

The PACMAN-AMI trial: a revolution in the treatment of acute coronary syndromes

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After an acute coronary syndrome (ACS), the risk of major adverse cardiovascular events (MACE) persists despite the reperfusion of the culprit lesion. The addition of proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i) to standard lipid-lowering therapies has been demonstrated to effectively reduce the levels of low-density lipoprotein cholesterol (LDL-C), with a consistent decrease of MACE in large, randomized clinical trials enrolling patients at high risk of cardiovascular events. There is a strong rationale for an immediate and aggressive LDL-C lowering with the use of PCSK9i in ACS patients. The PACMAN-AMI trial tested this hypothesis demonstrating that in ACS patients, the addition of subcutaneous biweekly alirocumab, compared with placebo, to high-intensity statin therapy resulted in significantly greater coronary plaque regression in non-infarct-related arteries after 52 weeks, as assessed by novel intra-coronary imaging modalities. These findings might provide the mechanistic rationale in favour of early initiation of very intensive LDL-C-lowering therapy in the acute setting of ACS, potentially modifying the actual common pattern of treatment.

Introduction

Cardiovascular illnesses continue to be the largest cause of disease burden worldwide.¹ In particular, acute coronary syndromes (ACS) remain one of the most relevant diseases worldwide in terms of frequency, mortality, and costs.¹

An initial therapy aimed at reducing myocardial damage is followed by a long-term therapy aimed at preventing recurrence. While statins are clear first-line drugs, new drug developments such as proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i) have been shown to improve cardiovascular outcomes when added to statins (\pm ezetimibe). PCSK9i are a new class of cholesterol-lowering medicines that have brought about a significant shift in lipid management. PCSK9 is a protease produced predominantly by hepatocytes that binds to low-density lipoprotein (LDL) receptors on the surface of hepatocytes and internalizes them, thereby increasing their destruction within

lysosomes.² This decreases the amount of LDL receptors available for the transport of LDL-cholesterol (LDL-C) into hepatocytes. Inhibition of PCSK9 increases the number of LDL receptors, hence facilitating the absorption of LDL-C into the liver and decreasing plasma LDL-C levels.

The PCSK9i alirocumab and evolocumab are fully human monoclonal antibodies that target the PCSK9 protein and interfere with the PCSK9/LDL receptor interaction.³ These new drugs lowered plasma LDL-C levels by approximately 60%, even in patients already receiving maximum-dose statin therapy.

In the last few years, large cardiovascular outcome trials were completed, showing that PCSK9i significantly reduce the risk of major vascular events. Reassuringly, this benefit comes with no major offsetting adverse events, such as an excess of myalgias, elevation of hepatic aminotransferases levels in the plasma, incident diabetes mellitus or neurocognitive adverse events.⁴ The clinical benefit of PCSK9i seen in these trials occurred in the setting of reducing LDL-C levels to unprecedentedly low levels, suggesting that more aggressive LDL-C targets should be adopted.

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PCSK9i and cardiovascular outcomes

A pre-specified exploratory review of data from two open-label extension studies [OSLER-1 and OSLER-2: (Open-Label Study of Long-Term Evaluation against LDL Cholesterol 1-2)] enrolling 4465 patients who had completed phase 2 or 3 lipid-lowering studies firstly suggested evolocumab might improve CV outcomes.⁵ After a median follow-up of 11.1 months, the evolocumab group had a lower composite CV endpoint rate than the control group.

The FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk) trial was the first successfully completed cardiovascular outcome trial of a PCSK9i⁶ (Figure 1). A total of 27 564 patients with clinically apparent atherosclerotic cardiovascular disease (ASCVD) were enrolled in this trial and randomized to evolocumab or placebo on top of high-intensity lipid-lowering therapy. These patients had either a history of myocardial infarction (MI), non-haemorrhagic stroke, or symptomatic peripheral arterial disease (PAD) and they were eligible for inclusion if they had an LDL-C level ≥ 70 mg/dL or a non-high-density lipoprotein cholesterol (non-HDL-C) level ≥ 100 mg/dL and were receiving optimized, stable high-intensity lipid-lowering therapy. Compared to placebo, evolocumab therapy lowered the risk of the primary endpoint (CV death, MI, hospitalization for unstable angina, stroke, or coronary revascularization) by 15% and the risk of the primary secondary endpoint (CV death, MI or stroke) by 20% (after a median follow-up of 2.2 years). The risks of fatal or nonfatal MI, fatal or nonfatal stroke, and coronary revascularization were reduced by 21-27% while there was no impact on cardiovascular mortality or hospitalization for unstable angina (Figure 2). The effect of evolocumab was consistent across subgroups based on baseline LDL-C level, presence/absence of diabetes mellitus, statin intensity and type of ASCVD (MI, stroke, PAD). Recently the results of 2 open-label extension studies [FOURIER-OLE (FOURIER Open-Label Extension)] in the US and Europe have been published. A total of 6635

patients were enrolled in FOURIER-OLE (3355 randomized to evolocumab and 3280 to placebo in the parent study). At a median of 5 years follow-up, patients originally randomized in the parent trial to evolocumab vs. placebo had a 15% lower risk of the primary endpoint [HR 0.85 (95% CI, 0.75-0.96); $P=0.008$], a 20% lower risk of secondary endpoint [HR 0.80 (95% CI, 0.68-0.93); $P=0.003$] and a 23% lower risk of CV death [HR 0.77 (95% CI, 0.60-0.99); $P=0.04$].⁷ Notably, a *post hoc* analysis of 22 351 FOURIER participants who had a prior MI found that the relative reduction in risk for the primary endpoint seen with evolocumab treatment was greater in patients with a MI within the previous 2 years (20%; HR 0.80, 95% CI 0.71-0.91), multiple prior MIs (18%; HR 0.82, 95% CI 0.72-0.93), or residual multi-vessel coronary disease (21%; HR 0.79, 95% CI 0.69-0.91) than in patients not meeting these criteria (5%, 8%, and 7%, respectively).⁸

The ODYSSEY LONG TERM study presented preliminary evidence that alirocumab might be associated with favourable CV outcomes. This randomized, double-blind trial enrolled 2341 patients at high risk of CV events (i.e. ASCVD or a ASCVD risk-equivalent) who had an LDL-C level 1.8 mmol/L (70 mg/dL) and were on maximally tolerated statin therapy⁹ (Figure 1). After 78 weeks, a *post hoc* analysis revealed that the alirocumab group had significantly fewer major adverse CV events (CV death, nonfatal MI, fatal or nonfatal ischaemic stroke, or unstable angina requiring hospitalization) than the placebo group (1.7% vs. 3.3%; HR 0.52; 95% CI 0.31-0.92; $P=0.02$).

The ODYSSEY OUTCOME trial offered more conclusive data.¹⁰ This randomized, double-blind, placebo-controlled trial examined the effects of alirocumab on CV events in ACS patients. A total of 18 924 patients were enrolled in this trial 1-12 months after hospitalization for MI or unstable angina. Inclusion criteria were LDL-C level ≥ 70 mg/dL, non-HDL-C level ≥ 100 mg/dL or Apolipoprotein B level ≥ 80 mg/dL despite high-intensity lipid-lowering therapy. Alirocumab significantly reduced the risk of the primary endpoint (a composite of death from coronary heart disease, nonfatal MI, fatal or nonfatal

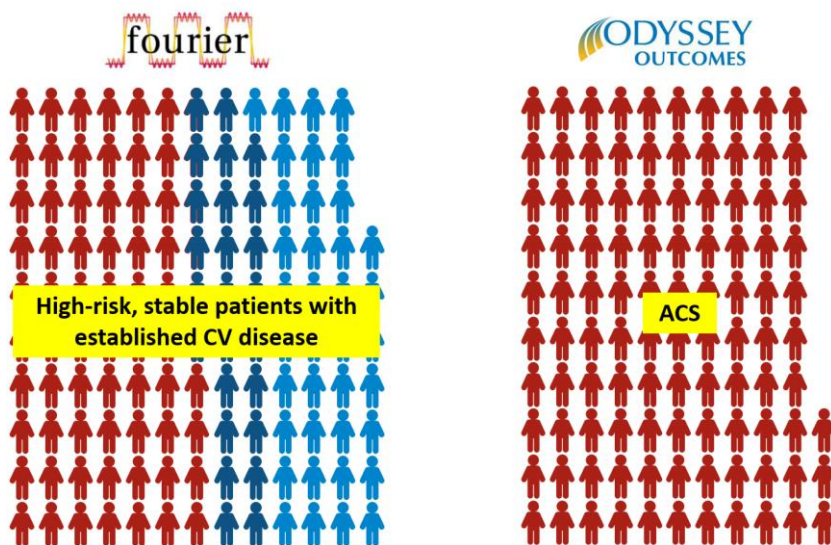




Figure 1 Populations of patients in the two largest phase III trial with PCSK9i.

Outcomes relative reduction		
Primary endpoint	15%	15%
MI	27%	14%
Stroke	21%	27%
Unstable angina	1%	39%
CV death	+5% increase (NS)	12% (NS)
All cause death	+4% increase (NS)	15% (p=0.026*)

* Nominal p value

Figure 2 Main outcomes of the two largest phase III trial with PCSK9i.

ischaemic stroke, or unstable angina requiring hospitalization) by 15% compared to placebo during the duration of the study (HR 0.85, 95% CI 0.78-0.93, $P=0.003$). The effects of alirocumab on the individual components of the composite endpoint were consistent in their direction¹⁰ (Figure 2).

Early initiation of PCSK9i in ACS

After an ACS, the risk of major adverse CV events persists despite the reperfusion of the culprit lesion. High levels of LDL-C enhance this risk, and lipid-lowering medication containing statins has been the cornerstone treatment for reducing it. Relative to ACS, immediate and aggressive lipid-lowering therapies are supported by the ESC/EAS dyslipidaemias guidelines, recommending initiation of lipid-lowering therapies including high-intensity statins during the first 1-4 days of hospitalization.¹¹

Both evolocumab and alirocumab suppress circulating PCSK9 (97% of the time) within 1 day of injection, indicating a very rapid initiation of effect. At least four confirmed findings in ACS reinforce the rationale for exploring the aggressive and quick pharmacological intervention with PCSK9i:¹² (i) PCSK9 levels in circulation are elevated during ACS; (ii) PCSK9 is related with intra-plaque inflammation, macrophage activation, and endothelial dysfunction; (iii) PCSK9 concentrations relate to inflammation in the acute phase of ACS; (iv) statins boost PCSK9 levels rapidly and, at times, substantially.

From a clinical standpoint, several studies demonstrated that PCSK9i therapy determines a significant reduction of CV events in post-ACS patients, through a process of plaque modification, by intervening in lipid metabolism and platelet aggregation and finally determining an improvement in endothelial function.

In the EVACS (Evolocumab in Acute Coronary Syndrome) study, patients with ACS without ST-segment elevation were enrolled and treated with evolocumab SQ 420 mg or placebo within 24 h of the event. Lipid parameters and primary endpoints were assessed at hospital discharge and 1 month after the event.¹³ Evolocumab enables >90% of patients to attain LDL-C 55 mg/dL in accordance with ESC/EAS criteria, compared to 11% of patients who receive only statins.

In the EVOPACS (Evolocumab for Early Reduction of LDL Cholesterol Levels in Patients With Acute Coronary Syndromes) research, effectiveness and safety of evolocumab were examined in 308 hospitalized patients during the early phases of ACS.¹⁴ Patients were randomized to receive placebo or evolocumab 420 mg in addition to high-intensity statin therapy. Evolocumab demonstrated a 40.7% reduction in LDL-C levels (95% CI: 45.2-36.2%; $P<0.001$) and allowed 95.7% of individuals to achieve target LDL-C values of 55 mg/dL.

Finally, the recently published EPIC-STEMI trial showed that alirocumab significantly reduces LDL-C levels compared with sham-control when given acutely during primary PCI.¹⁵ Among patients with ACS with ST-segment elevation undergoing primary PCI, alirocumab given at baseline, 2 weeks, and 4 weeks, was associated with a significant reduction in LDL-C level compared with sham-control at 6 weeks, without reporting side effects.

Effects of PCSK9i on plaque volume and composition

The composition of atherosclerotic plaques has a significant impact on their propensity to develop or to precipitate acute coronary events. *In vivo* coronary plaque morphology and content can be assessed using intracoronary imaging techniques.¹⁶

Large atheroma burden as measured by intra-vascular ultrasonography (IVUS), large lipid burden as measured by near-infrared spectroscopy (NIRS), and the presence of thin fibrous caps as measured by optical coherence tomography (OCT) have been associated with an increased risk of subsequent cardiovascular adverse events, as indicated by histological evidence.¹⁷ Interestingly, recurrent CV events occurring during follow-up in patients with ACS who have received percutaneous coronary intervention are equally related to recurrence at the locations of culprit and non-culprit lesions.¹⁷ In this context, thin-cap fibroatheroma (TCFA), detected by virtual-histology (VH) IVUS, is an independent predictor of later CV events associated with non-culprit lesions.

Intensive statin therapy has been demonstrated to prevent the evolution of coronary atheroma burden and may positively influence plaque composition by decreasing

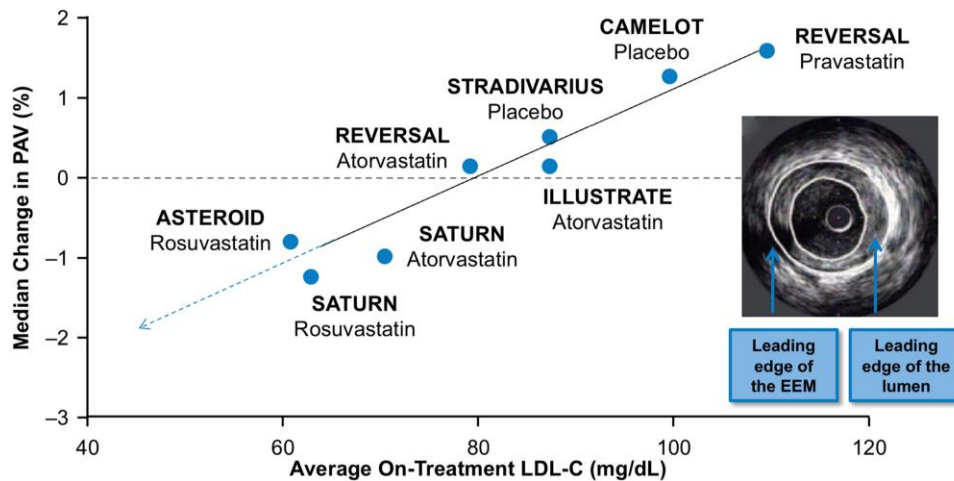


Figure 3 Median changes in percentage atheroma volume (PAV) vs. average on-treatment low-density lipoprotein cholesterol (LDL-C) in serial coronary intravascular ultrasonography (IVUS) trials.

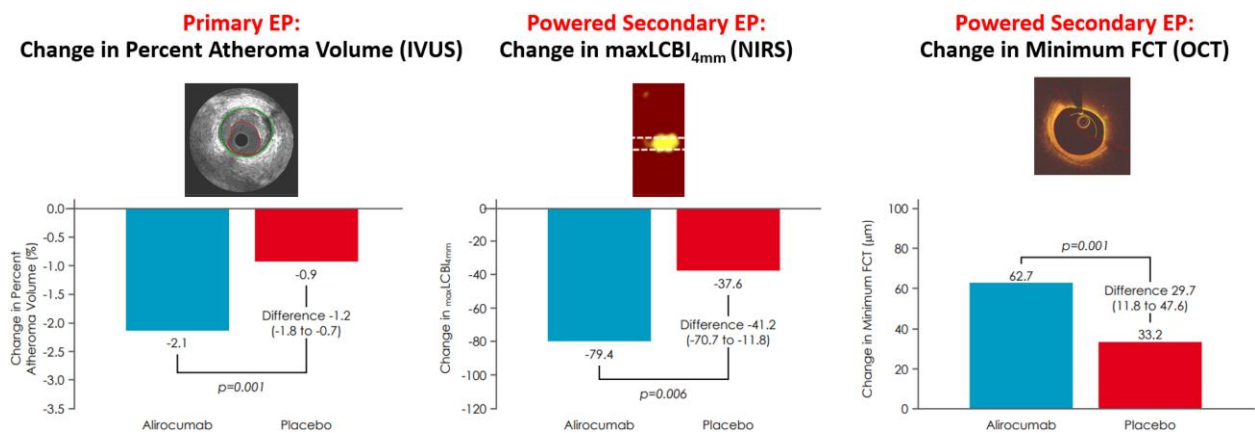


Figure 4 Primary and secondary outcomes of the PACMAN-AMI trial.

plaque lipid content and increasing fibrous cap thickness (FCT) (Figure 3). The GLAGOV (Global Assessment of Plaque Regression with a PCSK9 Antibody as Measured by IntraVascular Ultrasound) trial, a double-blind, placebo-controlled trial, found that adding evolocumab to statin medication in patients with angiographic coronary disease reduced IVUS-measured coronary atherosclerosis progression.¹⁸

After 76 weeks, evolocumab significantly reduced percentage atheroma volume (PAV) (-0.95% vs. +0.05% with placebo, $P < 0.001$; primary endpoint), total atheroma volume (TAV; difference -4.9 mm³, $P < 0.001$), and plaque regression in a greater proportion of patients than placebo (64.3% vs. 47.3% for PAV; 61.5% vs. 48.9% for TAV). Subsequently, the HUYGENS (High-Resolution Assessment of Coronary Plaques in a Global Evolocumab Randomized Study) trials randomized 160 patients with a non-ST-segment elevation MI to monthly evolocumab 420 mg or placebo for 52 weeks.¹⁹ Patients underwent serial OCT and intra-vascular ultrasound imaging within a matched arterial segment of a non-culprit vessel. The evolocumab group demonstrated a greater increase in

minimum FCT (+42.7 vs. +21.5 μm; $P = 0.015$) and decrease in maximum lipid arc (-57.5° vs. -31.4°; $P = 0.04$) and macrophage index (-3.17 vs. -1.45 mm; $P = 0.04$) throughout the arterial segment.¹⁹

The PACMAN-AMI trial

More recently, the PACMAN-AMI (Effects of the PCSK9 Antibody Alirocumab on Coronary Atherosclerosis in Patients With Acute Myocardial Infarction) trial enrolled 300 patients undergoing percutaneous coronary intervention for acute MI to determine the effect of early administration of alirocumab on coronary atherosclerosis assessed with multi-modality intra-coronary imaging (IVUS, NIRS, and OCT), in the non-infarct-related arteries (non-IRAs) of these patients.²⁰ This trial was an investigator-initiated, multi-centre, randomized, double-blind clinical trial conducted at nine centres in four European countries (Switzerland, Austria, Denmark, and the Netherlands). Patients 18 years or older who underwent urgent percutaneous coronary intervention of the culprit lesion for treatment of ACS were eligible for inclusion if they were considered suitable for intra-coronary imaging,

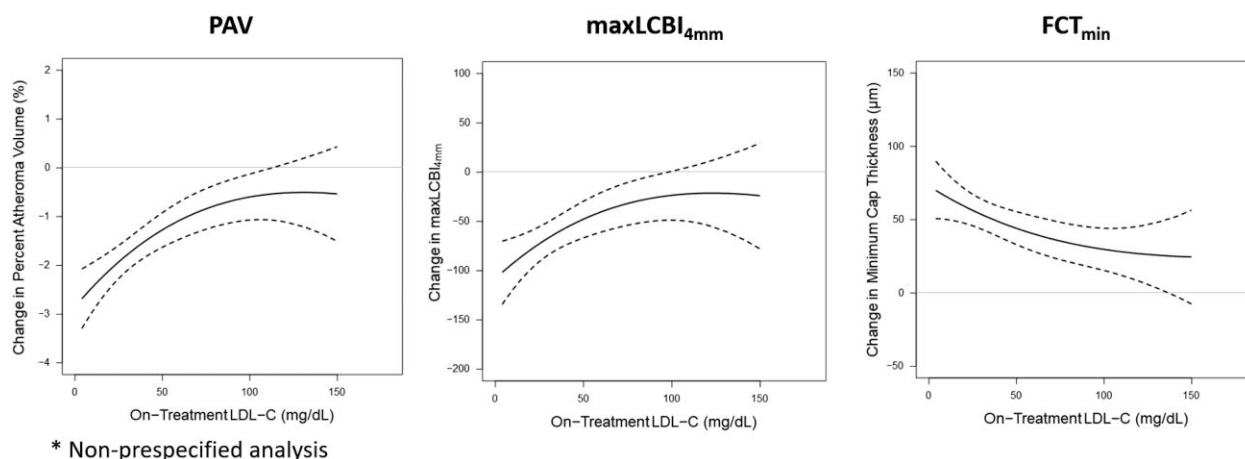


Figure 5 Primary and secondary outcomes according to low-density lipoprotein cholesterol LDL-C) levels in the PACMAN-AMI trial.

with angiographic evidence of coronary atherosclerosis but without significant obstructive disease in the proximal part of two non-IRAs. LDL-C levels, measured prior to revascularization, were required to be at least 125 mg/dL if patients had not been receiving a stable statin dose for at least 4 weeks or at least 70 mg/dL if patients had been receiving a stable statin dose for at least 4 weeks. Patients were excluded if they had left main or three-vessel coronary artery disease, history of coronary artery bypass surgery, severe kidney dysfunction, liver disease, or known statin intolerance. After the percutaneous coronary intervention of the culprit lesion in the IRA, eligible patients underwent intra-coronary imaging of the two non-IRAs and, if successful, they were randomly allocated in a 1:1 fashion to receive either 150-mg alirocumab or placebo, administered biweekly via subcutaneous injection for 52 weeks.²⁰ The first dose of the study drug was administered within 24 h after percutaneous coronary intervention, without dose adjustment during the study period. Intra-coronary imaging with the combined NIRS-IVUS catheter and OCT were performed in at least two proximal non-IRAs at baseline. At week 52, patients underwent a second intra-coronary imaging in the identical localization of the same arteries, using identical catheter types. For IVUS, lumen and external elastic membrane were analysed every 1 mm in matched regions of interest. For NIRS, identical regions of interest as those used for IVUS analyses were analysed and the 4-mm segment with maximum lipid core burden index (LCBI) was identified. OCT recordings were analysed every 0.4 mm within the matched regions of interest and FCT was measured using a validated, semi-quantitative method.

The primary IVUS-derived efficacy measure was change in PAV at 52 weeks; normalized TAV was the secondary IVUS efficacy measure. The main NIRS efficacy parameter was maximum LCBI within 4 mm; an additional secondary measure was total LCBI within the entire imaged regions. The main OCT efficacy measure was minimal FCT.²⁰

At week 52, the mean LDL-C level was 74.4 mg/dL in the placebo group and 23.6 mg/dL in the alirocumab group ($P < 0.001$). Patients receiving alirocumab also demonstrated significantly greater reductions in triglycerides, lipoprotein(a), and apolipoprotein B.

The primary efficacy end point, change in mean PAV from baseline, showed significantly greater reduction in the alirocumab group compared with the placebo group

(-2.13% [95% CI, -2.53% to -1.73%] vs. -0.92% [95% CI, -1.28% to -0.56%]; between-group difference, -1.21% [95% CI, -1.78% to -0.65%]; $P < 0.001$). Favourable changes were also observed for the powered secondary end points, including a greater reduction in lipid burden, assessed by NIRS, and greater increase in minimal FCT, assessed by OCT (Figure 4). These qualitative and quantitative changes in coronary plaque characteristics were directly related with LDL-C levels (Figure 5). Taken together, PCSK9 inhibition initiated early in the acute setting of AMI produced incremental benefits on coronary plaque evolution, composition, and phenotype compared with the favourable effects of intensive statin therapy alone.²⁰

Conclusions

PCSK9i have now been demonstrated to be valuable additions to the physicians' dyslipidaemia therapy arsenal. These medications cut plasma LDL-C levels by around 60%, greatly reduce the risk of severe vascular events, and have no adverse effects save injection-site responses.

Patients with a high burden of ASCVD are at a higher risk of major vascular events and benefit more from PCSK9 treatment in terms of relative and/or absolute risk reductions. The therapeutic effect shown in trials of PCSK9 inhibition was associated with plasma LDL-C levels below 20 mg/dL, suggesting that more aggressive LDL-C targets should be established.

Recent findings of the PACMAN-AMI trial indicate an incremental coronary plaque regression, lipid core reduction, and plaque stabilization with PCSK9i and provide a mechanistic rationale in favour of early initiation of very intensive LDL-C lowering, including PCSK9i, in ACS patients.

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Data availability

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

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