Lipid Lowering Treatment and Follow up in Recent Post Acute Coronary Syndrome Patients: Real-World Evidence from the Multicenter Observational Prospective - Post Acute Coronary Syndrome Italian Study (PACSI)

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Abstract

Background

Patients suffering from an acute coronary syndrome are at very high risk for recurrent events. Early targeted pharmacological intervention primarily aimed at controlling plasma LDL-cholesterol (LDL-C) levels can result in the reduction of recurrent cardiovascular events. This study aimed to evaluate real-life evidence from the Italian setting to document current practice of secondary prevention in patients after acute coronary syndrome (ACS), specifically assessing: (i) the rate of LDL-C target (<70 mg/dl) achievement after 6-10 weeks from index event and at later follow-up, (ii) the distance from LDL-C target during follow up, (iii) adherence rate and visit attendance.

Methods

Multicenter observational prospective clinical study ACS patients, evaluating target attainment rate at 6 weeks (V0) and 18 months (V2).

Results

Approximately 97.4% patients enrolled (N=524) received statin-based therapy, and 3.6% received ezetimibe at discharge; mean LDL-C values decreased from 113.0±44.7 mg/dL at discharge to 71.3±26.5 mg/dl at V0. Among patients with known LDL-C for main time-points, 51.7% achieved target LDL-C at V0, 45.8% at V2. Among patients not reaching the target, the mean distance from target was 23.5±20.7 mg/dL. Attainment of target LDL-C was similar in patients receiving intensive or low-moderate statin-based treatment (approximately 50%). LDL-C target attainment was associated with lower LDL-C value at discharge and smoking status. Adherence to statin treatment was high (96.2%) throughout, similarly to medical appointment attendance at V2 (84.7%).

Conclusions

Despite most ACS patients receiving intensive statin-based regimens, only approximately half achieved LDL-C target, suggesting the need for further optimizing drug selection, combination and dosage.

Introduction

In the last decades a large number of studies [1-4] and international guidelines have underlined the higher risk for future cardiovascular (CV) events among patients who have had an acute coronary syndrome (ACS) event, and emphasized the role of secondary prevention programs, including the control of modifiable risk factors and intensive treatment with cardio-protective drugs, with particular attention to lipid lowering therapies (LLT) to reduce CV mortality and morbidity [5].

Current ESC/EAS guidelines recommend [5,6] modulating the intensity of the preventive intervention based on clinical judgment, according to the individual level of total CV risk, setting less demanding targets for more moderate CV risk than those set for higher risk profiles. Specifically, the ESC/EAS guidelines established the treatment target for Low-Density-Lipoprotein Cholesterol (LDL-C) as <1.8 mmol/l (approximately <70mg/dl), recommending intensive LLT within the first 4 days from the ACS index event for those patients at very high CV risk, and a lower intensity LLT for patients at increased risk of side effects [1,5]. In addition, a recommendation for patients with baseline LDL-C between 1.8 and 3.5 mmol/L (70 and 135 mg/dL) was inserted, advising an LDL-C relative reduction from baseline of ≥50% [5] –as now recently endorsed also by AHA/ACC guidelines [7].

Nonetheless, international studies and registries evidence a large underutilization and suboptimal use of LLT among patients who are at high CV risk [8]. Indeed, as evidenced by the STAR (Statins Target Assessment in Real practice) study [9], which cross-linked official data from the Italian national pharmacy network with hospital charts and laboratories databases of over 3.000 patients, high potency statins are often used in patients who require only minor reductions in LDL-C levels, while low potency statins are frequently prescribed to patients with high CV risk who require a more aggressive treatment [9]. These findings were consistent with the observations by Hirsh et al, who underlined that only 1 in 3 patients included in two major US registries were prescribed statin doses based on their recommended target [8].

At the national level, the ESC/EAS guidelines on LDL-C goal achievement have been officially endorsed by the Italian Cardiological Societies, with the publication of the Consensus on the management of post-ACS patients [10], emphasizing the need for structured programs of CV risk through strict alignment to guideline recommendation and long-term management of treatment adherence. In fact, despite the improved management of dyslipidemia in ACS patients, discontinuation rates for intensive LLT are still high due to low compliance and side effects, which prevent patients from attaining treatment goals.

Given this background, this study had two main objectives. The first aim was to assess the effectiveness of the management of very high CV risk patients in secondary prevention, such as those discharged from the hospital after a recent ACS; the second objective was to evaluate, in these patients, the rate of LDL-C target achievement and the distance of LDL-C levels from target during follow up.

Patients and Methods

Study design and patient population

The present study was a multicenter observational prospective clinical study, performed between December 2015 and October 2017, enrolling patients with a recent ACS either naïve or previously treated with a lipid-lowering therapy. Patients were consecutively enrolled at 18 Cardiology centers across the country. Inclusion criteria were: age ≥ 18 years, hospitalization for acute coronary syndrome (STEMI, NSTEMI, UA) within the previous 6-10 weeks and informed consent. The only exclusion criteria were the presence of severe clinical conditions that would reduce patient's life expectancy, or presence of any condition (e.g. alcohol or substance abuse) that might have interfered with study completion.

Measurements and endpoints

The follow up (FU) calendar after patient assessment at discharge (D0) foresaw (1) the first follow up visit between 6-10 weeks after the ACS event (V0); (2) an intermediate non-mandatory visit at 5-7 months after ACS (V1) when available, and (3) a final visit at 12-14 months after the ACS (or in case of no-show, by phone after 15 months) (V2).

Parameters collected included socio-demographic variables, clinical (type of index ACS event, family history of CVD, BMI) and biochemical parameters (such as lipid profile, primarily LDL-C), presence of comorbidities (hypertension, chronic renal disease, diabetes mellitus), on-going LLT and concomitant medications with drug utilization pattern. The primary endpoint was the percentage of patients achieving the LDL-C target (<70 mg/dl) at V0 [5;10] and at follow up visit V2. Secondary endpoints were the mean distance to LDL-C among patients who did not reach the goal, visit attendance, drug utilization pattern, identification of possible risk profile for future ACS or predictors for target achievement.

Ethical considerations
The protocol of the study was approved by the Independent Ethics Committees (IECs) of all participating centers. This trial was conducted in agreement with Good Pharmaco-Epidemiology Practice requirements and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Statistical analysis
Categorical variables are presented as absolute numbers and percentages while numerical variables were measured using mean, standard deviation, median and range. Missing values were excluded from the statistical analysis. The distances to the target LDL-C value in patients who did not reach the goal at V0 and at V2 were measured as differences between the LDL-C value reported at each visit and the value 69 mg/dL; descriptive statistics of these distances were computed. Statistical analysis focused also on the percentage variation (reduction/increase) of LDL-C at V0 from baseline. Furthermore, comparison between the group of patients attaining the LDL-C target value at V0 and the group of patients who did not reach the goal was performed by using Chi-square or Fisher's exact test for categorical variables and the Mann-Whitney test for the value of LDL-C at discharge. In order to evaluate the differences in the percentage of patients with LDL-C goal achievement at V0 according to gender, age ≥ 65 and diabetes mellitus a multiple logistic regression model was built by considering the following potential predictors: smoking status (current/former/never smoking), BMI ≥25, hypertension, hypercholesterolemia, family history of cardiovascular disease, alcohol consumption, sedentary lifestyle, revascularization procedures, intensity of LLT therapy at discharge, and LDL-C value at discharge. A stepwise backward selection procedure was applied to identify statistically significant predictors. Intensive LLT dose was defined as either atorvastatin 40 or 80 mg with/without ezetimibe, rosuvastatin 20 or 40 mg with/without ezetimibe, simvastatin 40 mg with ezetimibe, atorvastatin 20 mg with ezetimibe, rosuvastatin 10 mg with ezetimibe. For all statistical tests, p-value (p) < 0.05 was accepted as statistically significant. Finally, for patients not reaching target LDL-C, the percent reduction of LDL-C value at discharge required for attaining target LDL-C value at V0 was also calculated. IBM SPSS Statistics version 23 was used for performing the calculations.

Results
Study sample
The study enrolled a total of 524 patients, recruited across the 19 participating centers, presenting for their first follow-up visit after ACS event (V0). At discharge (D0), only 402 patients (76.7%) had known LDL-C levels (Figure 1). At V0, 432 patients (82.4%) had a LDL-C level measurement; among them, 323 patients had known LDL-C levels both at D0 and V0. Data from this group were used for the primary analysis. V1 was an optional visit and was attended by 218 patients (41.6% of discharged patients), 143 of which had a measurement of LDL-C levels. V2 was attended by 444 patients (84.7% of discharged patients); among them, LDL-C levels were assessed in 253 patients. Only 179 patients had measured LDL-C levels at all visits (D0, V0 and V2) (Figure 1) and data from this group were used for the second set of analysis.

Among the enrolled patients, 6 died (massive pulmonary embolism, pancreatic cancer, probable heart attack, multiple complications due to several episodes of intra-stent thrombosis regardless of optimized medical therapy, cholecystitis, cancer). Eighteen non-fatal CV events were reported during the follow-up (1 NSTEMI and 4 UA between V0 and V1; 1 STEMI, 4 NSTEMI and 8 UA between V1 and V2).

Pharmacological treatments
Treatment patterns have been evaluated in 524 patients at D0 and V0, and in 444 patients at V2. At D0, almost all patients were on treatment with a statin (97.3%), and this percentage remained constant throughout the follow-up (96.2% at V2). Of these 22.2% were already on statin treatment prior to the ACS index event, while 77.8% started statin therapy after the event. The most frequently prescribed statin was atorvastatin (88.4%). With specific reference to the use of ezetimibe in monotherapy or association, the percentages of treated patients gradually increased over time throughout the follow up (3.6% at D0 to 16.9% at V2) (Figure 2). Most patients were concomitantly receiving other non-hypolipidemic drugs including aspirin, anti-platelets (other, non-aspirin), anticoagulants, beta-blockers, and ACE inhibitors (Table 1).
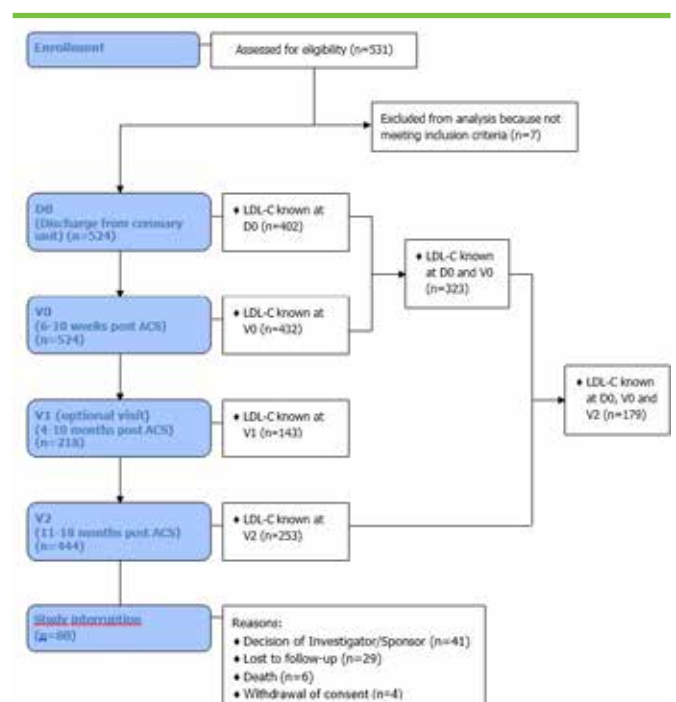

Figure 1
Patient flow chart

Table 1. Antiplatelets and other medication in use during the follow up

	D0	V0	V2
ANTIPLATELETS			
Aspirin	508 (97.1%)	493 (94.1%)	419 (94.4%)
Other antiplatelet	468 (89.5%)	464 (88.5%)	164 (36.9%)
OTHER MEDICATIONS			
Anticoagulant	51 (9.8%)	36 (6.9%)	29 (6.5%)
Beta-blockers	421 (80.5%)	412 (80.5%)	333 (76.0%)
Ace inhibitors	331 (63.4%)	309 (60.2%)	256 (58.7%)

The percentages for D0 and V0 refer to the entire dataset, whereas percentages for V2 refer to the number of patients for which data were available at that time point.

Analysis at V0

Table 2 summarizes the baseline socio-demographic and ACS-related clinical variables of interest, where known, for the 323 patients for whom all major clinical parameters were known at D0 and V0, and stratifies study sample by goal achievement (Yes "at target" or < 70 mg/dL/ No "not-at-target" or >70 mg/dL) at V0. Most patients were male (78,6%), under the age of 65 (58.2%) and had a BMI ≥ 25 (69.7%). The mean LDL-C at D0 was 113.02 ± 44.69 mg/dL (median 109.0 mg/dL, range: 25-252). Among these patients, there was a similar prevalence of STEMI (47.1%) and NSTEMI (41.2%), while UA was the presenting condition in a minority of patients (11.8%). Approximately 14% had had a previous myocardial infarction, 16.9% had known coronary heart disease (CHD), while 17.6% suffered previously from angina. Traditional risk factors for atherosclerosis were frequently present in these patients, including hypertension (68.5%), hypercholesterolemia (49.1%), diabetes (22.6%, with 5.3% of total were newly diagnosed cases upon D0) and current (18.1%) or former smoking (49.3%).
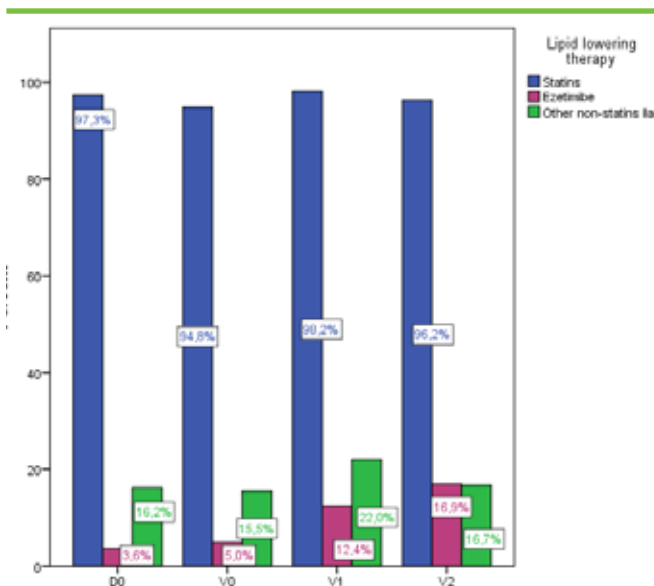

Figure 2
The percentages for D0 and V0 refer to the entire dataset, whereas percentages for V1 and V2 refer to the number of patients who attended the visits, 218 and 444 respectively.

Table 2. Baseline socio-demographic and ACS-related clinical variables.

	OVERALL (n=323)	LDL-C GOAL (<70 mg/dl) at V0		p
		YES (n=167)	NO (n=156)	
DEMOGRAPHY AND LIFESTYLE				
Male	254 (78.6%)	137 (82.0%)	117 (75.0%)	0.123
Caucasian	318 (98.5%)	164 (98.2%)	154 (98.7%)	1.000
Age ≥ 65 years	135 (41.8%)	75 (44.9%)	60 (38.5%)	0.240
BMI ≥ 25 kg/m2	205 (69.7%)	109 (71.7%)	96 (67.6%)	0.444
Sedentary lifestyle	161 (56.3%)	82 (55.4%)	79 (57.2%)	0.754
SMOKING STATUS				
Current smoker	55 (18.1%)	20 (12.4%)	35 (24.5%)	0.007*
Former smoker	150 (49.3%)	91 (56.5%)	59 (41.3%)	
Alcohol consumption	57 (20.2%)	34 (23.0%)	23 (17.2%)	0.225
INDEX ACS EVENT				
STEMI	152 (47.1%)	88 (52.7%)	64 (41.0%)	
NSTEMI	133 (41.2%)	61 (36.5%)	72 (46.2%)	0.109
UA	38 (11.8%)	18 (10.8%)	20 (12.8%)	
HISTORY OF CHD				
Prior myocardial infarction	45 (14.1%)	21 (12.6%)	24 (15.7%)	0.424
Prior Stable/Unstable Angina	55 (17.6%)	24 (14.6%)	31 (20.9%)	0.144
Previous CHD	53 (16.9%)	24 (14.7%)	29 (19.3%)	0.277
LDL-C AT D0				
LDL-C (mg/dL)	113.0 (±44.7)	103.3 (±44.6)	123.4 (±42.5)	<0.001*
COMORBIDITIES AND FAMILIARITY				
Diabetes mellitus	72 (22.6%)	41 (24.6%)	31 (20.4%)	0.375
Hypertension	220 (68.5%)	117 (70.1%)	103 (66.9%)	0.540
History of chronic renal failure/CKD	15 (4.7%)	12 (7.2%)	3 (1.9%)	0.033*
Family history of CVD	110 (35.5%)	46 (28.4%)	64 (43.2%)	0.006*
Hypercholesterolemia	156 (49.1%)	75 (44.9%)	81 (53.6%)	0.120
Revascularization procedures	93 (29.2%)	45 (26.9%)	48 (31.6%)	0.363
LLT INTENSITY AT D0				
Intensive	274 (85.4%)	141 (84.4%)	133 (86.4%)	0.625

*Statistically significant
ACS: Acute coronary syndrome; BMI: Body Mass Index; CHD: Coronary Heart Disease; CKD: chronic kidney disease; CVD: Cardio vascular disease. D0: discharge; LDL-C: Low-Density-Lipoprotein Cholesterol; NSTEMI:Non-ST-elevation myocardial infarction; STEMI:ST-elevation myocardial infarction; UA: unstable angina.

At V0, LDL-C was decreased by 29% (71.3±26.5 mg/dL); 30% of the patients (n=98) showed a reduction >50%, while 54.2% had a reduction <50%. Some patients (15.5%) showed an increase in LDL-C levels from discharge to V0.

At V0, only 51,7% of the patients achieved the LDL-C level goal suggested for their high cardiovascular risk category (<70 mg/dL) (Table 2); in this group, LDL-C levels were 51.6±12.3 mg/dL (40.7% reduction), compared to 92.5±20.7 mg/dL of the group

of patients who did not achieve the LDL-C level goal (16.4% reduction). These two subgroups had also significantly different LDL-C levels at baseline, with 103.3 mg/dL in those who reached the goal and 123.4 mg/dL in those who did not attain the LDL-C target value (p<0.001). Patients in the group at target were less likely to be current smokers (12.4% vs 24.5%, p=0.007) and had a lower incidence of family history of CVD (28.4% vs 43.2%, p=0.006), but presented a higher incidence of history of CKD (7.2% vs 1.9%, p=0.033).

The mean distance from LDL-C target among the 156 patients who did not reach LDL-C target at V0 was 23.5±20.7 mg/dL. At D0 about half of these patients had a percentage distance from target above 40%. Current guidelines recommend, for very high risk patients, a reduction of at least 50% if baseline LDL-C levels are between 70 and 135 mg/dL1; we found that 47.3% of patients in the group at target at V0 had a reduction of at least 50%, a percentage that was significantly lower in the group not at target (12.2%) (Figure 3).

At discharge, almost all patients (98.8%) were on statin therapy, including 77.4% who started taking a statin after the ACS event. A very small percentage of patients (3.4%) was given ezetimibe. High intensity lipid-lowering therapies were prescribed to 84.8% of patients (80.1% received atorvastatin 40 or 80 mg/day, 4.0% received rosuvastatin 20 or 40 mg/day and 0.6% received simvastatin 40 mg/day), while low-intensity regimen was prescribed to 14.6% of these patients. However, target LDL-C levels were achieved at similar rates in both the high intensity and low-moderate intensity groups (51.4% vs 55.3%). Among patients not at target at V0, 86.4% (Table 2) were receiving high intensity LLT, and 13.6% low-moderate LLT. Stratification of these patients by treatment intensity (high vs low-moderate) and distance from target showed that, at D0 in both groups, most of patients had a percentage distance from target above 40%, but this value was higher in low/moderate intensity group than in high intensity group (66.7% and 51.9% of patients) (Table 3).
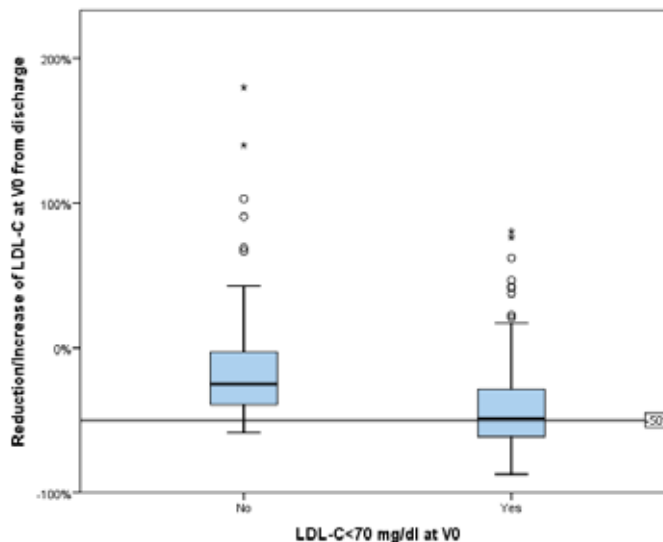
Table 3. Distribution of the percentage distances from LDL-C target value at D0 for patients who do not reach the goal by LLT intensity

		Intensity of LLT at discharge			
		High		Low/Moderate	
		Count	%	Count	%
Percentage distance from LDL-C target value	Reduction of at least 70,00	3	2.3%	0	0.0%
	Reduction 60,00-69,99	15	11.3%	2	9.5%
	Reduction 50,00-59,99	25	18.8%	4	19.0%
	Reduction 40,00-49,99	26	19.5%	8	38.1%
	Reduction 30,00-39,99	26	19.5%	2	9.5%
	Reduction 20,00-29,99	13	9.8%	3	14.3%
	Reduction 10,00-19,99	8	6.0%	0	0.0%
	Reduction 0,00-9,99	6	4.5%	1	4.8%
	Increase of at least 0,01	11	8.3%	1	4.8%
	Total	133	100.0%	21	100.0%

To assess whether CVD-associated risk factors could predict the achievement of LDL-C goal, the stepwise backward selection procedure was applied on multiple logistic regression analysis; this analysis showed that lower LDL-C value at discharge (OR: 0.984, 95% CI: 0.977-0.991, p<0.001) and smoking status (former vs current-smoker OR: 4.055, 95% CI:1.825-9.009, p=0.001) were associated with LDL-C target value attainment. Other potential predictors included in multivariate analysis were not statistically significant.

Target LDL-C at V2

This analysis was performed in the subgroup of patients who had known LDL-C levels at D0, V0 and V2 (179 patients). Baseline characteristics of this subgroup did not differ from those of
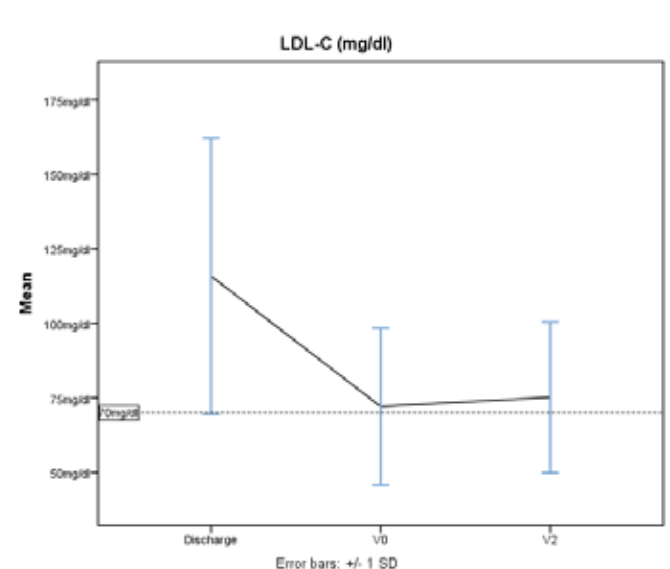

Figure 3
Percentage variations of LDL-C values from baseline, stratified by goal achievement (Yes/No)
The figure refers to the 323 patients who had known LDL-C levels both at D0 and V0.

Figure 4
Temporal trend of LDL-C values
The figure refers to the 179 patients who had known LDL-C levels at D0, V0 and V2.

the whole studied population (not shown). The LDL-C values decreased from 115.8±46.3 mg/dL to 72.1±26.2 mg/dL at V0 and 75.2±25.3 mg/dL at V2 (Figure 4).

The percentage of patients that attained target LDL-C was 51.4% (n=92) at V0 and 45.8% (n=82) at V2, but only 28.5% were a target both at V0 and V2, and almost half (44.6%) of the patients that were at target at V0 were not at target at V2. The mean distance from LDL-C target among the 97 patients who did not reach LDL-C target at V2 was 22.9 mg/dL (± 22.0).

Safety considerations
A total of 9 adverse events were reported for 7 patients, none of which ,however, was deemed to be related to LLT.
Discontinuation rates of LLT were extremely low: only 14 patients (2.7%) among those taking statins during the study discontinued statin treatment; the reasons for discontinuation were myalgia (1 patient, 7.1%), CK elevation (1 patient, 7.1%), other non-statin related reasons (6 patients, 42.9%), unknown reasons (6 patients, 42.9%). Out of 86 patients taking ezetimibe, 4 patients (4.7%) discontinued treatment; out of 3 patients taking fibrates, 2 patients (66.7%) discontinued treatment and out of 101 patients taking other non-statin lipid-lowering agents during the study, 23 patients (22.8%) discontinued treatment.

Discussion
The present study aimed to provide an updated snapshot of secondary prevention in patients experiencing acute coronary syndrome among Italian Cardiology Centers.

Given the observational nature of the study, it is not surprising that the timing of follow-up visits was not fully aligned with the established calendar, with V0 being within the expected 6-10 week range following the ACS event, V1 occurring within 4-10 months (versus 5-7 months), and V2 within 11-18 months (versus 12-14 months) after ACS event. Attendance to follow-up visits of overall population was 41.6% (218 patients) at V1 and 84.7% (444 patients) at V2. At V2, information was collected by phone for 44.6% of the patients.

Overall, findings described a widespread adoption of LLT for secondary prevention in ACS patients (with 97.3% patients on statin treatment at discharge), in agreement with the recommendations of national and international guidelines [5,10]. A major finding of this study is the suboptimal lipid profile control in these patients despite their very high risk of recurrent post-ACS events. In fact, about 40% of them had not their LDL-C levels measured either at discharge or V0, and an even lower percentage had their LDL-C levels measured at all three time points considered in this study. LDL-C-lowering represents a cornerstone in the management of patients after an acute coronary syndrome event. Current guidelines recommend that lipid management in these patients should be undertaken in a context of global risk management and LDL-C levels should be re-evaluated 4-6 weeks after the ACS event [5]. This should allow time to determine the effectiveness of the pharmacological treatment adopted after the acute event and, if necessary, to adjust it accordingly [5]. In addition, despite most of the post-ACS patients having been discharged with a high intensity statin therapy, only half of them were able to achieve the LDL-C goal recommended by current guidelines for their cardiovascular risk category (<70 mg/dL) [5].

The analysis of the patients with LDL-C levels measures available at both D0 and V0 showed a drop in the mean LDL-C level to levels not far from the goal, documenting the overall effectiveness of secondary prevention. This certainly is a long step forward when considering the findings of the review by Hirsh et al., which highlighted a broad underutilization of LLT after ACS [8]. According to their analysis, only 27% (23-38%) of ACS patients were prescribed a high-intensity statin at discharge and the most important predictor for the prescription of high dose statin treatment appears to be the pre-ACS statin dose [8,9]. On the other hand, in patients with baseline LDL-C >100 mg/dL, a more intensive LLT is associated with a greater reduction in the risk of cardiovascular and all-cause mortality, an association not present in patients with baseline LDL-C levels <100 mg/dL [11]. In our study, half of the enrolled patients did not attain target LDL-C suggesting a suboptimal use of LLTs; interestingly, these patients had baseline LDL-C levels >100 mg/dL and would have likely benefited from a more intensive treatment. Indeed, despite the majority of patients in our sample being prescribed a high dose statin, only a small percentage was prescribed the combination with ezetimibe (from 3.6% at D0 to approximately 16% at 18 months from discharge).

The use of ezetimibe in the treatment of high-risk patients is supported by the results of the IMPROVE-IT study [12], which quantified the benefit of adding ezetimibe to statin therapy in a 24% further decrease in LDL-C and related decrease in CV events. Recent subgroup analyses on the same database comparing high-intensity treatment with simvastatin-ezetimibe vs simvastatin monotherapy found the greatest absolute risk reduction to be among patients 75 years or older receiving simvastatin-ezetimibe [13]. Results from an international multicenter observational study [14,15] on patients from the DYSIS II registry, confirmed the potential for CHD patients in reaching LDL-C goals by adding ezetimibe to statin treatment and provided an estimate of the number of patients (actually double) from that population that could have potentially reached their goal or could have reduced the distance from their goal with ezetimibe [14].

On the same note, this could apply to our results as well, especially in considering the group of patients who did not reach target and who were treated with low-moderate intensity treatment (approx. 76%, Table 3), where there would be more room for improvement. For example, if we look at those patients in low-moderate regimen needing a reduction of at least 30% or above from value at discharge to reach the LDL-C target, we can hypothesize that the addition of ezetimibe (which alone contributes to a 20-24% LDL-C reduction) could have contributed to achieve the goal or to reduce distance from goal LDL-C. It is worth noting, however, that among patients who did not reach the LDL-C goal at V0, the percentage of those taking high intensity lipid-lowering therapy was comparable to that of patients in the "at target" group.

The analysis of specific subgroups showed that most patients with chronic kidney disease at V0 fell into the "at target" group, suggesting that the treatment was appropriately addressed in most cases; on the other hand, patients with familial history of CVD in the "at target" group were significantly less than those "not at target", suggesting the presence of additional risk factors that should be addressed properly 516].

Rate of therapy discontinuation during follow-up

Poor patient compliance is a common issue typically due to drug-related side effects as well as patient's distrust and personal decision to discontinue the treatment [8617]. In our study 96.2% of patients presenting at V2 were still taking the prescribed statin, and only 2.7% of patients discontinued due to side-effects, which may suggest an underlying attention to drug titration by the physician. Hence in consideration of the low drop-out rate and high percentage of patients continuing their prescribed statin treatment at one year, the high rate of patients "not at target" appears to be more likely explained by a suboptimal/inadequate use of combination therapies with other non-statin lipid lowering agents, rather than by intolerance to statin treatment.

Regarding patient compliance, it has been reported that only 53-60% of patients remain adherent within the first year of therapy initiation, as 10-25% of patients across observational studies manifest intolerance to statin treatment [8]. Another study providing data from real-life practice in Italy reports extremely low compliance at 1 year [9]. Yet, we cannot exclude that the high compliance observed in our study may reflect the specific characteristics of the studied population, i.e. post-ACS patients who may differ from patients of other studies, as well as an increasing patient empowerment and awareness on the importance of compliance, and, not least, a stricter follow up.

Adherence to post-acute follow up assessment

Post-discharge management of patients with ACS requires a comprehensive outpatient network and specific competence regarding risk factor control, optimal pharmacological therapy and adequate follow-up strategies. This combination should allow a significant outcome improvement with reduced rates of recurrent events. Cardiac rehabilitation programs have demonstrated significant improvement in drug titration, long-term adherence, recommended target attainment and outcome 718].

As evidenced in a national document commenting on real-life clinical practice across Italy, high risk patients seem to have a lower probability of accessing appropriate diagnostic tests, compared to low-risk patients (in particular stable angina patients), who are often subject to unnecessary assessments, and suggest the need for an individualized and clearly-defined follow-up program post-ACS to be explicitly written in the discharge records [10]. Results from our study show a higher attendance rate for visit V2 (84.7% of patients enrolled), at approximately one year from index event, compared with V1, which was an optional visit and was scarcely attended (41.6% of total population). Despite the high attendance rate to V0 and V2, the rate of LDL-C assessments was low. Considering that frequency of LDL-C monitoring is an important marker for the evaluation of the efficacy of prescribed LLTs and may also serve as an incentive for the patient in working towards a therapeutic goal, setting more frequent and mandatory LDL-C assessments during follow-up could provide the clinician additional information to adjust the LLTs accordingly [19,20].

Strengths and limitations

This study has strengths and limitations. This was a prospective investigation of patients receiving a complete baseline assessment and planned follow-up visits, with accurate evaluation of lipid profile and treatments. Inclusion bias or bias in treatment decision cannot be excluded, although recruitment of consecutive patients at each center was strongly suggested. Moreover, the use of chronic statin therapy at the time of the index event may have influenced the values of LDL-C at D0. Also, the analysis on the predictors for LDL-C target achievement was adjusted for possible confounding variables, but the lack of adjustment for variables not captured in the registry may represent a limitation. Finally, the fact that a considerable percentage of patients are not at goal may be explained in part due to compliance issues, as we were not able to measure compliance and adherence.

Clinical Implications

A large body of evidencet demonstrates the reduction of morbidity and mortality in the first year and beyond associated with the optimal control of risk factors responsible for recurrent cardiovascular events, fatal and nonfatal, after an ACS event. In addition to attainment of target LDL-C, optimal control includes adequate management of diabetes and hypertension, use of antiplatelet therapy and drugs for preventing left ventricular dysfunction onset or progression), and full adherence to healthy lifestyle measures, such as smoking cessation, physical activity and stress reduction. These goals must be pursued concomitantly rather than one at a time, and thus require the patient be supported by a multidisciplinary team and a structured secondary prevention program to face typical issues issues, that may arise over time, such as low patient motivation, lack of clear and updated goals, a dip in adherence pattern, ensuing comorbidities, aging and decreasing self sufficiency

Conclusions

In Italy secondary prevention for high-risk patients after ACS is aligned to current European guidelines recommending intensive LLT towards target LDL-C <70 mg/dl. The vast majority of patients is treated with intensive statin-based regimens, nonetheless only half achieve target values at 6 weeks from discharge and at 12 months. This suggests that the real-life practice is quite distant from an optimal management of secondary prevention patients after ACS and more should be done to improve LDL-C target achievement and outcome. At the time of the publication of this manuscript a new Edition of ESC Guidelines on Dyslipidemia has been just published (2019), introducing new goals of LDL-cholesterol in secondary prevention patients (< 55 mg/dl).

paper. Stefania Cercone and Laura Canullo are employees at MSD Italy. None of the co-authors have any conflict of interest to declare.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained for all patients prior to enrolment in the study.

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