European Heart Journal Supplements (2023) **25** (Supplement B), B55–B59
The Heart of the Matter
https://doi.org/10.1093/eurheartjsupp/suad068

ESC European Society of Cardiology

Hypocholesterolaemic treatment in coronary unit: from statins to anti PCSK9 therapies and bempedoic acid

Nicola Ferri[1,2], Alberto Corsini[3], and Massimiliano Ruscica[3]*

[1]Department of Medicine-DIMED, University of Padua, Padua, Italy; [2]Veneto Institute of Molecular Medicine, Padua, Italy; and [3]Department of Pharmacological and Biomolecular Sciences, University of Milan, Milan, Italy

KEYWORDS
Statin;
Hypocholesterolaemic treatment;
Bempedoic acid;
Anti-PCSK9 therapies

The knowledge that roughly 20% of survivors from an acute coronary syndrome (ACS) event experience a subsequent ischaemic cardiovascular event within 24 months with a 5-year mortality range between 19 and 22% highlights the importance of the lipid-lowering strategies in the secondary prevention after ACS. In this framework, statin treatment significantly improves clinical outcome after ACS. Within this remit, in the present review we critically discuss the use of statin and non-statin lipid-lowering approaches (ezetimibe, evolocumab, alirocumab, inclisiran, and bempedoic acid) in the early management of ACS patients. Relative to this latter aspect, the knowledge that circulating proprotein convertase subtilisin/kexin type 9 (PCSK9) levels are raised during ACS could be a generating hypothesis justifying the use of PCSK9 inhibitors in ACS. Thus, in a field fraught of uncertainty, the main barrier to the widespread prescription of non-statin agents (e.g. PCSK9 inhibitors) relates to their costs when compared with other lipid-lowering agents (e.g. statins and ezetimibe).

Introduction

Coronary artery disease remains a major cause of death in the developed world, although many improvements in its prevention and management. Acute coronary syndrome (ACS) [which includes unstable angina, non-ST-segment-elevation myocardial infarction (MI), and ST-segment-elevation MI] constitutes the most severe clinical manifestation of coronary artery disease. In this framework, immediate and aggressive lipid-lowering therapies are supported by the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) guidelines for the management of dyslipidaemias. They recommend initiating high-intensity statin therapy within the first 1–4 days of hospitalization. Indeed, risk of cardiovascular events appeared high beyond the first year post-MI, indicating a need for prolonged surveillance, particularly in patients with additional risk factors. This evidence is supported by the analysis of the GRACE (Global Registry of Acute Coronary Events) risk score highlighting that 5-year morbidity and mortality were high in patients following non-ST MI and unstable angina as seen following Non-ST elevation myocardial infarction (STEMI).[1]

Thus, it is mandatory to assess whether non-statin lipid-lowering agents, added to statin treatment, could produce a similar or even better reduction in the risk of major adverse cardiovascular events (MACE) is still unknown. On this regard, it is important to point out that different biochemical alterations occur during the ACS, including the induction of free fatty acid mobilization, hepatic very-low-density lipoprotein (VLDL) secretion, triglyceride (TG) elevation, and alteration in LDL and HDL particle composition.[2] More recently significant elevation of proprotein convertase subtilisin/kexin type 9 (PCSK9) has been observed during ACS.[3] Here, we summarized the current clinical evidence of a cardiovascular protective efficacy of hypocholesterolaemic drugs in the setting of ACS patients.

Statins and ezetimibe

The first evidence of the use of statins in ACS patients were derived from studies conducted between 2001 and 2004,

*Corresponding author. Email: massimiliano.ruscica@unimi.it

Table 1 Currently undergoing clinical trials testing evolocumab and alirocumab in ACS

Title	Status	No. of patients	Conditions	Interventions	Locations
Impact of evolocumab on the antiplatelet effects of ticagrelor and aspirin in patients with ACS (EvoACS) NCT05418166	Recruiting	$n = 30$	ACS	Evolocumab 140 mg s.c. after regular take ticagrelor and aspirin for 5 days	Harbin Medical University, Harbin, Heilongjiang, China
EVOLVE-MI: evolocumab very early after myocardial infarction NCT05284747	Not yet recruiting	$n = 4000$	Coronary artery Bypass graft surgery Atherosclerosis Vein Occlusion	Evolocumab + routine lipid management	USA and Canada
Evolocumab in ACS (EVACS) NCT03515304	Active, not recruiting	$n = 60$	ACS	Evolocumab 420 mg s.c. in NSTEMI patients within 24 h, or one day, of admission	Steven Paul Schulman, Baltimore, MD, USA
Evolocumab for early reduction of LDL-C levels in patients with acute coronary syndromes (EVOPACS) NCT03287609	Completed	$n = 308$	ACS	Evolocumab 140 mg/mL day 1 and at week 4	Multiple centres in Switzerland
Effect of evolocumab added to moderate-intensity statin therapy on LDL-C lowering and cardiovascular adverse events in patients with ACS (EMSIACS) NCT04100434	recruiting	$n = 500$	ACS	Statin alone therapy and evolocumab plus statin therapy	Tianjin Chest Hospital, Tianjin, China
Impact of evolocumab as an additional lipid-lowering therapy to changes in lipid core burden index of non-culprit vulnerable plaque in patients who underwent percutaneous coronary intervention for the acute coronary syndrome. NCT04719221	Recruiting	$n = 60$	ACS	Statin + ezetimibe for 2 months than evolocumab according to randomization	Korea University Anam Hospital, Seoul, Korea
Evolocumab in patients with acute MI (EVACS II) NCT04082442	Recruiting	$n = 100$	ACS	Evolocumab 420 mg s.c.	The Johns Hopkins Hospital, Baltimore, MD, USA
PCSK9 inhibitor on ACS patients with multivessel disease and relatively low LDL-C level in Chinese population. NCT05043740	Not yet recruiting	$n = 1360$	ACS	Evolocumab 140 mg or alirocumab 75 mg every 2 weeks, first s.c. injection at the time of randomization, followings for 12 months	
Markers of cardiovascular risk in patients with premature coronary artery disease and treatment (GEBI) NCT04613167	Recruiting	$n = 70$	ACS premature coronary heart disease Lipoproteinaemia Inflammation Genetic Polymorphisms	Evolocumab 140 mg every two weeks for 6 months, alirocumab 150 mg every 2 weeks s.c. for 6 months Placebo	University Medical Centre Ljubljana-Department of Vascular diseases and dept. of Cardiology, Ljubljana, Slovenia
Evaluation of effect of alirocumab on coronary atheroma	Completed	$n = 206$	Hypercholesterolaemia ACS	Alirocumab every 2 weeks on top of	Multiple centres Japan

Continued

Table 1 Continued

Title	Status	No. of patients	Conditions	Interventions	Locations
volume in Japanese patients hospitalized for acute coronary syndrome with hypercholesterolaemia (ODYSSEY J-IVUS) NCT02984982				stable statin therapy (atorvastatin or rosuvastatin)	
Effects of acute, rapid lowering of LDL-C with alirocumab in patients with STEMI undergoing primary PCI (EPIC STEMI) NCT03718286	Completed	$n = 97$	STEMI ACS Hypercholesterolaemia Hyperlipidaemias Dyslipidaemias	Alirocumab 150 mg administered prior to revascularization procedure, 2- and 4 weeks post-procedure	General Hospital, Hamilton, Ontario, Canada

namely the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL),[4] the Pravastatin or Atorvastatin and Infection Therapy—Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) trial[5], and the Aggrastat to Zocor (AtoZ) (10.1001/jama.292.11.1307). These studies demonstrated that early statin treatment (1–4 days or within 10 days after ACS) effectively reduced the incidence of MACE. Relevant results were also observed in the Atorvastatin for Reduction of Myocardial Damage during Angioplasty (ARMYDA) trial where patients with chronic stable angina, scheduled for elective coronary intervention, were randomized to receive atorvastatin (40 mg) or placebo days before the procedure (12 h pre-treatment). The study demonstrated a significant reduction of markers of myocardial injury in response to atorvastatin pre-treatment, suggesting a protective effect on procedural myocardial injury in elective coronary intervention.[6] This early window of protection, during which there is a lack of LDL-C lowering, suggests that the anti-inflammatory and pleiotropic properties of statins may be of clinical importance. The acute presentation of coronary artery disease may involve a complex interaction between the vessel wall, inflammatory cells, and the coagulation cascade. Indeed, in the PROVE IT-TIMI 22 trial, high dosage of atorvastatin (80 mg) not only achieved a better LDL-C reduction as compared with 40 mg of pravastatin, but strongly lowered CRP: an effect that was associated with clinically significant benefits in ACS patients.[5] Nevertheless, roughly 20% of ACS survivors experience a subsequent event of ischaemic nature within 24 months with a 5-year mortality ranging from 19% to 22%.[7] Achieving guidelines goals either <70 mg/dL or <55 mg/dL of LDL-C levels is not typically reached until 4 weeks after initiation high dose statins. Nevertheless, the initiation of statin therapy in the major trials conducted (i.e. PROVE-IT and A-to-Z) occurred 4–7 days after the event,[8] thus leaving open the possibility for taking further advantage of the pleiotropic effects of statins at the early and critical stage in ACS patients. The only study addressing the early benefits of statin therapy in ACS patients was MIRACL[4] where atorvastatin was initiated 24 to 96 h after the event. The results show a reduction of recurrent ischaemic events in the first 16 weeks, mostly recurrent symptomatic ischaemia requiring hospitalization.

Relative to ACS, immediate and aggressive lipid-lowering therapies is supported by the ESC/EAS dyslipidaemia guidelines, recommending initiation of high-intensity statin therapy during the first 1–4 days of hospitalization.[9] European and American guidelines highlighted the efficacy of an early and very aggressive statin therapy after ACS with monitoring of the LDL-C levels 4/12 weeks post-event. More recently, it has been proposed, for very high-risk patients, to start directly with triple therapy (statins, ezetimibe, and anti-PCSK9) in order to reduce LDL-C levels efficiently without hesitation.[10] This approach is also supported by the results of the IMPROVE-IT trial, where ezetimibe was added to simvastatin (40 mg) hospitalized within the preceding 10 days for an ACS.[11] The study enroled 18.144 ACS patients and 5314 patients over 7 years experienced a CV event; 170 fewer events (32.7 vs. 34.7%) were recorded in the group taking simvastatin plus ezetimibe ($P = 0.016$). The average LDL-C during the study was 1.8 mmol/L (70 mg/dL) in the simvastatin group and 1.4 mmol/L (55 mg/dL) in patients taking ezetimibe.

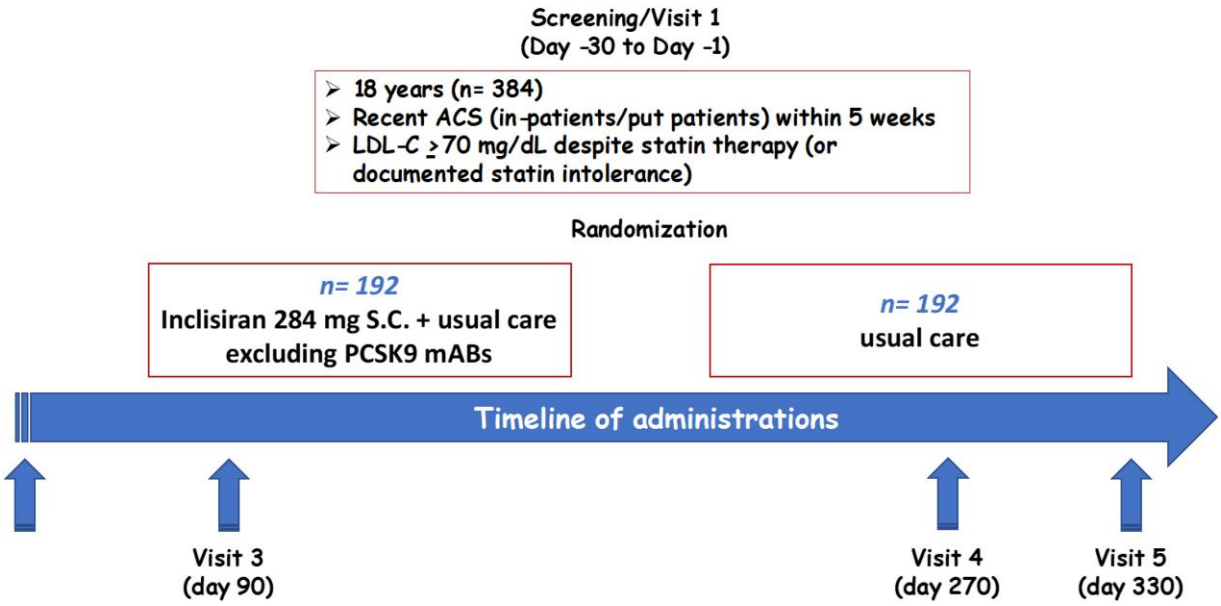

Figure 1 Schematic representation of the VICTORION-INCEPTION study.

Anti PCSK9 therapies: alirocumab, evolocumab, and inclisiran

The ODYSSEY OUTCOMES trial with alirocumab enroled 18 924 patients who were 1–12 months out from an ACS event.[12] After a run-in phase between 2 and 16 weeks on high-intensity statin therapy, participants were randomized to receive alirocumab every 2 weeks ($n = 9462$) or placebo (9462). Alirocumab was titrated between 75 and 150 mg to keep the LDL-C between 25 and 50 mg/dL, but above 15 mg/dL. After a median follow-up of 2.8 years, the hazard ratio (HR) for MACE was 0.85 (95%CI 0.78–0.93, $P < 0.001$) in favour of alirocumab. Patients who benefitted the most seemed to be those with baseline LDL-C ≥ 100 mg/dL, namely MACE were 11.5% and 14.9%, respectively, in the active group vs. placebo. Compared with patients with lower LDL-C, patients with baseline LDL-C ≥ 100 mg/dL had a greater absolute risk of death and a larger mortality benefit from alirocumab (HR = 0.71; 95%CI 0.56–0.90).[12] The superiority of alirocumab was irrespective of age with an increasing absolute benefit but not harm with advancing age. This aspect suggests that LDL-C lowering is an important preventive intervention for older patients after ACS. Relative risk reductions for MACE were consistent for patients ≥65 years (HR = 0.78; 95%CI 0.68–0.91) compared with those <65 years (HR = 0.89; 95% CI 0.80–1.00). At 3 years, the numbers-needed-to-treat was 43 in individuals aged 45 years, was 26 at age 75 years, and 12 for those aged 85 years.[13]

The benefit of alirocumab was also evident in patients with coronary artery bypass grafting (CABG) preceding the ACS event. Specifically, HR for MACE was 0.86 (95%CI 0.78–0.95) in patients without CABG, 0.85 (95%CI 0.54–1.35) in those with CABG performed after the index ACS but before randomization, and 0.77 (95%CI 0.61–0.98) in those with CABG performed prior to the index ACS.[14]

In the EVOPACS (Evolocumab for Early Reduction of LDL-cholesterol Levels in Patients With Acute Coronary Syndromes) study, evolocumab added to high-intensity statin therapy was well tolerated and resulted in substantial reduction in LDL-C levels, rendering >95% of patients within currently recommended target levels. Overall, the hypothetical positive clinical impact of evolocumab and alirocumab in patients with ACS are under investigation by ongoing and former clinical trials (*Table 1*). Positive results could determine a step forward in the current guidelines for the treatment of ACS patients.[15]

Targeting PCSK9 is now possible also by means of a gene-silencing agent (inclisiran) which allows a dosing schedule considerably different from that of common cholesterol-lowering drugs and potentially advantageous in terms of adherence and compliance to therapy. Although Phase 2 and 3 trials have demonstrated the efficacy of this agent in lowering LDL-C and the 4-year averaged mean reduction of LDL-C was 44.2% (95% CI: 47·1–41·4), with reductions in PCSK9 ranging from 62.2% to 77.8%, we need to wait for the results of the ORION-4 study (NCT03705234) to understand the efficacy of inclisiran to reduce major adverse cardiovascular events (MACE). This study plans to enrol ≥ 15 000 patients with pre-existing atherosclerotic cardiovascular diseases to be treated for a median duration of 5 years. Relative to the possible benefit of administrating inclisiran in the early phase of ACS, the VICTORION-INCEPTION study (*Figure 1*) has been planned (NCT04873934). The purpose of this Phase 3b trial (randomized, parallel-group, open-label, multicentre, and US-based) is to evaluate the effectiveness of implementation of a systematic LDL-C management pathway including treatment with inclisiran in participants who have experienced a recent ACS and have an increased LDL-C (≥70 mg/dL) despite being treated with a statin drug.

Bempedoic acid

Bempedoic acid is an oral, once daily, small molecule with an LDL-lowering efficacy similar to that of ezetimibe and

associated with a far lower percentage of muscular side effects. The safety and efficacy of the long-term use of bempedoic acid have been addressed in the CLEAR (Cholesterol Lowering via Bempedoic Acid, an ACL-inhibiting Regimen) program comprising four Phase 3 trials: statin-intolerant patients (CLEAR Tranquility); patients with LDL-C of at least 70 mg/dL despite maximum tolerated statin therapy (CLEAR Harmony); patients with ASCVD, heterozygous familial hypercholesterolaemia (HeFH), or both, on optimal statin treatment (CLEAR Wisdom); and statin-intolerant patients with ASCVD and inadequately controlled LDL-C (CLEAR Serenity). Although the data of the CVOT CLEAR Outcomes study will be presented in the early months of 2023, all the above-reported trials have excluded patients with a recent ACS. Thus, it is worth mentioning that the CLEAR ACS (Cholesterol Lowering Via Bempedoic Acid/Ezetimibe, an ACL-Inhibiting Regimen in Acute Coronary Syndrome Study) has been planned (NCT05263778). The overall objective of this Phase 4 study is to determine the efficacy, safety, and tolerability of bempedoic acid/ezetimibe in a contemporary and real-world population, enriched of older adults, women, and underrepresented racial/ethnic groups, of adults with a recent ACS event independent of use of statin therapy before the ACS event.

Conclusions

The benefit of intensive LDL-C lowering to reduce cardiovascular risk is recognized in international guidelines in patients after an ACS. Indeed, ~20% of ACS survivors experience a subsequent ischaemic cardiovascular event within 24 months and 5-year mortality ranges from 19% to 22%. The risk reduction management of patients with ACS is based on adapting lipid-lowering therapies according to the recommended treatment effect on LDL-C levels and patients' characteristics. Finally, the use of different therapeutic approaches to achieve a rapid hypocholesterolaemic effect could highlight the so called 'pleiotropic' effect of statins and possibly of bempedoic acid which is able to reduce C-reactive protein. Conversely, although PCSK9 therapies are not associated to an anti-inflammatory activity, they show an antiplatelet action or plaque modification that may contribute to a final cardiovascular protection in ACS patients.

Funding

None declared.

Conflict of interest: None declared.

Data availability

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

References

1. Claessen BE, Guedeney P, Gibson CM *et al*. Lipid management in patients presenting with acute coronary syndromes: a review. *J Am Heart Assoc* 2020;**9**:e018897.
2. Sposito AC, Chapman MJ. Statin therapy in acute coronary syndromes: mechanistic insight into clinical benefit. *Arterioscler Thromb Vasc Biol* 2002;**22**:1524–1534.
3. Burchardt P, Rzezniczak J, Dudziak J *et al*. Evaluation of plasma PCSK9 concentrations, transcript of LDL receptor, as well as the total number of monocyte LDL receptors in acute coronary syndrome patients. *Cardiol J* 2016;**23**:604–609.
4. Schwartz GG, Olsson AG, Ezekowitz MD *et al*. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. *JAMA* 2001;**285**:1711–1718.
5. Cannon CP, Braunwald E, McCabe CH *et al*. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004;**350**:1495–1504.
6. Pasceri V, Patti G, Nusca A *et al*. A randomized trial of atorvastatin for reduction of myocardial damage during coronary intervention: results from the ARMYDA (Atorvastatin for Reduction of Myocardial Damage During Angioplasty) study. *Circulation* 2004;**110**:674–678.
7. Jernberg T, Hasvold P, Henriksson M, Hjelm H, Thuresson M, Janzon M. Cardiovascular risk in post-myocardial infarction patients: nationwide real world data demonstrate the importance of a long-term perspective. *Eur Heart J* 2015;**36**:1163–1170.
8. Wiviott SD, de Lemos JA, Cannon CP *et al*. A tale of two trials: a comparison of the post-acute coronary syndrome lipid-lowering trials A to Z and PROVE IT-TIMI 22. *Circulation* 2006;**113**:1406–1414.
9. Mach F, Baigent C, Catapano AL; Group ESCSD *et al*. ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J* 2019;**2020**:111–188.
10. Ray KK, Reeskamp LF, Laufs U *et al*. Combination lipid-lowering therapy as first-line strategy in very high-risk patients. *Eur Heart J* 2022;**43**:830–833.
11. Cannon CP, Blazing MA, Giugliano RP; Investigators I-I *et al*. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med* 2015;**372**:2387–2397.
12. Steg PG, Szarek M, Bhatt DL *et al*. Effect of alirocumab on mortality after acute coronary syndromes. *Circulation* 2019;**140**:103–112.
13. Sinnaeve PR, Schwartz GG, Wojdyla DM; Investigators OO *et al*. Effect of alirocumab on cardiovascular outcomes after acute coronary syndromes according to age: an ODYSSEY OUTCOMES trial analysis. *Eur Heart J* 2020;**41**:2248–2258.
14. Goodman SG, Aylward PE, Szarek M *et al*. Effects of alirocumab on cardiovascular events after coronary bypass surgery. *J Am Coll Cardiol* 2019;**74**:1177–1186.
15. Ferri N, Ruscica M, Lupo MG, Vicenzi M, Sirtori CR, Corsini A. Pharmacological rationale for the very early treatment of acute coronary syndrome with monoclonal antibodies anti-PCSK9. *Pharmacol Res* 2022;**184**:106439.