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Review article

Lipid management in ACS: Should we go lower faster?

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ABSTRACT

Low-density lipoprotein-cholesterol (LDL-C) is a well-accepted causal risk factor for athero-thrombotic cardiovascular disease, as demonstrated in large epidemiological studies, including Mendelian randomization data. Several randomized controlled trials and meta-analyzes have shown that lipid lowering therapies, such as statins and more recently the non-statin agents ezetimibe and Proprotein Convertase Subtilisin Kexin type 9 (PCSK9) monoclonal antibodies (mAb), reduce cardiovascular events across a broad range of baseline LDL-C levels. Over time, the recommended target for LDL-C has become more stringent, moving from 2.6 mmol/l to 1.8 mmol/l in very high-risk patients. It is currently recommended to start high intensity statin treatment immediately after acute coronary syndromes (ACS) to maximally and rapidly reduce LDL-C. The novel treatment options enable the achievement of very low LDL-C levels below 1 mmol/l, with no reported safety issues, in particular with regard to neurocognitive events. However, current evidence supports the use of PCSK9 mAb treatment in ACS patients only after an initial 2–3 month run-up treatment adaptation period with maximally tolerated statin. The use of PCSK9 mAb immediately in the acute phase of ACS (<1 month) remains to be studied. Some data suggest that circulating PCSK9 increases coronary plaque vulnerability, inflammation as well as platelet aggregation in the acute phase of ACS, potentially justifying earlier PSCK9 mAb treatment initiation. As the use of novel treatment combinations in ACS is further explored to widen the perspectives of a more personalized approach for the management of ACS based on individual patient risk profile and baseline LDL-C values, their relative cost-effectiveness will also need to be assessed.

1. Introduction

Low-density lipoprotein-cholesterol (LDL-C) is a well-accepted causal risk factor for atherosclerotic cardiovascular disease, as demonstrated in large epidemiological studies, including Mendelian randomization data [1]. Several randomized controlled trials and meta-analyzes have shown that lipid lowering therapies including statins, and more recently the non-stating agents ezetimibe and Proprotein Convertase Subtilisin Kexin type 9 (PCSK9) monoclonal antibodies (mAb), reduce cardiovascular events across a broad range of baseline LDL-C levels [2]. Current treatment guidelines recommend an LDL-C target of 1.8 mmol/l after acute coronary syndromes (ACS), but these guidelines precede results from newer trials using novel treatment combinations, which have shown that lowering LDL-C below the recommended target is associated with additional cardiovascular benefits [3]. Overall, “Lower is better”, “less is more” or “lowest is best” are strong valid concepts for LDL-C treatment targets and are supported by a rapidly growing body of evidence [4]. In this clinical review paper, we will discuss the current evidence of lipid-lowering therapies in patients with ACS, and in particular the possible need to treat lower and faster (see Table 1).

1.1. Impact of lowering LDL-C on clinical outcomes

A meta-analysis including 312,175 participants (mean age 62 years, mean LDL-C 3.16 mmol/l) from 49 trials and totalizing 39,645 major cardiovascular events showed that the relative risk for each incremental reduction of 1 mmol/l LDL-C was reduced by 0.77 (95% CI 0.71–0.84, $p < 0.01$) for statins and 0.75 (95% confidence interval [CI] 0.66–0.86, p=0.002) for non-statin agents [5]. In addition to the relative reduction of LDL-C, the absolute achieved LDL-C value was also demonstrated to be significantly associated with an absolute risk reduction of cardiovascular events; for each incremental

Abbreviations: ACS, acute coronary syndromes; PCSK9, proprotein convertase subtilisin kexin 9.

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Table 1
Factors helpful in the decision to treat ACS patients with PCSK9 mAb [29].

1- Documentation of clinical ASCVD
Coronary artery disease, peripheral artery disease or ischemic stroke
2- Complete medical history for lipid-lowering therapy use
Maximally tolerated statin therapy
Use of ezetimibe
3- Presence of additional indices of risk severity
Familial hypercholesterolemia
Diabetes mellitus with target organ damage
Severe and/or extensive ASCVD (left main, three-vessels and proximal LAD)
Rapid progression of ASCVD (repeated ACS, unplanned coronary revascularization, ischemic stroke within 5 years of the index event)
4- Baseline LDL-C
Consider the percentage of reduction needed to reach the target < 1.8 mmol/l or a minimal reduction of LDL-C by 50%
5- LDL-C levels under maximally tolerated statin and ezetimibe
If LDL-C > 3.6 mmol/l, consider PCSK9 mAb
If LDL-C > 2.6 mmol/l, in presence of indices of risk severity, consider PCSK9 mAb

ACS, acute coronary syndromes; ASCVD, atherosclerotic cardiovascular disease; LAD, left anterior descending artery; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin kexin type 9.

reduction of 1 mmol/l LDL-C, the absolute risk reduction for coronary death or myocardial infarction was 4.6% (95% CI 2.9%–6.4%) in secondary prevention and 1.5% (95% CI 0.5–2.6%) in primary prevention [5]. Another recently published meta-analysis including 152,507 patients in secondary prevention from 19 trials (15 with statin, 3 with PCSK9 mAb and 1 with ezetimibe) compared more-intensive (N = 76′679) to less-intensive (N = 75′829) LDL-C lowering strategies [6]. Risk reduction was more pronounced in the more-intensive strategy, with a risk ratio (RR) of 0.81, 95% CI 0.77–0.86. The impact on clinical outcomes was greater in patients presenting high baseline LDL-C values and high cardiovascular risk scores [6]. Tables 2–4 summarize the various cardiovascular outcomes for the different lipid-lowering treatment strategies [1]: low-intensity statin [2]; high-intensity statin [3]; ezetimibe; and [4] PCSK9 mAb.

1.2. Statin

Statin is the first line recommended therapy to lower LDL-C after ACS. Large-scale evidence from randomized control trials and meta-analyses has shown that long-term statin therapy reduces cardiovascular events by about 25% per year for every incremental LDL-C reduction of 1 mmol/l [7]. The absolute benefits of statin therapy are proportionate to the absolute cardiovascular risk and absolute reduction in LDL-C. For example, the number needed to treat will be significantly lower in secondary prevention compared to primary prevention, and under high-versus low-intensity statin [7]. A meta-analysis of 27,548 patients from trials comparing high-*vs.* moderate-intensity statin showed a significant reduction by 16% of coronary death or myocardial infarction and a trend for decreased cardiovascular mortality by 12% (p=0.054) for the high-intensity statin treated patients [8]. In the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE-IT TIMI 22), 4162 patients with ACS treated with atorvastatin 80 mg *vs.* pravastatin 40 mg achieved significantly better LDL-C levels (1.80 mmol/l *vs.* 2.46 mmol/l, $p < 0.001$) and reductions of cardiovascular events (26.3% *vs.* 22.4%, hazard ratio [HR] 0.84, 95% CI 0.74–0.95, p=0.005) [9]. The European Society of Cardiology (ESC) guidelines for the management of acute coronary syndromes (ACS) recommend initiating high-intensity statin as soon as possible after diagnosis to achieve a target value of LDL-C < 1.8 mmol/l, or 50% LDL-C reduction from baseline [3]. The exact timing of initiating statin the context of ACS has not been determined and poorly studied. The recently published SECURE-PCI tested the hypothesis of preloading atorvastatin prior PCI in ACS patients [10]. 2087 received two doses of atorvastatin 80 mg and 2104 matching placebo, but finally only 64.7% underwent PCI. The incidence of major adverse cardiovascular events (MACE) was not significantly in both groups (6.2% *vs.* 7.1%, hazard ratio 0.88, 95% CI 0.69–1.11, p=0.27). However the subgroup of patients treated with PCI, preloading dose of atorvastatin was associated with a significant reduction of MACE (HR 0.72, 95% CI 0.54–0.96, p=0.02). Similarly in the STEMI subgroup (one quarter of the population) treated with PCI, effect of atorvastatin was significant (HR 0.54, 95% CI 0.35–0.84, p=0.01). The findings

Table 2
Incidence of major adverse cardiovascular events in 4 different lipid-lowering therapy trials.

	FOURIER [19]	IMPROVE-IT [14]	PROVE-IT 22 [9]	LIPID [37]
	PCSK9 mAb	Ezetimibe	Atorvastatin	Pravastatin
Median LDL-C (mmol/l)	0.78	1.40	1.60	2.90
Median follow-up (years)	2.2	6	2.0	6.1
Clinical outcomes per year				
CVD death	0.8%	1.2%	0.6%	1.2%
Myocardial Infarction	1.5%	2.2%	3.3%	1–2%
Stroke	0.5%	0.6%	0.5%	0.6%
Coronary revascularization	2.5%	3.6%	8.2%	2.1%
Unstable angina	0.8%	0.4%	1.9%	3.7%
Total CVD events	4.5%	5.8%	11.2%	NA
Hard CVD events	2.7%	3.4%	4.2%	¶

CVD, cardiovascular disease; FOURIER, Further Cardiovascular Outcomes Research with PCSK9 inhibition in Subjects with Elevated Risk; IMPROVE-IT, Improved Reduction of Outcomes: Vytorin Efficacy International Trial; LDL-C, low-density lipoprotein cholesterol; mAb, monoclonal antibody; NA, not available; PCSK9, proprotein convertase subtilisin kexin type 9; PROVE-IT 22, Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22.
Hard CVD events were defined as death due to CHD or nonfatal MI in the LIPID trial.

Table 3
Hazard ratios of major adverse cardiovascular events in 4 different lipid-lowering trials.

	FOURIER [19]	IMPROVE-IT [14]	PROVE-IT 22 [9]	LIPID [37]
	PCSK9 mAb	Ezetimibe	Atorvastatin	Pravastatin
Additional LDL-C reduction (%)	59	24	32	25
Median follow-up (years)	2.2	6	2.0	6.1
Clinical outcomes				
CVD death	HR 1.05 (95% CI 0.88–1.25)	HR 1.00 (95% CI 0.89–1.13)	HR 0.70 (95% CI 0.41–1.15)	HR 0.75 (95% CI 0.65–0.87)
Myocardial infarction	HR 0.73 (95% CI 0.65–0.82)	HR 0.87 (95% CI 0.80–0.95)	HR 0.87 (95% CI 0.75–1.10)	HR 0.71 (95% CI 0.62–0.82)
Stroke	HR 0.75 (95% CI 0.62–0.92)	HR 0.86 (95% CI 0.73–1.00)	HR 1.09 (95% CI 0.42–1.70)	HR 0.81 (95% CI 0.66–1.00)
Coronary revascularization	HR 0.78 (95% CI 0.71–0.86)	HR 0.95 (95% CI 0.89–1.01)	HR 0.84 (95% CI 0.76–0.98)	HR 0.80 (95% CI 0.72–0.90)
Unstable angina	HR 0.99 (95% CI 0.82–1.18)	HR 1.06 (95% CI 0.85–1.33)	HR 0.71 (95% CI 0.50–0.97)	HR 0.88 (95% CI 0.81–0.96)
Total CVD events	HR 0.85 (95% CI 0.79–0.92)	HR 0.95 (95% CI 0.90–1.00)	HR 0.84 (95% CI 0.77–0.96)	NA
Hard CVD events	HR 0.80 (95% CI 0.73–0.88)	HR 0.90 (95% CI 0.84–0.96)	HR 0.82 (95% CI 0.68.-1.01)	HR 0.76 (95% CIO 0.68–0.85)

CI, confidence intervals; CVD, cardiovascular disease; FOURIER, Further Cardiovascular Outcomes Research with PCSK9 inhibition in Subjects with Elevated Risk; HR, hazard ratio; IMPROVE-IT, Improved Reduction of Outcomes: Vytorin Efficacy International Trial; LDL-C, low-density lipoprotein cholesterol; NA, not applicable; mAb, monoclonal antibody; PCSK9, proprotein convertase subtilisin kexin type 9; PROVE-IT 22, Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22.
Hard CVD events were defined as death due to CHD or nonfatal MI in the LIPID trial.

Table 4
Reduction of cardiovascular events in 4 different lipid-lowering trials.

	FOURIER [19]	IMPROVE-IT [14]	PROVE-IT [9]	LIPID [32]
	PCSK9 mAb	Ezetimibe	Atorvastatin	Pravastatin
Median LDL-C (mmol/l)	0.78	1.40	1.60	2.90
LDL-C reduction (%)	59%	24%	32%	25%
Median follow-up (years)	2.2	6	2.0	6.1
ARR for total CVD events	−1.50%	−1.70%	−3.90%	−3.20%
NNT for total CVD events	67	59	26	31
Average NNT per year of follow-up	147	354	52	190

ARR, absolute risk reduction; CVD, cardiovascular disease; FOURIER, Further Cardiovascular Outcomes Research with PCSK9 inhibition in Subjects with Elevated Risk; IMPROVE-IT, Improved Reduction of Outcomes: Vytorin Efficacy International Trial; LDL-C, low-density lipoprotein cholesterol; mAb, monoclonal antibody; NNT, number needed to treat; PCSK9, proprotein convertase subtilisin kexin type 9; PROVE-IT 22, Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22.
Hard CVD events were defined as death due to CHD or nonfatal MI in the LIPID trial.

from the SECURE-PCI did not support routine use of loading doses of atorvastatin in the ACS patients, but raised the question of potential benefit in STEMI patients [10].

The use of ezetimibe or PCSK9 mAb is considered if target LDL-C levels are not achieved with statin alone, as described below in this article [3]. However, data from real life cohorts suggest that only one third of patients reach these targets one year after ACS [11]. There are multiple explanations for this poor rate of achievement, including lack of adherence to therapy, inertia surrounding treatment intensification, or fear of side effects [7,12]. It is of note that statin observance has also decreased following negative press reports and has been correlated with a significant increase in cardiovascular events [7]. Concerns around statin safety have proven to be unjustified for not trying to achieve recommended LDL-C targets or managing lipid disorders intensively, as the global negative effect of therapy discontinuation is far superior to the rate of observed serious side effects [7]. In addition, no association has been shown between the extent of achieved LDL-C levels and side effects [7]. Regarding the diabetic population with ACS, the use of high-intensity statin is also recommended, as diabetic patients are considered as a high-risk of worse prognosis after ACS by the guidelines [3]. In a randomized clinical trials including 591 ACS with diabetes, high-intensity statin with atorvastatin 40 mg a day has been associated with improved clinical outcomes (major adverse cardiovascular events) compared to atorvastatin 20 mg a day (8.4% *vs.* 14.6%, p=0.018), hazard rations (HR 0.61, 95% CI 0.36–0.91) [13]. In the PROVE-IT trial, the benefit of atorvastatin was also consistent in the subgroup of patients with diabetes [9].

1.3. Ezetimibe

In IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial), 18,144 patients hospitalized for ACS were randomized to [1] a combination of simvastatin 40 mg and ezetimibe 10 mg (median average value of 1.4 mmol/l) or [2] simvastatin 40 mg (median average value of 1.8 mmol/l) [14]. After a 6 years median follow-up period, the primary endpoint defined as a composite of cardiovascular death, nonfatal myocardial, re-hospitalization for unstable angina, coronary revascularization or nonfatal stroke, occurred in 32.7% in the simvastatin-ezetimibe group compared to 34.7% in the simvastatin group (HR 0.94, 95% 0.89–0.99, $p = 0.016$). IMPROVE-IT was the first study to show a benefit for a non-statin agent to lower LDL-C and improve prognosis after ACS [14]. The effect of ezetimibe was even more pronounced when taking into account the reduction of total events, including events beyond the first event (56% first events and 44% subsequent events), with a risk reduction of 9% (95% CI 3–15%, $p =$ 0.007), mainly driven by a decrease of nonfatal myocardial infarction and stroke [15]. Patients achieving both the targets for LDL-C < 1.8 mmol/l and hs-CRp < 2 mg/dL had significantly lower major adverse cardiovascular events (28.0% *vs.* 38.9%, HR 0.73, 95% CI 0.66–0.81, $p < 0.001$) [16]. Regarding the distribution of achieved LDL-C, 6.4% patients had less than 0.78 mmol/l, 31% between 0.78 and 1.29 mmol/l, 36% between 1.29 and 1.8 mmol/l and 26% above 1.8 mmol/l [17]. The adjusted risk of primary efficacy endpoint was lowest for those with LDL-C < 0.78 mmol/l (HR 0.79, 95% CI 0.69–0.91, $p = 0.001$) compared to those with LDL-C > 1.8 mmol/l [17]. Regarding safety outcomes, no significant differences were

observed across LDL-C ranges. Neurocognitive adverse events were 2.1% for patients with LDL-C below 0.78 mmol/l, 2.5% for patients with LDL-C between 0.78 and 1.29 mmol/l, 2.9% for patients with LDL-C between 1.29 and 1.8 mmol/l and 2.3% for patients with LDL-C above 1.8 mmol/l [17]. In the subgroup of patients with diabetes (N = 4933), ezetimibe was associated with a significant reduction of the primary endpoint (HR 0.85, 95% CI 0.78–0.94, p for interaction with non-diabetes = 0.02). The benefit of ezetimibe in the diabetic population was more pronounced compared to their nondiabetic counterparts [18].

1.4. Evolocumab

The impact of evolocumab on cardiovascular events was evaluated in the FOURIER trial that included 27,564 patients with atherosclerotic cardiovascular disease and LDL-C levels >1.8 mmol/l despite maximally tolerated statin treatment [19]. The addition of evolocumab (either 140 mg every 2 weeks or 420 mg monthly) was compared to placebo considering a primary composite efficacy endpoint of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina or coronary revascularization. At the term of a 2.2 years median treatment duration period, patients under evolocumab had achieved a 59% reduction in LDL-C (from 2.4 mmol/l to 0.78 mmol/l, $p < 0.0001$) and had significantly lower rates of cardiovascular events (9.8% *vs.* 11.3%, hazard ratio [HR] 0.85, 95% CI 0.79–0.92, $p < 0.001$, for the primary endpoint). When focusing on specific individual endpoints, cardiovascular death between both treatment arms was similar (1.8% *vs.* 1.7%, p=0.62), as was death from any cause (3.2% *vs.* 3.1%, p=0.54) [19]. The efficacy of evolocumab was mainly driven by a reduction of myocardial infarction (3.4% *vs.* 4.6%, HR 0.73, 95% CI 0.65–0.82, $p < 0.001$), coronary revascularization (5.5% *vs.* 7.0%, HR 0.78, 95% CI 0.71–0.86, $p < 0.001$) and ischemia stroke or transient ischemic attack (1.7% *vs.* 2.1%, HR 0.77, 95% CI 0.65–0.92, p=0.003). On the opposite, no effect was observed on cardiovascular mortality (1.8% *vs.* 1.7%, HR 1.05, 95% CI 0.88–1.25, p=0.62) nor on all-cause mortality (3.2% *vs.* 3.1%, HR 1.04, 95% CI 0.91–1.19, p=0.54). As also observed with statin therapy, the benefit of LDL-C lowering with evolocumab was more pronounced over time, with an accentuation of risk reduction beyond 12 months. Long-term data would be needed to clarify whether PCSK9 mAb could reduce mortality. No significant differences were found when comparing different subgroup analyses between treatments, such as baseline LDL-C levels. Of note, around 70% of patients were on high-intensity and 30% on moderate-intensity statin at baseline; less than 1% patients were on a suboptimal statin regimen. Regarding safety, no significant differences were reported compared to placebo, although injection-site reactions were higher for evolocumab. Findings from the FOURIER trial suggest that decreasing LDL-C below the current recommended target of 1.8 mmol/l could have an incremental benefit in terms of reducing cardiovascular events. These novel findings are in concordance with the intravascular ultrasound imaging results observed in the GLAGOV study, which demonstrated an additional beneficial effect on atherosclerotic plaque size reduction for LDL-C values between 0.52 and 0.65 mmol/l compared to higher values [20]. The clinical efficacy of achieving low LDL-C concentrations with PCSK9 inhibition follows a monotonic relationship, and major cardiovascular adverse events have been observed to be lowest in patients with LDL-C concentrations <0.2 mmol/l ($p = 0.0012$) [21]. In the FOURIER trial, the majority of patients on active treatment achieved LDL-C values below the recommended target of 1.8 mmol/l: 10% of patients reached very low LDL-C levels, with values < 0.5 mmol/, 31% patients reached levels between 0.5 and 1.3 mmol/l, and 13% between 1.3 and < 1.8 mmol/l; as a direct consequence, the rates of cardiovascular events recorded after ACS for these patients were additionally decreased compared to those of patients whose LDL-C targets were >1.8 mmol/l or above: 29% of patients achieved targets between 1.8 and 2.6 mmol/l and 17% had target values > 2.6 mmol/l [17].

The EBBINGHAUS (Evaluating PCSK9 Binding Antibody Influence on Cognitive Health in High Cardiovascular Risk Subjects) substudy of the FOURIER trial assessed the safety of low LDL-C values on cognitive function [22]. The Cambridge Neuropsychological Test Automated Battery was used to test specific executive functions for working memory (strategy and planning), and as secondary outcome psychomotor speed at baseline, 24 weeks and at the study completion (19 month median follow-up). No significant differences were found in cognitive functions between evolocumab and placebo and the primary endpoint met criteria for non-inferiority ($p < 0.001$). In addition, changes in cognitive functions in the group with very low LDL-C values (<0.65 mmol/l) were similar compared to those with higher LDL-C levels and were not clinically relevant. Of note, participants in the EBBINGHAUS were relatively young to develop cognitive dysfunctions, as their mean age at the start of the trial was 62.8 ± 8.7 years.

1.5. Bococizumab

In the SPIRE (Evaluation of Bococizumab in Reducing the Occurrence of Major Cardiovascular Events in High Risk Subjects) 1 and 2 trials, bococizumab reduced LDL-C levels by 55–60% in the short term, but in 10–15% of patients this effect was severely attenuated due to the development of anti-bococizumab antibodies [23]. The immunogenicity of these antibodies specific to bococizumab is probably explained by the nature of the drug, a partially humanized (chimeric) monoclonal antibody compared to the fully human monoclonal antibodies alirocumab and evolocumab. In the SPIRE 2 trial, although a wide variability in the LDL-C response was observed, a significant effect on the absolute event rates for major adverse cardiovascular events was achieved in favor of anti-PCSK9 monoclonal antibodies (mAb) (3.32% *vs.* 4.19%, relative risk reduction 21%, p=0.02) [23]. The development of bococizumab was discontinued in 2016.

1.6. Alirocumab

The efficacy alirocumab was tested in several phase II trials that included patients in primary and secondary prevention. The achieved levels of 55–60% LDL-C reduction are comparable to the results obtained both with evolocumab and bococizumab in all subgroups analyzed. These low LDL-C values were maintained over time, and no impact on efficacy due to anti-alirocumab antibodies has been raised so far. Regarding potential side effects, a recent meta-analysis that included data on cognitive functions did not raise any specific concerns [24]. A *post-hoc* analysis of the ODYSEEY LONG TERM study that included 2341 patients with familial hypercholesterolemia observed over a period of 78 weeks reported reductions both in major adverse cardiovascular events (1.7% *vs.* 3.3%, HR 0.52, 95% CI 0.31–0.90, $p = 0.02$) and LDL-C levels (1.5 mmol/l *vs.* 3.2 mmol/l) [25]. The findings of the ODYSSEY OUTCOMES (Evaluating of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) trial are expected to be presented in 2018 and will be determinant to clarify the impact of this additional PCSK9 inhibitor on clinical outcomes.

A network meta-analysis of randomized controlled trials in

patients with hypercholesterolemia assessed the impact of two PCSK9 mAb, alirocumab and evolocumab, on lipid levels and outcomes. The analysis included 17 trials with 13,083 patients (8250 received PCSK9 mAb, 3957 placebo and 846 ezetimibe). PCSK9 mAb was associated with a 57% LDL-C reduction compared to placebo and 36% compared to ezetimibe [26]. The use of PCSK9 mAb was also associated with a reduced incidence of all-cause mortality (odds ratios [OR] 0.43, 95% CI 0.22–0.82, $p = 0.01$). Recently, findings of the ODYSSEY OUTCOMES trial (Evaluating of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) have been presented during the American College of Cardiology (ACC) meeting. Post-ACS patients with LDL-C $\geq$ 100 mg/dL were randomized after a un-in period of 2–16 weeks on high-intensity statin to alirocumab 75 mg or 150 mg every 2 weeks (N = 9462) or placebo (N = 9462). Alirocumab was associated with a reduction of mean LDL-C by 54.7% (101.4 mg/dL *vs.* 53.3 mg/dL) and major adverse cardiovascular (CHD death, nonfatal MI, stroke or unstable angina) after a median follow-up of 2.8 years (9.5% *vs.* 11.1%, HR 0.85, 95% CI 0.78–0.93, p=0.0003). In secondary analyses, all-cause death was also reduced (3.5% *vs.* 4.1%, HR 0.85, 95% CI 0.73–0.98 p=0.026), as well as ischemia-driven coronary revascularization (7.7% *vs.* 8.8%, HR 0.88, 95% CI 0.79–0.97, p=0.009). No safety signal was reported.

1.7. Inclisiran

In addition to PCSK9 mAb, a chemically synthesized small interfering RNA to target PCSK9 messenger RNA has been tested in a phase 2 trial in 501 patients at high cardiovascular risk with elevated LDL-C [27]. The two-dose 300 mg of inclisiran produced the greatest reduction of LDL-C levels compared to placebo by 52.6% after a follow-up of 6 months. Further studies are needed to clarify the impact of inclisiran on outcomes.

1.8. Risk stratification

In order to identify patients who might most benefit most from ezetimibe therapy, the TIMI (Thrombolysis in Myocardial Infarction) Risk Score for Secondary Prevention was tested to predict major adverse cardiovascular events [28]. This score contains the following variables: congestive heart failure, hypertension, age $\geq$75 years, diabetes mellitus, prior stroke, prior coronary artery bypass graft, peripheral artery disease, chronic renal failure (eGFR < 60 ml/min) and smoking [16]. In the IMPROVE-IT trial, patients at high-risk were defined as having $\geq$3 risk factors and benefited most from ezetimibe (absolute risk reduction 6.3%, 95% CI 2.9–97%), which translated into a number needed to treat of 16 in order to prevent one cardiovascular event. In contrast, for patients at low risk (risk factor 0 or 1) there was no benefit in adding ezetimibe therapy. These findings suggest that besides the magnitude of LDL-C reduction and absolute achieved LDL-C values, specific patient characteristics and individual risk profile independently affect the efficacy of lipid-lowering treatments. Further data are needed to assess whether such risk stratifications can also be applied to PCSK9 mAb.

Another option for risk stratification could be the use of Dutch Lipid Clinic classification to identify patients with FH. In the Swiss SPUM ACS cohort, 4543 patients with ACS were classified as having HF according to the Dutch Lipid Clinic Definition the American Heart Association definition. Patients with FH and ACS showed a >2-fold adjusted risk of coronary events recurrence within the first year following discharge compared with patients without FH, despite concomitant use of high-intensity statin in many cases [24].

1.9. Guidelines

Following new evidence merging from trials assessing the efficacy of PCSK9 mAb, the European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) presented practical clinical consensus for the use of PCSK9 mAb for patients with atherosclerotic cardiovascular disease (ASCVD) or familial hypercholesterolemia (FH) [29]. The main aim of the consensus is to clearly define the profile of patients at very high risk of ASCVD events, the absolute LDL-C values and/or the extent of LDL-C reduction to be achieved with maximally tolerated statin with or without ezetimibe, and to describe an LDL-C threshold value for the initiation of PCSK9 mAb treatment. For example, for patients with ASCVD, the ESC/EAS consensus suggests PCSK9 mAb for LDL-C threshold values > 3.6 mmol/l, in other words a lipid value requiring a 50% reduction to achieve recommended targets. The presence of additional factors of severity was also taken into account, such as rapidly progressing ASCVD (through recurrence of ACS, unplanned coronary revascularization, or ischemic strokes within a timeframe of 5 years), FH, diabetes mellitus with target organ damage, complex multivessel or severe polyvascular atherosclerotic disease, and finally a lower threshold for LDL-C > 2.6 mmol/l. For patients with FH but without a clinically diagnosed ASCVD, an LDL-C threshold >4.5 mmol/l has been proposed for considering PCSK9 mAb. In the presence of additional factors of severity, such as diabetes mellitus with organ damage, lipoprotein(a) > 50 mg/dL, patients > 40 years of age without any previous lipid-lowering treatment, premature ASCVD in first-degree relatives (<55 years in males and <60 years in female) or imaging markers documented on tomography angiography (left main disease, proximal left anterior descending artery disease, 3-vessel disease), the threshold of LDL-C for considering PCSK9 mAb treatment has been adapted to > 3.6 mmol/l.

It is of note that eligible patients should always be on maximally tolerated statin therapy and the LDL-C response assessed only once patients have been under stable therapy for at least 4 weeks. If LDL-C goals are not achieved, the use of ezetimibe should be considered LDL-C levels measured after 4 weeks. If, after the use of both maximally tolerated statin and ezetimibe, LDL-C levels are still not at target, PCSK9 mAb should be considered. The first measurement of LDL-C following PCSK9 mAb injection should be scheduled 2 weeks after initiation of treatment.

1.10. Eligibility for PCSK9 mAb after ACS

In a Swiss cohort of 2023 patients hospitalized for ACS, the proportion of patients who would be eligible for PCSK9 mAb treatment at 1 year after ACS was 13.4% using the American College of Cardiology (ACC) criteria and 2.7% using ESC/EAS criteria [30]. There is a considerable gap between these values that can mainly be explained by the differences that exist between the ACC and the ESC/EAS with regard to treatment initiation thresholds for PCSK9 mAb. According to the ESC/EAS criteria, PCSK9 mAb eligibility is defined as LDL-C $\geq$ 3.6 mmol/l while on maximally tolerated statin in combination with ezetimibe, or LDL-C $\geq$ 2.6 mmol/l in case of rapid progression of ASCVD. According to the ACC criteria, eligibility for PCSK9 mAb is defined as LDL-C $\geq$ 2.6 mmol/l while on statin in combination with ezetimibe, and an achieved reduction of LDL-C < 50% from baseline; or LDL-C $\geq$ 1.8 mmol/l in case of diabetes mellitus or recurrent ASCVD events within 3 months. Patients both with possible or probable/definite FH were more systematically more eligible for PCSK9 mAb according to ACC *vs.* ESC/EAS criteria (27.6% *vs.* 8.8%, and 6.6% *vs.* 1.8%, respectively) [10].

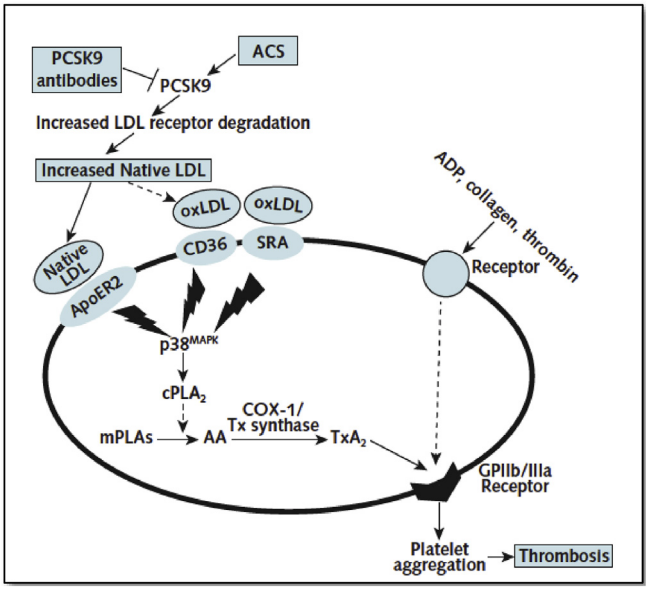

Fig. 1. PCSK9 increases coronary plaque vulnerability through several pathways, including pro-inflammatory low-density lipoprotein oxidation and direct modification of plaque composition.

1.11. Perspectives

The management of lipid disorders is characterized by the emergence of novel therapies acting on new biological targets. The combination of novel and established treatment agents adds new perspectives and options for the implementation of personalized medicine, based on individual risk profile and baseline LDL-C levels. Over time, the recommended target for LDL-C has become more stringent, moving from 2.6 mmol/l to 1.8 mmol/l for patients at very high-risk, including those with ACS [31]. A growing body of evidence is demonstrating that a decrease in LDL-C values beyond the recommended targets by combining agents, such as PCSK9 mAb with statin and/or ezetimibe improves the overall cardiovascular risk prognosis. Achievement of very low LDL-C levels to values less than 1 mmol/l is now possible for a majority of patients after ACS, and available data confirm the safety of such combinations, especially with regard to neurocognitive events at two-years' follow-up [19,21]. So far, the use of PSCK9 mAb has only been studied in ACS patients following an adaptation run-up period of 2–3 months with statin. No study has specifically assessed the use of PCSK9 mAb in the acute phase of ACS (<1 month). Some data suggest that circulating PCSK9 levels in the acute phase of ACS is increased with inflammation, potentially justifying earlier initiation of PSCK9 mAb treatment (Fig. 1). [32,33]. Therefore, secondary prevention in the outpatient setting has a major role for the medical decision regarding lipid-lowering therapies after ACS. There is a crucial need for improvement of risk prediction based on biomarkers or the use of clinical score to identify and personalize treatment. The current main issue in several countries is the cost-effectiveness of lowering LDL-C below recommended targets. In the United States, a cost-effectiveness analysis from the perspectives of the health system and based on the results from the FOURIER trial reported an incremental cost-effectiveness ratio for the use of PCSK9 mAb, in addition to statin, of 337,729$ per quality-adjusted life-years, and a low probability (<1%) of being cost-effective at the commonly accepted societal threshold of 100,000$ per quality-adjusted life-years [34]. In the future, an alternative scenario will be needed to clarify the impact of lowering LDL-C at levels below than recommended targets in term of efficacy, safety and costs. In addition, new clinical data may be convincing to lower even more the targets of LDL-C just after ACS. The EVOlocumab for Early Reduction of LDL-C Levels in Patients With Acute Coronary Syndromes (EVOPACS) study will specifically study the impact of LDL-C lowering using PCSK9 mAb in the acute phase of ACS (NCT03287609). This trial will add new evidence to the benefit of an earlier management of lipid-lowering therapy in the process of care of ACS patients. There is no doubt that discussions and controversies will continue for defining criteria for the reimbursement of those treatments. Selecting the best patients and the role of potential markers could aid in these decisions, as well as a systematic screening strategy to identify patients with FH at the time of ACS [35].Obviously, ACS patients have multiple risk factors and require a global preventive approach. In that sense, more data are needed to assess the incremental impact of lowering LDL-C besides improving life style. Finally, the exact timing of starting lipid-lowering therapy has to be defined. Guidelines recommend to start therapy as early as possible and "earlier is good" is accepted as a standard of care, but data need to be strengthened [36]. Table 5 summarized the main arguments supporting or not the advantages of earlier initiation of lipid-lowering in ACS (see Fig. 2).

2. Conclusion

LDL-C is a major therapeutic target in patients after ACS. Current evidence suggests that decreasing LDL-C to reach the recommended target of <1.8 mmol/l markedly improves prognosis and is not associated with safety concerns. The use of novel treatment combinations in ACS will need to be further explored to widen the perspectives of a more personalized approach for the management of ACS based on individual patient risk profile and baseline LDL-C values, and their relative cost-effectiveness will also need to be assessed.

Table 5
Arguments supporting the earlier lowering of LDL-C in ACS.

Pro	Con
Evidence in the reduction of long-term outcomes	Exact timing to initiate therapy not defined
Safety of low LDL-C values	Preloading dose of statin not supported
Indicator of quality of care at hospital	No data for PCSK9 inhibitors prior PCI
Pleotropic effect of statin	LDL-C not a prognostic marker after ACS
Counteract outpatient inertia of therapy	Baseline LDL-C prior ACS not always available
Effect on the plaque stabilization	Titration *vs.* high-intensity controversies
Statin not expensive therapy	Use of ezetimibe at hospital discharge not tested

ACS, acute coronary syndrome; LDL-C low-density lipoprotein cholesterol; PCI, percutaneous coronary intervention; PCSK9, proprotein convertase subtilisin kexin 9.

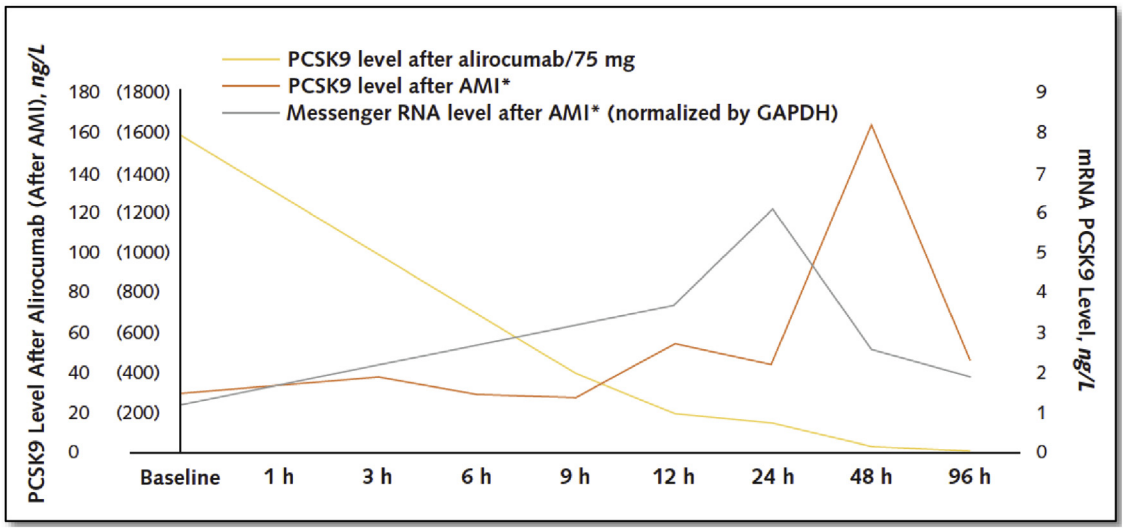

Fig. 2. PCSK9 peak levels during ACS, which relate to the time to maximal effect of PCSK9 antibodies.

Conflicts of interest

F.M. has received unrestricted research grants from Amgen, MSD and Sanofi, and was a Principal Investigator for the FOURIER, ODYSSEY OUTCOMES, and IMPROVE-IT trials. BG has no conflicts to declare.

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Levels of PCSK9 increase during ACS as a consequence of cardiac ischemia and could be a therapeutic target in this setting. With the permission of authors [33]. ADP, Adenosine diphosphate; ACS, acute coronary syndromes; LDL: low-density lipoprotein; PCSK9, proprotein convertase subtilisin kexin type 9.

Treatment with PCSK9 antibodies could be beneficial to patients with ACS by reducing low-density lipoprotein cholesterol levels and promoting early plaque stabilization via anti-inflammatory and antithrombotic mechanisms. With the permission of the authors [33].

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