European Heart Journal Supplements (2023) **25** (Supplement B), B114–B118
The Heart of the Matter
https://doi.org/10.1093/eurheartjsupp/suad086

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European Society
of Cardiology

Acute coronary syndromes: hospital management of dyslipidaemia with proprotein convertase subtilisin/kexin 9 inhibitors: time to act

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KEYWORDS
ACS;
Lipid-lowering therapy;
PCSK9 inhibitors;
Statins

Atherosclerotic cardiovascular disease (ASCVD) in its countless clinical presentations is, in industrialized countries, the most frequent cause of death and, in recent years, a leading role in the prevention of ASCVD has been attributed to the treatment of dyslipidaemias. If statins and ezetimibe remain the cornerstone of pharmacological treatment, an increasingly relevant role is attributed to the inhibitors of the proprotein convertase subtilisin/kexin 9 (PCSK9i), as a result of the excellent results obtained in their respective trials, not only on the reduction of low-density lipoprotein (LDL) or LDL cholesterol (LDL-C) but also on plaque stabilization and regression. The addition of PCSK9 inhibitors leads to a further reduction in LDL levels and a consequent improvement in prognosis and it is recommended in 'fast-track' administration (intrahospital/discharge) in patients with acute coronary syndromes (ACSs) or multiple cardiovascular events already on statin therapy and LDL >70 mg/dL and in statin-naïve ACS patients and LDL >140 mg/dL. By applying guidelines and fast-track, ~25% of patients with ACS should receive PCSK9i at discharge but unfortunately patients are currently undertreated.

Atherosclerotic cardiovascular disease (ASCVD) in its countless clinical presentations is, in industrialized countries, the most frequent cause of death, responsible for over 4 million deaths every year, only in Europe. According to estimates by the World Health Organization, aggressive control of modifiable risk factors could prevent up to 80% of premature deaths related to ASCVD, therefore the importance of maximizing the efforts of physicians and patients is evident in this direction (*Figure 1*, *Tables 1* and *2*).[1]

In recent years, a leading role in the prevention of ASCVD has been attributed to the treatment of dyslipidaemias. From the latest 2019 guidelines of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) on the management of dyslipidaemias, very ambitious targets have emerged and indications for a close follow-up for optimizing the therapy of patients at cardiovascular risk. If statins and ezetimibe remain the cornerstone of pharmacological treatment, an increasingly relevant role is attributed to the inhibitors of the proprotein convertase subtilisin/kexin 9 (PCSK9i), as a result of the excellent results obtained in their respective trials, not only on the reduction of low-density lipoprotein (LDL) or LDL cholesterol (LDL-C) but also on plaque stabilization and regression.[2]

However, the availability of highly effective drugs alone is not enough unless accompanied by appropriate prescribing by the cardiologist and strict patient compliance: recent data suggest that, in clinical practice, suboptimal management of hypercholesterolaemia is widespread and goals are achieved in only 30% of patients.[3]

The scientific evidence relating to the pivotal role of cholesterol in the pathogenesis of atherosclerosis has led, in recent years, to identify the treatment of dyslipidaemia as one of the fundamental pillars for the primary and secondary prevention of cardiovascular disease. Indeed, it has been extensively demonstrated through randomized trials and Mendelian randomization that the burden of atherosclerotic disease is not only dose-dependent but also time-dependent in a log-linear relationship with

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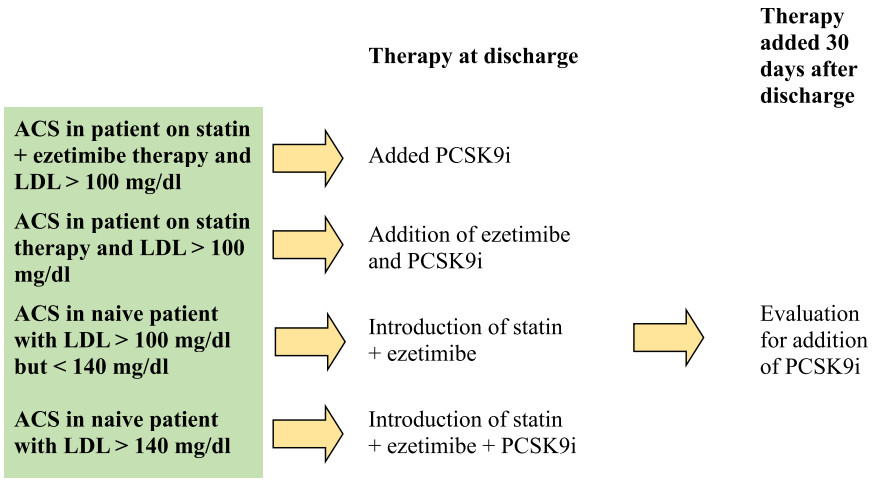

Figure 1 Therapeutic approach adopted by our Centre in relation to different clinical scenarios.

Table 1 Prescription trend of lipid-lowering therapy

	1 Jan 2020-31 Mar 2020 *N* = 118	1 Apr 2020-30 Jun 2020 *N* = 73	1 Jul 2020-30 Sept 2020 *N* = 95	1 Oct 2020-31 Dec 2020 *N* = 108	1 Jan 2021-31 Mar 2021 *N* = 108	1 Apr 2021-30 Jun 2021 *N* = 112	Variation (%)
Low statin intensity *n* (%)	9 (8)	4 (5)	4 (5)	2 (1.9)	3 (3)	3 (3)	−59
High statin intensity, *n* (%)	74 (63)	30 (41)	27 (28)	24 (22)	8 (8)	13 (12)	−77
Statin + ezetimibe, *n* (%)	31 (26)	29 (40)	52 (55)	64 (59)	69 (64)	65 (58)	+117
Plus Evolocumab, *n* (%)	4 (3)	10 (14)	14 (15)	19 (17)	27 (25)	30 (27)	+759

LDL-C levels.[4] If reducing LDL-C by 1 mmol/L reduces cardiovascular risk by 21%, Mendelian randomization studies show an even greater reduction (up to 50–55%) when considering the cumulative effect of prolonged exposure to low cholesterol levels.[5,6] Therefore, it is of paramount importance not only to reach the target but also to reach it early, as the effect on reducing cardiovascular events is greater the earlier the intervention, especially in secondary prevention. In fact, patients with a recent acute ischaemic event are the most likely to develop new cardiovascular events, as confirmed by a subanalysis of the FOURIER study.[7] These findings have been translated in the most recent ESC/EAS 2019 Guidelines on the Management of Dyslipidemia into goals that are all the more ambitious the higher the patient's cardiovascular risk, lowering the therapeutic target from 70 mg/dL (1.8 mmol/L) to 55 mg/dL (1.4 mmol/L) in addition to a reduction of at least 50% from baseline values, for patients at very high risk (a category in which virtually all of our patients with ischaemic heart disease fall).[2]

Although statins and ezetimibe remain the cornerstones of therapy, the expected LDL reduction with the aforementioned drugs does not exceed 50%. Instead, PCSK9 inhibitors, such as the monoclonal antibodies Alirocumab and Evolocumab, have been shown to reduce LDL-C by 43–76% more than placebo and 30% more than ezetimibe.[8] This reduction in LDL-C values translated into a significant reduction in cardiovascular events: in the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) study, Evolocumab resulted in a 27% reduction in the relative risk of myocardial infarction, 21% of stroke, and 22% of coronary revascularization and similar results were observed in the Occurrence of Cardiovascular Events in Patients Who Have Recently Experienced an Acute Coronary Syndrome (ODYSSEY OUTCOME) study for Alirocumab.[8,9] More recent studies, High-Resolution Assessment of Coronary Plaques in a Global Evolocumab Randomized Study (HUYGENS)[10] for Evolocumab and Effects of the PCSK9 Antibody AliroCuMab on Coronary Atherosclerosis in PatieNts with Acute Myocardial Infarction (PACMAN-AMI)[11] for Alirocumab, confirmed the data previously emerging in the GLobal Assessment of Plaque reGression With a PCSK9 antibOdy as Measured by intraVascular Ultrasound (GLAGOV) study,[12] demonstrating the ability of PCSK9i to reduce the progression of atherosclerotic disease with a stabilizing effect on the atheromatous plaque documented by an increase in the thickness of the fibrous cap and a reduction in its lipid arc.

Since April 2020, our Centre has adopted the treatment approach of the position paper of the Italian Society of Interventional Cardiology (GISE) by identifying patients who could benefit from in-hospital or discharge prescription of PCSK9i.[13] Subsequently, in line with the proposal of Ray *et al.*,[14] a prescribing procedure was also outlined in relation to patient risk, angiographic characteristics, and baseline LDL-C values. In July 2022, our experience translated into a study of a real population of patients discharged after an acute coronary syndrome (ACS) between January 2020 and June 2021, to assess how lipid-lowering

drug prescriptions changed in response to the new recommendations and the effectiveness of therapy in terms of achieving the goals recommended by guideline.[15]

Among the currently available PCSK9i, Evolocumab had features in terms of dosing and prescribing that led us to select it as the drug of choice during the study period. The dosing is unique and therefore does not require short-term reevaluation of the patient with blood tests for possible dose titration. This aspect proved to be critical in providing our patients with optimized medical therapy even during a complex period such as the pandemic, during which the management of short-term follow-ups was very complex and often logistically impossible. Moreover, solid safety data are available for Evolocumab even for very low LDL values (<25 mg/dL), since, already in the FOURIER study, 42% of patients achieved LDL values <25 mg/dL, with no differences in terms of total or serious adverse events leading to discontinuation of therapy.[8] These data were later confirmed by a *post hoc* analysis of the FOURIER study, in which LDL-C values <10 mg/dL were also achieved, with no evidence of serious adverse events or such as to result in drug discontinuation.[16] The safety of long-term exposure to low levels of LDL-C was then evaluated in the Open Label Study of Long-Term Evaluation Against LDL-C Trial (OSLER-1),[17] with a 5-year follow-up, dispelling initial clinical concerns about the potential risks, especially neurocognitive risks, associated with the use of PCSK9 inhibitors.

Despite the availability of highly effective drugs, the gap between guideline recommendations and clinical practice is still very wide. Among the many factors that may influence this suboptimal management of dyslipidaemia, inadequate prescribing and poor therapeutic compliance play a key role. In our population of consecutively hospitalized real-world ACS patients, at baseline, most patients were receiving hypolipidaemic therapy (62%), but only 17% achieved their target risk profile. Furthermore, while a significant percentage of patients with prior ACS were already taking lipid therapy at home prior to hospitalization (16 vs. 3.4%, $P < 0.001$), the same was not observed in patients diagnosed with peripheral arterial disease (33 vs. 29%, P 0.43), confirming a low treatment rate, even in patients identified by the guidelines as being at very high risk. These real-world data, derived from our study, highlight how dyslipidaemia and subsequent atherosclerosis are underdiagnosed problems, which, more often than not, physician and patient become aware of only during a hospitalization for an acute complication, be it coronary artery disease or limb ischaemia. The change in therapeutic strategy in response to the new guidelines published in late 2019 began to materialize with the introduction of fast-track, for patients with recent myocardial infarction (within 12 months) or a history

Table 2 Six months follow-up

	Total = 569 statin or statin + ezetimibe	Evolocumab
ACS recurrence, *n* (%)	5 (1)	1 (0.9)
Revascularization		
On the same vessel, *n*	4	0
On new vessel, *n*	2	1
Myalgias *n* (%)	21 (4.5)	2 (1.9)
Skin reaction at the injection site, *n* (%)	0 (0)	2 (1.9)
Discontinuation of therapy, *n* (%)	5 (1)	0 (0)

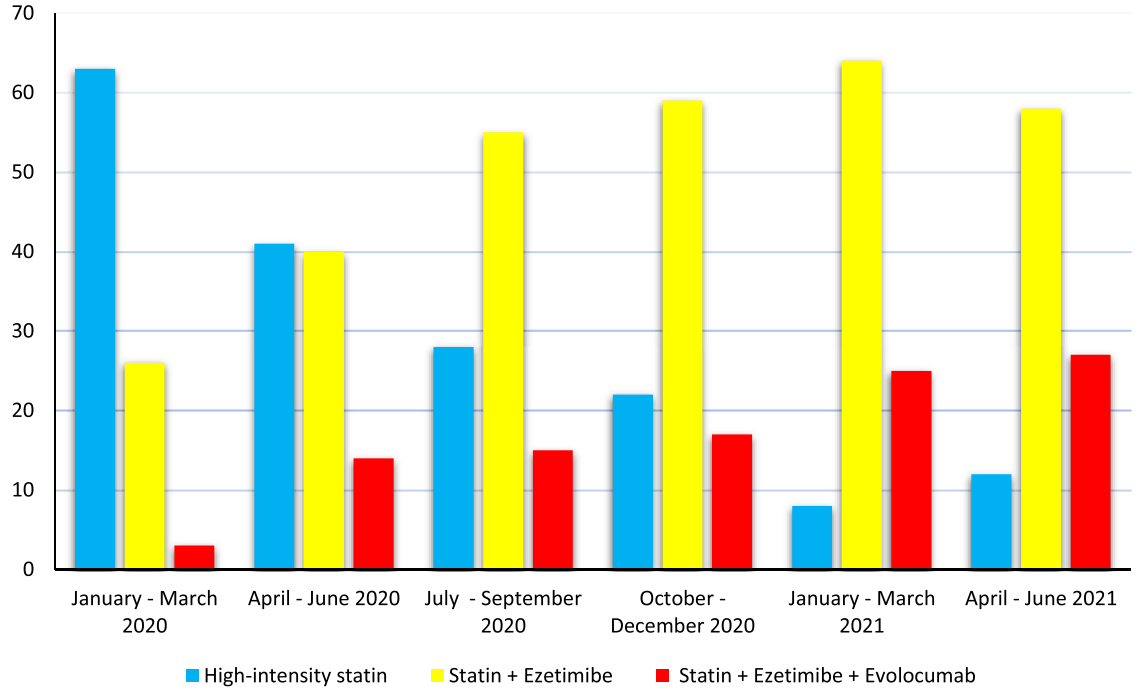

Figure 2 Prescription trends of various lipid-lowering therapies.

of multiple cardiovascular events.[13] In the wake of these indications, the prescribing of high-intensity statin monotherapy decreased from 63 to 12%, while the Evolocumab combination increased from 3 to 14% of discharged patients (*Figure 2*). While prescribing in this early period was in line with the stepwise approach proposed by the guidelines, the need to act intensively on high-risk patients has led to the establishment of a prescribing process with statin + ezetimibe combination therapy as the first step. In most cases, single statin therapy would not be sufficient to achieve the goal. Patients with very high cardiovascular risk and LDL values such that the therapeutic target could not be reached, either with statin therapy alone or in combination, were therefore candidates for Evolocumab prescription at discharge.

Out of a total of 621 patients treated from April 2020 to June 2021, 496 patients, 104 of whom were treated with Evolocumab (20%), were discharged from the Division of Cardiology of A. O. Mauriziano of Turin, arriving in the April–June 2021 quarter, affecting 27% of patients hospitalized for ACS. Patients who were candidates for PCSK9i were instructed as early as during hospitalization to properly manage subcutaneous administration of the drug.

This approach, in line with the flowchart of Ray *et al.*[14] also identifies additional risk elements that should guide the clinical cardiologist toward the immediate prescription of triple lipid therapy, such as multiple cardiovascular events, polyvascular disease, and multivessel coronary artery disease, parameters that in our study were in fact correlated with the prescription of PCSK9i, identifying patients at prohibitive risk, in whom LDL-C reduction should occur as quickly as possible.

Moreover, in our study, during the period from April 2020 to June 2021, the use of triple therapy at discharge in 20% of patients ensured that the 6-month LDL goal was achieved in 91% of patients. Adequate therapeutic adherence also plays a key role in achieving therapeutic goals. Low social status, the presence of comorbidities, and polypharmacotherapy are the factors that most frequently lead to discontinuation of therapy. Surprisingly, only in a minority of cases is discontinuation related to an undesirable drug effect, while up to 40% of patients discontinue therapy on physician's orders. The most frequent side effects reported by patients are muscle symptoms, particularly myalgias, muscle cramps, and muscle weakness. While statin-associated muscle symptoms (SAMS) have been found in some studies to occur in 10–15% of patients, recent work has pointed out that in many cases they are actually attributable to a nocebo effect.[18] Furthermore, SAMS are only rarely associated with an actual increase in creatine kinase values, warranting discontinuation of therapy, and serious adverse events such as rhabdomyolysis are extremely rare (1–3 cases/100 000 patients per year). In our population, side effects reported at 6-month follow-up were rare and did not lead to significant rates of discontinuation of therapy, this, in our opinion, to be related to the preponderant use of new generation statins, particularly rosuvastatin, associated with a lower incidence of side effects 6 months after discharge, 569 patients presented to the follow-up visit, among patients discharged with PCSK9i, due to proper information, therapeutic compliance was optimal and all patients discharged with Evolocumab took the drug correctly with excellent results in terms of therapeutic goals. In fact, patients on PCSK9i therapy, predominantly at very high cardiovascular risk [age <80 years, LDL-C >130 mg/dL, hospitalization for ST-elevation myocardial infarction (STEMI), multivessel coronary artery disease, previous cardiovascular events] achieved the goal of LDL-C < 55 mg/dL, with significantly greater reduction in cholesterol values than other treatment options. In terms of recurrence of cardiovascular events, six patients had re-hospitalization and underwent coronary revascularization (1%), including one patient on PCSK9i therapy (0.9%).

The results obtained are in line with what was observed in the EVOlocumab for Early Reduction of LDL-cholesterol Levels in Patients with Acute Coronary Syndromes (EVOPACS) study, which demonstrated a clear reduction in LDL-C with early introduction of Evolocumab, during the acute phase of an ACS.[19] More recently, FOURIER Open-label Extension (FOURIER-OLE)[20] confirmed incremental benefits in cardiovascular events, including cardiovascular mortality, with early use of Evolocumab, thus recommending early initiation of marked and sustained LDL-C reduction to maximize clinical benefit with persistently low rates of adverse events over 8 years.

In conclusion, there is increasing evidence of safety and efficacy for an intensive and early approach to post-ACS lipid reduction, 'strike early and strike strong',[21] with the combination of statin and ezetimibe as the first therapeutic step and possibly the prescription of PCSK9i as early as at discharge, to provide our patients with optimized therapy that can reduce mortality and morbidity rates through increasingly effective treatments while maintaining absolute safety profiles even with very low LDL-C values.

Funding

None declared.

Conflict of interest: None declared.

Data availability

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

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