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PCSK9 INHIBITION EARLY AFTER AN ACUTE CORONARY SYNDROME: RATIONALE AND CLINICAL EVIDENCE

Clinical Question

Early (in-hospital) initiation of PCSK9 inhibitor therapy in patients with acute coronary syndrome may provide additional clinical benefit when used on top of statin treatment.

DOCUMENT PURPOSE

To outline the current guideline recommendations regarding low-density lipoprotein cholesterol (LDL-C) targets in patients with acute coronary syndrome (ACS); the role of proprotein convertase subtilisin/kexin type 9 (PCSK9) and the rationale for its inhibition in ACS; and the expected clinical impact of PCSK9 inhibitors in the acute phase of ACS.

1.0 Introduction

ACS represents a group of **potentially life-threatening conditions that are associated with high morbidity and mortality** despite recent advances in treatment. ACS is classified into the following categories: **ST-elevation myocardial infarction** (STEMI) and **non-ST-elevation ACS** which can be further subdivided into unstable angina and non-ST segment elevation myocardial infarction (NSTEMI). The related healthcare costs are substantial because re-hospitalisations for repeated cardiac events are common.[1-3]

LDL-C is well established as a major cardiovascular (CV) risk factor. Accumulating evidence supports a **linear association between reductions in LDL-C levels and CV risk** in patients with atherosclerotic CV disease (**Figure 1**).[4-6] Therefore LDL-C reduction is an important treatment target in all relevant CV risk management guidelines.

PCSK9 inhibitors are a recently introduced, highly effective LDL-C lowering treatment which when used in addition to statin and/or ezetimibe treatment early after ACS, may achieve very low levels of LDL-C and further improve clinical outcomes.

Figure 1. Association between LDL-C and major CV events

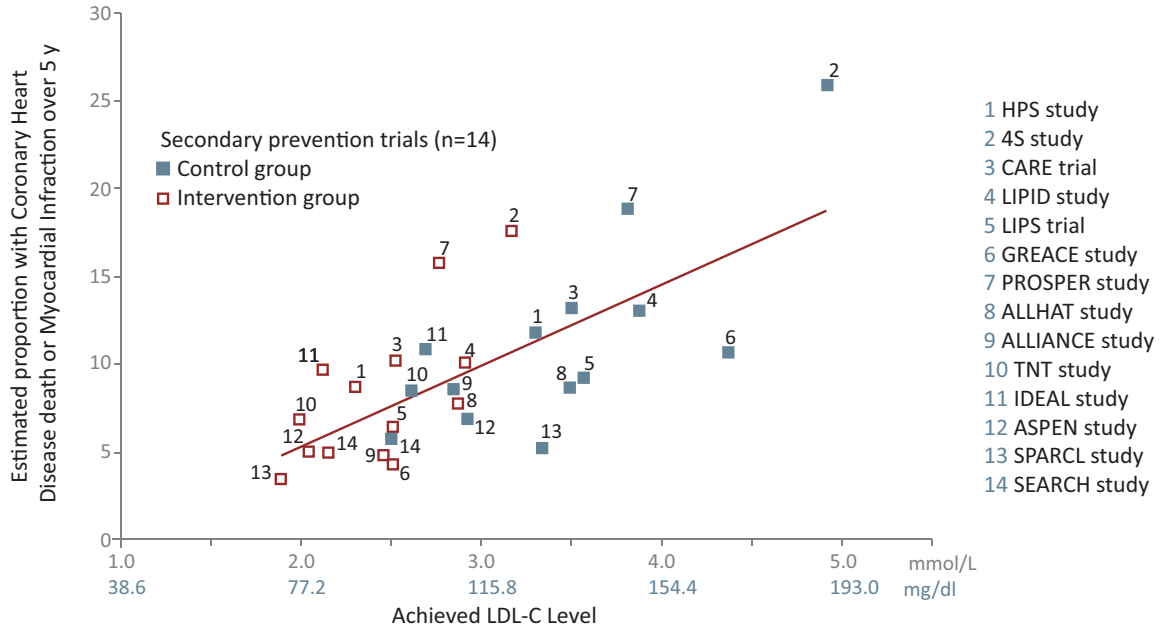


Figure adapted from Silverman et al, 2016.[5]

2.0 Current approaches to the management of LDL-C in ACS Patients

The acute management of ACS recommended by current European (European Society of Cardiology [ESC]) and US American College of Cardiology/American Heart Association [ACC/AHA]) guidelines[7-9] comprises revascularisation procedures such as percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) as well as antithrombotic medication and lipid-lowering therapies. After hospital discharge, lifestyle interventions (e.g. smoking cessation, exercise, healthy diet) are combined with **managing risk factors such as hypertension, diabetes and dyslipidaemia.**[7,8,10]

ACC/AHA guidelines[9] recommend high-intensity statin therapy in patients with clinical atherosclerotic CV disease (ASCVD) to **reduce LDL-C levels by ≥50%**, and in combination with ezetimibe, if necessary, to achieve a target LDL-C level <70 mg/dL (<1.8 mmol/L) for very-high-risk ASCVD patients. The 2017 ESC STEMI guidelines[7] recommend the same targets.

Target LDL-C levels are even lower in the 2020 ESC guidelines for the management of ACS in patients presenting without persistent ST-segment elevation:[8] it is recommended to reduce LDL-C levels by ≥50%, with a **target level <55 mg/dL (<1.4 mmol/L)** using high intensity statin therapy, in combination with ezetimibe, if necessary. In patients who have experienced several ischaemic events, the target is <40 mg/dL (<1.0 mmol/L).

In patients who do not reach these LDL-C targets despite maximal tolerated statin and ezetimibe therapy within 4-6 weeks after discharge, **addition of a PCSK9 inhibitor is recommended**.

However, in clinical practice only a minority of patients at high or very high-risk of CV events[11] achieve recommended LDL-C target levels (22-45% in a recent EU-wide cross-sectional observational study).[11-13]

3.0 The Role of PCSK9 inhibition in LDL-C reduction

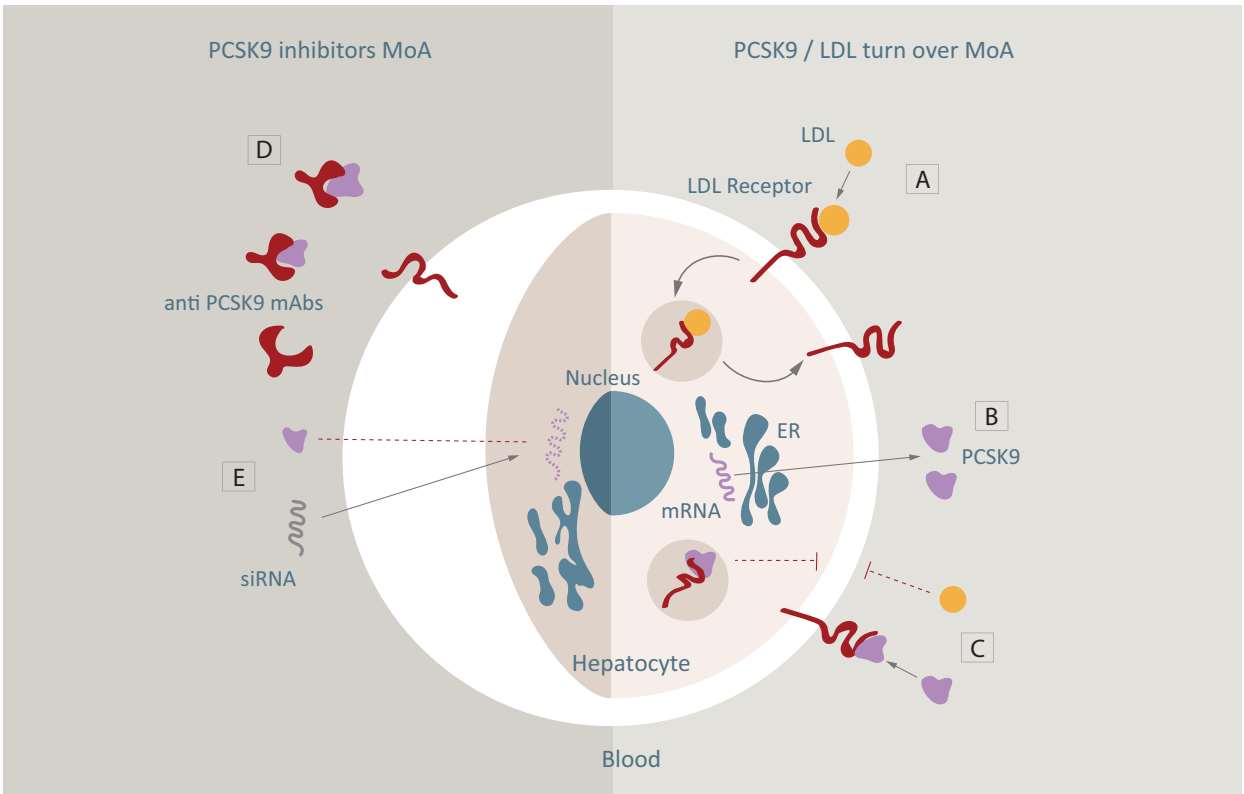
PCSK9 inhibition is a relatively new approach to reducing LDL-C levels. Whereas statins inhibit cholesterol synthesis in the liver and ezetimibe reduces LDL-C absorption from the small intestine, **PCSK9 inhibitors increase LDL-C uptake by the liver**, reducing LDL-C concentrations in the blood.

PCSK9 is a proprotein convertase enzyme involved in the degradation of LDL receptors on the surface of hepatic cells. Blocking PCSK9 increases the number of receptors allowing more LDL-C to be absorbed by the liver.

There are currently two strategies to inhibit PCSK9 activity (**Figure 2**) with differing mechanisms of action:

1. **Monoclonal antibodies (mAb's)** which bind to and inactivate PCSK9 in the blood[14]
2. **Small interfering RNA (siRNA)** molecules that suppress the synthesis of PCSK9 by binding to the messenger RNA, which is then degraded in the hepatic cell[15]

Figure 2. Mechanism of action of different PCSK9 Inhibitors



(A) In the absence of PCSK9, the LDL receptor is recirculated to the cell surface after carrying LDL into lysosomes. (B) PCSK9 is produced by the liver and enters the circulation. (C) When PCSK9 binds to the LDL receptor, it undergoes lysosomal degradation and is not recirculated to the cell surface, thereby preventing uptake of LDL (dashed lines). (D) Monoclonal antibodies to PCSK9 act by binding to PCSK9, thereby removing it from the circulation and preventing binding of PCSK9 to the LDL receptor (dashed line). (E) siRNAs act by degrading mRNA, thereby reducing PCSK9 release to the circulation (dashed line). ER, endoplasmic reticulum; mAb, monoclonal antibody. Adapted from Preiss et al, 2017.[16]

In early 2015, the monoclonal antibodies evolocumab and alirocumab were approved in the EU, the US, China, and Japan. The siRNA molecule inclisiran was approved in the EU in December 2020 and is currently awaiting approval in the US.

PCSK9 inhibitors are administered by subcutaneous injection; the mAb's, alirocumab and evolocumab, every 2-4 weeks, and the siRNA, inclisiran, at six-monthly intervals.

All currently available PCSK9 inhibitors achieve strong reductions in LDL-C levels beyond those achievable with conventional lipid-lowering therapies. However, to date only the mAb's alirocumab and evolocumab have also demonstrated CV risk reduction (**Section 4.0**).

Alirocumab has been shown to reduce LDL-C levels by 45-62%, and evolocumab has been shown to lower LDL-C levels by 55-75% when added to background statin treatment (**Table 1**).[17-20] For inclisiran, a meta-analysis indicates a 51% reduction in LDL-C levels in patients who do not reach treatment targets with maximum tolerated statin therapy.[21] These numbers compare favourably with the 10-20% additional reductions from ezetimibe when combined with statins (**Figure 3**).[22,23] PCSK9 inhibition has also been shown to be effective in patients with statin intolerance.[25-27]

A systematic review has estimated that, with the addition of PCSK9 inhibitors to conventional therapy, it is possible to achieve recommended LDL-C targets in about 90% of patients with hypercholesterolaemia.[23]

4.0 PCSK9 Inhibition and CV Risk Reduction

Randomised controlled double-blind trials have demonstrated **a reduction in CV endpoints** with alirocumab and evolocumab (**Table 2**).[17-20] Inclisiran has not yet reported a reduction in CV endpoints but this is currently under evaluation in the ORION-4 trial (NCT03705234) which is estimated to report at the end of 2024.

Specifically, in patients with a history of ACS, there is evidence of an **additional reduction in CV risk when PCSK9 inhibitors are administered on top of statin therapy** (**Table 2**):

- In the FOURIER trial[19] 80.9% of patients had a history of myocardial infarction (MI). The median duration of follow-up was 2.2 years. With evolocumab there was a 15% reduction in the risk of CV death, MI, stroke, hospitalisation for unstable angina, or coronary revascularisation. **The secondary endpoint of CV death, MI, and stroke was reduced by 20%**

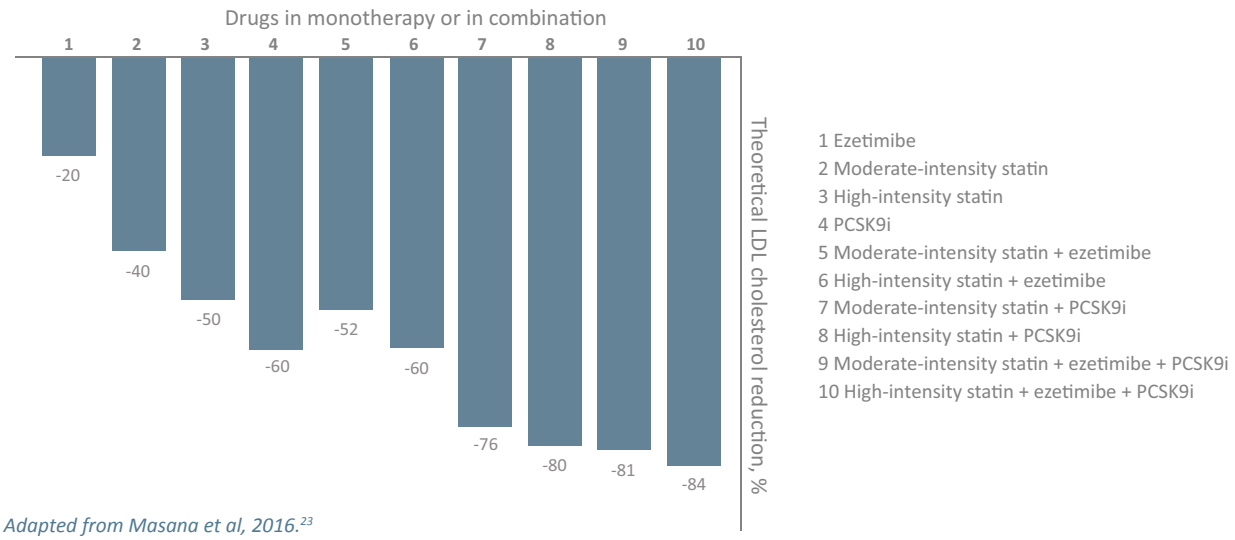
Table 1. Percentage reduction in plasma LDL-C with different PCSK9 inhibitors

	Per cent reduction in plasma LDL-C (%)[a]		
	Monotherapy	**Added to statin therapy**	**Statin-intolerant patients**
High-intensity statin	50-60	ND	ND
Ezetimibe	20-25	20-25[22]	15[24]
PCSK9 inhibitor			
Evolocumab 140 mg every 2 weeks or 420 mg monthly	55-57	63-75	55-56
Alirocumab 150 mg every 2 weeks	ND	62	45[b]
Alirocumab 300 mg every 4 weeks	59	56	ND
Inclisiran	50	52[21]	ND

Adapted from Sabatine, 2019.[14]

[a] Not based on head-to-head studies; [b] 75 mg every 2 weeks, increased to 150 if LDL-C levels ≥70 mg/dL (≥1.8 mmol/L); ND, no data

Figure 3. Theoretical percentage reduction in LDL-C



Adapted from Masana et al, 2016.[23]

Table 2. CV outcomes trials with PCSK9 inhibitors

Trial name and reference	PCSK9 inhibitors	Number of patients	Patient profile	Baseline LDL- C level mg/dL (mmol/L)	Mean absolute reduction in plasma LDL-C level mg/dL (mmol/L)	Mean percent reduction in plasma LDL-C level (%)	Median follow-up	Key results
FOURIER[19]	Evolocumab	27,564	Patients with MI, stroke or peripheral artery disease	92 (2.38)	56 (1.44) at 48 weeks	59	2.2 years	15% reduction in CV death, MI, stroke, hospitalisation for unstable angina or coronary revascularisation 20% reduction in the secondary endpoint of CV death, MI and stroke.
ODYSSEY Outcomes[20]	Alirocumab	18,924	Patients with history of ACS	92 (2.38)	53 (1.37) at 48 weeks	54.7	2.8 years	15% reduction in CHD death, MI, ischaemic stroke or hospitalisation for unstable angina 14% reduction in CV death, MI or stroke
ODYSSEY Long-term[18]	Alirocumab	2,341	Patients with familial hypercholesterolaemia or with established CHD or CHD equivalent	122 (3.15)	74 (1.91) at 24 weeks	61.9	1.5 years[a]	48% reduction in death from CHD, nonfatal MI, fatal or nonfatal ischaemic stroke, or unstable angina requiring hospitalisation[b]
OSLER-extension[17]	Evolocumab	4,465	Varying characteristics[c]	120 (3.10)	70.5 (1.82) at 48 weeks	58.4	0.93 years	53% reduction in major adverse CV events (death, coronary events, cerebrovascular events or heart failure requiring hospitalisation)

[a] Mean; [b] Post-hoc analysis; [c] The trials included patients with familial hypercholesterolaemia; patients with elevated LDL-C while on statin or with LDL-C ≥100 mg/dL (≥2.6 mmol/L) not on statins, and statin-intolerant patients

- In the ODYSSEY-OUTCOMES trial[20] the median duration of follow-up was 2.8 years. Alirocumab administered between 1 to 12 months after index ACS reduced the risk of death from coronary heart disease, nonfatal MI, fatal or nonfatal ischaemic stroke, or unstable angina requiring hospitalisation by 15%. **The endpoint of CV death, MI and stroke was reduced by 14%**

The cost-effectiveness of reducing CV risk in ACS patients with PCSK9 inhibition is a consideration in clinical practice. A number of analyses have addressed the issue for different patient and reimbursement conditions, with the greatest cost-effectiveness typically found among patients with the highest LDL-C levels at baseline.[28-34]

5.0 Early Reduction of LDL-C with PCSK9 inhibition post-ACS

ACS patients are at increased risk of recurrent ischemic events, particularly during the early period following the index event[35] but many of them do not reach recommended LDL-C treatment targets.[36]

Several meta analyses[37-39] and a recent randomised trial[38] have shown that high-dose statin treatment before PCI in patients with STEMI, NSTE-ACS or stable angina can reduce the risk of periprocedural MI within 30 days. However, more studies are needed to confirm the benefits as not all available studies agree on this outcome,[41] and long-term data are lacking.

Although data are still relatively limited, several studies have shown very early reduction of LDL-C levels with evolocumab in the acute phase of ACS:

- In the EVACS trial, NSTE-ACS patients received evolocumab on top of high-intensity statin therapy within 24 hours of presentation. **LDL-C levels started to decrease within 24 hours** and were lower than with placebo after three days (46% reduction with evolocumab vs 12% reduction with placebo).[42]
- In the EVOPACS trial, patients with NSTE-ACS or STEMI received evolocumab in-hospital (within 72 hours of symptom onset) and after 4 weeks, on top of statin therapy. This experimental strategy reduced LDL-C levels by 77% as early as within 4 weeks and brought **>95 % of patients to target levels within 8 weeks.**[35]

A number of ongoing trials will provide further evidence (**Table 3**) to support the early reduction of LDL-C with evolocumab and potentially alirocumab. Presently, there are no ongoing trials exploring inclisiran in the acute phase of ACS.

Table 3. Ongoing and planned trials of PCSK9 inhibitors in the acute ACS setting

Study name (NTC number)	Description	Number of patients	Estimated completion date
EVACS II (NCT04082442)	Evolocumab administered during early hospitalisation in STEMI patients	100	Late 2021
EPIC STEMI (NCT03718286)	Alirocumab administered to STEMI patients before they undergo a revascularisation procedure	100	Mid-2021
PACMAN-AMI (NCT03067844)	Effects of alirocumab in patients with NSTE-ACS or STEMI undergoing PCI	294	Late 2021
EMSIACS (NCT04100434)	Effects of evolocumab in ACS patients	500	Mid-2023
AMUNDSEN REAL (https://www.action-groupe.org/en/etude/amundsen-action)	Planned randomised real-world study in NSTE-ACS and STEMI patients who will receive evolocumab before undergoing PCI	1,660	Late 2023

6.0 Safety of PCSK9 inhibition

Current evidence has not supported earlier safety concerns around achieving very low LDL-C levels (<30 mg/dL; the median in the FOURIER trial).[43-45] Large scale trials also support the **good safety profile** of PCSK9 inhibition.

- In the FOURIER and ODYSSEY OUTCOMES trials, which together included >45,000 patients, evolocumab and alirocumab demonstrated very favourable safety profiles (**Table 4**). PCSK9 inhibition showed **similar rates to placebo** for relevant side effects such as muscle-related events, incidence of cataract, neurocognitive adverse events, or haemorrhagic stroke[19,20]
- For all PCSK9 inhibitors, there seems to be slightly more injection-site reactions than with placebo, but most of these are mild[46]

The findings are supported by specific analyses[47] and real-world evidence.[48,49]

The long term safety of evolocumab is being evaluated in the FOURIER open label extension trial (NCT03080935) which is due to complete late 2021.

7.0 Additional benefits of PCSK9 inhibition

There are data supporting the benefits of PCSK9 inhibition on **slowing the progression of coronary atherosclerosis;** these benefits are related to the additional effect on LDL-C levels on top of statins.

The GLAGOV trial reported a significant reduction in percent atheroma volume (indicating atherosclerosis regression) when evolocumab was added to statin therapy over 18 months in subjects with coronary disease.[50]

The ODYSSEY J-IVUS study found that alirocumab (non-significantly) reduced atheroma volume in patients hospitalised for ACS and inadequately controlled with statin therapy.[51]

8.0 Summary

PCSK9 inhibition can powerfully and rapidly reduce LDL-C levels, and therefore there may be a case for initiation of PCSK9 inhibition therapy during the acute in-hospital phase of ACS. Whether intensive LDL-C reduction with PCSK9 inhibitors early after ACS will translate into better clinical outcomes requires further studies.

Table 4. Rates of adverse events in the outcomes trials with PCSK9 inhibitors in ACS patients

	Adverse event rate (%)			
	FOURIER[19]		ODYSSEY Outcomes[20]	
	Evolocumab	Placebo	Alirocumab	Placebo
AEs thought to be related to the study agent and leading to discontinuation	1.6	1.5	N/A	N/A
AEs leading to discontinuation	N/A	N/A	3.6	3.4
Injection-site reaction	2.1	1.6	3.8	2.1
Allergic reaction	3.1	2.9	7.9	7.8
Muscle-related event	5.0	4.8	N/A	N/A
Rhabdomyolysis	0.1	0.1	N/A	N/A
Cataract	1.7	1.8	1.3	1.4
Adjudicated new-onset diabetes	8.1	7.7	9.6	10.1
Diabetes worsening or diabetic complication among patients with diabetes at baseline	N/A	N/A	18.8	21.2
Hepatic disorder	N/A	N/A	5.3	5.7
Neurocognitive event	1.6	1.5	1.5	1.8
Adjudicated haemorrhagic stroke	N/A	N/A	<0.1	0.2

N/A, not available

Glossary

Acute coronary syndrome(s) (ACS), broadly defined class of acute conditions ranging from cardiac arrest, or electrical or haemodynamic instability with cardiogenic shock to patients who are already pain-free again at the time of presentation. Important ACS events include NSTE-ACS and STEMI.

Coronary artery bypass grafting (CABG), procedure to bypass native coronary arteries that have high-grade stenosis or occlusion by grafting the left internal mammary artery or segments of saphenous vein to the coronary artery.

Low-density lipoprotein cholesterol (LDL-C), cholesterol transported in the circulation by low-density lipoprotein, the elevation of which is directly related to the risk of coronary artery disease and cholesterol-related morbidity

Non-ST-segment elevation ACS (NSTE-ACS), term comprising non-ST-segment elevation myocardial infarction (NSTEMI) and unstable angina

Percutaneous coronary intervention (PCI), the opening of narrowed or blocked coronary arteries by means of balloon angioplasty (with or without placement of stents), atherectomy (arterial plaque removal), or other techniques involving use of a catheter

Proprotein convertase subtilisin/kexin type 9 (PCSK9), enzyme which binds to the receptor for LDL-C on liver and other cell membranes, assisting in their breakdown and reducing the ingestion of LDL-particles from extracellular fluid into cells

RNA (ribonucleic acid), nucleic acid generally composed of a single polynucleotide strain of ribonucleotides, which is found in cells of both prokaryotes and eukaryotes. RNA is a vital component of protein synthesis

ST-elevation myocardial infarction (STEMI), patients presenting with acute chest pain and persistent (>20 min) ST-segment elevation, generally reflecting an acute total or subtotal coronary occlusion.

Abbreviations

ACS	Acute coronary syndromes	**MI**	Myocardial infarction
ACC	American College of Cardiology	**MoA**	Mechanism of action
AHA	American Heart Association	**NSTE-ACS**	Non-ST-segment elevation ACS
ASCVD	Atherosclerotic cardiovascular disease	**NSTEMI**	Non-ST-segment elevation myocardial infarction
CABG	Coronary artery bypass graft	**PCI**	Percutaneous coronary intervention
CV	Cardiovascular	**PCSK9**	Proprotein convertase subtilisin/kexin type 9
ESC	European Society of Cardiology	**RNA**	Ribonucleic acid
LDL	Low-density lipoprotein	**siRNA**	Small interfering RNA
LDL-C	Low-density lipoprotein cholesterol	**STEMI**	ST-segment elevation myocardial infarction
mAb	Monoclonal antibody		

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