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REVIEW
Acute Coronary Syndromes

Acute LDL-C reduction post ACS: strike early and strike strong: from evidence to clinical practice. A clinical consensus statement of the Association for Acute CardioVascular Care (ACVC), in collaboration with the European Association of Preventive Cardiology (EAPC) and the European Society of Cardiology Working Group on Cardiovascular Pharmacotherapy

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After experiencing an acute coronary syndrome (ACS), patients are at a high risk of suffering from recurrent ischaemic cardiovascular events, especially in the very early phase. Low density lipoprotein-cholesterol (LDL-C) is causally involved in atherosclerosis and a clear, monotonic relationship between pharmacologic LDL-C lowering and a reduction in cardiovascular events post-ACS has been shown, a concept termed 'the lower, the better'. Current ESC guidelines suggest an LDL-C guided, step-wise initiation and escalation of lipid-lowering therapy (LLT). Observational studies consistently show low rates of guideline-recommended LLT adaptions and concomitant low rates of LDL-C target goal achievement, leaving patients at residual risk, especially in the vulnerable post-ACS phase. In addition to the well-established 'the lower, the better' approach, a 'strike early and strike strong' approach in the early post-ACS phase with upfront initiation of a combined lipid-lowering approach using high-intensity statins and ezetimibe seems reasonable. We discuss the rationale, clinical trial evidence and experience for such an approach and highlight existing knowledge gaps. In addition, the concept of acute initiation of PCSK9 inhibition in the early phase is reviewed. Ultimately, we focus on hurdles and solutions to provide high-quality, evidence-based follow-up care in post-ACS patients.

Keywords Acute coronary syndrome • Acute myocardial infarction • LDL-C • Residual risk • Statins • Ezetimibe • PCSK9 • Bempedoic acid

Introduction

Patients experiencing an acute coronary syndrome (ACS) are at high risk for recurrent cardiovascular events, especially within the first year after hospital discharge.[1–3] A large body of evidence has demonstrated a clear relationship between levels of LDL-C and risk of atherosclerotic cardiovascular disease (ASCVD).[4] Furthermore, the reduction in ASCVD risk has been shown to be proportional to absolute LDL-C reductions.[5–7]

The 2019 *ESC/EAS Guidelines for the management of dyslipidaemias* and the *2020 ESC Guidelines for the management of non-ST-segment elevation acute coronary syndromes (NSTE-ACS)* recommend a stepwise approach to lipid-lowering therapy (LLT) with re-evaluation of LDL-C goals after 4–6 weeks.[8,9] A high-intensity statin therapy should be initiated in all ACS patients, regardless of initial LDL-C values, with a goal LDL-C of <55 mg/dL (<1.4 mmol/L) and a reduction of at least 50% from baseline.[9] If these goals are not met with high-intensity statin therapy alone, ezetimibe, and, if goals are still not met, a proprotein convertase subtilisin/kexin type 9 (PCSK9)-inhibitor, should be added. In patients with ASCVD experiencing a second event while on maximally tolerated statin-based therapy, guidelines suggest an even lower LDL-C goal of <40mg/dL (<1.0 mmol/L). The *2021 ESC guidelines on cardiovascular disease prevention in clinical practice* recommend a stepwise approach to LDL-C goals, including patients with established ASCVD, with an initial LDL-C goal of <70 mg/dL (1.8 mmol/L) and a subsequent goal of <55 mg/dL (<1.4 mmol/L).[10] The recommended lipid-lowering treatment algorithm is similar for patients with stable ASCVD and patients in the early phase after an ACS across current ESC guidelines, despite strong differences in residual risk.

As the extent of LDL-C reduction in response to pharmacologic interventions is predictable based on baseline LDL-C levels, it is reasonable to assume that a significant proportion of ACS patients will not achieve their target goal with high-intensity statin treatment alone prescribed at discharge.[11] Observational data shows that few lipid-lowering drugs are prescribed and few dose adjustments are performed after hospital discharge[12,13] and that the majority of patients do not achieve their goals.[13,14] The reasons for this are multifactorial and include prescription inertia, systemic barriers, and delays or losses to follow-up after discharge.

Observational data shows a 10% cumulative incidence of a second MI, a stroke or cardiovascular death within the first 100 days after experiencing an MI.[1] Even in an ideal post-ACS scenario, it can take up to 12 weeks for patients to receive optimal LLT when following the current stepwise approach to lipid-lowering suggested by the guidelines, which corresponds to the most vulnerable phase after a major coronary event. Taken together with 'the lower the better' principle for LDL-C reduction now clearly supported by RCTs, and recent data suggesting improvements in plaque size and composition in response to acute and strong LDL-C reduction in the vulnerable post-ACS population,[15,16] we believe that a 'strike early and strong' approach is reasonable. Within this clinical consensus document, we aim to highlight the rationale and biology as well as the available medication for such an approach. We discuss the current evidence and experience with acute, early, and fast LDL-C reduction after ACS using upfront medication combinations and propose a state-of-the-art approach. In conclusion, we summarize the current knowledge gaps and need to obtain the evidence necessary to make 'strike early and strong' the standard approach.

Rationale and biology behind (acute) LDL-C reduction in ACS patients

Platelets, monocytes, and lipids along with endothelial dysfunction are the major driving forces in atherogenesis that ultimately cause atherosclerotic coronary artery disease.[17,18] Local build-up of atherosclerotic plaques led by lipid rich cores filled with macrophage foam cells and cell debris caused by apoptotic cells may ultimately destabilize the lesion and lead to plaque rupture, exposing the highly pro-coagulant plaque content to the bloodstream, which may result in thrombotic vessel occlusion and myocardial infarction. Plaque rupture is mainly prevented and controlled by the fibrous cap rich in extracellular matrix overlying the plaque.

Improvements in primary preventive interventions within the last decades, including lipid-lowering therapies, have potentially shifted the underlying cause of ACS away from plaque rupture towards superficial erosion of plaques. It is estimated that nowadays superficial erosion is responsible for up to one third of ACS cases.[19] The mechanism of superficial erosion is not fully understood. The interplay of matrix metalloproteases, components of the innate immune system, and neutrophils in concert with activated platelets are thought to play a major role.[19,20] Interestingly, LDL-C has recently been associated with the number and pro-inflammatory status of circulating monocytes, establishing a new link between high LDL-C levels and the progression of

atherosclerosis.[21,22] Monocytes of patients with familial hypercholesterolemia were characterized by increased expression of a key receptor required for extravasation into atherosclerotic plaques.[22] The same receptor is suggested to be necessary for the typical sequential monocyte extravasation into infarct tissue upon myocardial infarction.[23–25] Treatment with PCSK9 inhibitors reduced monocyte cholesterol content, reversed its pro-inflammatory status and reduced its migratory potential, providing further evidence to the interplay between elevated circulating cholesterol, inflammatory activation and atherosclerotic disease progression.

A clear association between intensive lipid-lowering therapies and better outcomes in patients after ACS was demonstrated almost two decades ago.[26] More recently, a linear reduction in cardiovascular adverse events has been described even when LDL-C reduction surpassed current guideline-recommended treatment goals, thus postulating 'the lower the better' as a therapeutic strategy in patients with ACS.[27]

Two recent randomized clinical trials of modest size evaluated the effects of very early addition of alirocumab or evolocumab on top of a standard lipid-lowering regimen in ACS patients undergoing percutaneous coronary intervention (PCI) at the infarct-related artery (IRA) with angiographic evidence of non-significant atherosclerotic disease in non-IRA vessels.[15,16] Patients were followed for 1 year, and the primary endpoints of minimal fibrous cap thickness[16] or plaque atheroma volume[15] in non-IRA were significantly improved in patients who received a PCSK9 inhibitor on top of standard treatment. It is important to highlight that those trials suggested disease-modifying effects of PCSK9 inhibitors beyond simply stopping disease progression by causing regression of coronary atherosclerosis. Importantly, most patients in the control arms receiving standard lipid-lowering therapy did not reach goal LDL-C levels. Both trials demonstrated a clear relationship between achieved LDL-C levels and improvements in plaque phenotype, although these analyses were done *post hoc*. The results suggest that such an approach to early PCSK9 inhibition in ACS patients is safe, feasible, and offers plaque stabilizing effects that may translate into preventing plaque rupture and subsequent ACS. Several drugs and drug combinations with various efficacy and rapidity of action are available for such a 'strike early and strong' approach.

Table 1 Expected effects of various lipid-lowering classes and their combination on LDL-c levels

Drug class	Expected proportional LDL-C lowering compared with placebo	LDL-C lowering effect after 2 weeks of treatment[a]
Moderate-intensity statin	30%	25%[84]
High-intensity statin	50%	45%[85]
ezetimibe	20%	20%[86]
PCSK9 antibody	60%	50–60%[28,30,87,88]
PCSK9 siRNA	50%	40%[32]
Bempedoic acid	15–25%	15–25%[89]
Combination therapy		
High-intensity statin plus ezetimibe	65%	
High-intensity statin plus PCSK9 antibody	75%	
High-intensity statin plus ezetimibe plus PCSK9 antibody	85%	
Bempedoic acid plus ezetimibe	35%	

Examples for high-intensity statins, defined as an expected LDL-C reduction of ~50%: atorvastatin 40–80 mg; rosuvastatin 20–40 mg
Examples for moderate-intensity statins, commonly defined as an expected LDL-C reduction of 30 (−50)%: atorvastatin 10 (−20 mg); rosuvastatin (5−)10 mg; simvastatin 20–40 mg; and others
Available PCSK9 antibodies: alirocumab, evolocumab
Available PCSK9 siRNA: inclisiran
PCSK9, proprotein convertase subtilisin kexin-9; LDL-C, low-density lipoprotein cholesterol; siRNA, small interfering ribonucleic acid
[a]Obtained from RCTs specifically reporting 2 weeks levels.

Available lipid-lowering drugs: pharmacodynamic profile, effectiveness, and safety

Most previous studies focused on the degree of LDL-C lowering instead of the rapidity of lipid lowering. However, in the immediate aftermath of an ACS, patients are at elevated risk of recurrent events,[1–3] and the rapidity of LDL-C lowering has therefore become a new focus.

Table 1 summarizes the data on the magnitude of LDL-C lowering achieved by various drugs. As a rule of thumb, high-intensity statin treatment will cause a 50% reduction of LDL-C, and combination with ezetimibe will result in a 65% reduction of LDL-C from baseline. The rapidity of LDL-C lowering has not been systematically assessed, we have therefore reported the effects at 2 weeks after therapy initiation (*Table 1*).

Three small studies have assessed the concept of acute LDL-C reduction by initiating PCSK9 inhibitor treatment in the acute phase after an ACS and demonstrated such an approach's safety, feasibility, and efficacy.[28–30] Two trials evaluated evolocumab treatment in the very early phase after ACS. In the EVACS trial ($n = 57$), a significant LDL-C reduction was evident 24 h after application, with two-thirds of patients achieving guideline-recommended LDL-C levels <55 mg/dL (<1.4 mmol/L) at discharge (around Day 4, *Figure 1A*).[28] At Days 4–7, maximal LDL-C lowering effects were seen in the PCSK9-group, which had LDL-C levels approximately 50% lower as compared with the standard group. The larger EVOPACS trial ($n = 308$) demonstrated a 90% rate of LDL-C goal achievement 8 weeks after an ACS when initiating evolocumab therapy during index hospitalization for ACS compared with 11% in the standard treatment group.[29] A similar study administering alirocumab within 24 h of NSTEMI presentation (VCU-AlirocRT, $n = 20$) resulted in a significant LDL-C reduction evident on day three and a dramatic reduction to a mean LDL-C level of 28 mg/dL (0.72 mmol/L) only 14 days after treatment initiation.[30] (*Figure 1B*) Inclisiran is a novel small interfering RNA (siRNA) inhibiting the translation of the PCSK9 protein reducing LDL-C by ~50%.[31] Approximately 14 days after the first injection, LDL-C reductions in the magnitude of 40% were seen reaching its peak reduction of 50% after around 30 days. With a two-dose regimen with a second injection 90 days after the initial one, slightly more pronounced effects were seen.[32,33]

Considering safety, there is an unproven myth that aggressive LDL-C lowering could promote haemorrhagic stroke.[34] However, in a prespecified analysis from ODYSSEY OUTCOMES (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab), the rate of haemorrhagic stroke after ACS was almost negligible and not increased by the PCSK9 antibody alirocumab vs. placebo.[35] It has to be noted that randomization

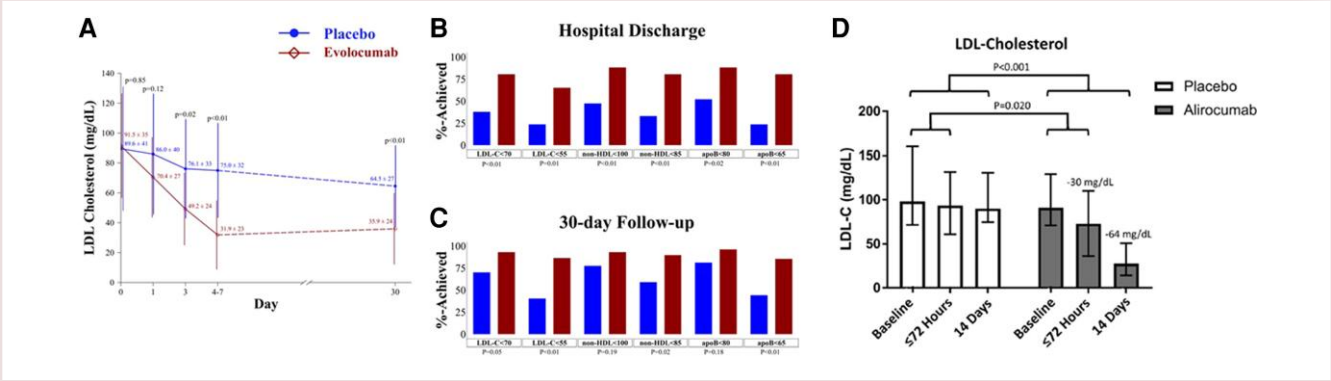

Figure 1 Time course of LDL-C levels after PCSK9 inhibition in ACS patients. (*A*) LDL-C levels upon administration of 420 mg evolocumab or placebo on top of standard lipid-lowering therapy in 57 patients with NSTEMI in the EVACS trial. Note that evolocumab reduced LDL-C levels already by day 1 as compared with standard therapy after 1 week. By Day 3, mean LDL-C levels were below target goals with nearly two-thirds of patients being discharged with LDL-C levels reaching recommended goals. Patients (in %) achieving various lipid goals when given standard treatment or evolocumab on top of standard treatment at hospital discharge (*B*) and at 30 days (*C*). Reprinted with permission from.[28] (*D*) LDL-C levels 72 h and 14 days after ACS in 20 patients on pre-ACS high-intensity statin therapy in the VCU-AlirocRT trial. Patients were 1:1 randomized to placebo or one dose of 150 mg alirocumab. Reprinted with permission from.[30] LDL-C, low-density lipoprotein cholesterol; NSTEMI, non-ST elevating myocardial infarction.

was carried out on average 2.6 months after the ACS, thus after the critical peri-interventional phase associated with most bleeding events, as seen elsewhere.[3] In a recent meta-analysis including 11 trials with more than 20 000 patients comparing more with less intensive LDL-C lowering after ischaemic stroke, more intensive LDL-C lowering was associated with an increased risk of haemorrhagic stroke, while the rate of recurrent stroke and major adverse cardiovascular events were reduced.[36] The number needed to treat to prevent a recurrent stroke within 4 years was 90 and for preventing a major adverse cardiac events (MACE) was 35, while the number needed to harm for a haemorrhagic stroke was 242. The authors concluded that the benefits and risks of more intensive LDL-C lowering might be more favourable overall as compared with less intensive LDL-C lowering, especially in patients with atherosclerotic disease. Moreover, there are no further signals of harmful effects induced by early and strong lipid lowering in ACS as compared with conventional LLT.[37]

In conclusion, and based on the knowledge that thrombo-ischaemic secondary events after an ACS frequently occur within 1–3 months after the index event and that early plaque stabilization might be important for secondary prevention, the 'strike early and strong' strategy using an optimal combination of effective and safe lipid-lowering agents may represent a therapeutic tool that needs further investigation. Several trials have provided evidence for early, solid and acute LDL-C reduction that should be highlighted.

Evidence and experience of acute and early LDL-C reduction after ACS

Strong LDL-C reduction post-ACS and outcome

The most robust evidence that strong LDL-C reduction post-ACS is associated with improved outcomes comes from the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering trial comparing atorvastatin 80 mg daily with placebo, initiated 1–4 days after hospitalization and continued for 4 months.[38] (*Table 2*). Together with a more substantial LDL-C reduction, atorvastatin treatment was associated with a 16% risk reduction for MACE, with event curves diverging after as early as 4 weeks.[38] The PROVE-IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy) trial compared atorvastatin 80 mg with pravastatin 40 mg daily initiated up to 10 days after ACS and continued for a median of 2 years.[26] MACE occurred significantly less frequently with atorvastatin 80 mg (16% risk reduction), with a clinical benefit already becoming evident 4 months after randomization. The phase Z of the A-to-Z trial compared a regimen of early initiation of an intensive statin (simvastatin 40 mg for 1 month followed by simvastatin 80 mg daily) with a regimen of delayed initiation using less intensive statin treatment (placebo for 4 months followed by simvastatin 20 mg once daily) and followed patients for 2 years.[39] The trial missed its primary endpoint, a composite of MACE. Of note, almost half of the patients were randomized after PCI.

In the last decade, two trials demonstrated a reduction of adverse cardiovascular events with non-statin lipid-lowering therapies added to statins after ACS. IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) compared treatment with ezetimibe (10 mg) with placebo, each added to simvastatin 40 to 80 mg daily, within 10 days after experiencing an ACS.[40] A benefit of ezetimibe began to appear after 1 year of treatment, with a significant 6% relative risk reduction for MACE at six years (8).

The ODYSSEY OUTCOMES trial compared the PCSK9 inhibitor alirocumab with placebo in patients 1–12 months after experiencing an ACS with LDL-C levels above 70 mg/dL while on stable high-intensity statin treatment. Median time from ACS to randomization was 2.6 months.[41] Alirocumab reduced MACE compared with placebo (relative risk reduction 15%) with efficacy becoming apparent at ~1 year. Importantly, a goal LDL-C of 25–50 mg/dL, lower than current guideline goals, was defined, and the dose of alirocumab was adjusted accordingly. This trial design with recruitment and randomization on average two and a half months after ACS differs from the herein discussed 'strike early' approach, that was recently tested in smaller trials with surrogate endpoints, that initiated PCSK9 inhibitors within the first days after ACS.[15,16] Importantly, the recently presented ODYSSEY OUTCOMES longer-term follow-up data (up to 5 years) was consistent with the main trial results with respect to efficacy, safety, and tolerability.[42]

A subgroup analysis of the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial revealed that patients experiencing a MI within 12 months of randomization ($n = 5\,711$) had a higher event rate, and

Table 2 Trial evidence supporting early and strong LDL-c reduction

Name	Design	Study population	Follow-up	Primary outcome	Primary results	Laboratory results
MIRACL[38]	Atorvastatin (80 mg) 1x/day vs. placebo initiated within the first 4 days after ACS (median 2.6 days)	Patients with unstable angina or non-Q-wave MI without planned revascularization $n = 3\,086$	16 weeks	Composite endpoint: death, non-fatal MI, cardiac arrest, recurrent unstable angina requiring rehospitalization	HR: 0.84 (0.70–1.00) $P = 0.048$	LDL-C: 72 mg/dL vs. 135 mg/dL
PROVE-IT TIMI-22[26]	Atorvastatin (80 mg) 1x/day vs. pravastatin (40 mg) 1x/day initiated within the first 10 days after ACS	ACS (AMI and unstable angina) $n = 4\,162$	Median of 24 months	Time to composite endpoint: Death, MI, stroke, unstable angina requiring hospitalization, any revascularization (PCI; CABG) beyond 1 month	HR: 0.84 (0.74–0.95) $P = 0.005$	LDL-C: 62 mg/dL vs 95 mg/dl
IMPROVE-IT[40]	Ezetimibe 10 mg & simvastatin (40 mg) 1x/day vs. Placebo & simvastatin (40 mg) 1x/day Randomization at a median of 5 days after index event	ACS $n = 18\,144$	Median 6 years	Composite endpoint: Death, non-fatal stroke or major coronary event (non-fatal MI, unstable angina requiring hospitalization or any revascularization beyond 1 month)	HR 0.94 (0.89–0.99) $P = 0.016$	LDL-C: 53.7 mg/dL vs. 69.5 mg/dL
ODYSSEY OUTCOMES[41]	Alirocumab & standard treatment vs. placebo & standard treatment Randomization at a median of 2.6 months after ACS	ACS $n = 18\,924$	Median 2.8 years	Composite endpoint: Death from coronary heart disease, non-fatal MI, all stroke, unstable angina requiring hospitalization	HR 0.85 (0.78–0.93) $P < 0.001$	LDL-C: 53 mg/dL vs. 92 mg/dL (at 48 months on treatment)

Primary outcomes given as hazard ratio (95% confidence interval)
ACS, acute coronary syndrome; MI, myocardial infarction; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; IVUS, intravascular ultrasound; AMI, acute myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; CV, cardiovascular.

treatment with evolocumab was associated with a stronger reduction of the primary composite endpoint by 19%, as compared with 8% in patients with a remote MI ($n = 16\,609$).[43] Within the FOURIER open-label extension study with a median follow-up of 5 years, more than 3 000 patients initially treated with placebo were switched to evolocumab and compared with a similar sized group with continuing evolocumab exposure. The latter group was characterized by a 20% lower rate of CV death, MI or stroke, a strong signal for the importance of early, strong treatment.[44]

Of interest, in the Cholesterol Treatment Trialist's main analyses of 27 trials including 174 000 patients, treatment effects were less pronounced in the first year as compared with the following years.[5,7] However, a large proportion of trials included patients with stable atherosclerotic disease, where such a gradual effect has been observed owed to the nature of stable ASCVD.[45]

Acute/early LDL-C reduction and outcome

While several large-scale cardiovascular outcome trials have proven strong LDL-C reductions using potent lipid-lowering therapies after ACS as beneficial, less data are available on the benefits of acute LDL-C reduction. The placebo-controlled SECURE PCI trial did not show a clinical benefit of periprocedural administration of two loading doses of 80 mg of atorvastatin in ACS patients with intended invasive management. However, in the pre-specified subgroup of patients undergoing PCI (65% of all patients), MACE was significantly reduced by 28% while in the non-PCI group, a trend to an increase in MACE was observed (*P*-interaction of 0.02). As these effect are only hypothesis generating, additional data are required.[46] The observed beneficial effects in the PCI group remained consistent irrespective of time of atorvastatin pre-treatment including the two hours before PCI, suggesting additional protective effects besides LDL-C lowering.[47] In accordance, a meta-analysis including RCTs conducted before SECURE PCI indicated that preprocedural administration of statins in ACS patients (but not postprocedural initiation) prominently reduced the 30-day MI rate by 62% compared with no statin or low-dose statin.[48]

National registry data from the United States, including 300 000 patients, confirmed that early (within 24 h) administration of statins (new or continued prescription) after AMI is associated with a markedly reduced in hospital mortality (4.0% and 5.3% compared with 15.4% for no statin treatment within the first 24 h).[49] Early statin use was also

associated with a lower incidence of cardiogenic shock, arrhythmias, cardiac arrest, and cardiac rupture. Recently published propensity score matched observational data from Korea confirm that administration of statins within 24 h after admission for AMI is associated with a 22% reduction of MACE rate during a follow-up of almost 4 years.[50]

Taken together, very early, pre-PCI initiation of high-intensity statin treatment may be beneficial. In-hospital start of PCSK9 inhibitors ensures LDL-C target goal achievement in most patients within the early and vulnerable phase. Whether such achieved LDL-C lowering using PCSK9 inhibitors translate into a reduction of adverse cardiovascular events in the very early phase needs to be tested by dedicated outcome trials.

Early/acute high-intensity LDL reduction and rapid adherence to LDL-C goals

In a large observational study from Sweden among 40 607 patients with a recent AMI, evaluation of the relationship between changes in LDL-C between the index event and an outpatient visit after 6–10 weeks and the risk of cardiovascular outcomes was reported.[51] The median follow-up time was 3.78 years. Those patients discharged with high-intensity statins and achieving >50% LDL-C reduction had a lower incidence of all CV outcomes than those using lower doses of statins. The authors concluded that more significant early LDL-C reduction and more intensive statin therapy after MI was associated with a reduced risk of all CV outcomes.

Moreover, another study investigated adherence to statins and LDL-C goal achievement rates in a high CV risk population in Italy.[52] The large majority of patients had a previous major CV event (99.9%), but adherence (proportion of days covered, ≥80%) after 3 and 6 months was only 61% and 55.14%, respectively. High adherence to lipid-lowering drugs was associated with almost a three times higher probability of reaching the LDL-C goals.

Importantly, few drug or dose adjustments are performed in ACS and stable ASCVD patients after discharge from the hospital throughout geographic regions.[12,13] This finding underscores the importance of starting high-intensity lipid-lowering before hospital discharge to attain the guideline-recommended LDL-C levels.

Main challenges precluding achievement of lipid profile goals in clinical practice

Several barriers can potentially hinder reaching the LDL-C goal after an ACS. These can be broadly classified as physician, healthcare system, and patient related and are listed in *Table 3*.

Prescription of inadequate LLT is consistently being observed upon hospital discharge. For instance, in the EUROASPIRE V study, only half of the patients have been prescribed treatment with high-intensity LLT.[53] Similarly, in the more recent DA VINCI study, the proportion of patients with established atherosclerotic cardiovascular disease and, therefore by definition at very high cardiovascular risk, that was being treated with high-intensity statins, combined treatment with ezetimibe or PCSK9 inhibitors was 36.7%, 9%, and 1.2% respectively.[54] This can be related to therapeutic inertia, lack of adherence to guideline recommendations, and administrative barriers to drug prescription. As stated above, tailoring LLT according to a structured protocol considering the individualized cardiovascular risk is of paramount importance.

After hospital discharge, the limited access to cardiac rehabilitation programmes and/or the lack of a structured clinical pathway can result in poor coordination between healthcare providers, delayed reassessment of the lipid profile, and even loss at follow-up, leading to loss of opportunities to achieve an optimal secondary prevention strategy.

Life-long risk reduction in secondary prevention is strongly dependent on medication adherence. Thus, poor adherence to treatment is a significant concern for all long-term drug therapies such as LLT. Patient empowerment, defined as how people gain greater control over decisions and actions affecting their health, has been recognized as critical for better adherence. Physicians should promote patient education during hospitalization and follow-up through effective communication and providing educational material in different formats (booklets; educational videos; hospital and scientific societies websites). In addition, educational efforts targeting at physicians and providers caring for post-ACS patients focusing on evidence and guidelines and effective strategies increasing adherence are required. Interactive e-health interventions may offer novel ways of improving medication adherence.[55] However, further research is needed to better identify the type of intervention with the strongest impact, with several recent trials showing mixed results.[56,57]

The availability of generic combination pills of high-intensity statins and ezetimibe may improve adherence and LDL-C lowering and should therefore be the primary form of prescription.[58,59] The once- or twice monthly injection scheme for PCSK9 antibodies and twice yearly injection scheme for PCSK9-silencing RNA (siRNA) may further improve adherence and ultimately outcomes.

Table 3 Barriers preventing evidence-based and guideline-directed therapy may have reasons on the physician, patient and system level

Physician	Healthcare system	Patient
Inadequate LLT prescription at discharge	Administrative barriers to drug prescription	Poor adherence to treatment
Lack of adherence to guideline recommendations	Cost of novel advanced LLT	Limited knowledge about secondary prevention goals
Lack of structured clinical pathway	Barriers to reimbursement	Lack of educational opportunities during hospital admission
Therapeutic inertia	Limited availability of cardiac rehabilitation programmes	Increased statin intolerance awareness
Knowledge gap between different levels of care	Poor coordination among healthcare stakeholders	Lack of trusted educational sources on the internet and misinformation

LLT, lipid-lowering therapy.

Optimal lipid lowering after ACS

Tailoring lipid-lowering in the acute phase

How should clinicians navigate between guidelines, strained care systems, cost issues, and novel evidence supporting acute and intense LDL-C reduction? At admission for ACS, a (non-fasting)[60] lipid panel should be drawn as early as possible. This lipid panel should include measurement of Lipoprotein(a), if previously unknown, as part of the overall risk estimation.[61] All patients should be treated with a high-intensity statin (defined as statin treatment with expected LDL-C lowering >50%, examples are atorvastatin 40–80 mg; rosuvastatin 20–40 mg 1x/day, with best trial evidence for atorvastatin 80 mg

and rosuvastatin 20 mg, by decreasing order) and treatment should preferably be initiated before coronary angiography (*Figure 2*) and before the results of the lipid panel are available. In patients already on statin therapy, it is fundamental to continue high-intensity statin therapy without interruption or to escalate to high-intensity statin therapy.

In addition to high-intensity statins, the systematic addition of ezetimibe early after ACS, and irrespective of the LDL-C under statin therapy, is reasonable. Ezetimibe is well-tolerated when given early post-ACS and associated with a clinical benefit, explained by the reduction in LDL-C.[40] With trial evidence for a monotonic relationship between achieved LDL-C levels and adverse cardiovascular outcomes without any safety signals, the observed low rate of medication intensification after discharge, the high rate of secondary events in the very early phase, and the availability of generic ezetimibe and combination pills with high-intensity statins, discharge of every post-ACS patient on a combination pill of a high-intensity statin and ezetimibe appears reasonable.[62] Particularly, patients with a baseline LDL-C > 100 mg/dL, in whom it is expected that high-intensity statins will not be sufficient to achieve a LDL goal <55 mg/dL, will benefit most from this early combined treatment.

Ultimately, initiation of PCSK9 inhibitor treatment could be particularly beneficial in the setting of ACS, as it has been shown to be safe, feasible and associated with small beneficial effects on surrogate endpoints obtained by intravascular imaging in two small RCTs. The high rate of LDL-C target goal achievement with such an approach makes it attractive, especially for the early phase after ACS. Patients with additional (ischemic) risk factors such as multivessel CAD or polyvascular disease as well as patients with familial hypercholesterolemia (FH) with strongly elevated LDL-C levels, unlikely achieving LDL-C goals with conventional therapy alone represent a potentially interesting subset for such an approach.[63,64]

Latest guidelines suggest an LDL-C goal of <40 mg/dL in patients experiencing a recurrent major vascular event within 2 years after the first event while taking a maximally tolerated statin.[9] We believe such patients are at extremely high risk and unlikely to achieve LDL-C goals with conventional therapy, justifying escalation to PCSK9 inhibitors during their index hospitalization, despite a lack of dedicated cardiovascular outcome trials.[62] We acknowledge that such an approach may not be feasible in various systems due to reimbursement restrictions (*Table 3*).

In addition, all ACS patients, especially those with elevated LDL-C, premature AMI and a family history for premature AMI[65,66] should be screened for potential FH during the index hospitalization.[67] Screening should include established scoring systems such as the Dutch Lipid Clinic Network score[68] and should be verified by genetic testing.[69] When diagnosing FH, family cascade screening should be undertaken, a cost-effective measure[70] which may identify up to 6–8 additional FH mutation carriers.[69] In patients with a high likelihood of FH and LDL-C > 190 mg/dL, upfront triple therapy with a high-intensity statin, ezetimibe, and a PCSK9 inhibitor seems reasonable.

Statin intolerance

The ideal care pathway for suspected statin intolerance has yet to be established,[71] especially in a high-risk situation such as the immediate phase after an ACS. Several studies suggested that observed muscle symptoms may in fact be nocebo effects and a large percentage of patients were successfully restarted on statins after trial completion.[72–74] In clinical practice, to ensure effective lipid-lowering in the critical phase, initiating a PCSK9 inhibitor in combination with ezetimibe and re-challenge with a statin in parallel seems reasonable. We acknowledge that in some systems, PCSK9 inhibitors are not reimbursed or only upon failure of conventional therapies. Upfront combination therapy of ezetimibe with bempedoic acid and statin re-challenge and re-evaluation after 4–6 weeks appears to be a reasonable approach in such a scenario.

Bempedoic acid is a novel lipid-lowering drug, inhibiting an enzyme involved in hepatic cholesterol biosynthesis upstream of HMG-CoA reductase. The CLEAR OUTCOMES trial (NCT02993406) is currently evaluating the effects of once daily bempedoic acid on major cardiovascular events in 14 000 patients with or at high risk of cardiovascular disease deemed statin intolerant. In such patients, bempedoic acid may therefore be an ideal agent in form of a combination therapy consisting of ezetimibe, bempedoic acid and a PCSK9 inhibitor. In patients not achieving target LDL-C goals while on dual LLT with a high-intensity statin and ezetimibe, addition of bempedoic acid appears reasonable if PCSK9 inhibitors are not available or not reimbursed.[75] No cardiovascular outcome data are currently available for bempedoic acid.

Post-discharge management

ACS patients often experience gaps in care early in their transition from hospital to home. Lack of adequate communication and uncoordinated support after discharge from the hospital negatively impact patient experiences and follow-up care.[76]

In all patients, a lipid improvement plan should be formulated before discharge, including the acute and discharge phase and a clear referral pathway for early follow-up and definite treatment. Patients should be re-evaluated 4–6 weeks after discharge, if possible, at the admission hospital or another dedicated secondary prevention clinic caring for (high-risk) post-ACS patients. Achieved LDL-C, tolerability, compliance, knowledge, and other secondary prevention measures should be assessed, escalation of therapy evaluated, and rehabilitation promoted. From 6 months to 1 year after the ACS, achieved goals and critical areas of difficulties identified should be evaluated.[77] Adherence to guideline-recommended treatment after ACS affects the patient's prognosis. Telemedicine, ranging from simple phone check-ups to single or group teleconferences or even the use of dedicated apps, can help improve adherence.[78,79] Simplification of LLT, like the use of generic single pill combination of high-intensity statins + ezetimibe has been shown to increase the adherence and the percentage of patients at LDL-C goal.[80]

Lifestyle management

In addition to pharmacological LDL-C management, strong emphasis should be put on education in lifestyle adaptions, during the initial hospital stay and in the form of continued rehabilitation programmes, both in in-patient and outpatient settings. Lifestyle interventions to reduce LDL-C include dietary changes such as avoidance of trans-fats, reduction of dietary saturated fats, and increased intake of dietary fibre and functional foods. Other lifestyle factors influencing LDL-C include reduction of excessive body weight, reduction of dietary cholesterol and an increase in habitual physical activity. For further details, we refer the readers to the *2021 ESC Guidelines on cardiovascular disease prevention in clinical practice*.[10]

Gaps in knowledge and future perspectives

Across current ESC guidelines, a 'one size fits all' lipid-lowering treatment algorithm for all patients with ASCVD is being postulated, independent of additional risk factors or acuity of presentation, with recent guidelines even taking a step back and introducing a two-step approach to LDL-C goals.[8–10] A recent expert viewpoint document challenged this approach and suggested a further differentiation between patients at very high risk and those at extremely high risk, in whom upfront triple LLT should be considered.[62] A similar approach grading

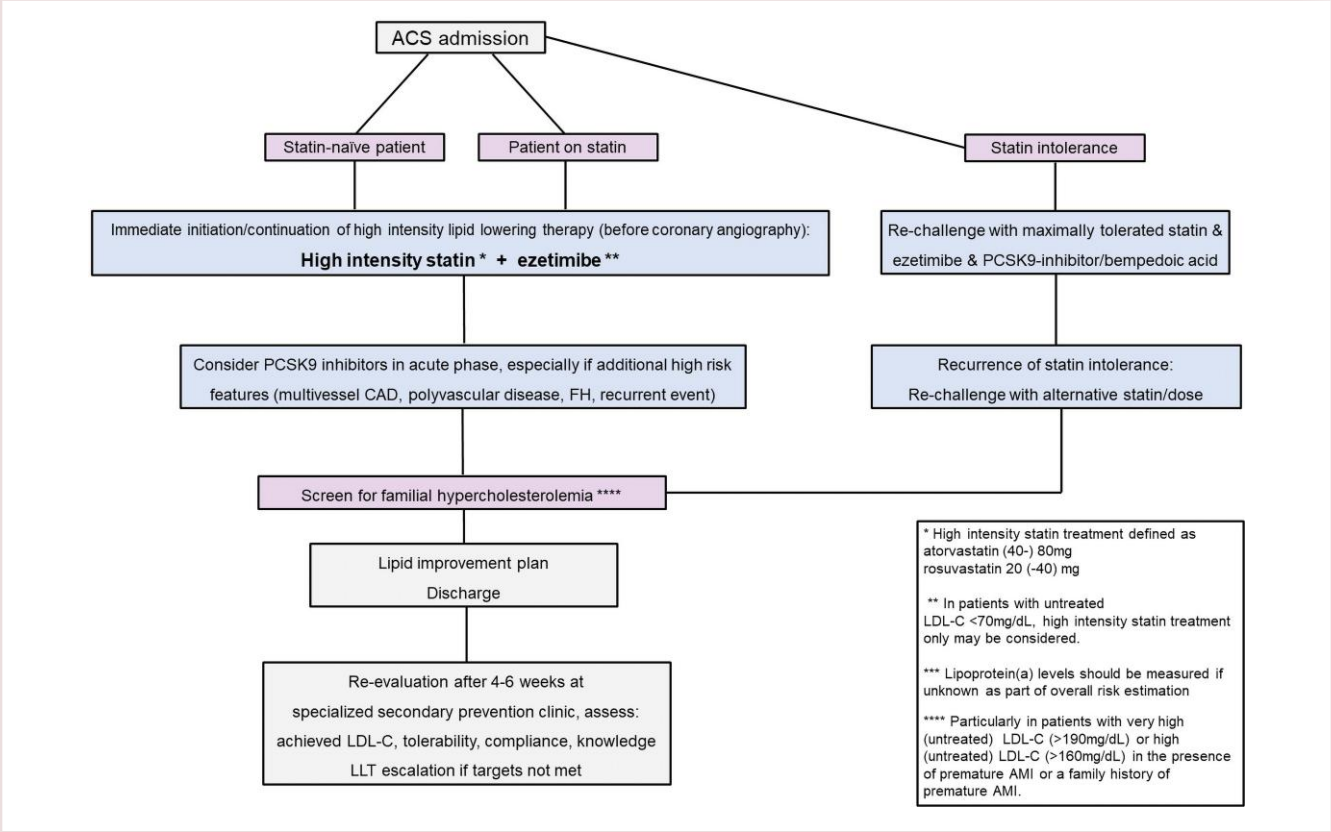

Figure 2 Proposed lipid-lowering algorithm after ACS. A combination therapy consisting of a high-intensity statin and ezetimibe, preferably as a combination pill, should be initiated as soon as possible, preferably before coronary angiography, irrespective of LDL-C levels or pre-existing statin therapy. A lipid panel should be obtained as early as possible. Treatment with PCSK9 inhibitors in the acute phase may be discussed, especially in patients exhibiting additional high-risk features such as multivessel coronary disease, polyvascular disease or familial hypercholesterolemia. In patients experiencing a second major vascular event while treated with a high-intensity statin, current ESC guidelines suggest a LDL-C goal of <40 mg/dL for which a PCSK9 inhibitor would be necessary in most patients. All patients, particularly those with very high untreated LDL-C of >190 mg/dL or >160 mg/dL in the presence of premature AMI or family history of premature AMI, should be screened for FH. All patients should be discharged with a clear lipid improvement plan and be re-evaluated after 4–6 weeks in a specialized secondary prevention clinic and achieved LDL-C, treatment tolerability, compliance and knowledge about disease and therapies should be assessed. Lipid-lowering therapy should be escalated if goals are not met. In patients with known statin intolerance, statin treatment should be re-initiated at the maximally tolerated dose in combination with ezetimibe and a PCSK-9 inhibitor. If PCSK9 inhibitors are not available, bempedoic acid may represent an alternative. In case of a recurrence of symptoms suggestive of recurrent statin intolerance, re-challenge with an alternative statin should be attempted. In patients prescribed a PCSK9 inhibitor in the acute phase for fast LDL-C goal achievement and/or stabilization of the remaining coronary vasculature, de-escalation of triple therapy (high-intensity statin, ezetimibe and PCSK9 inhibitor) should be discussed during follow-up. ACS, acute coronary syndrome; PCSK9, proprotein convertase subtilisin/kexin type 9; CAD, coronary artery disease; FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; AMI, acute myocardial infarction; ESC, European Society of Cardiology.

ASCVD patients into several risk levels is also being postulated by the current US guidelines.[81]

A cornerstone of the ESC guidelines on dyslipidaemias is the definition of LDL-C goals. Such an approach however has not been tested in dedicated outcome trials but instead are based on achieved LDL-C levels in recent positive recent outcome trials, including FOURIER (30 mg/dL) and ODYSSEY OUTCOMES (38–53 mg/dL).[41,45] We believe that formulating clear LDL-C goals may be helpful for both providers and patients to create a lipid plan. Whether different LDL-C goals should be formulated for patients after ACS or characterized by more severe disease or recent events at higher overall risk remains a debate, we do however firmly believe that we should be fast and efficient in achieving currently formulated goals.

Several small trials have evaluated PCSK9 inhibitor therapy in the acute phase and have demonstrated rapid LDL-C goal achievement within a few days, as well as favourable effects on coronary atherosclerotic disease after a 1-year treatment course.[15,16,28–30] Whether the indication for such a triple therapy (high-intensity statin, ezetimibe, and PCSK9 inhibition) should be re-evaluated after the acute phase and potentially de-escalated in response to clinical course and achieved LDL-C, comparable with antithrombotic combination therapies, warrants further discussion. Dedicated cardiovascular outcome trials for such an approach are warranted. The AMUNDSEN trial (NCT04951856) is currently randomizing 1666 patients with STEMI or NSTEMI to a one-year treatment with evolocumab 140 mg s.c. every 2 weeks, with the first dose given prior to PCI. The primary endpoint is obtained LDL-C reduction at 12 months, clinical endpoints will only be

collected as tertiary endpoints. EVOLVE-MI (EVOLocumab Very Early After Myocardial infarction) will include 4,000 adult patients hospitalized for STEMI or NSTEMI which will be randomized to routine post-ACS lipid management or evolocumab added to routine post-ACS lipid management (NCT05284747, clinicaltrials.gov). The primary endpoint is a composite of AMI, stroke arterial revascularization and all-cause mortality and the trial is expected to close the evidence gap in the area of early and acute LDL-C reduction using PCSK9-inhibitors.

A novel, revolutionary approach is the use of siRNA targeted against PCSK9. Twice yearly injections with inclisiran reduce LDL-C by approximately 50% within 2–4 weeks.[31] Two cardiovascular outcome trials (ORION-4; NCT03705234 and VICTORION-2 PREVENT; NCT05030428) are underway that both aim to include 15 000 patients with a history of AMI, stroke, or presence of peripheral arterial disease. A twice yearly inclisiran injection administered by healthcare professionals may help overcome several barriers, including non-compliance and presumed statin intolerance. Administering inclisiran in the acute phase would lower LDL-C by 50% for about three months, bridging the highest risk phase. The aforementioned cardiovascular outcome trials should be awaited before adopting such a strategy.

Poor treatment adherence, limited knowledge, and wide-spread misinformation regarding lipid-lowering therapies remain significant barriers to secondary prevention. In addition, treatment inertia and knowledge gaps on the provider side further aggravate the problem. We believe that strategic information campaigns for both providers and patients are necessary to overcome these barriers. Such low-key campaigns should be rolled out on several channels, including print, television, brochures, and social media, to counter frequently coordinated misinformation campaigns. This also underlines the importance of drug initiation before leaving the hospital after an ischaemic event.

Use of PCSK9 inhibitors in heart failure patients remains controversial, with a *post hoc* analysis of ODYSSEY OUTCOMES evaluating the effects of alirocumab on clinical outcomes in patients with or without a history of heart failure suggested that the former group (14.9% of all patients) did not benefit from PCSK9 inhibition.[82] Treatment with alirocumab was even associated with an increased rate of non-fatal myocardial infarction in patients with a history of heart failure.[83] Currently, the EVO-HF Pilot study aims to test the effects of evolocumab vs. placebo on top of guideline-directed medical treatment in patients with heart failure with reduced ejection fraction of ischaemic aetiology on troponin levels after 12 months (NCT03791593).

Conclusions

Patients experiencing an ACS are at heightened risk of recurrent events, especially in the very early phase. Over the last decades, a clear monotonic relationship between achieved LDL-C levels and cardiovascular outcomes has been described, with no apparent lower threshold and no serious safety signals described thus far, especially not in the early phase after an ACS. Despite current guidelines suggesting a step-wise lipid-lowering approach, data from many systems suggest a very low rate of medication changes following hospital discharge after ACS. Even in the best-case scenario, with LDL-C assessments and therapy escalations undertaken every 4–6 weeks, it might take up to 3 months for a patient to achieve target goals, coinciding with the highest risk period for recurrent cardiovascular events. We, therefore, propose a lipid-lowering strategy of 'strike early and strike strong' to be discussed in all patients with ACS, with immediate initiation of statin therapy and a dual lipid-lowering strategy as a default strategy. Acute PCSK-9 inhibition is a novel strategy that deserves consideration, especially in patients exhibiting high risk features. Identifying hurdles in daily clinical practice and strategies to ensure high-quality follow-up care of our high-risk patients should constitute a significant focus in our healthcare systems.

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Data availability

No new data were generated or analysed in support of this research.

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