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SHORT COMMUNICATION

PCSK9 Inhibitors: Is the Time Ripe for the "Fast Track" Use Independently on the LDL-C Baseline Values in Acute Coronary Syndrome?

Alessandro Bellis[1] · Ciro Mauro[1] · Emanuele Barbato[2] · Bruno Trimarco[3] · Carmine Morisco[3]

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Abstract
The low-density lipoprotein cholesterol (LDL-C) lowering decreases the risk to develop major adverse cardiovascular events (MACE) in patients with acute coronary syndrome (ACS). Therefore, the "fast track" use of PCSK9 inhibitors (PCSK9i) has been introduced in ACS patients not achieving LDL-C target (70 mg/dl) despite an ongoing lipid lowering therapy with statin at maximum tolerated dosage plus ezetimibe or stain-naïve (LDL-C > 130 mg/dl). PCSK9i "fast track" use has shown to achieve the regression of "non-culprit" atherosclerotic plaques leading to a further MACE decrease. Interestingly, it has been also hypothesized a role of PCSK9i beyond the LDL-C lowering in ACS. PCSK9i have been demonstrated to decrease the inflammation of atherosclerotic plaques and myocardium, inhibit platelet aggregation, and improve the cardiomyocyte survival against the reperfusion injury. All these findings may positively impact on the prognosis and suggest the PCSK9i use in the acute phase of ACS independently on the baseline LDL-C values.

Keywords Acute myocardial infarction · Atherosclerosis · Secondary prevention · Cardiovascullar risk · Lipid lowering therapy

1 Introduction

The 2019 guidelines of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) on the management of dyslipidaemias, suggested, for the first time, the addition of PCSK9 inhibitors (PCSK9i) in "fast track" after the acute coronary syndrome (ACS) event (during hospitalisation; Class IIa, Level of Evidence C), in patients with low density lipoprotein cholesterol (LDL-C) > 100 mg/dl despite an ongoing lipid lowering therapy (LLT) with statin at maximum tolerated dosage plus ezetimibe [1]. The 2023 ESC Guidelines for the management of ACS have further reinforced this indication by lowering the LDL-C cut-off to values < 55 mg/dl (Class I, Level of Evidence A) [2]. The aim was to achieve the therapeutic target of LDL-C in the highest percentage of patients before the discharge and the regression of "non-culprit" atherosclerotic plaques. In fact, it is well known the tight link between high LDL-C levels and the risk of atherosclerotic cardiovascular disease progression, as well as that one between LDL-C lowering and the decrease of the risk to develop major adverse cardiovascular events (MACE) [3]. The switch from the concept "the lower, the better" to that "strike early, strike strong" has pushed to test the use of PCSK9i in addition to statin independently on previous LLTs, if LDL-C is > 130 mg/dl. This wider PCSK9i "fast track" use has shown to achieve the concomitant decrease of atheroma volume and of plaque lipid content, and increase in fibrous cap thickness in "non-culprit" plaques (triple regression endpoint) leading to a more significant reduction of MACE compared to the statin therapy alone [4].

✉ Carmine Morisco
carmine.morisco@unina.it

[1] Unità Operativa Complessa Cardiologia con UTIC ed Emodinamica - Dipartimento Emergenza e Accettazione, Azienda Ospedaliera "Antonio Cardarelli", Via Cardarelli n.9, Napoli 80131, Italy

[2] Dipartimento di Medicina Clinica e Molecolare, Sapienza Università di Roma, Azienda Ospedaliera Sant'Andrea, Roma, Italy

[3] Dipartimento di Scienze Biomediche Avanzate, Università FEDERICO II, Via Pansini n.5, Napoli 80131, Italy

More interestingly, a benefit by the PCSK9i on the MACE incidence has been also hypothesized independently on the LDL-C lowering. Indeed, it has been previously evidenced how the graphical progression of relative risk reduction to develop new MACE was linear with the decrease of LDL-C values for all LLTs, whereas it became hyperbolic with PCSK9i [5].

In our opinion, there's a strong pathophysiological fundament supporting this hypothesis. In type 1 ACS, the potentially irreversible myocardial reperfusion injury is determined by micro-vascular obstruction (MVO), which is dependent on non-modifiable factors, such as genetic predisposition and pre-existing coronary micro-vascular dysfunction, and on modifiable factors, such as ischemic injury, micro-embolization of thrombotic debris, and intramyocardial haemorrhage (IMH) [6]. The early recanalization of culprit coronary artery reduces the myocardial ischemic injury, but often determines the micro-embolization phenomenon and the IMH onset. Thus, the therapeutic strategies aimed to reduce coronary micro-embolization and IMH may have more impact on clinical outcomes in this clinical setting. Here, we try to synthetically resume the current literature showing that PCSK9i decrease the inflammation of atherosclerotic plaque and myocardium, inhibit platelet aggregation, and improve the cardiomyocyte survival against the reperfusion injury. All these findings may positively impact on the prognosis and suggest the PCSK9i use in the acute phase of ACS independently on the baseline LDL-C values.

2 The Potential Role of PCSK9i "Fast Track" Use Beyond the Lipid Lowering Effect

In the first 24–48 h following an ACS, there is an increase of PCSK9 values that correlates with an higher incidence of MACE [7]. This phenomenon is partially due to ACS, but it seems to be also induced by statin therapy. In particular, PCSK9 levels significantly rise up after LLT with statins in ACS patients. PCSK9 up-regulation feeds the inflammation of atherosclerotic plaque that becomes more prone to the rupture [8]. PCSK9i determine the maximum reduction of circulating PCSK9 within 4 h since their first administration. The early alirocumab or evolocumab plus statin administration have significantly lowered the macrophage grade in "non-culprit" plaques [9, 10]. Moreover, the reduction of intra-myocardial macrophage quote by PCSK9i has been shown to attenuate the transformation of cardiac fibroblasts in myofibroblasts, thereby ameliorating the cardiac fibrosis [11]. Thus, the PCSK9i "fast track" administration may contribute to the decrease of inflammation inside the "non-culprit" atherosclerotic plaques and directly prevent the ventricular fibrosis post-myocardial infarction.

Furthermore, PCSK9 enhances platelet activation and in vivo thrombosis, as well as myocardial necrosis expansion after ligation of anterior descending artery in mice, by binding to platelet CD36. PCSK9i abolish these enhancing effects of PCSK9, supporting the potential use of these drugs in order to reduce the MVO and no-reflow phenomenon [12]. Intriguingly, it has been recently demonstrated that, in patients affected by stable atherosclerotic cardiovascular disease with high platelet reactivity who were on clopidogrel treatment and presented LDL-C values > 70 mg/dl, evolocumab determined a significant decrease in platelet aggregation at 14 days follow-up, whereas this effect disappeared at 30 days follow-up, without affecting the lipid lowering power [13]. Overall, these results seem to suggest a relevant anti-platelet effect of PCSK9i in the first days since their administration, thereby supporting the "fast track" use of these molecules in order to reduce the extension of MVO in acutely infarcted myocardium, where platelet aggregation is significantly increased.

Finally, several evidences seem to indicate PCSK9 as an actor in the direct reperfusion injury that is the main responsible of post-ischemic left ventricular remodelling (LVR) [14]. LVR is a dynamic phenomenon affecting almost the half of STEMI patients and leading to an high rate of hospitalizations for heart failure (HF). In patients with STEMI, PCSK9 levels after 48 h are significantly associated with IMH, MVO, and infarct size leading to LVR and worse subsequent clinical outcomes [15].

In cardiomyocytes exposed to hypoxia and reperfusion, the increase of PCSK9 expression activates Caspase 9 leading to Caspase-3 cleavage and to apoptotic death. At the same time, mitochondria produce reactive oxygen species (ROS) and LDL-C triggers IRE1/JNK pathway: both these events determine autophagy. PCSK9 may also provoke the damage of mitochondrial DNA, thereby inducing pyroptosis. At the end, the excessive accumulation of ferrous ions and of PCSK9 causes functional stress of mitochondria, thus producing lipid peroxidation of intracellular lipid and cell membrane, and then ferroptosis. All these molecular mechanisms may justify the progression to HF.

In vivo models of myocardial infarction and reperfusion have revealed an increased expression of PCSK9 and of the autophagy marker LC3 in both ischemic and surrounding area. This event has determined a thinning of the ischemic myocardial wall leading to LVR that was prevented by the pretreatment with PCSK9i, independently on LDL-C decrease [16]. It is possible to hypothesize an analogue effect in humans, because an increased expression of PCSK9 and LC3 has been also found in hearts from patients affected by recent (< 7 days) lethal myocardial infarction [16]. Thus, the early PCSK9 antagonism during myocardial infarction

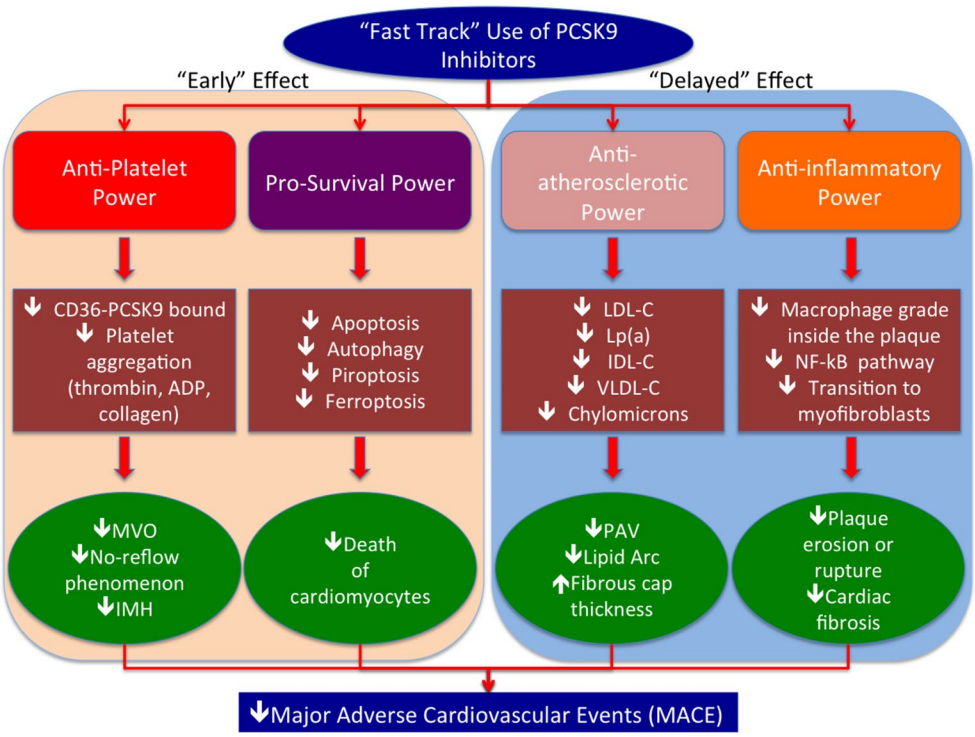

Fig. 1 Effects of the PCSK9 Inhibitors "Fast Track" Use in ACS. The decreased incidence of MACE observed with PCSK9i "fast track" administration is induced by the LDL-C lowering-dependent effect determining the regression of "non-culprit" atherosclerotic plaques, but it may be also potentially mediated by LDL-C lowering-independent effects triggering the cardiomyocytes survival and reducing the MVO and the IMH following the reperfusion injury. IDL-C: intermediate density lipoprotein-cholesterol; IMH: intramyocardial haemorrhage; LDL-C: low density lipoprotein-cholesterol; Lp(a): lipoprotein (a); MVO: micro-vascular obstruction; PAV: percentage atheroma volume; VLDL-C: very low density lipoprotein-cholesterol

may significantly favour the cardiomyocyte survival rate thereby reducing the risk of post-ischemic LVR.

3 Conclusions and Perspectives

PCSK9i "fast track" use has shown to decrease the atheroma volume, to blunt the inflammatory state of "non-culprit" atherosclerotic plaques and of myocardium, to exert an inhibitory effect on platelet aggregation and on molecular pathways inducing the death of cardiomyocytes. All these findings allow us to speculate that the decreased incidence of MACE observed in ACS patients achieving the triple regression endpoint with PCSK9i "fast track" administration in the PACMAN-AMI trial is potentially induced by an "early" effect (independent by LDL-C lowering) triggering the cardiomyocytes survival and reducing the MVO and the IMH in response to the reperfusion injury, and by a "delayed" effect (dependent by LDL-C lowering) determining the regression of "non-culprit" atherosclerotic plaques thereby affecting the recurrence of ACS (Fig. 1). Hopefully, the data from ongoing large randomized trials investigating the effects of PCSK9i "fast track" strategy on myocardial salvage and LVR (Table 1) could further support this pathophysiological hypothesis and suggest the PCSK9i as a drug of the acute phase of ACS independently on the baseline LDL-C values.

It is intuitive that the extended administration of PCSK9i to all acute ACS patients implies an higher economic impact on the national healthcare system. However, although no one cost-effectiveness analysis has been performed about the "fast track" use of these drugs independently on the baseline LDL-C values, few studies have yet demonstrated that both alirocumab and evolocumab improve cardiovascular outcomes at costs considered of good value in patients with recent ACS (1–12 months) and baseline LDL-C ≥ 100 mg/dl [17, 18]. Interestingly, evolocumab has also provided economic benefits in recent ACS patients with baseline LDL-C ≥ 70 mg/dl, if they presented an additive risk factor (diabetes mellitus type 1 or 2, age from 65 to 85 years, previous ischemic stroke or peripheral artery disease within 6 months) or a second event within 2 previous years [18]. Because it is very likely that the price of PCSK9i will significantly lower in few years, it is conceivable that the "fast track" use of PCSK9i independently on the baseline LDL-C values may be more largely cost-effective in the next future.

In the meantime, to address the cost-reduction of PCSK9i "fast-track", it is possible to imagine a PCSK9i "one-shot" strategy where the second drug injection will be allowed only if the baseline LDL-C values, measured on a blood sample performed before the first drug administration, were above the thresholds established by the ESC Guidelines. The efficacy of this therapeutic hypothesis on the post-ischemic LVR and MACE incidence has obviously to be tested in randomized clinical trials.

Table 1 Randomized Trials Testing the Potential LDL-C Independent Effects of PCSK9 Inhibitors "Fast Track" Use in ACS. In this table are reported the characteristics of ongoing randomized trials testing the potential LDL-C independent effects of PCSK9 inhibitors "fast track" use in ACS patients. The primary endopoints are represented by the entity of myocardial salvage and the onset of left ventricular remodelling. Both these parameters significantly influence the incidence of MACE

Title	Status	Number of Patients	Conditions	Interventions	Endpoint
EVOLVE-MI: EVOLocumab Very Early After Myocardial Infarction	Not yet recruiting	N = 4000	ACS	Evolocumab 140 mg s.c. + Routine Lipid Management	Total of myocardial infarction, ischemic stroke, any revascularization, all-cause death
Effect of Evolocumab Added to Moderate-Intensity Statin Therapy on LDL-C Lowering and Cardiovascular Adverse Events in Patients With Acute Coronary Syndrome (EMSIACS)	Recruiting	N = 500	ACS	Statin alone therapy and Evolocumab 140 mg plus statin therapy	LDL-C lowering and cardiovascular adverse events
Impact of Early PCSK9 Inhibitor on Heart After Acute Myocardium Infarction (PERFECT-AMI)	Not yet recruiting	N = 20	ACS	Alirocumab 75 mg versus standard of care lipid management	Left ventricular remodeling (myocardial salvage and ejection fraction by MRI at 1 week and 6 months after primary PCI)
The Impact of Early PCSK9 Inhibitor Treatment on Heart After Acute Myocardium Infarction (PERFECT II)	Not yet recruiting	N = 160	ACS	Alirocumab 75 mg versus standard of care lipid management	Myocardial salvage index assessed by MRI at 1 week post-PCI

ACS: acute coronary syndrome; MRI: magnetic resonance imaging

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Data Availability As a review article, no new data were generated or analysed in support of this research.

Declarations

Conflict of Interest None declared.

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