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Pharmacological rationale for the very early treatment of acute coronary syndrome with monoclonal antibodies anti-PCSK9

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ABSTRACT

Immediate and aggressive lipid lowering therapies after acute coronary syndromes (ACS) and percutaneous coronary interventions (PCI) are supported by the ESC/EAS dyslipidemia guidelines, recommending the initiation of high-intensity statin therapy within the first 1–4 days of hospitalization. However, whether non statin lipid-lowering agents, added to statin treatment, could produce a further reduction in the risk of major adverse cardiovascular events (MACE) is still unknown. Thus, the efficacy of early treatment post-ACS with monoclonal antibodies (mAbs) anti PCSK9, evolocumab and alirocumab, is under investigation. The rationale to explore the rapid and aggressive pharmacological intervention with PCSK9 mAbs is supported by at least five confirmatory data in ACS: 1) circulating PCSK9 levels are raised during ACS 2) PCSK9 may stimulate platelet reactivity, this last being pivotal in the recurrence of ischemic events; 3) PCSK9 is associated with intraplaque inflammation, macrophage activation and endothelial dysfunction; 4) PCSK9 concentrations are associated with inflammation in the acute phase of ACS; and 5) statins raise PCSK9 levels promptly and, at times, dramatically. In this scenario, appropriate pharmacodynamic characteristics of anti PCSK9 therapies are a prerequisite for an effective response. Monoclonal antibodies act on circulating PCSK9 with a direct and rapid binding by blocking the interaction with the low-density lipoprotein receptor (LDLR). Evolocumab and alirocumab show a very rapid (within 4 h) and effective suppression of circulating unbound PCSK9 (− 95 % ÷ − 97 %). This inhibition results in a significant reduction of LDL-cholesterol (LDL-C) after 48 h (− 35 %) post injection with a full effect after 7–10 days (55–75 %). The complete and swift inhibitory action by evolocumab and alirocumab could have a potential clinical impact in ACS patients, also considering their potential inhibition of PCSK9 within the atherosclerotic plaque. Thus, administration of evolocumab or alirocumab is effective in lowering LDL-C levels in ACS, although the efficacy to prevent further cardiovascular (CV) events is still undetermined. The answer to this question will be provided by the ongoing clinical trials with evolocumab and alirocumab in ACS. In the present review we will discuss the pharmacological and biological rationale supporting the potential use of PCSK9 mAbs in ACS patients and the emerging evidence of evolocumab and alirocumab treatment in this clinical setting.

1. Introduction

Acute coronary syndrome (ACS) is an operational term that refers to a spectrum of conditions compatible with acute myocardial ischemia and/or infarction that are usually due to an abrupt reduction in coronary blood flow [1]. As early as 10–15 min after the onset of ischemia, cellular glycogen reduction, myofibrils relaxation, sarcolemmal disruption, and mitochondrial abnormalities are observed. Patient's history, symptoms and electrocardiogram alterations contribute to confirm the diagnosis [2].

Regarding the biochemical alterations that may occurs during the myocardial infarction (MI), already in 1971, Fyfe et al. observed an apparent decreases in total cholesterol during hospitalization of patients with an ACS [3]. Since then, a variety of reports indicated relevant alterations in serum lipids associated to ACS. In some patients a significant reduction (18 % ÷ 53 %) of low-density lipoprotein cholesterol (LDL-C) levels was observed between day 1 and days 7 post-MI, while in others it was reported an LDL-C increased by 13–32 % [4]. The reason for these changes can be related to the acute phase response to MI [5,6], increase of whole body cholesterol biosynthesis as judged by the lathosterol/cholesterol ratio [7] and reduction in the expression of high-density lipoprotein (HDL) regulatory proteins [8,9]. In addition, myocardial injury and necrosis facilitate adrenergic mediated adipocyte lipolysis leading to free fatty acid mobilization, increase hepatic very-low-density lipoprotein (VLDL) secretion, triglyceride (TG) elevation, and alteration in LDL and HDL particle composition [10,11].

More recently, the LUNAR (Limiting UNdertreatment of lipids in ACS with Rosuvastatin) trial evaluated lipid levels in adults hospitalized for acute ST-segment elevation myocardial infarction (STEMI), non-STEMI, or unstable angina (UA) [12]. This prospective study, that compared the efficacy of LDL-C lowering with 2 different statins (rosuvastatin and atorvastatin) after hospitalization, observed that lipid levels remain relatively stable during the first 96 h after ACS [12]. Since the alteration in lipid parameter seems due to the extent and severity of myocardial necrosis [3], the exclusion of complicated patients (*e.g.*, type 3/4 MI, ventricular dysrhythmia) in the LUNAR trial probably underestimated the potentially greater lipid alterations that may have otherwise resulted with their inclusion. Indeed, it is not surprising that older studies, especially those performed in the pre-thrombolytic and pre-PCI era [3,13,14], were associated with bigger lipid effects after ACS compared with more recent ones [15,16]. Very recent observations indicated that cardiac ischemia during ACS may drive up the levels of PCSK9

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(Proprotein Convertase Subtilisin/Kexin type 9) [17,18], a pivotal regulator of LDL-C levels as well as with relevant biological actions that may contribute to plaque vulnerability in coronary vessels. This increase was similar between patients with STEMI and NSTEMI [18].

2. Pathogenesis of ACS: role of PCSK9 from thrombosis to inflammation

As previously indicated, the main biological function of PCSK9 is the degradation of the LDL receptor (LDLR) in hepatocytes, thus leading to lower LDL-C uptake by the liver [19]. PCSK9 is transcriptionally regulated by the sterol regulatory element binding proteins (SREBP) and by the hepatocyte nuclear factor 1α (HNF1α) [20–23]. Thus, in response to cell cholesterol depletion or inhibition of sterol intracellular synthesis (*i.e.,* by statins) PCSK9 promoter activity is induced, determining an increase of PCSK9 transcription, and circulating levels [24–26].

In humans, plasma levels of PCSK9 vary over a very wide range (~100-fold) among normal, apparently healthy individuals, from a minimum of 20.1 ng/ml to 1133.9 ng/ml [27]. Higher median levels are found in women (331 ± 105 ng/ml) *vs* men (290 ± 109 ng/ml) [27]. A significant proportion of circulating PCSK9 (30 %) is associated with lipoproteins, LDL and lipoprotein (a) [Lp(a)] [28–32]. The mature (62 kDa) and furin-cleaved (55 kDa) forms are both present in the circulation [33], and mass spectrometry analysis reported a total mean PCSK9 concentration of 309 ± 126 ng/ml (mean ± SD), 30 % of which in the cleaved form [34]. Tissue distribution analysis in adulthood and during ontogeny in mouse and rat revealed that PCSK9 mRNAs are mainly expressed in the liver but also in other tissues including kidney, small intestine, cerebellum, and arteries [35–37]. The half-life for plasma PCSK9 has been recently determined in mice and was found to be equal to 15.6 h [38].

The potential role of PCSK9 in ACS has been raised from the determination of its plasma levels in CVD patients. Indeed, raised circulating PCSK9 levels have been directly associated with platelet reactivity, with a significant increase in the highest *vs* lowest tertile of PCSK9 levels [39]. In the upper tertile 22 % of the patients experienced major adverse cardiovascular events (MACE) at one year, *vs* 3.4 % in the lowest tertile [39]. This study revealed that at one-year follow-up, PCSK9 was independently associated with increased ischemic MACEs [39]. These findings suggest that higher PCSK9 levels are associated with platelet reactivity, this being a possible predictor of ischemic events in ACS patients undergoing PCI [39].

In line with the clinical data, human recombinant PCSK9 added to platelet-rich plasma significantly enhanced platelet aggregation induced by subthreshold concentrations of epinephrine (Fig. 1) [40]. Additionally, loss of PCSK9 reduced the formation and stability of arterial thrombus and platelet function in mice [40]. Very similar results were obtained by another research group, documenting how the PCSK9 enhanced *in vivo* thrombosis in a $FeCl_3$-injured mesenteric arteriole thrombosis mouse model [41], effect that was partially blocked by evolocumab [41].

Mechanistic studies have revealed that PCSK9 binds to platelet CD36 and activates Src kinase, MAPK (mitogen-activated protein kinase)-ERK5 (extracellular signal-regulated kinase 5), and JNK (c-Jun N-terminal kinase). Activation determines a raised generation of reactive oxygen species as well as activation of the cytosolic phospholipase A2/cyclooxygenase 1/thromboxane A2 (PLA2/COX1/TXA2) signaling pathways downstream of CD36 to enhance platelet aggregability (Fig. 1) [41]. Finally, PCSK9 enhances MI expansion post-MI in a CD36-dependent manner [41]. These results suggest that PCSK9 contributes to platelet hyperactivity, *in vivo* thrombosis, and worsened heart function post-MI.

Additional data indicate that platelet activation and *in vivo* thrombosis is antagonized by both evolocumab and alirocumab [42]. Indeed, anti-PCSK9 mAbs significantly decreased platelet aggregation detected in platelet-rich plasma and in whole blood platelet from

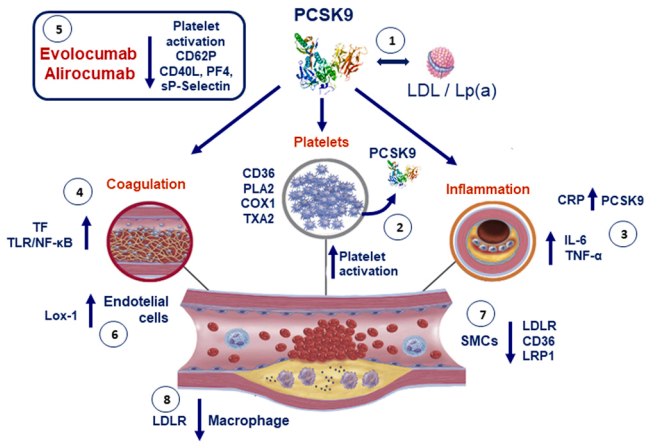

Fig. 1. Schematic representation of the potential direct involvement of PCSK9 in ACS. 1) PCSK9 is present in the systemic circulation in free form and bound to lipoproteins [LDL and Lp(a)]; in bound form it could accumulate in the atherosclerotic plaque, affecting its composition. 2) PCSK9 induces platelet aggregation by interacting with CD36 and activating the PLA2/COX1/TXA2 pathway. PCSK9 in present in platelets and it is release in response to CRP and other proinflammatory cytokines. 3) PCSK9 itself can stimulate the release of IL-6 and TNFα from macrophages. 4) PCSK9 acts positively also on coagulation by inducing the expression of tissue factor (TF) through the toll-like receptor (TLR) nuclear factor kappa B (NF-κB) pathway. 5) The effect on platelet activation is inhibited by the monoclonal antibodies evolocumab and alirocumab. This activity action correlates with reduced levels of CD40L, PF4, soluble P-Selectin and expression of CD62P. 6) PCSK9 induces the expression of lectin-like oxidized LDL receptor-1 (LOX-1), the primary scavenger receptor for oxidized LDL (oxLDL) on endothelial cells. PCSK9 is present in atherosclerotic plaques and is expressed by SMCs. 7) PCSK9 modulates the proliferation and migration of SMCs and the expression of surface receptors, such as LDLR, LDL receptor-related protein 1 (LRP1) and CD36. 8) PCSK9 released from these cells directly affects the expression of LDLR on macrophages.

hypercholesterolemic patients (Fig. 1) [42]. This effect is associated, and potentially due to, a decreased platelet membrane expression of CD62P and plasma levels of the *in vivo* platelet activation markers soluble CD40 Ligand (CD40L), Platelet Factor-4 (PF-4), and soluble P-Selectin [42].

Inflammation may also contribute to the effect of PCSK9 on platelet function. For instance, C reactive protein (CRP) has been found to induce surface expression of PCSK9 in platelets, that is then released in a cleaved form of 53 kDa at the concentration of 500 pg/ml per 300,000 plt/μl (Fig. 1) [43]. In a subgroup of patients (n = 100) with coronary artery disease, platelet PCSK9 correlated with CD62P surface expression both on non-activated and *ex vivo* CRP-stimulated platelets [43]. Even more intriguingly, monoclonal antibodies anti PCSK9 attenuated the ADP- and CRP-induced platelet aggregation and thrombus formation [43]. Thus, the release of platelet derived PCSK9 is a prominent prothrombotic factor, that augments thrombus formation under flow.

The same platelet derived PCSK9 has been found to induce monocyte migration, and differentiation into macrophages/foam cells [43]. A direct pro-inflammatory action of PCSK9 in macrophages has been also shown and found to be dependent from the LDLR [44]. PCSK9 enhances the release of pro-inflammatory cytokines IL-6 and TNF-α, the latter being directly correlates with PCSK9 plasma levels in humans [44].

The two players, platelets and PCSK9, were shown to accumulate in atherosclerotic carotid arteries in areas occupied by macrophages [45,46]. The pro-inflammatory cytokine TNFα, locally released mainly by this immune cell, enhances PCSK9 expression in vascular endothelial cells and smooth muscle cells [47]. In patients with myocardial ischemia, especially in the acute phase, there is a massive release of pro-inflammatory cytokines, including hsCRP, TNFα, IL-6, IL-1β, sLOX-1, and others [47,48]. Thus, the inflammatory status observed in

ACS may be the trigger of increased PCSK9 levels observed in this clinical setting [17,18]. Further, PCSK9 affects the coagulation cascade by increasing the expression of procoagulant tissue factor (TF) expression in peripheral blood mononuclear cells through the toll-like receptor (TLR)/NF-kB pathway (Fig. 1) [49].

Taken together, considering the emerging role of PCSK9 as a player in platelet reactivity, thrombus formation, MI expansion and inflammation, its pharmacological inhibition may exert significant beneficial effects in ACS.

3. Mechanism of action of mAbs anti PCSK9

Evolocumab and alirocumab are human mAbs directed against human PCSK9 [50]. *In vitro*, evolocumab binds PCSK9 with high affinity, with equilibrium dissociation constants of 4, 4, and 160 pM, for human, cynomolgus, and mouse PCSK9, respectively [50]. Evolocumab sterically hinders binding of PCSK9 to the LDLR, with a 50 % inhibitory concentration (IC_{50}) of 2.08 ± 1.21 nM [50]. Evolocumab alone increases the LDLR expression in cultured hepatocytes (HepG2), this effect is significantly higher in combination with statins [50]. Thus, the binding of evolocumab to PCSK9 inhibits circulating PCSK9 from interacting with the LDLR, preventing PCSK9-mediated LDLR degradation and allowing the LDLR to recycle back to the liver cell surface with higher efficiency.

Single subcutaneous (s.c.) administration of evolocumab in healthy volunteers determined a complete decrease of unbound PCSK9, more than 97 %, within 15 min after injection; inhibition that remained at this level through 3 days, and then gradually returned to baseline by 14 days (Fig. 2).

Evolocumab 140 mg or 420 mg shows a maximum suppression of circulating unbound PCSK9 within 4 h post-injection [51]. Unbound PCSK9 concentrations returned toward baseline when evolocumab concentrations went below the limit of quantitation. No increase in PCSK9 above baseline was observed during washout. This inhibition resulted in a significant reduction of LDL-C after 24–48 h (− 30 %) [52], with a peak at 14 and 21 days, for 140 mg or 420 mg, respectively [51].

The effect of baseline PCSK9 on reductions in LDL-C were evaluated using pooled data from four phase III randomized clinical studies [53]. Across all quartiles of baseline PCSK9 concentrations, evolocumab 140 mg Q2W and 420 mg QM suppressed circulating free PCSK9 levels by 90–100 % within 1 week of administration. Regardless of baseline PCSK9, both evolocumab 140 mg Q2W and 420 mg QM were associated with significant and consistent reductions in LDL-C [53].

A very similar pharmacodynamic effect was observed with alirocumab with a maximal reduction of mean free PCSK9 observed between day 3 and day 4 after *s.c.* injection, but already evident few hours post injection [54]. After this suppression, serum concentrations of free PCSK9 started to gradually increase after 15 days and returned within the baseline range at 30 days. From the pharmacodynamic point of view, LDL-C declined reaching a nadir on day 15 [54]. At this time point, the percentage decrease in LDL-C was approximately 50 % after 15 days, associated to a significant reduction of ApoB and non-HDL-C. Interestingly, in patients under chronic treatment with both evolocumab and alirocumab a massive increase (3 ÷ 7 fold) of total PCSK9 plasma levels has been reported [55]. This effect is due to the reduced clearance of PCSK9 bound to mAbs by the liver through the LDLR and by an unexpected, and still debated, post-translational increase in PCSK9 secretion [56].

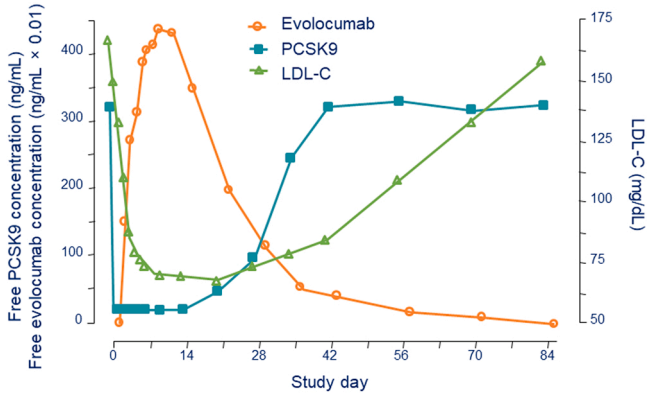

Fig. 2. Changes of from baseline in LDL-C and unbound PCSK9 in healthy subjects after s.c. injection of evolocumab 120 mg.
Modified from Kasichayanula et al. [51].

4. Current guidelines for lipid lowering therapies after ACS

First evidence of the use of statins in ACS patients derived from two studies conducted respectively in 2001 and 2004, the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) [57] and the Pravastatin or Atorvastatin and Infection Therapy - Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) trial [58]. 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 ARMYDA (Atorvastatin for Reduction of Myocardial Damage during Angioplasty) 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. The study demonstrated a significant reduction of markers of myocardial injury in response to atorvastatin pretreatment, suggesting a protective effect on procedural myocardial injury in elective coronary intervention [59]. Nevertheless, roughly 20 % of ACS survivors experience a subsequent event of ischemic nature within 24 months with a 5-year mortality ranging from 19 % to 22 % [60,61]. Achieving guidelines goals either < 70 mg/dl [62] or < 55 mg/dl [63] of LDL-C levels is not typically reached until 4 weeks after initiation high dose statins. Relative to ACS, immediate and aggressive lipid lowering therapies is supported by the ESC/EAS dyslipidemia guidelines, recommending initiation of high-intensity statin therapy during the first 1–4 days of hospitalization [63].

In Table 1 are summarized the current guidelines from the American Heart Association (AHA) [64], ESC/EAS [65], and International Lipid Expert Panel (ILEP) [66]. The European guideline consider all patients with an ACS as at very high risk, whereas in American guideline, a patient with ACS must also have multiple high-risk features or more than one previous atherosclerotic cardiovascular disease event. Although the LDL-C targets differ between the European (EAS/ESC and ILEP) and American (AHA) societies, all three documents 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 [67].

5. mAbs anti PCSK9 in ACS

The use of anti PCSK9 therapies have not been included in the very short period after ACS but only if the final (4/12 weeks after ACS) LDL-C target is not reached with statin plus ezetimibe therapies (Table1). Thus, current guidelines do not include the use of evolocumab or alirocumab in ACS patients during the first 1–4 days of hospitalization, as indicated for statins. Nevertheless, evolocumab and alirocumab exert a complete inhibition of circulating PCSK9 (− 97 % of free PCSK9) within 1-day post injection, thus suggesting a very rapid onset of action [54,68]. On the contrary, inclisiran, the recently approved small interfering RNA (siRNA) anti PCSK9, determines a liver specific inhibition of PCSK9 synthesis which leads to a reduction of total PCSK9 levels by about 25–30 % after 1-day and 65 % at 4/5 days post-injection [69,70]. A non-complete inhibition of PCSK9 by inclisiran is potentially due to the

Table 1
Comparison of the treatment strategies in patients with ACS as recommended by the American and European cholesterol guidelines. MVD, Hepatic microvascular dysplasia; FH, familial hypercholesterolemia; PVD, Peripheral vascular disease; DM, diabetes mellitus.

Guidelines	Risk classification	Lipid management immediately after ACS	LDL-C target	If not at target at 4/12 weeks
AHA 2018	ACS patients not at very high risk (age ≤ 75 years)	Initiation or continuation of high-intensity statin	LDL-C reduction ≥ 50 %	Add ezetimibe if LDL-C still ≥ 70 mg/dl (≥ 1.81 mmol/l)
	ACS patients not at very high risk (age ≥ 75 years)	Initiation or continuation of high or moderate-intensity statin		Add ezetimibe if LDL-C still ≥ 70 mg/dl (≥ 1.81 mmol/l)
	ACS patients at very high risk (history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions)	Initiation or continuation of high-intensity statin	LDL-C reduction ≥ 50 %	Add ezetimibe if LDL-C still ≥ 70 mg/dl (≥ 1.81 mmol/l) ***OR*** non-HDL ≥ 100 mg/dl (≥ 2.6 mmol/l)
	Risk classification	**Lipid management immediately after ACS**	**LDL-C target**	**If not at target at 4/6 weeks follow-up**
ESC/EAS 2019	All ACS patients are considered at very high risk	high dose statin therapy during the first 1–4 days of hospitalization	LDL-C ≤ 55 mg/dl (≤ 1.42 mmol/l) ***AND*** LDL-C reduction ≥ 50 %	Add ezetimibe. If goal not achieved after 4–6 weeks add PCSK9 inhibitors
	Risk classification	**Lipid management immediately after ACS**	**LDL-C target**	**If not at target at 4/6 weeks follow-up**
ILEP 2021	ACS patients at very high risk already on statin therapy and LDL-C < 100 mg/dl (< 2.5 mmol/l)	Continuation of maximal tolerated statin dose	LDL-C ≤ 55 mg/dl (≤ 1.42 mmol/l) ***AND*** LDL-C reduction ≥ 50 %	Add ezetimibe
	Statin naive ACS patients at very high risk with LDL-C < 120 mg/dl (< 3 mmol/l)	Initiation with high doses of atorvastatin or rosuvastatin	LDL-C ≤ 55 mg/dl (≤ 1.42 mmol/l) ***AND*** LDL-C reduction ≥ 50 %	Add ezetimibe
	Any ACS patient at very high risk with LDL-C ≥ 300 mg/dl (≥ 7.5 mmol/l)	Initial triple therapy with statin + ezetimibe + PCSK9 inhibitor might be initiated in hospital	LDL-C ≤ 55 mg/dl (≤ 1.42 mmol/l) ***AND*** LDL-C reduction ≥ 80 %	
	ACS patients at extremely high risk (MI + previous vascular event in the past 2 years; ACS + MVD; ACS + PVD; ACS + FH; ACS + DM + one additional risk factor)	Initial dual therapy with maximal tolerated statin dose and ezetimibe	LDL-C ≤ 40 mg/dl (≤ 1 mmol/l)	Add PCSK9 inhibitors

fact that circulating PCSK9 is mainly, but not exclusively, from hepatic origin, whereas evolocumab and alirocumab bind almost totally plasma PCSK9 (approximately 97 %). Thus, a more complete and faster inhibitory action of PCSK9 by mAbs could have a potential clinical impact in ACS patients. Conversely, the more rapid inhibition of PCSK9 by evolocumab and alirocumab does not seem to determine a faster LDL-C lowering effect with a − 50 % after 5–6 days for both drugs [54,68]. This effect was recently confirmed in a small single-center, prospective, open-label randomized controlled trial conducted in Japan [71]. The change in LDL-C levels from the baseline to 4 weeks was − 76.1 % and − 33.1 % in the evolocumab and pitavastatin groups, respectively [71]. The kinetics of evolocumab and statins are very similar and reflects the long half-life time of LDL-C in the circulation (48 h)[72]. It is also important to note that statins rapidly induce PCSK9 levels (24–48 h) in atherosclerotic patients [73], and in ACS [74], thus further supporting a rapid intervention with anti-PCSK9 therapies, *i.e.* mAbs.

6. Clinical evidence supporting the use of mAbs anti PCSK9 in ACS patients

Although the ODYSSEY OUTCOMES study demonstrated the superiority of alirocumab *vs* placebo in patients with a recent ACS [75,76] the trial compared treatments in patients that experienced ACS 1–12 months (median 2.6) prior to randomization [77]. In addition, patients with MI within 30 days of randomization were excluded in FOURIER trial. Thus, justification of early use of PCSK9 inhibition soon after an ACS event is under investigation (Table 2).

Early results were those relative to the EVOPACS (evolocumab for early reduction of LDL-cholesterol levels in patients with ACS) study [78]. Aim of the trial was to evaluate the feasibility, safety, and efficacy of evolocumab for very early LDL-C lowering (within 24 h) in ACS patients with LDL-C levels that were either above the recommended targets (at that time) [79], or were not projected to be reduced below these targets under high-intensity statin therapy. The rationale was based on the knowledge that during the early period of ACS the risk of recurrent ischemic events is greater [57]. However, although evolocumab allowed to reach LDL-C < 1.8 mmol/l in 95.7 % of patients compared to a 37.6 % in the placebo group, the study was not powered for cardiovascular outcomes. The inflammatory biomarkers, *e.g.*, C-reactive protein (CRP), interleukin (IL)-1β and IL-6 were not statistically modified between-groups. Whether or not the lack of activity of PCSK9 inhibition on the inflammatory milieu matters is an aspect worth of consideration in the recurrence of ACS [80]. Indeed, a very recent report, from a small case-crossover pilot study in patients hospitalized for ACS, showed a significant reduction of IL-1β and IL-6 after 72 h of evolocumab treatment [81]. Although PCSK9 inhibitors do not reduce CRP [82], experimental research reports an association among higher PCSK9 plasma levels, high on-treatment platelet reactivity, and elevated factor VIII levels [83]. The potential impact of PCSK9 inhibitors on platelet reactivity has been explored in the NCT03096288 trial (Impact of Evolocumab on the Effects of Clopidogrel in Patients With High On-Treatment Platelet Reactivity) and results are awaited.

Data from EVACS trial (Evolocumab in Acute Coronary Syndrome), enrolling patients with NSTEMI MI and troponin I ≥ 5 ng/ml, showed that in-hospital initiation of evolocumab (420 mg), early after ACS, rapidly and significantly reduced LDL-C within 24 h, namely, LDL-C dropped from 91.5 ± 35 mg/dl to 70.4 ± 27 mg/dl. At day 3, LDL-C levels in the group given evolocumab were significantly lower than those achieved in the placebo group and remained lower until day 30 reaching values of 35.9 ± 24 mg/dl *vs* 64.5 ± 27 mg/dl [52]. At hospital discharge, evolocumab allowed 80 % of patients to reached secondary prevention AHA targets and 65 % to reach those recommended by EAS [52].

The feasibility, safety, and efficacy of evolocumab (140 mg every two weeks) in ACS patients of Chinese descent is the goal of the EMSIAC (Effect of Evolocumab Added to Moderate-Intensity Statin Therapy on LDL-C Lowering and Cardiovascular Adverse Events in Patients With Acute Coronary Syndrome) study. The primary outcome is the

Table 2
Currently undergoing clinical trials testing evolocumab and alirocumab in ACS.

Title	Status	Number of patients	Conditions	Interventions	Locations
Impact of Evolocumab on the Antiplatelet Effects of Ticagrelor and Aspirin in Patients With Acute Coronary Syndrome (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	United States and Canada
Evolocumab in Acute Coronary Syndrome (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, Maryland, United States
EVOlocumab for Early Reduction of LDL-cholesterol Levels in Patients With Acute Coronary Syndromes (EVOPACS) NCT03287609	Completed	N = 308	ACS	Evolocumab 140 mg/ml day 1 and at week 4	Multiple centers in Switzerland
Effect of Evolocumab Added to Moderate-Intensity Statin Therapy on LDL-C Lowering and Cardiovascular Adverse Events in Patients With Acute Coronary Syndrome (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, Maryland, United States
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 two 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 Lipoproteinemia Inflammation Genetic Polymorphisms	Evolocumab 140 mg every two weeks for 6 months, Alirocumab 150 mg every two 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 Volume in Japanese Patients Hospitalized for Acute Coronary Syndrome With Hypercholesterolemia (ODYSSEY J-IVUS) NCT02984982	Completed	N = 206	Hypercholesterolemia ACS	Alirocumab every 2 weeks on top of stable statin therapy (atorvastatin or rosuvastatin)	Multiple centers Japan
Effects of Acute, Rapid Lowering of LDL Cholesterol With Alirocumab in Patients With STEMI Undergoing Primary PCI (EPIC STEMI) NCT03718286	Completed	N = 97	STEMI ACS Hypercholesterolemia Hyperlipidemias Dyslipidemias	Alirocumab 150 mg administered prior to revascularization procedure, 2- and 4-weeks post-procedure	General Hospital, Hamilton, Ontario, Canada

percentage changes in LDL-C at week 4 and 12 after treatment. The secondary outcome is the occurrence of major adverse cardiac events (MACE) after 12 weeks and 1 year of treatment [84]. Very recently, the feasibility and safety of the early treatment of mAbs anti PCSK9 in lipid-lowering therapy has been investigated in patients with extremely high cardiovascular risk with LDL-C levels $\geq$3.0 mmol/l. The results indicated that evolocumab can reduce the cumulative incidence of cardiovascular events as early as 20 days after the initiation of the treatment without increasing adverse reactions [85]. Nevertheless, these results required further confirmatory studies with larger patient population. A second analysis of the ODYSSEY OUTCOMES trial highlighted another important evidence regarding the possible use of PCSK9 inhibitors alirocumab in ACS patients. Indeed, alirocumab showed to reduce the relative risk of MACE after ACS irrespective of the dose and the use of statins. In addition, patients not under statin treatment have the highest absolute risk for recurrent MACE and alirocumab substantially reduces that risk. This data indicates PCSK9 inhibition as a very effective therapeutic strategy for statin-intolerant patients with ACS [86]. After all, the efficacy of anti PCSK9 therapy has been considered very effective in many aspects of clinical practice from the beginning of the approval of both alirocumab and evolocumab [87].

The approach for ACS patients with heart failure is another important issue to be considered. Although statins reduce cardiovascular events in primary and secondary prevention, they did not show any benefit in patients with a history of HF, as found in the GISSI-HF [88] and the CORONA studies [89]. A secondary analysis of the ODYSSEY study found that alirocumab reduced MACE in ACS patients without a history of HF but not in those with a history of HF, respectively, a HR of

0.78 (95 %CI 0.70–0.86) *vs* a HR of 1.17 (95 %CI 0.97–1.40). Thus, lipid lowering therapies based on statins and PCSK9 inhibitors seem to be ineffective or even detrimental and potentially to be avoided in patients with HF.

In conclusions, current knowledge on the pathophysiological action of PCSK9 suggests that the rapid pharmacological inhibition might provide an effective intervention in ACS to prevent further cardiovascular events. An effective and complete inhibition of PCSK9 with mAbs, together with the use of statins, might reduce platelet activation and control the inflammatory response associated to ACS. These hypothetical actions and a possible positive clinical impact in patients with ACS are under investigation by the ongoing clinical trials with both evolocumab and alirocumab. Positive results could determine a change in the current guidelines for the treatment of ACS patients.

Declaration of Interest

Prof. Alberto Corsini and Prof. Nicola Ferri have received an honorarium from Amgen S.r.l.

Data Availability

No data was used for the research described in the article.

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