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REVIEW

Lipid-Lowering Strategies After Acute Coronary Syndrome: From Guidelines to Bedside

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ABSTRACT

Acute coronary syndrome (ACS) induces a pro-inflammatory and pro-atherogenic state, increasing the risk of recurrent major adverse cardiovascular events (MACE). Rapid reduction of low-density lipoprotein cholesterol (LDL-C) is an important therapeutic strategy for stabilizing vulnerable atherosclerotic plaques and reducing inflammation. Current clinical guidelines classify patients with a recent ACS as being at extremely high risk and recommend an LDL-C target of <55 mg/dl, together with a reduction of >50% from baseline. This paper evaluates lipid-lowering therapies, including statins, ezetimibe, PCSK9 monoclonal antibodies, inclisiran, and bempedoic acid. It examines their efficacy in lowering LDL-C, their effects on major adverse cardiovascular events (MACE), the management of statin intolerance, and their mechanisms of action. High-dose statin therapy has lipid-lowering and anti-inflammatory effects. Ezetimibe reduces LDL-C levels and cardiovascular events by selectively inhibiting the intestinal protein Niemann-Pick C1-Like 1. PCSK9 inhibitors, such as evolocumab and alirocumab, provide substantial additional reductions in LDL-C when used in combination with standard therapy, promoting plaque regression and reducing the rate of MACE. Inclisiran provides sustained hepatic inhibition of PCSK9 via small interfering RNA (siRNA), with a twice-yearly dosing regimen, helping to address issues related to treatment nonadherence. Patients with statin intolerance require alternative lipid-lowering strategies, such as bempedoic acid, which provides an option for achieving LDL-C targets. Early implementation of combination therapy during the acute phase optimizes vascular remodeling, reduces inflammation, and reduces the risk of recurrent ischemic events.

Keywords: acute coronary syndrome, low density lipoprotein, statins, ezetimibe, PCSK9 inhibitors

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INTRODUCTION

Systemic amyloidosis comprises a heterogeneous group Atherosclerotic cardiovascular diseases remain among the leading causes of morbidity and mortality worldwide. Following an episode of acute coronary syndrome (ACS), the coronary artery wall enters a state of biological instability characterized by inflammation, endothelial dysfunction, and plaques at risk of rupture or erosion.[1] Despite advances in percutaneous coronary interventions and antithrombotic therapy, the residual risk of MACE remains high during the first year after ACS.[2] International guidelines published by the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) classify patients with a recent ACS as having an extremely high cardiovascular risk,[3] recommending a low-density lipoprotein cholesterol (LDL-C) target of <55 mg/dl (<1.4 mmol/L), along with a reduction of at least 50% from baseline plasma levels.[3] For patients who experience a second cardiovascular event within 2 years while receiving

therapy at maximally tolerated doses, the guidelines set an even lower target of <40 mg/dl (<1.0 mmol/L). Achieving these target levels in clinical practice requires a clear understanding of the available lipid-lowering agents, their mechanisms of action, and their effectiveness in promoting plaque regression and stabilization.

To address these objectives and provide a scientifically grounded narrative review, an exhaustive search of the literature was conducted in the PubMed/MEDLINE, Embase, and Cochrane databases through 2026. The selection prioritized phase III randomized controlled clinical trials evaluating cardiovascular outcomes, intracoronary imaging studies assessing plaque phenotype, and major clinical guidelines.

STATINS: FIRST-LINE PHARMACOLOGICAL THERAPY AND THEIR PLEIOTROPIC EFFECTS

Statins are the first-line pharmacological therapy for the secondary prevention of ACS.[3,4] Guidelines recommend initiating treatment at the highest tolerated doses as early as possible during hospitalization, regardless of baseline LDL-C levels.[3,4] High-dose statin therapy, particularly atorvastatin 80 mg/day, provides a substantial reduction in lipid levels compared with moderate-dose regimens.[5] The reduction in MACE correlates directly with the decrease in LDL-C levels.[6] A 38.7 mg/dl reduction in LDL-C lowers the annual rate of major vascular events by approximately 20%.[6] The MIRACL study demonstrated an early reduction in recurrent ischemic events within 16 weeks of an ACS with atorvastatin 80 mg/day.[7] The long-term benefits were validated by the PROVE IT-TIMI 22 study, which showed that high-dose atorvastatin provides a substantial reduction in lipid levels compared with moderate-dose regimens, achieving LDL-C reductions of approximately 50% or more and thereby contributing to a lower risk of recurrent cardiovascular events.[5] The ASTEROID study further supported these findings, demonstrating through serial intravascular ultrasound that high-dose statin therapy can induce regression of coronary atherosclerosis.[8]

The clinical benefits of statins in the acute phase are based on their direct pleiotropic effects on the vascular wall.[9] Statins exert an anti-inflammatory effect by inhibiting the synthesis of isoprenoids, intermediates in the cholesterol synthesis pathway, which, in turn, modulates intracellular signaling pathways.[10] This process significantly reduces levels of high-sensitivity C-reactive protein (hs-CRP) and lowers proinflammatory cytokines such as IL-1β, IL-6, and TNF-α.[10] In addition, intracoronary imaging studies using intravascular ultrasound and optical coherence tomography have shown that high-dose statin therapy reduces atherosclerotic plaque volume.[8] Statins also inhibit matrix metalloproteinases (MMPs), thereby preventing degradation of the fibrous cap.[9] At the endothelial level, statins enhance nitric oxide bioavailability and reduce oxidative stress. These pleiotropic effects have also been associated with a reduction in myocardial fibrosis in heart failure.[9,11]

Statins also modulate the risk of thrombosis and the proliferation of vascular smooth muscle cells following acute coronary ischemia.[9] By reducing the expression of tissue factor in circulating monocytes, they decrease local thrombin production and attenuate platelet aggregation at sites of plaque erosion.[9] In addition, statins reduce the expression of plasminogen activator inhibitor-1 to restore normal fibrinolysis.[12] These pleiotropic actions are rapid, providing vascular protection during the critical initial period following an ACS, when the risk of recurrent thrombotic occlusion is highest.

Clinical management is often complicated by statin-associated muscle symptoms, which affect approximately 5% to 10% of patients in large controlled trials, with a similar frequency reported among those receiving placebo.[3,13] The risk increases at high doses compared with moderate doses. These symptoms range from mild myalgia to severe myopathy.[3,13] Discontinuing statin therapy without immediately switching to alternative lipid-lowering agents increases the risk of recurrent cardiovascular events.[3,14] When patients cannot tolerate high-dose statin therapy, management strategies include reducing the daily dose or switching to a hydrophilic statin with a prolonged half-life, such as rosuvastatin.[13] For patients with complete statin intolerance, statin-free treatment regimens should be initiated promptly.[14,15]

EZETIMIBE: SELECTIVE INHIBITION OF INTESTINAL ABSORBTION

Ezetimibe works in combination with statin therapy by selectively inhibiting the Niemann-Pick C1-Like 1 protein located on the brush border of jejunal enterocytes.[16,17]

By inhibiting cholesterol uptake in enterocytes, ezetimibe reduces the transport of intestinal cholesterol to the liver.[17] The resulting decrease in hepatic cholesterol leads to an increase in hepatic LDL receptor expression, which effectively removes low-density lipoprotein particles from the bloodstream.[16] When administered as monotherapy, ezetimibe reduces LDL-C by 15% to 22%,[3] and when combined with high-dose statin therapy, it provides an addi-

tional reduction of 23% to 24%, resulting in a significantly greater reduction from baseline levels.[17]

The clinical efficacy of adding ezetimibe to statin therapy following an acute coronary syndrome was evaluated in the IMPROVE-IT study, which followed 18,144 patients for an average of 6 years. Adding 10 mg of ezetimibe to 40 mg of simvastatin resulted in a statistically significant reduction in MACE compared with statin monotherapy.[17] The greatest clinical benefits were observed in patients with diabetes and older patients.[18] Additional secondary analyses from the IMPROVE-IT study revealed that a 16 mg/dl reduction in LDL-C levels resulted in an 18% decrease in the rate of ischemic events.[19]

At the cellular level, ezetimibe reduces arterial inflammation by decreasing the production of chylomicrons and lowering circulating levels of high-sensitivity C-reactive protein.[16,20] Intravascular ultrasound data from the PRECISE-IVUS study demonstrated that dual therapy with statins and ezetimibe induces greater regression of atheroma volume than statin monotherapy in patients with ACS.[21] By reducing the accumulation of LDL-C esters in macrophages, ezetimibe limits their transformation into foam cells and reduces the expansion of the necrotic core.[22]

Current guidelines recommend the prompt initiation of ezetimibe therapy in combination with high-dose statins during hospitalization in patients with elevated baseline LDL-C levels.[3,4] This immediate approach avoids delays, ensuring that patients following an ACS are more likely to achieve the guideline-recommended LDL-C target of <55 mg/dl.[23,24]

PCSK9 INHIBITORS: HIGHLY EFFECTIVE BIOLOGIC MONOCLONAL ANTIBODIES

Biological therapies such as evolocumab and alirocumab target PCSK9, a circulating serum protease that promotes the degradation of LDL receptors in hepatocytes.[25,26] Blocking PCSK9 prevents this degradation, significantly increasing receptor density on cell membranes.[26,27] Monoclonal PCSK9 inhibitors result in significant reductions in LDL-C, ranging from 50% to 60%, when added to statin therapy.[26] When used in a triple-therapy regimen, alongside high-dose statins and ezetimibe, LDL-C reductions have the potential to reach exceptional levels, substantially exceeding the limits of monotherapy.[28]

The clinical impact of PCSK9 inhibition on cardiovascular events was established in the FOURIER study, which evaluated evolocumab, and in the ODYSSEY OUTCOMES study, which evaluated alirocumab.[26,27] Both studies demonstrated a statistically significant relative reduction of 15% in MACE.[26,27] The ODYSSEY OUTCOMES study showed that treatment with alirocumab initiated 1–12 months after an ACS resulted in a significant reduction in mortality among patients with baseline LDL-C levels of 70 mg/dl or higher.[27] The EVOPACS study confirmed the safety and lipid-lowering efficacy of initiating treatment with evolocumab directly during hospitalization for ACS.[28] Ultimately, a 15–28% lifetime reduction in LDL-C was safe, while providing ongoing protection against ischemic events.[25]

High-resolution intracoronary imaging studies have provided essential insights into how PCSK9 inhibitors alter plaque morphology.[29] Specifically, the HUYGENS study, which used optical coherence tomography, demonstrated that early administration of evolocumab thickens the fibrous cap and reduces the lipid arc in vulnerable coronary plaques.[30] Similarly, the PACMAN-AMI study, which used intravascular ultrasound and near-infrared spectroscopy, confirmed that alirocumab initiated during acute myocardial infarction resulted in a twofold greater regression of atheroma volume compared with statin therapy alone.[18] In addition to lowering LDL-C, PCSK9 inhibition also suppresses TLR4-mediated inflammation to protect the endothelium.[31] In atherosclerotic plaques, neovascularization occurs, allowing an accumulation of mast cells that triggers inflammation. A significant reduction in LDL-C decreases inflammation within vulnerable plaques and reduces the risk of intraplaque hemorrhage.[32]

Treatment with PCSK9 inhibitors requires subcutaneous administration every 2 weeks or once monthly.[26,27] In patients with a recent ACS who are classified as being at extremely high cardiovascular risk, early initiation of PCSK9 inhibitors is highly cost-effective because of the substantial reduction in absolute risk and the prevention of recurrent hospitalizations.[3] Guidelines recommend considering PCSK9 inhibitors during the initial hospitalization for ACS or during early follow-up in patients whose lipid levels remain above target values despite oral therapy at the maximum tolerated dose.[4,28]

INCLISIRAN: TARGETED GENE INHIBITION VIA SMALL INTERFERING RNA

Inclisiran uses siRNA technology to achieve targeted gene silencing in hepatocytes.[33,34] Inclisiran is conjugated to triantennary N-acetylgalactosamine, which specifically binds to asialoglycoprotein receptors on the surface of hepatocytes, ensuring its uptake.[34] After entering the cell via receptor-mediated endocytosis, inclisiran is incorporated into the RNA-induced silencing complex.[34] Its antisense strand cleaves the PCSK9 messenger RNA, preventing

TABLE 1. Comparative summary of lipid lowering therapies

Drug class	Mean LDL-C reduction	Route & dosing schedule	Key clinical outcome evidence	Primary vascular mechanism & plaque effects
High-dose statins	Substantial lowering (50–60%)[3]	Oral (daily)	PROVE-IT TIMI-22,[5] MIRACL,[7] ASTEROID[8]	Pleiotropic anti-inflammatory effects, hs-CRP reduction, increased fibrous cap collagen, MMP inhibition[8–10]
Ezetimibe	Incremental (15–25%)[3,19]	Oral (daily)	IMPROVE-IT,[19] PRECISE-IVUS[21]	NPC1L1 intestinal absorption blockade, reduced percent atheroma volume[19,21]
PCSK9 inhibitors	Substantial (50–60%)[27]	Subcutaneous (every 2–4 weeks)	FOURIER,[26] ODYSSEY OUTCOMES,[27] PACMAN-AMI[18]	Fibrous cap thickening on OCT, total plaque volume regression, Lp(a) reduction[29,30]
Inclisiran	Sustained (48–52%)[33]	Subcutaneous (initial, 3 months, then 6 months)	ORION Trial Program[34,37,38]	Targeted hepatic siRNA gene silencing, elimination of short-term lipid fluctuations[35,36]
Bempedoic acid	15–25% monotherapy[14,15]	Oral (daily)	CLEAR Outcomes,[14] CLEAR Harmony[15]	Hepatic ATP-citrate lyase inhibition, hs-CRP lowering, muscle-sparing pathway[14,37]

translation and thereby inhibiting protein production.[33,34]

A major clinical advantage of inclisiran is its extended dosing schedule, with administration initially on day 1, then after 3 months and subsequently every 6 months.[35] This regimen directly addresses the issue of patient non-adherence to daily oral therapies or biweekly injections, which is a leading cause of treatment failure in secondary prevention.[36] Data from the ORION Phase III clinical trial program confirmed the efficacy, tolerability, and safety profile of inclisiran over extended treatment periods.[34] In addition, data from the ORION-3 study demonstrated a sustained reduction in LDL-C over four years of continuous treatment.[37] A combined analysis of patients in the ORION program indicated a 25–30% relative reduction in major adverse cardiovascular events.[35,38]

Semiannual administration of inclisiran eliminates the short-term lipid fluctuations associated with irregular daily dosing. Long-term inhibition of PCSK9 in the liver prevents vascular smooth muscle cell remodeling, lowers levels of inflammatory cytokines, and supports stable vascular recovery following an ACS.[35] Safety assessments in the ORION studies did not reveal significant hepatic toxicity or muscle-related adverse reactions.[34,37] By ensuring reliable, long-term control of lipid levels through biannual injections administered by healthcare providers, inclisiran provides a mean of maintaining patients with a recent ACS within guideline-recommended lipid target ranges.[36]

ALTERNATIVES TO STATINS AND MANAGEMENT OF STATIN INTOLERANCE

For patients who are intolerant to statins or who fail to achieve guideline-recommended targets despite combination therapy, non-statin alternatives offer important clinical benefits.[14] Bempedoic acid acts on ATP-citrate lyase, an enzyme upstream of HMG-CoA synthetase-1.[14] Because this enzyme is found exclusively in the liver but is absent from skeletal muscle, bempedoic acid reduces LDL-C synthesis without causing the muscle-related side effects associated with statins.[14,15] When administered orally at a dose of 180 mg per day, bempedoic acid reduces LDL-C by 15% to 25% in combination with statins at maximally tolerated doses.[15]

The cardiovascular benefits of bempedoic acid were demonstrated in the CLEAR Outcomes study, which evaluated 13,970 patients at high cardiovascular risk who were intolerant to statins.[14] Bempedoic acid significantly reduced the risk of MACE by 13% and the incidence of fatal or nonfatal myocardial infarction by 23%.[14] Bempedoic acid also significantly reduced circulating levels of hs-CRP, demonstrating both lipid-lowering and anti-inflammatory properties.[14,39] Secondary analyses confirmed that bempedoic acid was well tolerated, with low rates of muscle-related side effects, offering an important statin-free oral treatment option for patients with a recent ACS.[14,15]

CLINICAL PERSPECTIVE AND FUTURE DIRECTIONS

Lipid-lowering therapy remains an indispensable component of secondary prevention following an acute coronary syndrome.[3,4] Rapidly achieving guideline-recommended targets requires a shift from the traditional step-by-step approach to intensive combination strategies implemented early after an ACS.[23,40] Initiating combination therapy during hospitalization with high-dose statins at the max-

imum tolerated dose, together with ezetimibe and PCSK9 inhibitors, allows rapid lipid control during the critical period following an ACS.[24,28] However, real-world data from sources such as the DA VINCI observational study indicate that combination therapies remain underutilized in routine clinical practice.[23]

Future approaches to secondary cardiovascular prevention will increasingly integrate advanced intracoronary imaging techniques and circulating biomarkers to guide personalized treatment.[41] Combining intensive LDL-C reduction with targeted anti-inflammatory agents, such as low-dose colchicine, represents a promising approach to addressing residual inflammatory risk in patients following an ACS.[42] By simultaneously reducing vascular inflammation, promoting fibrous cap thickening, and reducing the size of the necrotic core, these combination therapies may help limit the progression of atherothrombotic disease.

CONCLUSIONS

Patients who survive an ACS remain at extremely high risk of recurrent ischemic events because of persistent atherosclerotic burden, plaque instability, and residual inflammation. Rapid, sustained LDL-C reduction is therefore a cornerstone of secondary prevention and should be initiated during the index hospitalization. The therapeutic objective is to achieve an LDL-C level of <55 mg/dl, together with a reduction of at least 50% from baseline, while minimizing the time patients remain above target.

High-intensity statins remain the foundation of treatment, providing substantial LDL-C reduction as well as favorable anti-inflammatory, endothelial, antithrombotic, and plaque-stabilizing effects. However, statin monotherapy is frequently insufficient to achieve current LDL-C targets. Early addition of ezetimibe is a simple and effective intensification strategy, whereas PCSK9 monoclonal antibodies provide substantial LDL-C lowering and proven cardiovascular benefits in patients with persistently elevated LDL-C levels or particularly high residual risk.

Inclisiran may improve long-term lipid control in patients with poor adherence because of its twice-yearly maintenance schedule, although definitive cardiovascular outcome data are still awaited. In patients with confirmed statin intolerance, treatment should not be delayed; ezetimibe, PCSK9-targeted therapies, and bempedoic acid provide effective alternatives or complementary options.

Overall, lipid management following an ACS should move beyond delayed stepwise escalation toward early, individualized combination therapy. Regular lipid monitoring, adherence support, and timely treatment intensification are necessary to translate guideline targets into real-world reductions in recurrent MACE.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

I.T. and V-.B.H. contributed equally to the conception and design of this review, literature search and interpretation of the evidence, drafting and critical revision of the manuscript, and approval of the final version. Both authors agree to be accountable for all aspects of the work.

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