentration (LDL-C) Targets for Patients post CABG

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IRB: Not applicable

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## Abbreviations:

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACC</td>
<td>American College of Cardiology</td>
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<tr>
<td>AHA</td>
<td>American Heart Association</td>
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<tr>
<td>ARR</td>
<td>Absolute Risk Reduction</td>
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<tr>
<td>ASCVD</td>
<td>Atherosclerotic cardiovascular disease</td>
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<td>CABG</td>
<td>Coronary artery bypass grafting</td>
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<tr>
<td>EACTS</td>
<td>European Association of Cardiothoracic Surgery</td>
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<tr>
<td>eGFR</td>
<td>Estimated glomerular filtration rate</td>
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<tr>
<td>ESC</td>
<td>European Society of Cardiology</td>
</tr>
<tr>
<td>IPE</td>
<td>Icosapent Ethyl</td>
</tr>
<tr>
<td>MACE</td>
<td>Major adverse cardiovascular events</td>
</tr>
<tr>
<td>MI</td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>NST</td>
<td>Non statin therapies</td>
</tr>
<tr>
<td>OMT</td>
<td>Optimal medical therapy</td>
</tr>
<tr>
<td>PCSK9i</td>
<td>Proprotein convertase subtilisin/kexin type 9 inhibitor</td>
</tr>
<tr>
<td>RRR</td>
<td>Relative Risk Reduction</td>
</tr>
<tr>
<td>SASE</td>
<td>Statin associated side effects</td>
</tr>
<tr>
<td>SI</td>
<td>Statin intolerance</td>
</tr>
<tr>
<td>TIA</td>
<td>Transient Ischemic accident</td>
</tr>
<tr>
<td>siRNA</td>
<td>Small interfering Ribonucleic acid</td>
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</table>
Central picture: Flowchart for LDL-C reduction post CABG as per AHA/ACC and the ESC guidelines.

Central message: Wider use of recently introduced non-statin agents should help to reduce the residual risk of adverse cardiac events in high-risk post CABG patients.

Perspective statement: Post CABG patients are at high risk for adverse cardiovascular events. Secondary prevention, particularly LDL-C reduction has demonstrated significant benefit in reducing these risks. We hope that the wider use of recently introduced non-statin agents and more attention towards triglyceride reduction will help to reduce residual risk for adverse cardiac events in high-risk coronary artery bypass patients.

Keywords: atherosclerosis, coronary artery disease, coronary artery bypass grafting, PSCK9 inhibitor, ezetimibe, Inclisiran, Bempedoic acid, statin intolerance, statin associated muscle symptoms
Introduction:

Coronary artery bypass grafting (CABG) is a common cardiac surgical procedure with approximately 400,000 cases done annually in the US alone. Over the years, the comorbidity of patients undergoing CABG has increased with more patients having pre-existing diabetes mellitus, heart failure, chronic kidney disease, peripheral artery or cerebrovascular disease with higher utilization of emergent surgery.

Contemporary post-operative outcomes among patients who undergo CABG are excellent with low in-hospital mortality (1.8%), but avoiding recurrent major adverse cardiovascular events (MACE) largely depends on adopting appropriate secondary prevention measures. To increase the uptake of secondary prevention strategies after CABG, in 2015 (American Heart Association - AHA) and 2018 (European Association of Cardiothoracic Surgery - EACTS) provided a clear guidance on the therapies considered optimal medical therapy (OMT) after surgery. Along with lifestyle modifications, as per these guidelines, OMT consisted of anti-platelet therapy (aspirin, P2Y12 inhibitors), blood pressure control (beta-blockers, angiotensin receptor blockers, angiotensin converting enzyme inhibitors), glycemic control, and effective low density lipoprotein cholesterol (LDL-C) reduction. Among these measures, one could argue that LDL-C reduction may likely be one of the most important for post CABG patients. We have clear evidence that lipid lowering after CABG is associated with better graft patency and improved outcomes. In the Post-Coronary Artery Bypass Graft trial (post-CABG) trial, compared to patients with LDL-C concentrations between 132 – 136 mg/dl (3.4 mmol/L), those with LDL-C concentrations < 100 mg/dl (2.6 mmol/L) had improved saphenous vein graft patency on coronary angiography. Over a 7-year follow-up, this trial also reported a lower incidence of MACE in patients with LDL-C concentrations < 100 mg/dl. A more contemporary analysis of 3
randomized trials showed a dose-response relationship between attained LDL-C and MACE outcomes in patients with type 2 diabetes undergoing CABG. We already have randomized trial data on the effectiveness of statin therapy for many decades, yet most post CABG patients are grossly under-treated.

More recently, the importance of treating elevated LDL-C in secondary prevention was further supported by recent genetic studies that reported a causal relationship between low-density lipoprotein cholesterol (LDL-C) concentrations and atherogenesis. Furthermore, initiating appropriate lipid lowering therapies immediately after surgery may promote better long-term medication adherence and substantial life-years gained.

Therefore, in this review, we aim to:

(i) Introduce the ‘very-high risk’ definition and updated intensity of LDL-C lowering in CABG patients.

(ii) Discuss recent updates on statin intolerance (statin associated side effects (SASE)).

(iii) Provide an overview of the recent advances in non-statin therapy (NST).

(iv) Briefly discuss the relevance of triglycerides in secondary ASCVD prevention, and lastly

(v) Present current opinions regarding possible concerns of an extremely low LDL-C concentration.

The very high-risk patient and new LDL-C targets:

The European Society of Cardiology (ESC) and the American Heart Association/American College of Cardiology (AHA/ACC) recently introduced guidelines regarding the choice of coronary revascularization. However, they provide little guidance regarding secondary prevention strategies after CABG. Therefore, our strategies on secondary prevention are based on the 2018 AHA/ACC and the 2019 ESC Scientific committee statements for the treatment of
blood cholesterol $^{13,14}$. Both (ACC/AHA and ESC) identify LDL-C as the primary therapeutic target in secondary prevention and created a new group of ‘very high-risk’ ASCVD patients that they consider are at highest risk to have recurrent major adverse cardiovascular events (MACE) (Table 1). From table 1, clearly the ESC definition for a ‘very high-risk’ patient is more liberal than that provided by the AHA/ACC. In our recent study using data from US Veterans, using the 2018 AHA/ACC criteria, approximately a third (32%) of the patients undergoing CABG were classified as ‘very high-risk’ by the ACC/AHA criteria $^{15}$. However, according to the ESC criteria, all patients would be classified as ‘very high-risk’. Even if we hypothesize that US Veterans have a higher comorbidity burden than non-Veterans and apply the stricter ACC/AHA criteria, we expect that at least 20% of all post CABG patients treated at non-VA hospitals in the US are likely ‘very high-risk’ for recurrent MACE. Therefore, accurate risk-stratification after surgery is the first step towards initiating intensive secondary prevention measures. Another important difference between guidelines is the lower target (LDL-C < 55 mg/dl; 1.42 mmol/L per ESC guideline) vs a threshold of 70 mg/dl; 1.81 mmol/L to consider non-statin therapies as per the AHA/ACC guideline. (Figure 1 A/B). In the latter sections, we discuss the available therapies to achieve such extremely low LDL-C concentrations.

The problem of statin intolerance (statin-associated side effects [SASE]):

While statins remain the first line therapy for LDL-C reduction, poor long-term adherence, high rates of discontinuation, and statin intolerance (SI) due to perceived side effects often limit effective risk reduction $^{16}$. Depending upon the data sources, statin-associated muscle symptoms (SAMS) and SI may occur in 5-30% people receiving statin therapy, with observational studies reporting higher event rates than randomized trials $^{17,18}$. While definitions of SAMS/SI vary (Table S1) multiple studies reported that Black or Asian race, age $\geq 65$ years, female sex, statin
intensity, intense exercise and increased alcohol intake were associated with increased SI\textsuperscript{18, 19, 20}. Furthermore, SI was associated with a 50% increase in the relative risk for MI among 56,000 Medicare beneficiaries\textsuperscript{22} and SI patients were 85% less likely to meet recommended LDL-C thresholds of < 100 mg/dl (patients with CHD, ischemic stroke, PAD, or diabetes) and <70 mg/dL (patients with recent ACS).\textsuperscript{23} Due to the higher MACE rates, compared to patients tolerating high-intensity statins, SI patients also incurred higher overall treatment costs\textsuperscript{23}. But the recently introduced NST (proprotein convertase subtilisin/kexin type 9 inhibitors [PCSK9i] monoclonal antibodies, small interfering RNA therapies, and Bempedoic acid) will help to bridge this gap.

**Non-statin therapies for LDL-C reduction after CABG:**

Statin agents (simvastatin, atorvastatin, lovastatin, pravastatin, pitavastatin and rosuvastatin) have been the first line agents for reducing LDL-C. They inhibit hydroxy-methyl coenzyme-A reductase, which is the rate limiting step in de-novo cholesterol synthesis (Figure S1). Based on their projected LDL-C reduction from the untreated baseline concentration, drugs can be classified as low-intensity (< 30% LDL-C reduction), moderate intensity (30 – 49%) and high-intensity (≥ 50% LDL-C reduction) (Table 2). A large patient-level pooled meta-analysis of 27 trials reported that every 1 mmol/L (38 mg/dl) reduction in LDL-C concentration resulted in a 21% relative risk reduction (RRR) for MACE\textsuperscript{24} Currently, Ezetimibe, Bempedoic acid, PCSK9i monoclonal antibodies (Evolocumab, Alirocumab), and Inclisiran are the NST that are approved in the United States for lowering LDL-C concentration. While Ezetimibe and Bempedoic acid require daily oral dosing, the PCSK9i are subcutaneous injections that can be administered either bi-weekly or monthly (Evolocumab, Alirocumab) while Inclisiran (an siRNA molecule) needs 6-monthly dosing after the initial doses at days 0 and 90. The ORION-4 (NCT 03705234)
randomized trial evaluating the clinical benefit of Inclisiran, an siRNA molecule, is currently ongoing, while all other drugs have demonstrated cardiovascular benefit (https://clinicaltrials.gov/ct2/show/NCT03705234). Table 3 provides summary information on NST outcomes trials.

**Ezetimibe**: Ezetimibe is a selective cholesterol inhibitor which targets the Niemann-Pick CI-Like 1 (NPC1L1; SLC65A2) (Figure S1). In the IMPROVE-IT trial (2015), a combination of moderate intensity simvastatin monotherapy versus combination therapy (moderate intensity simvastatin + 10 mg oral daily Ezetimibe) resulted in a 24% relative reduction in LDL-C compared to the baseline. At 6 years median follow up, Ezetimibe resulted in a 6% relative risk reduction for MACE. Currently, both AHA/ACC and ESC recommend Ezetimibe as an inexpensive add-on therapy with statins. Importantly, in this trial, post CABG patients seemed to derive a greater benefit from Ezetimibe (absolute risk reduction (ARR) 8.8% for CABG vs 2% in the overall trial). However, a small fraction of eligible post CABG patients currently receive Ezetimibe. A single center study of 484 post-CABG patients from Australia reported that despite only 50% patients at LDL-C thresholds according to 2018 AHA/ACC guidelines, less than 1% of total patients received Ezetimibe as a second-line agent. In our analysis of 8,948 ‘very high-risk’ post-CABG US Veterans only 1.4% received Ezetimibe therapy and only 30% were at the recommended threshold LDL-C concentrations before CABG. Thus, increasing the use of Ezetimibe is a relatively inexpensive way to get more post CABG patients at their recommended LDL-C thresholds prior to discharge.

**PCSK9 inhibitors (Alirocumab, Evolocumab)**: PCSK9, a protein, binds to hepatocyte LDL receptors and prevents the hepatic uptake of circulating LDL particle. PCSK9 inhibitors (PCSK9i) are monoclonal antibodies that bind and inhibit the activity of PCSK9 which results in
increased hepatocyte uptake of circulating LDL (Figure S1). Both drugs can be given biweekly or monthly. In trials that enrolled high-risk ASCVD patients, evolocumab (FOURIER), and alirocumab (ODYSSEY OUTCOMES) resulted in a 1.6% and 1.5% ARR (both trials reported a 15% RRR) for MACE respectively. While the ARR estimates may appear small, this was on the background of high intensity statin therapy with average baseline LDL-C concentrations in both trial around 92 mg/dl (2.38 mmol/L) and the trial were of short duration. In a pre-specified analysis of 2,028 patients post CABG from the ODYSSEY Outcomes trial, a high absolute risk reduction (6.4%) for MACE was observed in patients with prior CABG and the gradual separation in the cumulative incidence curves beyond the second year highlighted a possible incremental benefit of low LDL-C in high-risk patients. A trial to evaluate whether evolocumab administration early after CABG will improves saphenous vein graft patency (NEWTON-CABG) is currently underway (NCT03900026). Data from recent glucagon like peptide-1 receptor agonist trials suggest that the subcutaneous route is well accepted and after appropriate training, patients can safely self-administer both evolocumab and alirocumab. While PCSK9i use among patients post CABG could improve outcomes, presently cost and refusal of pre-authorization from private insurers remain hurdles to wider use clinical practice.

Bempedoic Acid: Among NST, Bempedoic acid is the most recent medication to demonstrate clinical benefit in patients with established ASCVD (CLEAR Outcomes). Bempedoic acid is a prodrug that is converted to its active form by the very-long-chain acyl-CoA synthetase in the liver and kidney. Like statins, it inhibits de-novo cholesterol synthesis resulting in increased clearance of circulating LDL (Figure S1). As skeletal muscle does not have very-long-chain acyl-CoA synthetase, it is well tolerated in SASE patients. The CLEAR Outcomes trial, in fact, only enrolled high-risk statin intolerant ASCVD patients. Starting with a mean LDL-C
concentration of 139 mg/dl at randomization, trial participants receiving Bempedoic acid had a 21% decline in LDL-C concentrations over the 40-month median follow-up. Results of the CLEAR Outcomes were reported in March 2023 but real-world experience with Bempedoic acid is, at present, extremely limited. In the pivotal trial, investigators observed higher rates of hyperuricemia and gout among study drug recipients. However, more real-world evidence is needed regarding treatment related adverse events before we can make any specific conclusions regarding its safety profile.

Inclisiran: Inclisiran, an siRNA molecule, is a long-acting double-stranded RNA molecule. It inhibits PCSK9i mRNA in the hepatocyte by interacting with the RNA-induced silencing complex \(^{38}\). After doses at days 0 and 90, Inclisiran reaches a steady plasma concentration and requires to be re-administered every 6 months. In December 2021, the US Food and Drug Administration approved Inclisiran as a second line agent after statins for LDL-C reduction in patients with heterozygous familial hypercholesteremia or ASCVD. In a real-world experience of 80 patients, the drug was well tolerated and resulted in a 50% reduction in LDL-C concentrations over the 2 month study period \(^{39}\). The ORION-4 trial evaluating its cardiovascular benefit is currently ongoing (NCT03705234).

Some practical guidance:

In the supplementary appendix, we further provide a brief framework for initiating LDL-C reduction after surgery (Table S2).

Recommendations regarding triglyceride (TG) concentrations:

While much focus has hitherto been on LDL-C, despite lowering LDL-C concentrations the residual risk of MACE in some ASCVD patients remain high. Furthermore, Mendelian randomization studies have recently reported a possible causal role for TG in ASCVD \(^{40}\). While
earlier trials reducing TG levels failed to report cardiovascular benefits \(^4\), the REDUCE-IT trial

using Icosapent ethyl (IPE, an omega-3 fatty acid product) versus mineral oil (as placebo) reduced MACE in patients with elevated TG levels \(^2\). In this trial, 8179 ASCVD patients, already on statin therapy, received high dose IPE (4 gms/day). Over the 5-year median follow up, MACE rates were 5% lower with IPE therapy (25% RRR). IPE is currently approved for use in the US for reducing CV risk in patients with elevated TG (\(\geq 150\) mg/dL). In a subgroup analysis of the REDUCE-IT trial, MACE reduction in IPE treated patients with history of CABG (Hazard Ratio - 0.76) was comparable to that observed in the overall trial \(^3\). However, the similarly designed STRENGTH trial, using another fish oil (omega-3 fatty acid) formulation (combination of Eicosapentanoic acid/Docosahexanoic acid) vs corn oil (placebo) failed to reduce CV risk \(^4\). Subsequently, the use of mineral oil as placebo in the REDUCE-IT created controversy given the observed increase in LDL-C and higher inflammatory signals among patients that received the mineral oil placebo \(^5\). A recent study further reported that both mineral and corn oil showed similar rates of atherosclerosis progression; however, the issue of statin absorption among placebo treated patients remains a cause for concern \(^6\).

**Safety of extremely low LDL-C:**

Totality of evidence clearly demonstrates that LDL-C concentration reduction directly results in MACE reduction. PCSK9i and Inclisiran can reduce LDL-C to extremely low levels (<30 mg/dL). Potential risks with such low LDL-C levels are new onset diabetes, hemorrhagic stroke and cataract development. Although increased risk of diabetes appears to be supported by consistent evidence, other side effects remain controversial. While mendelian randomization points towards a possible link between extremely low LDL-C and diabetes \(^7\), this has yet not been observed in any of the PCSK9i trials. In a pooled analysis of 14 trials from the Odyssey
program, alirocumab treated patients with LDL-C < 25 mg/dl had higher rates of cataract formation but not neurological emergencies. Thus, until further research tells us differently, the cardiovascular benefit of extremely low LDL-C concentrations presently greatly outweighs the small possibility of adverse events linked to extremely low LDL-C. Targeting Lipoprotein (a) may be the path forwards towards achieving zero MACE events. Trials and drugs (Pelacarsen, Olpasiran) reducing Lp (a) levels are still ongoing, and we await more data regarding their cardiovascular benefit.

**Summary:**

In this review, we hope to provide practicing cardiac surgeons information regarding the importance of actively promoting aggressive LDL-C reduction therapies in their patients after coronary artery bypass surgery. Although we often consider leaving medication choices to cardiologists and primary care clinicians, the authors believe that cardiac surgeons have an important opportunity to positively impact our patients’ long-term outcome by advocating for the aggressive initiation of optimal medical therapy immediately after surgery. We hope that our review will help to underline the importance of LDL-C reduction after CABG and increase the proportion of patients receiving optimal LDL-C management worldwide.
Figure Legend:

Figure 1.

Caption – Overview of LDL-C reduction strategy.

Legend – We present the flowchart for LDL-C reduction strategy as a part of the secondary prevention measures for patients with pre-existing atherosclerotic vascular disease.
Figure S1. We present the various pathways that are influenced by statin and non-statin therapies outlined in our review. In the intestine, dietary cholesterol is absorbed via the Niemann Pick C1-like-1 protein receptor. Ezetimibe inhibits this receptor and prevents oral cholesterol absorption. In the liver, de-novo cholesterol synthesis pathway converts glucose to cholesterol. In this pathway, Bempedoic acid inhibits the adenosine triphosphate-citrate lyase (ACL) enzyme, while statins inhibit the hydroxy-methyl CoA reductase enzyme, which is the rate limiting step in de-novo cholesterol synthesis. LDL-C receptors in the liver take in the circulating LDL-C. These receptors are degraded by proprotein convertase subtilisin/kexin type 9 (PCSK9). Therefore, PCSK9 inhibitors prevent PCSK9 from attaching to and degrading the LDL-C receptors. In the hepatocyte, the PCSK9 production is governed...
by PCSK9 mRNA. Inclisiran inhibits PCSK9 mRNA by interacting with the RNA-induced silencing complex, thereby reducing PCSK9 concentrations in the liver.

Abbreviations: ACL – adenosine triphosphate-citrate lyase, HMGCR – hydorxy-methyl coenzyme A reductase, LDL-C – low density lipoprotein cholesterol, NPC1L1 – Niemann Pick C1 like 1 protein, mRNA – messenger ribonucleic acid, PCSK9 – proprotein convertase subtilisin/kexin type 9
Table 1. The ACC/AHA and ESC criteria for *very high risk*:

<table>
<thead>
<tr>
<th>Major ASCVD events</th>
<th>High-risk Conditions</th>
</tr>
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<tbody>
<tr>
<td>Recent acute coronary syndrome (within the past 12 months)</td>
<td>Age &gt; 65 years</td>
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<tr>
<td>Prior history of myocardial infarction (other than the recent acute coronary syndrome)</td>
<td>Heterozygous familial hypercholesterolemia</td>
</tr>
<tr>
<td>Prior history of ischemic stroke</td>
<td>History of prior CABG / percutaneous revascularization</td>
</tr>
<tr>
<td>Symptomatic peripheral arterial disease / Prior history of lower limb revascularization / Prior lower limb amputation for vascular disease</td>
<td>Diabetes mellitus</td>
</tr>
</tbody>
</table>

**The 2018 AHA/ACC ‘very high risk’ definition**

Multiple major ASCVD events OR one ASCVD event + multiple high-risk conditions.

**Major ASCVD events**

Recent acute coronary syndrome (within the past 12 months)
Prior history of myocardial infarction (other than the recent acute coronary syndrome)
Prior history of ischemic stroke
Symptomatic peripheral arterial disease / Prior history of lower limb revascularization / Prior lower limb amputation for vascular disease

**High-risk Conditions**

Age > 65 years
Heterozygous familial hypercholesterolemia
History of prior CABG / percutaneous revascularization
Diabetes mellitus
Hypertension
Chronic kidney disease (eGFR < 60 ml/min/1.73 m²)
Current smoking
LDL-C > 100 mg/dl (> 2.6 mmol/L) despite maximally tolerated statin therapy
Prior congestive heart failure

**The 2019 ESC ‘very high risk’ definition**

Clinically documented ASCVD (having at least one of the following)
Prior acute coronary syndrome (myocardial infarction or unstable angina)
Stable angina
Prior revascularization (coronary or peripheral vascular)
Prior stroke/TIA
Peripheral arterial disease
Documented ASCVD using imaging (unequivocal)
Significant plaque on a coronary angiogram or CT scan (at least two major epicardial vessels having > 50% stenosis)
Significant carotid stenosis on a carotid ultrasound
Diabetes mellitus with target organ damage (microalbuminuria, retinopathy or neuropathy)
Severe Chronic kidney disease (eGFR < 30 ml/min/1.73 m²)
A calculated SCORE predicting > 10% risk of fatal ASCVD at 10 years.

This table presents the criteria to define a ‘very-high risk’ patient according to the professional society guidelines.
Table 2.

<table>
<thead>
<tr>
<th>Low-intensity Statin therapy</th>
<th>Moderate Intensity Statin therapy</th>
<th>High Intensity Statin therapy</th>
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<tbody>
<tr>
<td>Daily dose lowers LDL-C by &lt; 30% (on average)</td>
<td>Daily dose lowers LDL-C by 30 – 49% (on average)</td>
<td>Daily dose lowers LDL-C by ≥ 50% (on average)</td>
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<tr>
<td>Simvastatin 10mg</td>
<td>Atorvastatin 10 – 20 mg</td>
<td>Atorvastatin 40 – 80 mg</td>
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<tr>
<td>Pravastatin 10 – 20 mg</td>
<td>Rosuvastatin 5 – 10 mg</td>
<td>Rosuvastatin 20 – 40 mg</td>
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<tr>
<td>Lovastatin 20 mg</td>
<td>Simvastatin 20 – 40 mg</td>
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<tr>
<td>Fluvastatin 20 – 40 mg</td>
<td>Pravastatin 40 – 80 mg</td>
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<td></td>
<td>Lovastatin 40 mg</td>
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<td></td>
<td>Fluvastatin XL 80 mg</td>
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<td></td>
<td><strong>Fluvastatin 40 mg BID</strong></td>
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<td></td>
<td>Pitavastatin 2-4 mg</td>
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</table>

This table groups statin drugs according to their LDL-C reducing intensity. It created from data provided in the 2018 AHA/ACC Guidelines on the management of blood cholesterol. Bold face denotes those therapies that were included in randomized trials of statin therapy.
Table 3. Summary of the trials included in this review

<table>
<thead>
<tr>
<th>Drug</th>
<th>Pivotal Trial</th>
<th>Trial overview</th>
<th>Results</th>
<th>Drug related Adverse Events</th>
</tr>
</thead>
</table>
| Ezetimibe        | IMROVE-IT     | • 18,144 patients with acute coronary syndrome and an LDL-C > 50 mg/dl  
• Simvastatin 40mg vs Simvastatin 40mg + Ezetimibe 10 mg  
• Dosing: 10mg Ezetimibe orally daily  
• Median duration: 6 years  
• Primary endpoint: composite of CV death, major coronary event (non-fatal MI, unstable angina, coronary revascularization 30 days beyond randomization) | • 2% absolute risk reduction favoring Ezetimibe therapy  
• HR 0.94 (95%CI:0.89, 0.99) | • No difference observed in the pre-specified safety endpoints  
• Discontinuation of study medication due to adverse events similar in both arms |
| PCSK9 inhibitors |               |                                                                                                                                                                                                                                                                  |                                                                        |                                                                                                                   |
| Evolocumab       | FOURIER       | • 27,564 patients with established ASCVD already on stable statin therapy and LDL-C > 70 mg/dl  
• 70% and 5% received high-intensity statin and Ezetimibe at baseline  
• Dosing: Evolocumab subcutaneous injection, 140mg bi-weekly or 420mg | • 1.5% absolute risk reduction favoring Evolocumab  
• HR 0.85 (95%CI:0.73, 0.88) | • No difference observed in the pre-specified safety endpoints  
• Injection site reactions more frequent with Evolocumab (2.1% vs 1.6%)  
• Rate of new onset diabetes comparable between arms [HR 1.05 (95%CI:0.94, 1.17)] |
<table>
<thead>
<tr>
<th>Drug</th>
<th>Study</th>
<th>Patients Description</th>
<th>Dosing</th>
<th>Primary Endpoint</th>
<th>Risk Reduction</th>
<th>Safety Endpoints</th>
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<tbody>
<tr>
<td>Alirocumab</td>
<td>ODYSSEY OUTCOMES</td>
<td>18,924 patients with remote acute coronary syndrome already on high-intensity statin therapy with LDL-C &gt; 70 mg/dl (1.8 mmol/lit)</td>
<td>Dosing: Alirocumab subcutaneous injection, 75 – 150mg biweekly to ensure LDL-C 25 – 50 mg/dl, but above 15 mg/dl.</td>
<td>Composite of CV death, major coronary event (non-fatal MI, unstable angina, coronary revascularization)</td>
<td>1.6% absolute risk reduction</td>
<td>HR 0.85 (95%CI:0.78, 0.93) No difference observed in the pre-specified safety endpoints. Local injection site reactions higher with Alirocumab (3.8% vs 2.1%). Rate of new onset diabetes comparable in both arms.</td>
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<tr>
<td>Bempedoic Acid</td>
<td>CLEAR Outcomes</td>
<td>13,970 patients with established, or at high risk for ASCVD and statin intolerant at randomization</td>
<td>Tolerated statin therapy vs tolerated statin therapy + Bempedoic acid</td>
<td>1.6% absolute risk reduction</td>
<td>HR 0.87 (95%CI:0.76, 0.96)</td>
<td>The overall incidence of serious adverse events and adverse events leading to study drug discontinuation was similar between groups.</td>
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<td>Triglyceride reduction</td>
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<tr>
<td><strong>Icosapent ethyl (IPE)</strong></td>
<td>8179 ASCVD patients on statin therapy with elevated fasting TG (135 – 499 mg/dl; 0.52 – 5.64 mmol/lit)</td>
<td>5% absolute risk reduction</td>
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<td><strong>REDUCE-IT</strong></td>
<td>Dosing: IPE 4gms twice day versus placebo</td>
<td>HR 0.75 (95%CI:0.68, 0.83)</td>
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<td></td>
<td>Primary endpoint: composite of CV death, major coronary event (non-fatal MI, unstable angina, coronary revascularization)</td>
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- Renal events (11.6% vs 8.6%), hyperuricemia (10.9% vs 5.6%), gout (3.1% vs 2.1%) and cholelithiasis (2.2% vs 1.2%) higher in patients treated with Bempedoic acid

This table presents a summary of trials included in our review. The cardiovascular outcomes trial for Inclisiran is currently ongoing (ORION-4; NCT03705234).
References:


2018 AHA/ACC Guidelines

Post-CABG patient

Not 'very high-risk'

Age ≤ 75 years

High-intensity statin

If on maximal-dose statin therapy and LDL-C ≥ 70

Add Ezetimibe (Class IIb)

Age > 75 years

Very-high Risk

High-intensity or maximal statin (Class I)

If on maximal-dose statin therapy and LDL-C ≥ 70

Add Ezetimibe (Class IIb)

2019 ESC Guidelines

Post-CABG patient

All patients deemed Very-high Risk

Target

LDL-C reduction ≥ 50% and target LDL-C < 1.4 mmol/L (< 55 mg/dl)

Apo-B levels < 65

Therapy

High-intensity Statin (if tolerated)
Repeat LDL-C in 8-6 weeks / above target, start Ezetimibe
Repeat LDL-C in 8-6 weeks / above target, start PCSK9i
2018 AHA/ACC Guidelines

**Post-CABG patient**

**2018 AHA/ACC Classification**

**Not ‘very high-risk’**
- Age ≤ 75 years
  - High-intensity statin (Class I)
  - If on maximal statin therapy and LDL-C ≥ 70, add Ezetimibe (Class III)

**Very-high Risk**
- Age > 75 years
  - High-intensity or maximal statin (Class I)
  - Include moderate-intensity or high-intensity statin (Class IIb)
  - With maximal statin therapy, if LDL-C ≤ 70 mg/dL, add Ezetimibe (Class IIa)
  - Add Ezetimibe before PCSK9i (Class I)

2019 ESC Guidelines

**Post-CABG patient**

**2019 ESC Criteria**

**All patients deemed Very-high Risk**
- Target LDL-C reduction ≥ 50% and target LDL-C < 1.4 mmol/L (< 55 mg/dL)
- Apo-B levels < 65

**2019 ESC Therapy**
- High-intensity Statin (if tolerated)
- Repeat LDL-C in 6-8 weeks / above target, start Ezetimibe
- Repeat LDL-C in 6-8 weeks / above target, start PCSK9i
Title: Novel Therapies to Achieve the Recommended Low-density Lipoprotein Cholesterol Concentration (LDL-C) Targets for Patients post Coronary Artery Bypass Grafting

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SUPPLEMENTARY APPENDIX
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Table S2. Some simulated scenarios that provide a pathway for initiating LDL-C reduction after CABG ............................................................... 5
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Table S1. Definition of Statin Intolerance

<table>
<thead>
<tr>
<th>Scientific society</th>
<th>Definition</th>
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<tr>
<td>National Lipid Association (NLA)</td>
<td>Adverse effects related to the quality of life leading to decisions to decrease or stop the use of statins</td>
</tr>
<tr>
<td>European Atherosclerosis Society (EAS)</td>
<td>They prefer to use the term statin-associated muscle symptoms (SAMS). EAS defines SAMS as the occurrence of all muscle-related complaints (eg. Pain, weakness, or cramps) irrespective of documented creatine kinase elevation</td>
</tr>
<tr>
<td>International Lipid Expert Panel (ILEP)</td>
<td>Inability to tolerate the dose of statin required to sufficiently reduce the patient’s cardiovascular risk</td>
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</table>

This table presents the different definitions for statin intolerance (SI), statin associated muscle symptoms (SAMS) or statin associated side effects (SASE) adopted by the various professional societies.
Figure S1. We present the various pathways that are influenced by statin and non-statin therapies outlined in our review. In the intestine, dietary cholesterol is absorbed via the Niemann Pick C1-like-1 protein receptor. Ezetimibe inhibits this receptor and prevents oral cholesterol absorption. In the liver, de-novo cholesterol synthesis pathway converts glucose to cholesterol. In this pathway, Bempedoic acid inhibits the adenosine triphosphate-citrate lyase (ACL) enzyme, while statins inhibit the hydroxy-methyl CoA reductase enzyme, which is the rate limiting step in de-novo cholesterol synthesis. LDL-C receptors in the liver take in the circulating LDL-C. These receptors are degraded by proprotein convertase subtilisin/kexin type 9 (PCSK9). Therefore, PCSK9 inhibitors prevent PCSK9 from attaching to and degrading the LDL-C receptors. In the hepatocyte, the PCSK9 production is governed by PCSK9 mRNA. Inclisiran inhibits PCSK9 mRNA by interacting with the RNA-induced silencing complex, thereby reducing PCSK9 concentrations in the liver.

Abbreviations: ACL – adenosine triphosphate-citrate lyase, HMGCR – hydroxy-methyl coenzyme A reductase, LDL-C – low density lipoprotein cholesterol, NPC1L1 – Niemann Pick C1 like 1 protein, mRNA – messenger ribonucleic acid, PCSK9 – proprotein convertase subtilisin/kexin type 9
Table S2. Some simulated scenarios that provide a pathway for initiating LDL-C reduction after CABG

Patient A admitted for CABG. Preoperatively patient A is tolerating rosuvastatin 40mg well and has a pre-operative LDL-C 94 mg/dl.

**ESC criteria**

- patient A is very high risk
- After surgery and oral medications resumed, start on Rosuvastatin 40mg as per preoperative dosing
- Add oral Ezetimibe
- Provide education regarding PCSK9 inhibitor self-injection and start first dose prior to discharge
- repeat lipid profile at 90 days from discharge to confirm that LDL-C \( \leq 55 \) mg/dl

**AHA/ACC criteria**

- Evaluate if patient A is ‘very high risk’
- If not high-risk, then we may continue without any changes OR consider oral Ezetimibe to provide further lowering of LDL-C.
- If very-high risk, then initiate oral Ezetimibe
- repeat lipid profile at first post-operative visit
- if LDL-C > 70 mg/dl, then start PCSK9 inhibitor therapy.
- Provide education for self-injection of PCSK9 inhibitors.
Patient B admitted for CABG. Preoperatively patient B has received atorvastatin 40mg previously but refused to take that after 2 weeks because of muscle ache. Since then, the patient has not been on any LDL-C lowering medications and has a pre-operative LDL-C 124 mg/dl.

Patient B may have statin intolerance due to muscle symptoms. However, even if they cannot tolerate a lipophilic statin like atorvastatin, they may tolerate a hydrophilic drug like rosuvastatin.

- Post-operatively initiate rosuvastatin at low dose 5-10mg and evaluate for symptoms. Explain to the patient the rationale for choosing an alternative statin agent and the possibility that this drug may not affect the patient in the same manner that atorvastatin did.
- Initiate oral Ezetimibe / Bempedoic acid.
- If rosuvastatin is well tolerated for 2 weeks, then discuss and double the dose, if possible. However, it is better to have the patient on some statin therapy rather than no therapy.
- If following ESC criteria, then PCSK9 inhibitors should be started before discharge.
- If following AHA/ACC criteria and the patient is not very high risk, then a combination of rosuvastatin + oral Ezetimibe may reduce LDL-C below 100 mg/dl.
- If very high risk, then PCSK9 inhibitors may be needed. We can repeat LDL-C at the first post-operative visit and then decide depending upon the LDL-C concentrations.
References

These references are provided in the supplement as per journal manuscript guidelines, only 25 references are allowed in the main document.


