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FULL RESEARCH PAPER
Lipids & atherosclerosis

Strike early–strike strong lipid-lowering strategy with proprotein convertase subtilisin/kexin type 9 inhibitors in acute coronary syndrome patients: real-world evidence from the AT-TARGET-IT registry

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Aims No data are available on early initiation of proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i) in patients with acute coronary syndrome (ACS) in the real world. This study investigates the effects of PCSK9i started at time of ACS hospitalization on lipid control and major cardiovascular (CV) events in the real world.

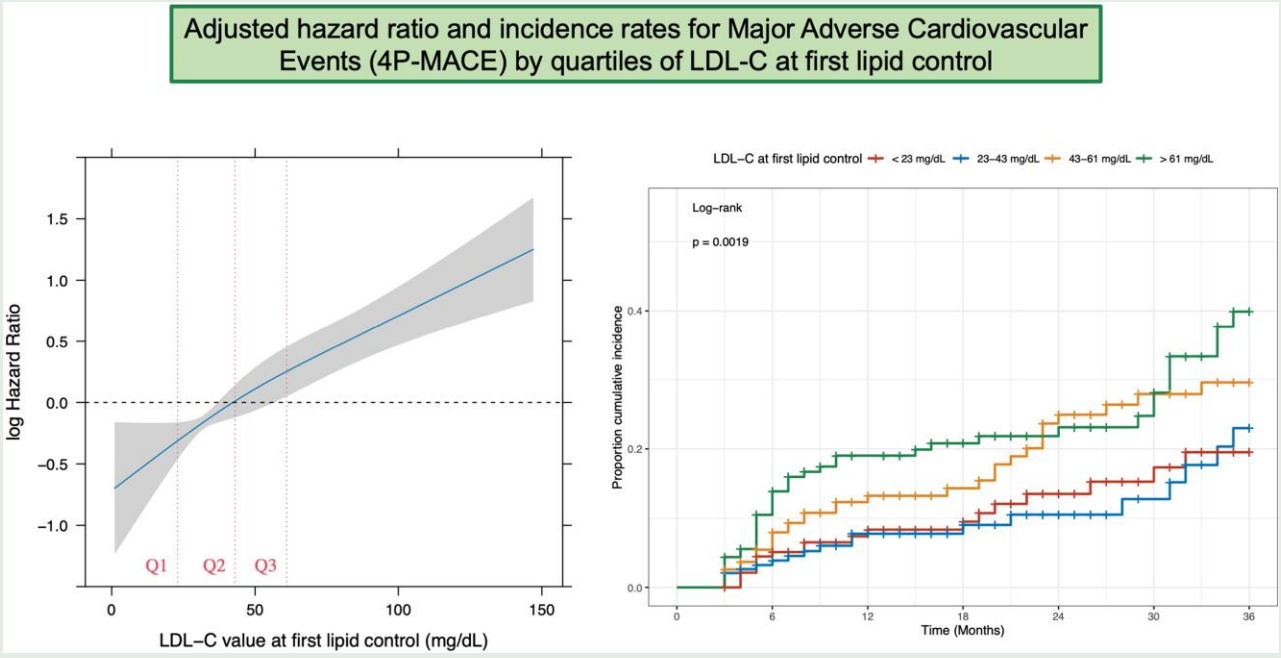
Methods and results The lipid control outcome was the percentage of patients reaching the LDL-C target of <55 mg/dL at first lipid control. The clinical outcome was the incidence of composite major CV events (all-cause death, non-fatal MI, non-fatal stroke, and ischaemia-driven revascularization) during a follow-up in relation to quartiles of LDL-C at first lipid control. We included 771 patients with ACS from the AT-TARGET-IT registry, receiving PCSK9i prescription during hospitalization or at discharge. Median LDL-C was 137 mg/dL and decreased to 43 mg/dL at first lipid control. 527 (68.3%) patients achieved LDL-C target at the first lipid control at a median time of 37 days from hospitalization; of them, 404 (76.8%) were discharged on statin plus ezetimibe background therapy. Event curves through a median follow-up of 11 months across quartiles of LDL-C showed a stepwise lower risk of 4P-MACE, 3P-MACE, all-cause mortality, and ischaemia-driven revascularization in lower quartile of LDL-C values at first lipid control (<23 mg/dL) and in patients reaching LDL-C < 55 mg/dL.

Conclusion Intensive and early lipid-lowering therapy using PCSK9i in patients with ACS (strike early–strike strong strategy) is safe and effective in clinical practice and associated with a reduction of residual CV risk.

Lay summary This study, from the AT-TARGET-IT registry, investigates the effects of PCSK9i started at time of ACS hospitalization on lipid control and major CV events in the real world.

- Intensive and early PCSK9i therapy reduces composite major cardiovascular (CV) events in patients reaching LDL-C target values.
- A *strike early–strike strong* strategy is safe and effective.

Graphical Abstract



Keywords Acute coronary syndrome • LDL cholesterol • Lipid-lowering therapy • PCSK9 inhibitors • Efficacy • Safety

Introduction

Patients with acute coronary syndromes (ACS) are at increased risk of recurrent atherothrombotic events early after the index event.[1,2] In ACS patients, lowering low-density lipoprotein cholesterol (LDL-C) reduces cardiovascular (CV) morbidity and mortality, with a clinical benefit proportional to the degree of LDL-C decrease.[3] In fact, in clinical trials, early initiation of intensive lipid-lowering therapy (LLT) in patients with ACS, with statins,[4,5] statins plus ezetimibe,[6] or proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i)[7] reduces the incidence of recurrent events and, therefore, is recommended by the current guidelines.[1,2,8] The clinical benefit is linearly related to the absolute reduction of LDL-C and extends to very low LDL-C values.[9] Recent intravascular imaging studies with either evolocumab[10] or alirocumab[11], in

which PCSK9i were administrated in patients with ACS on top of statins and compared with placebo, demonstrated that those treated with PCSK9i, in whom LDL-C values were lowered to a mean value of 28.1 mg/dL[10] and 23.6 mg/dL,[11] showed a significant increase of the minimum fibrous cap thickness, volume atheroma,[10] and lipid core,[11] in remote non-culprit plaques within 50[10] and 52[11] weeks, respectively, indicating favourable changes in the composition of coronary atherosclerotic lesions. Two small randomized trials[12,13] reported that the majority (90.1 and 92.1%, respectively) of patients with ACS-initiating PCSK9i during in-hospital stay, on top of statins, reached the LDL-C target of <55 mg/dL recommended by the guidelines[2,8] within 8 weeks from randomization. Thus, in clinical practice, a strategy of early initiation of PCSK9i would be feasible and of potential benefit in patients with ACS.[14]

Yet, no data are available on implementation in the real-world setting of the guidelines' recommendations in patients with ACS.[1,2] The AT-TARGET-IT study is an investigator-promoted, multicentre, single-country registry on use of PCSK9i in the Italian real-world practice that recently reported findings on PCSK9i use in our country. The aim of the present analysis was to investigate the population of ACS patients enrolled in the registry who received initial PCSK9i therapy within their in-hospital stay or at discharge for ACS, reporting effects on lipid control and major CV events.

Methods

Study population

The study design has been previously described.[15] In brief, AT-TARGET-IT (NCT05430828) is a single-country, multicentre, observational, phase IV registry of Italian patients initiating PCSK9i as part of their routine clinical management, based on the ESC/EAS guidelines' indications[8] and national reimbursement criteria[16] at time of enrolment. The registry included 22 Italian sites listed in Supplementary material. The present analysis includes patients with ACS who received PCSK9i prescription during in-hospital stay or at hospital discharge for ACS or within 4 weeks from ACS hospitalization, according to national reimbursement rules.[16] Enrolment period started on 01 March 2020 and ended on 31 May 2023.

Clinical characteristics of patients at initiation of PCSK9i, including demographics, CV risk factors, laboratory values, comorbidities, time of prescription, diagnosis of familial hypercholesterolaemia (FH), and other LLTs, lipid levels, PCSK9i, and LLTs type and dose, were collected by investigators in all sites using electronic health records.

Statin intolerance was determined primarily through patient-reported symptoms, at the discretion of the investigator. LDL-C measurements were collected as per clinical practice, and changes in LLTs were recorded. Adverse drug reactions (ADRs) were collected on the evaluation of the investigator.

Endpoints

(1) Lipid control: the main outcome of the analysis was the percentage of patients reaching the LDL-C target of <55 mg/dL at first lipid control.

Additional analysis included the adherence to treatment, defined as the extent, to which a patient takes prescribed medications according to the dosage and frequency recommended by the provider. The adherence was expressed as 'medication possession ratio' (MPR), defined as the ratio between the drug units dispensed during the treatment period and the duration of the treatment period itself. As reported in literature, we considered high adherence to therapy if MPR ≥ 80%, partial adherence if MPR <80% but ≥40%, and poor adherence if MPR < 40%.[17]

Patients were considered to have discontinued drugs if they permanently stopped therapy during the observation period. Persistence was defined as therapeutic continuity from the start of treatment upon enrolment.[18] Self-discontinuation was defined as a patient-driven discontinuation without a clinical reason.

(2) CV outcomes: the endpoint of the study was the incidence of composite major adverse CV events (MACE) during a follow-up in relation to quartiles of LDL-C at first lipid control. Composite clinical endpoint included death, non-fatal stroke, non-fatal myocardial infarction (MI), and ischaemia-driven revascularization (four-point MACE, 4P-MACE). We also tested the correlation between LDL-C at first lipid control and composite clinical endpoint of death, non-fatal stroke, and non-fatal MI (three-point MACE, 3P-MACE) and on single components of the composite endpoints.

Incidence of CV events was compared between patients achieving the LDL-C target of 55 mg/dL vs. those who did not and between patients below and above the LDL-C median value at first lipid control.

Statistical analysis

Continuous variables are presented as medians and interquartile range (IQR) or mean and standard deviation (SD) based on the normality of the distribution. Summaries are based on observed data, with no imputation applied for patients who did not have data at specific time points. Groups are compared using the Kruskal–Wallis tests. Categorical variables are presented as counts and percentages and groups compared using χ^2 tests. The difference in LDL-C between first lipid control and last lipid control was calculated. The patients were stratified according to the LDL-C at target status, quartile of LDL-C, and median value of LDL-C at first and last lipid control.

The relation between LDL-C at first lipid control to each clinical outcome is presented as cumulative Kaplan–Meier curves and analysed with Cox proportional hazards models with LDL-C value as a continuous variable, LDL-C at target status (LDL-C not at target as reference), and LDL-C median value (LDL-C above the median value as reference).

Analyses were adjusted for age, sex, body mass index, estimated glomerular filtration rate, smoking, previous coronary revascularization, history of diabetes, heart failure, hypertension, peripheral artery disease, and familial hypercholesterolaemia.

The relationships between LDL-C at first lipid control and outcomes were explored using restricted cubic splines to allow for non-linearity. Tests are two-sided throughout and a *P*-value <0.05 was considered as significant.

Ethical conduct of the study

The study was approved by Campania 3 Ethics Committee and reviewed by an independent ethics committee in each centre. The study was performed according to ethical principles that had their origin in the Declaration of Helsinki and was consistent with the International Council for Harmonisation. Written informed consent was provided by all patients. AT-TARGET-IT has been registered on ClinicalTrials.gov (NCT05430828) and on AIFA Observational Studies Registry.

Results

Demographical and baseline clinical characteristics

From 1836 patients on PCSK9i therapy included in the AT-TARGET-IT registry, we extracted data on 802 patients who received a prescription for PCSK9i at the time of ACS hospitalization. From 802 patients, 31 were subsequently excluded due to incomplete laboratory data; all 31 patients excluded were alive at the time of analysis. We therefore included 771 in the final analysis. Of 771 patients included in this analysis, 731 received a prescription for PCSK9i during in-hospital stay and 40 within 4 weeks from discharge after hospitalization for ACS (see Supplementary material online, *Figure S1*).

Mean age was 62 years (9.9 SD), and the majority was male (79.1%). Median time from baseline to first lipid control was 37 days (IQR 25, 77 days), whereas last lipid control occurred at 11 months (IQR 6, 26 months). Complete demographical and baseline clinical characteristics for the entire population and stratified for PCSK9i type are listed in Supplementary material online, *Table S1*.

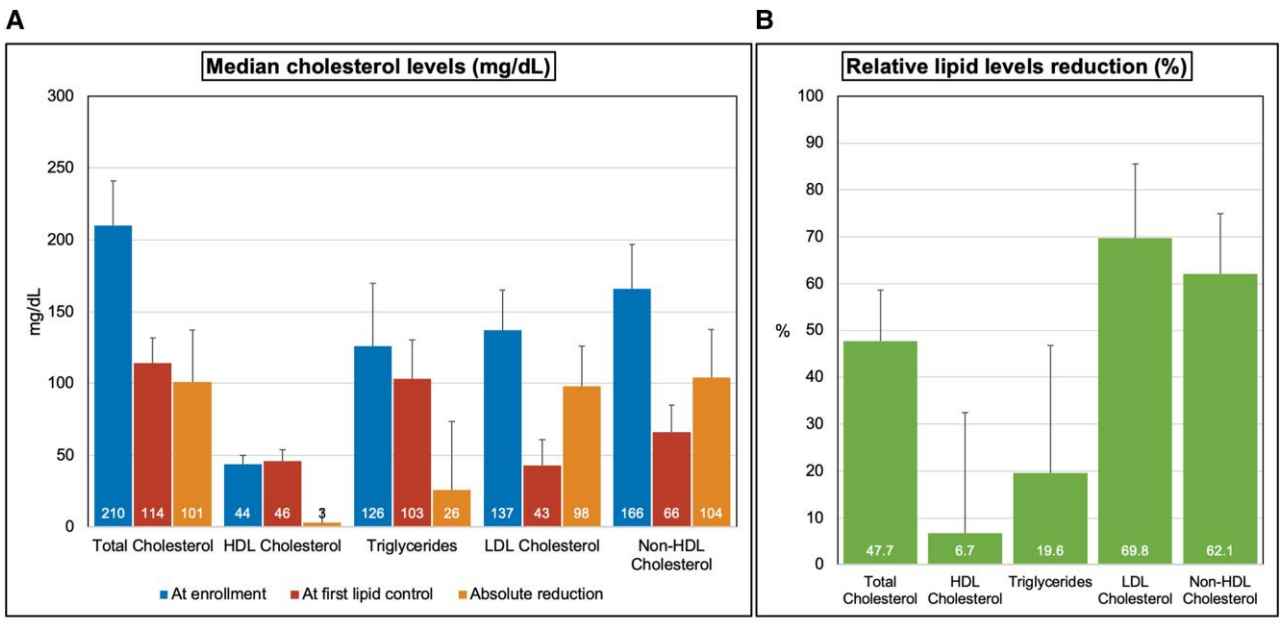


Figure 1 Low-density lipoprotein cholesterol values. On the left (*A*), median LDL cholesterol levels at enrolment and at first lipid control with median absolute reduction. On the right (*B*), median percentage reductions in the cholesterol values.

Background lipid-lowering therapies

Of 771 patients, 725 (93.9%) received LLTs at time of hospital discharge; of them 66 (9.1%) were on ezetimibe alone, 113 (15.6%) on statin alone, and 546 (75.3%) on a statin and ezetimibe combination (reflecting the reimbursement rule for early PCSK9i prescription in our country). The remaining 46 patients were discharged on PCSK9i alone. Type and dose of statin stratified by PCSK9i are detailed in Supplementary material online, *Table S2*. History of statin intolerance was reported in the 112 patients not receiving statin at discharge (46 with any LLTs and 66 with ezetimibe alone), with the most common reason being statin-induced myalgia (74 patients, 66.1%), followed by statin-induced elevation of creatine phosphokinase (29 patients, 25.9%) or transaminases (9 patients, 8%).

Efficacy, safety, adherence, and persistence of proprotein convertase subtilisin/kexin type 9 inhibitors

Complete data on the effect of PCSK9i on lipid profile at the first lipid control are shown in Supplementary material online, *Table S3*.

Median LDL-C at hospital admission was 137.0 mg/dL (IQR 115.0, 165.0 mg/dL) and reached 43 mg/dL (IQR 23.0, 61.0 mg/dL) at the first lipid control that occurred at a median of 37 days (IQR 26, 77 days) (*Figure 1A*). Median LDL-C levels remained substantially unchanged (49 mg/dL, IQR 28.0, 60.5 mg/dL) at the last lipid control at 11 months (IQR 6, 26 months). Median absolute reduction in LDL-C value at first lipid control was 98.0 mg/dL (IQR 64.0, 126.0 mg/dL) (*Figure 1A*), while median relative reduction in LDL-C was 69.8% (IQR 54.2%, 84.6%) (*Figure 1B*). In addition, when the reduction of LDL-C values was analysed by quartiles at first lipid control (Q1: 15–26 days, Q2: 27–37 days, Q3: 38–77 days, and Q4: 78–180 days) (*Figure 2A*) or by quartiles at last lipid control (Q1: 3–6 months, Q2: 7–11 months, Q3: 12–26 months, and Q4: 27–36 months) (*Figure 2B*), no significant differences were found in the percentage of LDL-C reduction in comparison to baseline values. The percentage reduction of LDL-C was significantly higher with more intense LLTs (see Supplementary material online, *Figure S2*; Supplementary material online, *Table S4*).

Of 771 patients included in the study, 527 (68.3%) achieved LDL-C target at first lipid control (see Supplementary material online, *Table S5*). Of 527 patients achieving LDL-C target, 73 (13.8%) were on statin therapy alone, 35 (6.6%) on ezetimibe alone, 404 (76.8%) on a statin and ezetimibe combination, and 15 (2.8%) were not on LLT (see Supplementary material online, *Figure S3*). Of 771 patients, 608 (78.8%) patients achieved 50% LDL-C reduction at first lipid control, while 503 (65%) achieved LDL-C target of <55 mg/dL and 50% LDL-C reduction at the time of the first lipid control. Characteristics of patients achieving 50% LDL-C reduction and of patients achieving 50% LDL-C reduction and LDL-C target of <55 mg/dL in comparison with those not achieving are presented in Supplementary material online, *Tables S6 and S7*.

At last lipid control, that occurred at a median time of 11 months, 701 of 771 enrolled patients (90.9%) showed high adherence to therapy (MPR ≥ 80%), 38 (4.9%) partial adherence (MPR < 80%, ≥ 40%), and 32 (4.1%) poor adherence (MPR < 40%) (see Supplementary material online, *Figure S4*).

Persistence was assessed at 6, 12, and 18 months from prescription. At 6 months, 99.1% of patients enrolled in the study remained on therapy, with this value being consistent at 12 months (98.3% on 380 available patients) and 18 months (96.4% on 298 available patients) (see Supplementary material online, *Figure S5*). Overall, 37 patients (4.8%) discontinued therapy, 25 patients self-discontinued treatment (67.5%), and 12 patients discontinued PCSK9i according to medical advice (in 10 cases due to perceived 'too low' LDL-C values and in two cases due to adverse drug reactions). In addition, 4 patients reported local reaction at the injection site not leading to discontinuation.

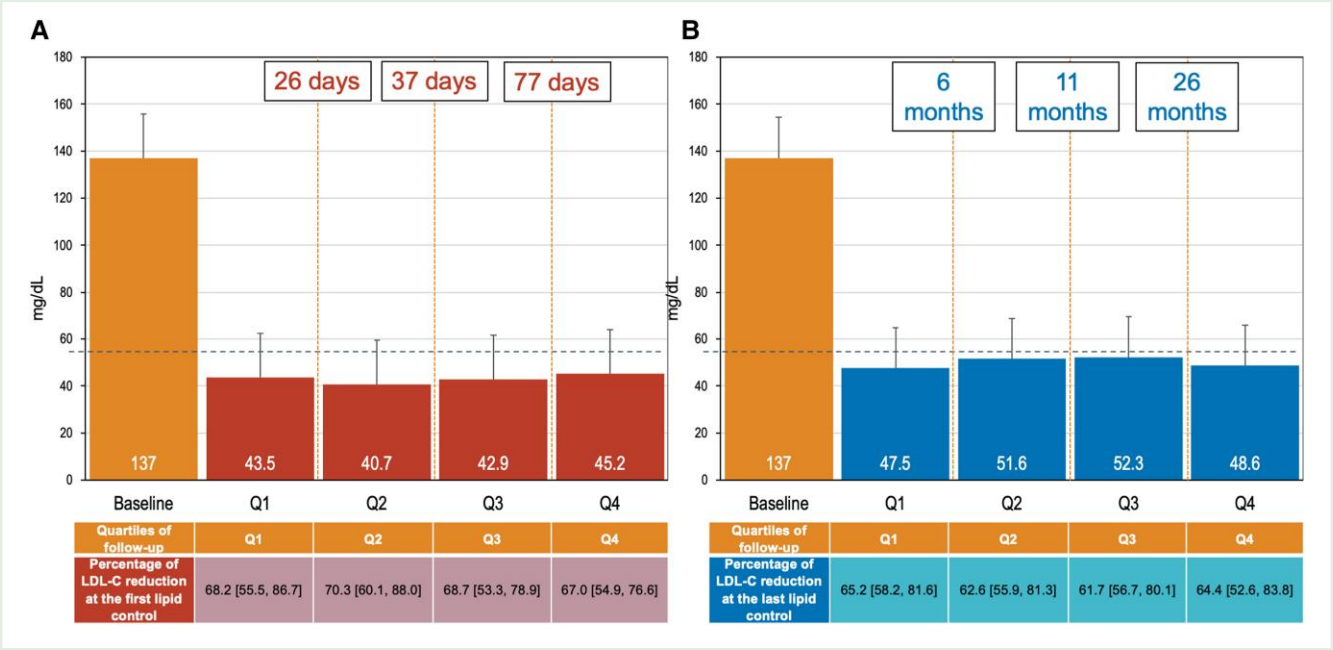


Figure 2 Low-density lipoprotein cholesterol values stratified by quartiles of a follow-up. LDL cholesterol values stratified by quartiles of a follow-up at first lipid control (red, on the left, *A*) and last lipid control (blue, on the right, *B*).

Cardiovascular events during a follow-up

During a median follow-up of 11 months, 116 (15.2%) patients developed 4P-MACE. In particular, 43 (5.6%) patients died from any cause, 30 (3.9%) had a recurrent MI, 2 (0.2%) had a stroke, and 41 (5.3%) had an ischaemia-driven revascularization.

The unadjusted frequency of 4P-MACE, 3P-MACE, all-cause mortality, and ischaemia-driven revascularization was significantly correlated to interquartile range of LDL-C at first lipid control and to interquartile range of relative LDL-C reduction at first control in comparison to baseline (*Table 1*). When patients were stratified by interquartile range of LDL-C at first lipid control, they differ for the most intense LLT in lower LDL-C quartile and for the lower frequency of type 2 diabetes mellitus in lower LDL-C quartile (see Supplementary material online, *Table S8*). Hazard ratio (HR) for the 4P-MACE, 3P-MACE, all-cause mortality, and ischaemia-driven revascularization by LDL-C at first lipid control was also adjusted for clinical characteristics and established CV risk factors, as reported in Supplementary material online, *Table S9*, confirming the independent association between LDL-C value and 4P-MACE, 3P-MACE, ischaemia-driven revascularization, and all-cause mortality. The reduction in HR appeared linear across the interquartile range of LDL-C at first lipid control for 4P-MACE, 3P-MACE, all-cause mortality, and ischaemia-driven revascularization (*Figure 3A*). The distribution of event curves through a follow-up across quartiles of LDL-C change showed a stepwise lower risk of 4P-MACE, 3P-MACE, all-cause mortality, and ischaemia-driven revascularization (*Figure 3B*) with lower LDL-C values at first lipid control.

Of 771 patients included in the study, 527 (68.3%) achieved LDL-C target at the first lipid control (see Supplementary material online, *Table S7*). The unadjusted frequency of 4P-MACE, 3P-MACE, and all-cause mortality was significantly different in patients reaching LDL-C < 55 mg/dL (*Table 2*). The distribution of event curves through a follow-up between patients reaching and those not reaching LDL-C target showed lower risk of 4P-MACE, 3P-MACE, and all-cause mortality (*Figure 4*, upper panel) in patient with LDL-C < 55 mg/dL.

When patients were stratified according to the median LDL-C value at first lipid control (43 mg/dL) (as reported in Supplementary material online, *Table S10*), the unadjusted frequency of 4P-MACE, 3P-MACE, all-cause mortality, and ischaemia-driven revascularization was significantly different in patients reaching LDL-C ≤ 43 mg/dL (*Table 2*). The distribution of event curves through a follow-up between patients above and below median value of LDL-C at first lipid control showed lower risk of 4P-MACE, 3P-MACE, all-cause mortality, and ischaemia-driven revascularization (*Figure 4*, lower panel) in patients below median value of LDL-C at first lipid control.

These results were also confirmed when HR for the 4P-MACE, 3P-MACE, and all-cause mortality by achievement of LDL-C target and by median LDL-C at first lipid control was also adjusted for clinical characteristics and established CV risk factors (see Supplementary material online, *Table S9*).

In 503 (65%) patients who achieved LDL-C target of <55 mg/dL and 50% LDL-C reduction at the time of the first lipid control, the unadjusted frequency of 4P-MACE, 3P-MACE, and all-cause mortality was significantly reduced compared with those who did not (see Supplementary material online, *Table S11*).

Comparison between evolocumab and alirocumab

Of 771 patients enrolled, 506 (65.6%) patients were on evolocumab and 265 (34.4%) were on alirocumab (of them, 153 patients were on alirocumab 75 mg and 112 were on alirocumab 150 mg). LDL-C absolute and relative reduction did not significantly differ between the evolocumab and alirocumab groups (see Supplementary material online, *Figure S6* and Supplementary material online, *Table S3*). No difference in CV outcomes was observed between the two drugs, as shown in Supplementary material online, *Table S12*.

Table 1 Cardiovascular events during the entire follow-up period stratified by quartiles of low-density lipoprotein cholesterol, relative low-density lipoprotein cholesterol reduction, and absolute low-density lipoprotein cholesterol reduction at first and last lipid control

LDL-C values	First lipid control					Last lipid control				
	Q1 ($n = 193$)	Q2 ($n = 193$)	Q3 ($n = 193$)	Q4 ($n = 192$)	*P*-value	Q1 ($n = 193$)	Q2 ($n = 193$)	Q3 ($n = 193$)	Q4 ($n = 192$)	*P*-value
LDL cholesterol	<23 mg/dL	23–43 mg/dL	43–61 mg/dL	>61 mg/dL	<0.001	<35 mg/dL	35–49 mg/dL	49–74 mg/dL	>74 mg/dL	<0.001
Non-fatal MI	8 (4.1)	8 (4.1)	5 (2.6)	9 (4.7)	0.737	5 (2.6)	10 (5.2)	6 (3.1)	9 (4.7)	0.499
Non-fatal stroke	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.5)	0.570	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.5)	0.570
Ischaemia-driven revascularization	5 (2.6)	6 (3.1)	14 (7.3)	16 (8.3)	0.022	6 (3.1)	6 (3.1)	14 (7.3)	15 (7.8)	0.056
All-cause mortality	6 (3.1)	5 (2.6)	15 (7.8)	17 (8.9)	0.011	5 (2.6)	6 (3.1)	13 (6.7)	19 (9.9)	0.005
3P-MACE (non-fatal MI, non-fatal stroke, and all-cause mortality)	15 (7.8)	13 (6.7)	20 (10.4)	27 (14.1)	0.042	11 (5.7)	16 (8.3)	19 (9.8)	29 (15.1)	0.016
4P-MACE (non-fatal MI, non-fatal stroke, ischaemia-driven revascularization, and all-cause mortality)	20 (10.4)	19 (9.8)	34 (17.6)	43 (23.6)	<0.001	17 (8.8)	22 (11.4)	33 (17.1)	44 (24.2)	<0.001

LDL-C relative reduction	First lipid control					Last lipid control				
	Q1 ($n = 193$)	Q2 ($n = 193$)	Q3 ($n = 193$)	Q4 ($n = 192$)	*P*-value	Q1 ($n = 193$)	Q2 ($n = 193$)	Q3 ($n = 193$)	Q4 ($n = 192$)	*P*-value
LDL cholesterol relative reduction	<54.2%	54.2–69.8%	69.8–84.6%	>84.6%	<0.001	<43.8%	43.8–61.4%	61.4–75.5%	>75.5%	<0.001
Non-fatal MI	10 (5.2)	8 (4.1)	5 (2.6)	7 (3.6)	0.616	11 (5.7)	11 (5.7)	2 (1.0)	6 (3.1)	0.048
Non-fatal stroke	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.5)	0.570	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.5)	0.570
Ischaemia-driven revascularization	15 (7.8)	15 (7.8)	7 (3.6)	4 (2.1)	0.021	14 (7.3)	15 (7.8)	8 (4.1)	4 (2.1)	0.041
All-cause mortality	15 (7.8)	20 (10.4)	3 (1.6)	5 (2.6)	<0.001	16 (8.3)	16 (8.3)	5 (2.6)	6 (3.1)	0.013
3P-MACE (non-fatal MI, non-fatal stroke, and all-cause mortality)	26 (13.5)	28 (14.5)	8 (4.1)	13 (6.8)	<0.001	28 (14.5)	27 (14.0)	7 (3.6)	13 (6.8)	<0.001
4P-MACE (non-fatal MI, non-fatal stroke, ischaemia-driven revascularization, and all-cause mortality)	41 (22.0)	43 (22.6)	15 (7.8)	17 (8.9)	<0.001	42 (22.5)	42 (22.2)	15 (7.8)	17 (8.9)	<0.001

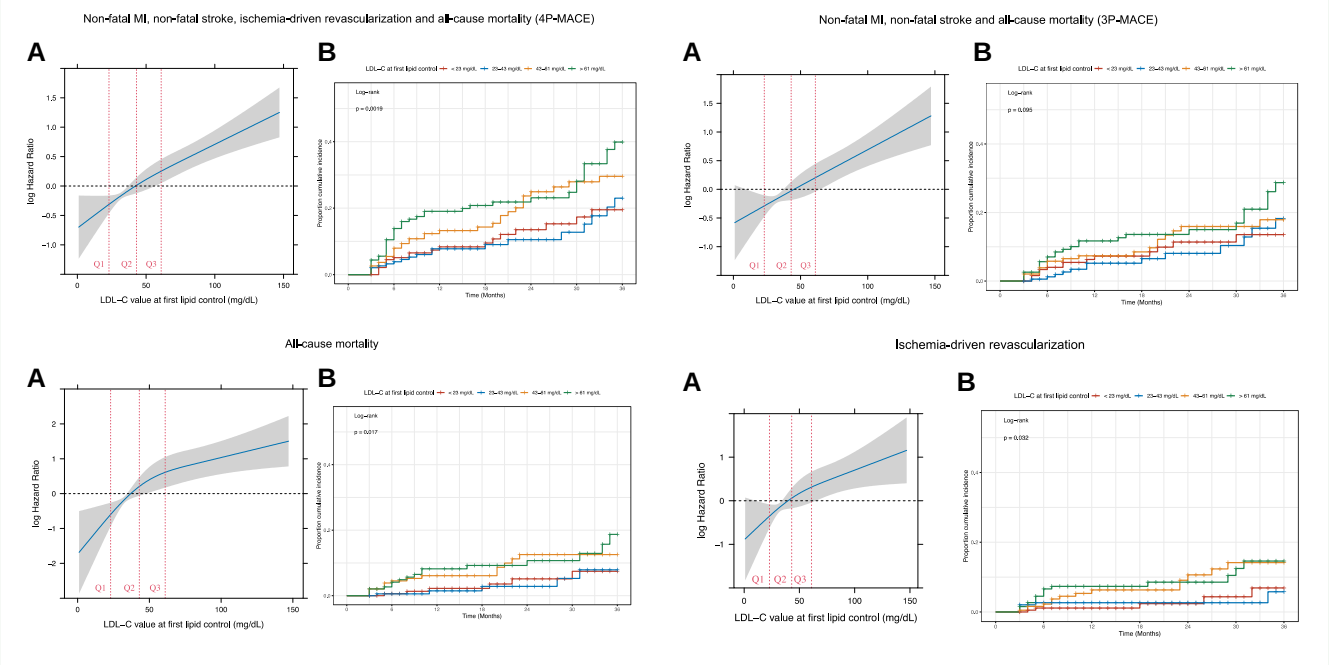


Figure 3 Hazard ratio and Kaplan–Meier curves for clinical endpoints. (*A*) Hazard ratio (HR) for the 4P-MACE, 3P-MACE, all-cause mortality, and ischaemia-driven revascularization by low-density lipoprotein cholesterol (LDL-C, mg/dL) at first lipid control, adjusted for clinical characteristics, and established cardiovascular risk factors. Solid line: hazard ratio with 95% confidence interval (CI), shadowed area, in relation to low-density lipoprotein cholesterol levels at first lipid control using restricted cubic splines with three knots. Vertical dotted lines: percentiles. *X*-axis presented on a linear scale and *Y*-axis on a logarithmic scale (logHR). (*B*) Kaplan–Meier curves of the cumulative incidence rates by quartile of low-density lipoprotein cholesterol at first lipid control. Outcomes are assessed after the first lipid control.

Discussion

The findings of the present study show that real-world patients with ACS, receiving in-hospital prescription of PCSK9i to optimize LLT, show intensive and safe reduction of LDL-C, and the majority achieves LDL-C target recommended by the ESC and ACC/AHA guidelines[1,2] at a median time of 37 days from index event. Remarkably, over a median follow-up of 11 months, incidence of major CV events resulted significantly correlated with the level of on treatment LDL-C level measured at first lipid control, and patients reaching LDL-C target showed a significantly lower incidence of major CV events compared with patients who did not.

To our knowledge, this is the first report from real-world clinical practice that, in a subset of patients that substantially differs from those enrolled in clinically randomized studies, demonstrates that the benefit of achieving very low levels of LDL-C early after ACS is associated with a significant clinical benefit without noticeable side effects.

Background studies and comparison with current data

The linear relationship between LDL-C absolute reduction and incidence of CV events has been standing since several years.[9,19] This relationship applies to different population subsets, including people without ASCVD,[20,21] patients with stable coronary artery disease,[22] and patients with recent ACS,[4–7] who represent the highest risk population. With the availability of PCSK9i for clinical use, the correlation between LDL-C levels and incidence of major CV events has been extended to very low levels of LDL-C, as reported in Fourier trial,[22] where patients randomized to evolocumab achieved a median LDL-C value of 30 mg/dL. In addition, the benefit of reaching very low level of LDL-C was showed in a meta-analysis[9] including patients with a baseline LDL-C < 70 mg/dL who were enrolled in clinical lipid-lowering studies. Yet, in the real-world context, ASCVD patients treated with PCSK9i are substantially different from those enrolled in clinical trials, as reported in the recent multi-country registry of patients receiving evolocumab[23,24] and in the largest single-country registry of patients treated with either alirocumab or evolocumab,[15] where LDL-C values at initiation of therapy were much higher than those reported in trials, resulting in higher baseline CV risk.

Strike strong and strike early strategy in patients with acute coronary syndrome

Based on evidence from trials, a new strategy has been recently proposed to mitigate the excess of risk that characterizes the post-ACS period consisting of as-early-as-possible initiation of intensive LLT after the event to rapidly achieve LDL-C targets recommended by the guidelines.[1,25] This strategy ('strike early, strike strong') that includes in-hospital prescription of PCSK9i in selected patients was recommended by the 2019 ESC dyslipidaemia guidelines[8] and more recently by the ESC ACS[1] and ACC/AHA[2] guidelines.

The feasibility of this strategy was assessed in three small, randomized studies reporting early initiation of PCSK9i in patients with ACS. The EVOPACS study[12] ($n = 308$) randomized ACS patients within 72 h to evolocumab 420 mg s.c. monthly vs. placebo, on top of atorvastatin 40 mg, and reported that at 8 weeks 90.1% of patients achieved the <55 mg/dL LDL-C target and 95.7% of the <70 mg/dL target in the evolocumab group compared with 10.7% (<55 mg/dL) and 37.6% (<70 mg/dL) in the placebo group. In the smaller EVACS study,[26]

Table 2 Cardiovascular events during the entire follow-up period stratified by the LDL-C at target status at first and last lipid control

At target status	First lipid control			Last lipid control		
	Not at target ($n = 244$)	At target ($n = 527$)	*P*-value	Not at target ($n = 275$)	At target ($n = 496$)	*P*-value
Non-fatal MI	10 (4.1)	20 (3.8)	0.998	12 (4.4)	18 (3.6)	0.756
Non-fatal stroke	1 (0.4)	1 (0.2)	1.000	1 (0.4)	1 (0.2)	1.000
Ischaemia-driven revascularization	17 (7.0)	24 (4.6)	0.224	18 (6.5)	23 (4.6)	0.335
All-cause mortality	28 (11.5)	15 (2.8)	<0.001	25 (9.1)	18 (3.6)	0.003
3P-MACE (non-fatal MI, non-fatal stroke, and all-cause mortality)	39 (16.0)	36 (6.8)	<0.001	38 (13.8)	37 (7.5)	0.006
4P-MACE (non-fatal MI, non-fatal stroke, ischaemia-driven revascularization, and all-cause mortality)	56 (23.9)	60 (11.4)	<0.001	56 (21.1)	60 (12.1)	0.001
LDL-C values	**First lipid control**			**Last lipid control**		
	M1 ($n = 386$)	**M2 ($n = 385$)**	***P*-value**	**M1 ($n = 386$)**	**M2 ($n = 385$)**	***P*-value**
LDL cholesterol	≤43 mg/dL	>43 mg/dL	<0.001	≤49 mg/dL	>49 mg/dL	<0.001
Non-fatal MI	16 (4.2)	14 (3.6)	0.858	15 (3.9)	15 (3.9)	1.000
Non-fatal stroke	1 (0.3)	1 (0.3)	1.000	1 (0.3)	1 (0.3)	1.000
Ischaemia-driven revascularization	11 (2.8)	30 (7.8)	0.004	29 (7.5)	12 (3.1)	0.010
All-cause mortality	11 (2.8)	32 (8.3)	0.002	32 (8.3)	11 (2.8)	0.002
3P-MACE (non-fatal MI, non-fatal stroke, and all-cause mortality)	28 (7.3)	47 (12.2)	0.028	48 (12.5)	27 (7.0)	0.015
4P-MACE (non-fatal MI, non-fatal stroke, ischaemia-driven revascularization, and all-cause mortality)	39 (10.1)	77 (20.5)	<0.001	77 (20.5)	39 (10.1)	<0.001

57 patients with MI were randomized to a single dose of evolocumab 420 mg s.c. or placebo within 24 h and 65.4% achieved the <55 mg/dL LDL-C target at hospital discharge compared with 23.8% in the placebo group ($P = 0.01$). Yet, baseline LDL-C in this study was 91 mg/dL, a value substantially lower than that observed in real-world studies[15,23,27] and in the current one. Finally, in the EPIC-STEMI study[13] ($n = 68$), a strategy of early administration of alirocumab 150 mg s.c. before PCI in STEMI patients compared with sham control resulted in a placebo-corrected 22% reduction of LDL-C at 45 days and 92.1% of patients achieving <55 mg/dL LDL-C target compared with 56.7% in the control group ($P = 0.001$), starting from a baseline LDL-C level of 114 mg/dL. In addition, two intravascular imaging studies that randomized patients with ACS received PCSK9i or placebo, on top of high-intensity statins, demonstrated favourable plaque modification effects in non-culprit lesions of patients receiving either evolocumab[10] or alirocumab[11] at 50 and 52 weeks, respectively, that included reduced atheroma volume at IVUS, increased minimum fibrous cap thickness at OCT,[10] and reduced lipid core at IVUS[11] compared with placebo. Notably, baseline median LDL-C levels were 140.4 mg/dL[10] and 152.8 mg/dL[11] and reached very low level during PCSK9i treatment (28.1 and 23.6 mg/dL in the HUYGENS[10] and PACMAN-AMI[11] studies, respectively). However, none of these studies reported effects on clinical outcomes. A subsequent analysis of the PACMAN-AMI trial[28] reported that over 52 weeks of a follow-up, the incidence of major CV events (all-cause death, MI, and revascularization) in patients achieving a favourable modification in all three imaging parameters (reduced atheroma volume, increased minimum fibrous cap thickness, and reduced lipid core) was significantly lower (8.3%) compared with those who did not achieve 'triple' plaque regression (18.2%; $P = 0.04\%$). Notably, reduction of CV events was mostly driven by reduction of coronary revascularization, a finding that was consistently confirmed in our analysis. However, no correlation with LDL-C levels was reported that would be quite informative for clinical practice.

Evidence from the current study

There are no studies that investigated the efficacy, safety, and clinical impact of the 'strike strong and strike early strategy' in patients with ACS in a real-world setting. As recognized in the ESC recent position paper,[25] these data would be much needed to support implementation in clinical practice, where real-world patients substantially differ from trial patients.

Our study reports the first population of patients with ACS receiving PCSK9i within in-hospital stay for ACS in a real-world setting that is being collected in a single-country multicentre Italian registry. The most relevant findings of the study can be summarized as follows: (i) early use of PCSK9i in addition to oral therapy, mostly on top of statin–ezetimibe combination, is able to achieve <55 mg/dL target in the majority of patients (68.3%) at first lipid control that occurred at median time of 37 days from event; (ii) PCSK9i therapy in ACS patients demonstrates very high adherence and stable intensive lipid-lowering effects without clinically significant side effects; and (iii) intensity of lipid-lowering effects is associated with significant reduction of major CV effects, including all-cause death.

The latter is obviously the most relevant finding of the study. When the population of patients was grouped into quartiles of LDL-C levels at first lipid control or into quartiles of absolute LDL-C reduction from baseline, a stepwise significant lower incidence of major CV events

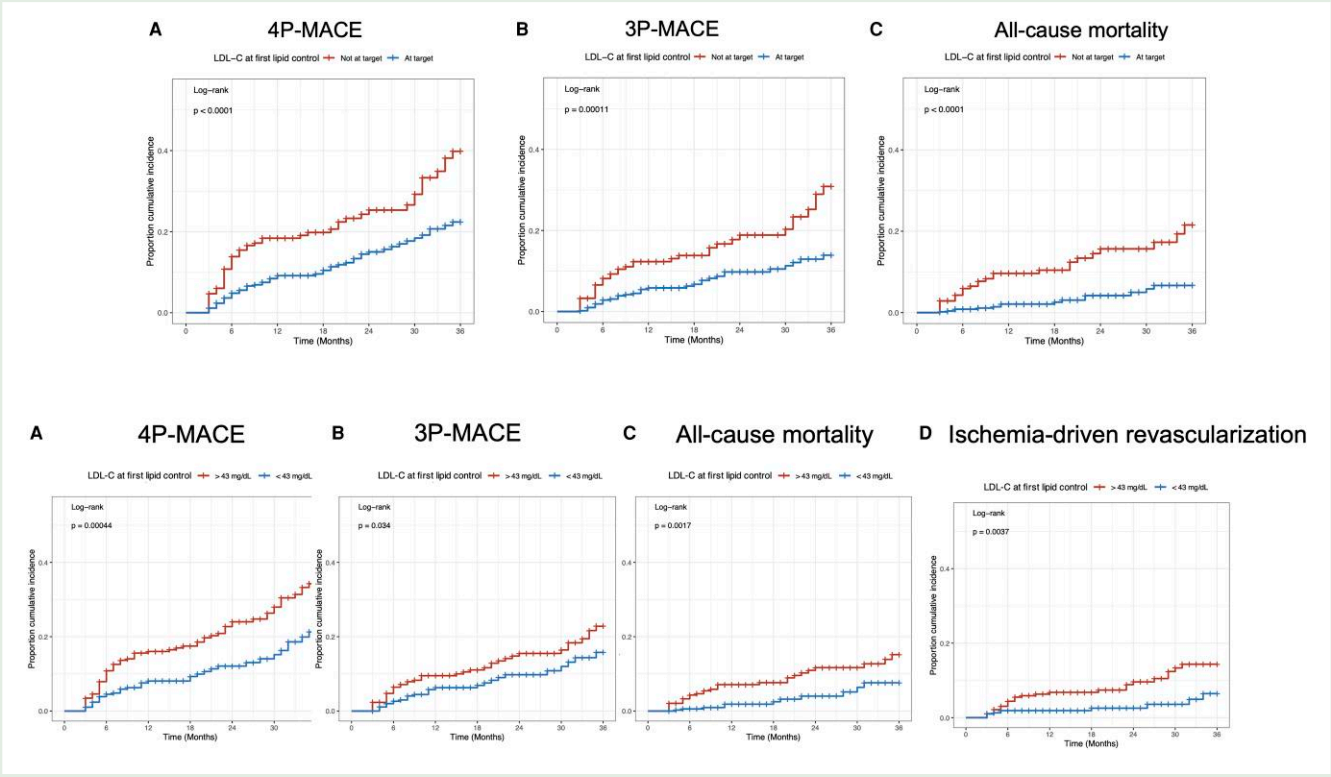


Figure 4 Kaplan–Meier curves for clinical endpoints. Upper panel: Kaplan–Meier curves of the cumulative incidence rates of (*A*) 4P-MACE, (*B*) 3P-MACE, and (*C*) all-cause mortality by LDL-C target status at first lipid control. Outcomes are assessed after the first lipid control. Lower panel: Kaplan–Meier curves of the cumulative incidence rates of (*A*) 4P-MACE, (*B*) 3P-MACE, (*C*) all-cause mortality, and (*D*) ischaemia-driven revascularization, by median LDL-C value at first lipid control. All outcomes are assessed after the first lipid control.

was observed (*Table 1*, *Figure 3*). Notably, a significant reduction in all-cause death and ischaemia-driven revascularization was observed from the highest to the lowest LDL-C quartile. Our data are highly consistent with those from the Sweden registry[19] where patients with acute MI and with a first post-MI lipid control within 6 to 10 weeks were enrolled and followed up for 3.6 years. In that study, similarly to our findings, a significant association between quartiles of LDL-C reduction and incidence of major CV events was observed, using statins as LLT. However, due to the lack of PCSK9i therapy, the median LDL-C at a follow-up was 77 mg/dL, a value substantially higher than that reported in the current study.

The observed reduction of all-cause death is very consistent with previous findings from the ODYSSEY trial that randomized post-ACS patients to alirocumab vs. placebo, on top of statin therapy.[29] In that analysis, a significant reduction of mortality was observed in patients with baseline LDL-C > 100 mg/dL and a significant correlation was observed between mortality rate and quartile LDL-C during treatment. These findings are quite similar to our results, observed in a different clinical context and on top of a different LLT.

Thus, achievement of target LDL-C value is a powerful driver of residual CV risk reduction, especially in the very early post-ACS phase, and needs to be considered as a crucial aim of antilipidic therapy. In our study, incidence of CV events was significantly lower in patients who reached the LDL-C target compared with those who did not and in patients with LDL-C below the median value of 43 mg/dL compared with those above and was most evident in the lowest LDL-C quartile that corresponded to an LDL-C value below 23 mg/dL. These observations are relevant for clinical practice as they clearly indicate that reducing LDL-C at values even lower than recommended target is feasible using optimized combination LLT and is associated with additional relevant clinical benefit.[2,8,30] Remarkably, the effects on clinical outcomes were evident despite the relatively short follow-up of 11 months.

Finally, the success of a *strike early–strike strong* lipid-lowering strategy with PCSK9i is strictly dependent on adherence to background LLT. In this study, the majority (75.3%) of our patients received PCSK9i on top of statin–ezetimibe combination therapy, reflecting the national reimbursement PCSK9i policy that allows prescription when ACS patients show LDL-C values >70 mg/dL on combination therapy (unless statin intolerant) in a 30-day interval before the index event. Of 527 patients reaching LDL-C target, 404 (76.8%) were on oral combination therapy, showing that combination of oral and injectable LLT is needed in the majority of very high-risk patients. Thus, we believe that a fast-track therapeutic approach, as the one adopted in our country and reported in the current study, based on early prescription of PCSK9i on top of optimized oral LLT, might be informative to reduce residual CV risk in clinical practice.

Limitation of the study

The observational design of the study has inherent limitations. In fact, apart from death, misclassification of CV events may occur due to lack of centralized adjudication committee. Yet, this is unlikely to have any influence on the reported findings, since non-fatal MI or stroke and ischaemia-driven revascularization represent easily classifiable events requiring hospitalization with precise diagnostic coding. The non-randomized design of the study is also a limitation, making our observations hypothesis-generating for randomized clinical trials.

In this registry, all-cause mortality and not CV mortality was assessed, as reported in other recent studies.[28] Yet, although CV mortality would

have been informative, adjudication would have been hampered by the observational design of the study. However, early after ACS, CV mortality represents by far the leading cause (70%) of death in a population of mean age comparable to our population,[29] suggesting that the effects observed on mortality are plausibly sustained by reduction of CV mortality.

Conclusions

The findings of the present study from a real-world registry indicate that an intensive optimized early LLT using PCSK9i ('strike early and strong strategy') in patients with ACS is safe and effective in clinical practice, and that reducing LDL-C even lower than recommended targets is associated with a significant reduction of residual CV risk.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology*.

Author contribution

P.G.: conceptualization, methodology, visualization, investigation, data curation, writing—original draft, writing—review, and editing. Ch.B.: visualization and investigation. G.G.: visualization and investigation. Mi.B.: visualization and investigation. D.D.: visualization and investigation. Giu.P.: visualization and investigation. Ma.B.: visualization and investigation. Mat.P.: visualization and investigation. G.A.: visualization and investigation. F.C.: visualization and investigation. G.T.: visualization and investigation. P.C.: visualization and investigation. Ar.C.: visualization and investigation. F.F.: visualization and investigation. Ang.C.: visualization and investigation. F.V.: visualization and investigation. Ant.C.: visualization and investigation. F.B.: visualization and investigation. S.M.: visualization and investigation. G.M.: visualization and investigation. F.D.: visualization and investigation. F.G.: visualization and investigation. R.N.: visualization and investigation. I.P.: visualization and investigation. A.P.: visualization and investigation. R.Q.: visualization and investigation. Al.M.: visualization and investigation. P.A.M.: visualization and investigation. L.D.L.: visualization and investigation. Ga.C.: visualization and investigation. N.D.B.: visualization and investigation. M.C.: visualization and investigation. L.P.: visualization and investigation. Cl.B.: visualization and investigation. C.I.: visualization and investigation. F.M.: visualization and investigation, writing—original draft, writing—review, and editing. S.F.: visualization and investigation. D.B.: visualization and investigation. A.L.M.P.: visualization and investigation. E.N.: visualization and investigation. Mar.P.: visualization and investigation. A.S.: visualization and investigation. M.S.: visualization and investigation. S.P.: conceptualization, methodology, visualization, investigation, data curation, writing—original draft, writing—review, and editing. P.P.F.: conceptualization, methodology, visualization, investigation, data curation, writing—original draft, writing—review, editing, supervision, and project administration.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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