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LIPID ABNORMALITIES AND CARDIOVASCULAR PREVENTION (G DE BACKER, SECTION EDITOR)

Low-Density Lipoprotein Cholesterol After an Acute Coronary Syndrome: How Low to Go?

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Abstract

Purpose of Review Recent advances in low-density lipoprotein cholesterol (LDL-C) lowering therapy have now enabled reducing LDL-C safely to very low levels. This review summarizes evidence from recent randomized clinical trials of intensive LDL-C lowering in patients with acute coronary syndrome (ACS) and provides a practical approach for LDL-C lowering to reduce the risk of recurrent ischemic events in this population.

Recent Findings The risk of atherothrombotic events falls linearly with LDL-C level extending to very low achieved LDL-C levels (< 10 mg/dL) without apparent safety concerns. The addition of ezetimibe or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors (i.e., evolocumab or alirocumab) to statin therapy lowers LDL-C to very low levels (≤ 30–50 mg/dL) with safety under the conditions studied and reduces the risk of recurrent cardiovascular events in patients with atherosclerotic cardiovascular disease.

Summary Current data support LDL-C lowering to levels below 70 mg/dL in patients post-ACS. Combination of high-intensity statins, ezetimibe, and if needed PCSK9 inhibitors merits consideration in such patients with ACS to optimize outcomes.

Keywords LDL cholesterol · Acute coronary syndrome · Secondary prevention · Atherothrombosis

Abbreviations

LDL-C	low-density lipoprotein cholesterol
ACS	acute coronary syndrome
PCSK9	proprotein convertase subtilisin/kexin type 9
ASCVD	atherosclerotic cardiovascular disease
HR	hazard ratio
CI	confidence interval
ARR	absolute risk reduction
NNT	number needed to treat

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Introduction

Low-density lipoprotein cholesterol (LDL-C) indubitably causes atherosclerotic cardiovascular disease (ASCVD.) Fortunately, we possess an expanding palette of evidence-based interventions to modify this causal risk factor [1]. The last two decades have witnessed substantial progress in lowering LDL-C for primary and secondary prevention of cardiovascular events. Among patients with acute coronary syndromes (ACS), intensive LDL-C lowering with high-intensity statin therapy has figured prominently in the prevention of atherothrombosis for over a decade. The target level of achieved LDL-C has evolved to progressively lower levels with successful completion of randomized clinical trials examining different combination of statin and nonstatin therapies (i.e., ezetimibe and PCSK9 inhibitors). The recently published 2018 multisociety clinical practice guideline on the management of blood cholesterol in patients with history of

ACS has recommended a LDL-C target of 70 mg/dL [2]. Although no trial of LDL-C-lowering therapeutics has titrated treatment to achieve a particular LDL-C target, several secondary analyses of primary and secondary prevention lipid-lowering trials have demonstrated lower risk of cardiovascular events with lower achieved LDL-C levels below the current guideline recommendation of 70 mg/dL, and even lower ischemic events with further attainment of very low levels (< 40–50 mg/dL) without apparent safety concerns [3–5].

Recent development in pharmacotherapies for LDL-C lowering has enabled lowering of LDL-C to much lower levels than those achieved with high-intensity statin monotherapy. To this end, recent randomized clinical trials have established that addition of these nonstatin LDL-C-lowering therapies (i.e., ezetimibe or PCSK9 inhibitors) to statin therapy provides further lowering of LDL-C (median achieved levels of ~ 30–50 mg/dL) and greater reduction in cardiovascular events compared with statin therapy alone [6•, 7•, 8•]. These trials have consistently affirmed the efficacy and the safety of lowering LDL-C to levels below the currently recommended target of 70 mg/dL and a greater reduction in cardiovascular events. Taken together, the current evidence strongly supports a clinical strategy of tailoring LDL-C-lowering therapy to achieve optimal LDL-C level comparable to those seen in recent clinical outcomes trials of combination of ezetimibe or PCSK9 inhibitor to statin therapy. This review discusses evidence that has evolved the optimal target of LDL-C in patients with ACS and provides a practical approach for optimizing LDL-C lowering for reduction of recurrent cardiovascular events in patients post-ACS.

Evolution of Target Level of LDL-C After an ACS: Lessons from Randomized Clinical Trials

Target LDL-C 100 mg/dL

Although several observational analyses and clinical trials have made significant contributions to our understanding of benefits of LDL-C lowering in patients with ACS, we discuss select large-scale randomized clinical trials that have advanced the target of achieved LDL-C for secondary prevention in patients with ACS (Fig. 1). Randomized clinical trials of intensive LDL-C lowering with statin therapy have consistently shown reduction in cardiovascular events. The Scandinavian Simvastatin Survival Study (4S) randomly assigned 4444 patients with ASCVD (79% with prior ACS) and mean baseline LDL-C > 160 mg/dL to simvastatin or placebo. Compared with placebo, simvastatin lowered LDL-C by 35% (mean) resulting in a 30% reduction in all-cause mortality (hazard ratio [HR] 0.70, 95% confidence interval [CI] 0.58–0.85) over the median follow-up of 5.4 years [9]. The Cholesterol and Recurrent Events (CARE) trial randomized 4159 patients with myocardial infarction (MI) and LDL-C levels of 115–174 mg/dL to pravastatin 40 mg/day or placebo [10]. Compared with placebo, pravastatin 40 mg/day lowered LDL-C by ~ 30% resulting in an achieved LDL-C of ~ 100 mg/dL and 24% reduction (HR 0.76, 95% CI 0.64–0.91) in the incidence of coronary death or MI during a 5-year follow-up. These findings from CARE laid the foundation for establishment of target LDL-C goal of 100 mg/dL for secondary prevention by the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) [11].

Target LDL-C 70 mg/dL

The Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE IT–TIMI 22) trial investigated the effect of lowering LDL-C to 100 mg/dL versus 70 mg/dL on cardiovascular events in patients with ACS [12]. In PROVE IT-TIMI 22, 4162 patients with ACS and median baseline LDL-C of 106 mg/dL randomly received high-intensity statin therapy with atorvastatin 80 mg/day or standard-dose pravastatin 40 mg/day. During a 2-year follow-up, the median achieved LDL-C was 95 mg/dL and 62 mg/dL with pravastatin 40 mg/day and atorvastatin 80 mg/day, respectively. Compared with pravastatin, intensive LDL-C lowering with atorvastatin 80 mg/day resulted in a 16% relative reduction (HR 0.84, 95% CI 0.84–0.95) in the risk of primary end point composite of death, MI, unstable angina requiring rehospitalization, coronary revascularization, and stroke. Patients who achieved LDL-C < 70 mg/dL had lower risk of cardiovascular events than those with LDL-C > 70 mg/dL [13]. Participants who achieved both LDL-C < 70 mg/dL and high-sensitivity C-reactive protein (hs-CRP) < 2 mg/L had even lower rates of recurrent cardiovascular events than those with either LDL-C > 70 mg/dL or hs-CRP > 2 mg/L [13]. On the basis of evidence of clinical benefit of achieving levels of LDL-C to 70 mg/dL in PROVE IT-TIMI 22, an update to the clinical practice guideline on the management of cholesterol introduced a more intensive, but optional, LDL-C goal of 70 mg/dL for patients with ACS [14, 15]. Furthermore, a post hoc analysis of PROVE IT-TIMI 22 demonstrated a lower incidence of recurrent cardiovascular events among patients who achieved LDL-C < 40 mg/dL as compared with patients with standard achieved LDL-C (80–100 mg/dL) without any safety concern with achieving LDL-C < 40 mg/dL [5].

The clinical trials of LDL-C lowering after ACS have not only informed us about the benefits of high-intensity statin therapy for secondary prevention, but they have also emphasized the advantage of early initiation of intensive LDL-C-lowering therapy during hospitalization with ACS. The peak in the risk of recurrent atherothrombotic events in the early

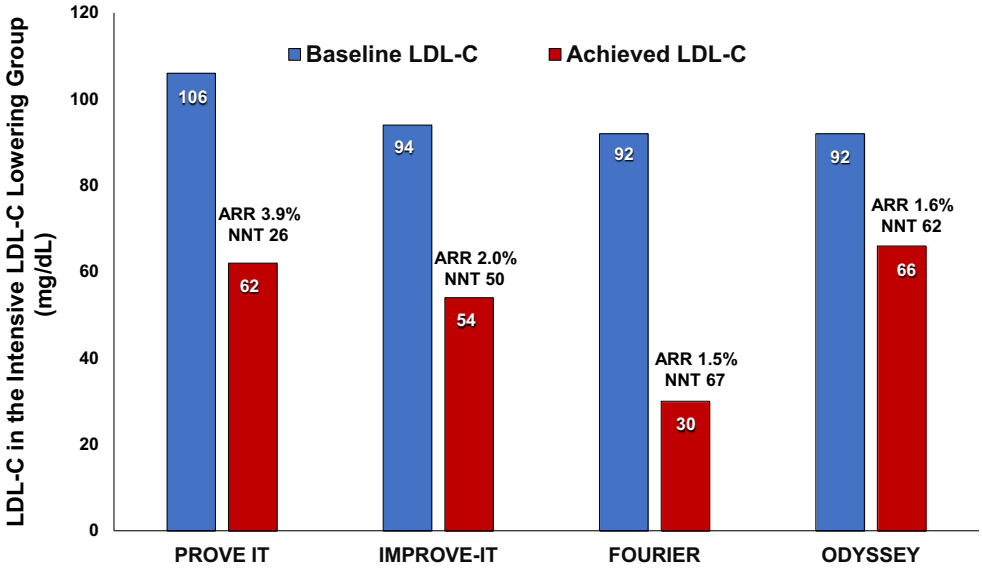

Fig. 1 Summary of baseline and achieved LDL-C in the treatment arm, absolute risk reduction, and number needed to treat for the primary efficacy end point with intensive LDL-C lowering in PROVE IT, IMPROVE-IT, FOURIER, and ODYSSEY OUTCOMES trials. LDL-C = low-density lipoprotein cholesterol; ARR = absolute risk reduction; NNT = number needed to treat to prevent 1 primary efficacy end point

period after an ACS warrants initiation of high-intensity statin therapy as soon as possible after the confirmation of diagnosis of ACS. Among patients with ACS in PROVE IT-TIMI 22, the benefit of intensive LDL-C reduction on lowering ischemic events emerged as early as 15 days after randomization and persisted through the end of the trial [12]. Evidence from several other randomized controlled trials has also supported the concept of early initiation of high-intensity statin therapy in patients with ACS. For instance, in the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study, 3086 patients with ACS and mean baseline LDL-C level of 124 mg/dL randomly received atorvastatin 80 mg/day or placebo within 1–4 days of presentation [16]. At 16 weeks after ACS, early treatment with atorvastatin 80 mg/day lowered LDL-C to a mean level of 72 mg/dL and resulted in a 16% relative reduction (HR 0.84, 95% CI 0.70–1.0) in recurrent ischemic events than placebo. Similarly, in the phase Zocor (Z) of the Aggrastat (A) to Z (A2Z) trial, among patients with ACS [17], the early initiation of an intensive statin therapy (simvastatin 40 mg/day for 1 month followed by 80 mg/day) resulted in a lower rate of cardiovascular events and lower median achieved LDL-C at 8 months (63 mg/dL versus 77 mg/dL) as compared with delayed initiation of a less intensive statin regimen (placebo for 4 months followed by simvastatin 20 mg/day) during a 2-year follow-up.

Target LDL-C 30–50 mg/dL

The robust evidence regarding the safety and efficacy of lowering levels of LDL-C to < 50 mg/dL in patients with ACS have mostly emerged from recent cardiovascular outcomes trials which added ezetimibe or PCSK9 inhibitors to background statin therapy. Preceding these trials, most data regarding the safety and cardiovascular benefit of achieving very low levels of LDL-C derived from exploratory analyses which were prone to residual confounding despite multivariable adjustment. These issues precluded causal inference between very low levels of achieved LDL-C and reduction in cardiovascular events.

Ezetimibe, an inhibitor of the Niemann–Pick C1–like 1 (NPC1L1) protein in the intestine, decreases absorption of cholesterol and reduces LDL-C by an additional ~ 20% when combined with statin therapy was examined in the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) trial [6•]. IMPROVE-IT enrolled 18,144 patients with an ACS within 10 days of randomization and an LDL-C of 50–100 mg/dL if on statin therapy, or an LDL-C of 50–125 mg/dL if not on statin therapy and randomly allocated patients to receive either simvastatin 40 mg/day plus ezetimibe 10 mg/day or simvastatin 40 mg/day alone. The simvastatin/ezetimibe group had a lower median time-weighted average achieved LDL-C level compared with the simvastatin alone group (54 mg/dL versus 69 mg/dL). Combined ezetimibe and simvastatin therapy significantly reduced the incidence of primary end point composite of cardiovascular death, nonfatal MI, unstable angina requiring hospitalization, coronary revascularization, or nonfatal stroke by 6% relative to simvastatin alone during a median follow-up of 6 years. The addition of ezetimibe yielded an absolute risk reduction in the primary end point of 2% translating into a number needed to treat of 50 patients to prevent 1 event over 6 years. IMPROVE-IT provided the first randomized controlled trial evidence of efficacy of an addition to statin-based LDL-C lowering therapy that showed reduction in cardiovascular events. The findings in favor of addition of ezetimibe in this trial highlighted that clinical benefit from intensive LDL-C lowering extended beyond statin therapy

and demonstrated the benefit of the addition of other LDL-C-lowering approaches to statins.

In a prespecified analysis in IMPROVE-IT, patients attaining an LDL-C level < 30 mg/dL at 1 month had a significantly lower rate of cardiovascular events and similar safety profile than those with LDL-C > 70 mg/dL [18]. Consistent with the findings in PROVE IT-TIMI 22, the achievement of prespecified dual thresholds of LDL-C < 70 mg/dL and hsCRP <2 mg/L and an exploratory dual level of LDL-C < 50 mg/dL and hsCRP <1 mg/L at 1 month after randomization associated with reduced risk of recurrent cardiovascular events as compared with not meeting any 1 of these thresholds [19]. Furthermore, more patients receiving the combination of simvastatin and ezetimibe achieved the prespecified LDL-C and hs-CRP targets as compared with patients receiving simvastatin alone.

The monoclonal antibodies evolocumab and alirocumab, administered subcutaneously, inhibit PCSK9 and lower LDL-C by > 50% in most patients on or off background statin therapy. Recent randomized clinical trials have proved that intensive LDL-C lowering with PCSK9 inhibitors improves cardiovascular outcomes. The Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) and the ODYSSEY OUTCOMES trial evaluated the efficacy and safety of PCSK9 inhibitor addition to background statin therapy [7•, 8]. In FOURIER, 27,546 patients with ASCVD including 81% with prior MI and LDL-C levels ≥ 70 mg/dL on background statin therapy randomly received evolocumab (140 mg every 2 weeks or 420 mg every 4 weeks subcutaneously) or placebo [7•]. Relative to placebo, the mean percentage reduction in LDL-C with evolocumab was 59% at 48 weeks resulting in a median achieved LDL-C of 30 mg/dL. Compared to placebo, evolocumab significantly reduced the risk of the primary end point composite of cardiovascular death, MI, stroke, hospitalization for unstable angina, or coronary revascularization by 15% (HR 0.85, 95% CI 0.79–0.92) and the key secondary outcome composite of cardiovascular death, MI, or stroke by 20% (HR 0.80, 95% CI 0.73–0.88). The absolute risk reduction in cardiovascular death, MI, or stroke in the evolocumab group was 1.5% translating to a number needed to treat of 67 patients to reduce 1 event over 2.2 years. Evolocumab consistently prevented cardiovascular events in patients with ASCVD irrespective of whether the baseline LDL-C was < 70 mg/dL or ≥ 70 mg/dL and whether they were treated with high-, moderate-, or low-intensity statin therapy [20]. Among trial participants in FOURIER, 10% of patients achieved LDL-C < 20 mg/dL, 31% achieved 20–50 mg/dL, 29% achieved 50–70 mg/dL, and remaining achieved > 70 mg/dL. In a prespecified analysis, the investigators found a monotonic relationship between low achieved LDL-C level and the lower risk of cardiovascular events extending to extremely low achieved LDL-C levels (< 10 mg/dL) without any safety concerns [21]. Since the median achieved LDL-C was ~ 30 mg/dL in FOURIER, it has paved the path to consider further LDL-C lowering following ACS to levels below (~ 30 mg/dL) current guideline recommendation of 70 mg/dL and even below a median achieved level of ~ 50 mg/dL in the ezetimibe/simvastatin arm in IMPROVE-IT.

ODYSSEY OUTCOMES randomized 18,924 patients who had an ACS in the preceding 1–12 months and LDL-C level of ≥ 70 mg/dL on background maximally tolerated statin therapy to alirocumab (75 mg every 2 weeks subcutaneously) or placebo [8•]. The dose of alirocumab was adjusted to target LDL-C level of 25–50 mg/dL. As compared with placebo, alirocumab reduced the primary end point composite of death from coronary heart disease, nonfatal MI, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization by 15% (HR 0.85, 95% CI 0.78–0.93) during the median follow-up of 2.8 years. At 4 months, the average achieved LDL-C was 40 mg/dL in the alirocumab group and 93 mg/dL in the placebo group. The absolute benefit of alirocumab in reducing cardiovascular events was greater among patients who had a baseline LDL-C ≥ 100 mg/dL (number needed to treat of 16 patients over 4 years) than patients who had baseline LDL-C < 100 mg/dL.

In addition to individual randomized clinical trials of LDL-C lowering therapies, several patient-level meta-analyses have consistently demonstrated the efficacy and safety of intensive LDL-C lowering in patients with ACS. In 2010, the Cholesterol Treatment Trialists Collaboration (CTTC) conducted a patient level meta-analysis of 170,000 individuals from 26 randomized trials comparing more versus less intensive LDL-C lowering with statin therapy and found a 20% reduction in the 5-year risk of cardiovascular events with every 40-mg/dL reduction in LDL-C [22]. Moreover, the benefits of intensive LDL-C lowering did not depend on baseline LDL-C levels and applied to patients who had baseline LDL-C values < 80 mg/dL [22]. Subsequently, a trial-level meta-analysis of 49 randomized trials including statin and nonstatin therapies comprising 312,175 participants showed that the magnitude of relative reduction of vascular events with LDL-C lowering related directly to the absolute reduction in LDL-C and achieved LDL-C [23]. In this meta-analysis, treatment with statin and nonstatin therapy that act via augmentation of LDL receptor (i.e., ezetimibe, bile acid sequestrants, ileal bypass, and diet) to lower LDL-C conferred a similar magnitude of relative reduction in cardiovascular events per change in LDL-C as documented by the CTT collaborators (20% relative reduction in vascular events per 40 mg/L reduction in LDL-C over 5 years). Additionally, lower achieved LDL-C levels associated with lower incidence of cardiovascular events in patients with ASCVD including those with ACS (4.6% lower event rate per each 40 mg/dL lower LDL-C) [23]. Since most randomized trials of LDL-C lowering in patients with ASCVD have enrolled patients who have

baseline LDL-C > 70 mg/dL, whether intensive LDL-C lowering would also be safe and effective in reducing cardiovascular events in patients with initial LDL-C level of < 70 mg/dL has engendered debate. To this end, a recent meta-analysis examining further lowering of LDL-C in patients presenting with LDL-C levels ≤ 70 mg/dL and achieving levels as low as a median of 21 mg/dL demonstrated a consistent reduction in cardiovascular events per mg/dL change in LDL-C, as observed by CTT investigators, without any significant adverse effects [24].

Addressing Patient and Practitioner Concerns Regarding Very Low LDL-C

Despite extensive evidence regarding the efficacy and safety of achieving very low LDL-C levels, many physicians and patients remain reluctant to optimize lipid-lowering therapy to achieve LDL-C target of 70 mg/dL or even lower. First, since the human body needs cholesterol for steroid hormone synthesis and cell membrane function, many are concerned that achieving very low levels of LDL-C would deplete them of cholesterol required for normal cellular function [25]. Contrary to this concern, genetic data have shown that individuals with loss-of-function variants of PCSK9 that result in lifelong reduction in levels of LDL-C to < 20 mg/dL remain healthy [26], have healthy offspring and low rates of cardiovascular events than the general population. Comparative data among human populations and among species further affirm the safety of cholesterol concentrations well below 70 mg/dL [27]. Furthermore, recent trials have raised no safety concerns with the achievement of levels of LDL-C to as low as < 10 mg/dL over the duration of exposure [21]. These considerations should reassure patients and clinicians regarding the clinical benefit of achieving very low LDL-C levels, particularly in patients with ACS who remain at very high risk for recurrent cardiovascular events.

Second, concerns persist regarding an increased risk of development of diabetes with intensive statin therapy in the primary prevention population [28, 29]. Indeed, in Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER), the statin caused a small but statistically significant 0.1% rise in hemoglobin A1c in a population preselected for increased inflammation [28]. Incident diabetes in JUPITER occurred almost exclusively in those with preexisting dysglycemia and hastened crossing the arbitrary threshold of diabetes diagnosis less than 6 weeks than those not receiving rosuvastatin [30]. Analyses showed that other statins shared augmented risk of developing diabetes [29]. But the magnitude of cardiovascular benefit with intensive statin therapy in this population offsets the small risk of diabetes [30]. Furthermore, there were no significant increases in the risk of new-onset diabetes in IMPROVE-IT, FOURIER, or ODYSSEY OUTCOMES in which a large proportion of patients achieved very low LDL-C levels.

Third, early stage clinical studies of PCSK9 inhibition raised some concerns that the very low levels of LDL-C achieved with PCSK9 inhibition might associate with neurocognitive deficits [31]. Yet, a trial of 1204 patients randomized to evolocumab or placebo in addition to background statin therapy who underwent comprehensive neurocognitive assessment found no significant difference in cognitive function between the two groups over a 19-month follow-up

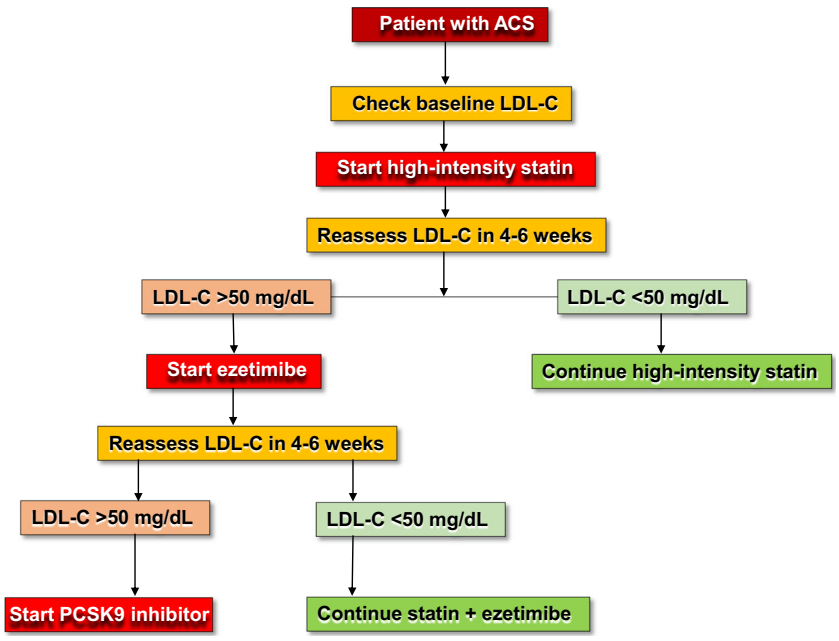

Fig. 2 Suggested algorithm for management of LDL-C in patients post-ACS guided by results of recent randomized trials. ACS = acute coronary syndrome; LDL-C = low-density lipoprotein cholesterol

period [32]. Similarly, no significant increases in the risks of cognitive deficits were seen with the attainment of very low LDL-C levels in IMPROVE-IT, FOURIER, or ODYSSEY OUTCOMES [6•, 7•, 8•].

Precision LDL-C-Lowering Therapy After an ACS

Although all patients with ACS have an elevated risk for ischemic events, their individual risk for recurrent cardiovascular events can vary considerably. As a result, patients with ACS may derive different degrees of absolute benefit from intensive LDL-C lowering. A "Precision LDL-C Lowering" approach may help tailor lipid-lowering therapy based on a particular patient's future risk for cardiovascular events. To this end, risk prediction tools using clinical characteristics and polygenic genetic risk scores can identify subgroups of patients with ACS who may derive greater absolute benefit from intensive LDL-C lowering with high-intensity statin therapy or with the addition of ezetimibe to simvastatin. For instance, in IMPROVE-IT, atherothrombotic risk stratification using nine clinical variables identified subset of high-risk patients who gained greatest absolute benefit from the addition of ezetimibe to statin therapy independent of achieved levels of LDL-C [33]. Correspondingly, in CARE and PROVE IT-TIMI 22, risk stratification using a 27 genetic variant risk score identified individuals at increased risk for recurrent ischemic events who derived the largest relative and absolute benefit from statin therapy [34]. These hypothesis-generating findings point the way toward pursuit of personalized allocation of lipid-lowering therapy in patients with ACS. Such strategies, however, will require prospective validation in other cohorts, including targeting PCSK9 inhibitors, before their adoption in routine clinical practice.

Practical Approach for Optimizing LDL-C Risk in Patients with ACS Based on Recent Trials

Figure 2 describes a suggested practical approach for the management of LDL-C in patients with ACS based on evidence from recent secondary prevention lipid-lowering trials. In addition to the management of LDL-C, post-ACS all patients should also receive other guideline-directed medical therapies as tolerated and referral to cardiac rehabilitation programs. Statin-naive patients who present with ACS merit initiation of high-intensity statin therapy. Patients who take moderate or low-intensity statins on presentation should also receive high-intensity statin therapy. ACS patients already receiving high-intensity statin therapy who have LDL-C measured within the first ~ 24 h after symptom onset of greater than 50 mg/dL, merit consideration for addition of ezetimibe.

In ACS patients 4–6 weeks following initiation of an initial LDL-lowering regimen, if LDL-C exceeds 50 mg/dL, consider addition of ezetimibe if not already started. Those whose LDL-C remains > 50 mg/dL in the stable phase post-ACS, despite being compliant with maximally tolerated statin therapy and ezetimibe, warrant a shared decision-making conversation regarding initiation of monoclonal antibodies that inhibit PCSK9 (i.e., evolocumab or alirocumab). Post-ACS patients unable or unwilling to take statins, or those who have very high LDL-C levels that will not likely decrease below 50 mg/dL with high-intensity statin therapy alone should have consideration of initiation of ezetimibe and/or PCSK9 inhibitors upon index presentation with ACS. Each ambulatory encounter should include discussion of the benefits of compliance to lipid-lowering therapy, healthy lifestyle, and diet in all patients with history of ACS.

Future Directions

Despite accruing data about the benefits of intensive LDL-C lowering in patients with ACS, the adherence to high-intensity statin therapy remains low [35, 36]. Thus, post-ACS patients require ongoing efforts to improve adherence such as patient education, assistance with access to medications. System approaches to deploy and test novel approaches to improve adherence and access to statin therapy are underway. In spite of significant reduction in cardiovascular events with PCSK9 inhibitors in two recent clinical trials, these agents remain underutilized due to high cost and barriers to access. Nevertheless, the recent decrease in the cost of both evolocumab and alirocumab in the last year in the USA may facilitate their utilization in eligible patients. Furthermore, the development and assessment of novel and convenient approaches to LDL-C lowering continue [37]. For example, inclisiran, a small interfering RNA that inhibits PCSK9 messenger RNA causing robust lowering in LDL-C with less frequent dosing (twice a year), has shown promise in phase 1 and 2 studies [38]. Another approach, bempedoic acid, an orally active small molecule inhibitor of ATP citrate lyase, can lower LDL as well, albeit to a lesser extent. Clinical outcome trials have begun using these novel agents [39].

Conclusions

Among patients with ACS, intensive LDL-C lowering to very low levels has shown safety and more effective reduction of atherothrombotic events than the current guideline-recommended target of 70 mg/dL. High-intensity statins, ezetimibe, or PCSK9 inhibitors enable most patients with ACS to achieve LDL-C levels (≤ 30–50 mg/dL) shown superior in the prevention of recurrent cardiovascular events.

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Compliance with Ethical Standards

Conflict of Interest Arman Qamar declares that he has no conflict of interest.

Peter Libby reports other from Kowa Pharmaceuticals, other from Amgen, other from AstraZeneca, other from Esperion Therapeutics, other from Ionis Pharmaceuticals, grants and other from Novartis, other from Pfizer, other from Sanofi-Regeneron, other from XBiotech, Inc., other from Corvidia Therapeutics, personal fees from DalCorPharmaceuticals, other from IFM Therapeutics, other from Olatec Therapeutics, other from Medimmune, and other from XBiotech, Inc.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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