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Low density lipoprotein target achivement in very high and extreme cardiovascular risk patients during a cardiac rehabilitation program

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ABSTRACT

Background and aims: Studies demonstrate that Low Density Lipoprotein (LDL) cholesterol targets are largely unreached in real-life, particularly in the higher cardiovascular (CV) risk classes. Our aim was to evaluate LDL target achievement in very high and extreme CV risk patients at the end of a Cardiac Rehabilitation (CR) program.

Methods and results: A total of 940 patients with recent acute or chronic coronary syndrome participating in a CR program were enrolled between January 2012 and December 2023. LDL targets were <70 mg/dL for patients treated before August 2019, <55 mg/dL after this date and <40 mg/dL for extreme CV risk subjects. Mean age was 66.9 ± 10.6 years, 82.9 % of the subjects were males and LDL cholesterol decreased from 107.3 ± 39.3 to 64.5 ± 24.6. 88.0 % of the subjects were taking high-intensity statins, 38.1 % ezetimibe while only 4.6 % PCSK9-inhibitors and 0.9 % bempedoic acid. 53.1 % of the patients reached the LDL target with particularly positive peaks in 2018 (72.8 %), 2022 (78.8 %) and 2023 (75.7 %). 29.8 % of the patients had extreme CV risk and they achieved the target of LDL <40 mg/dL only in 16.4 %, with a higher prevalence in the latest years (32 % in 2022 and 22.7 % in 2023).

Conclusions: Our results are highly encouraging compared to those reported in previous observational studies. The further we move from guideline publication, the higher the proportion of patients achieving LDL targets, supported by increased clinical awareness and new pharmacological options. However, more attention should be paid to extreme CV risk patients, both in term of correct dentification and treatment.

1. Introduction

CardioVascular (CV) diseases are the leading cause of death worldwide and are primarily driven by atherosclerotic vessel involvement [1]. Among their modifiable risk factors, the most significant one is Low Density Lipoprotein (LDL) cholesterol.

The 2019 European Society of Cardiology (ESC) guidelines [2,3] further lowered the LDL target, adhering to the principle of "the lower, the better", especially in the secondary prevention setting.

However, some observational studies (such as the DA VINCI and the SANTORINI ones) highlighted that the recommended LDL cholesterol targets are not adequately met in most patients, particularly those in the higher risk categories [4,5]. Both studies suggested that this may be due to insufficient use of statins and ezetimibe combination therapies, as well as new Lipid Lowering Therapies (LLT) such as Pro*protein Convertase Subtilisin/Kexin type 9* inhibitors *(PCSK9-i) and bempedoic acid*.

Cardiac Rehabilitation (CR) programs are an essential secondary prevention strategy, strongly recommended by guidelines [6]. Beyond physical exercise, CR programs are settings where patients' disease awareness and engagement can be improved, and drug therapies can be optimized and tailored [7]. In fact, higher rates of LDL cholesterol target achievement have been reported in these settings, although results remain suboptimal [8,9]. Furthermore, the target achievement of the recently described subgroup of extreme CV risk subjects has never been evaluated [10].

The objective of our study was to evaluate LDL cholesterol levels and

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the achievement of the corresponding targets at the end of a CR program in Acute and Chronic Coronary syndrome (ACS and CCS respectively). Furthermore, we aimed to evaluate the achievement of the 40 mg/dL LDL cholesterol target of extreme CV risk patients.

2. Methods

2.1. Study population

We evaluated a total of 940 patients who attended the CR of our institution for a recent ACS or CCS hospitalization, between January 1, 2012, and December 31, 2023.

The diagnosis of ACS followed the Fourth Universal Definition of Myocardial Infarction [11], which defines ACS as the presence of acute myocardial injury alongside clinical evidence of acute myocardial ischemia. Ischemia was characterized by a rise and/or fall in high-sensitivity Troponin T levels with at least one value exceeding the 99th percentile upper reference limit (>14 ng/L), along with at least one of the following features: (i) symptoms of myocardial ischemia; (ii) new ischemic changes on the electrocardiogram; (iii) development of pathological Q waves; (iv) imaging evidence of new loss of viable myocardium or newly abnormal wall motion in a context compatible with ischemic etiology; and (v) coronary thrombus identified via coronary angiography.

CCS was defined according to the ESC 2024 Guidelines [12]: (i) symptomatic patients with stress-induced angina or ischemia with epicardial obstructive coronary arteries diseases; (ii) patients with angina or ischemia caused by epicardial vasomotor abnormalities or functional/structural microvascular alterations in the absence of epicardial obstructive coronary arteries diseases; (iii) non-acute patients post-ACS or after a revascularization; (iv) non-acute patients with heart failure of ischemic or cardiometabolic origin; and (v) asymptomatic individuals in whom epicardial CAD is detected during an imaging test for refining cardiovascular risk assessment, screening or as an incidental finding.

For the present analysis patients without epicardial coronary arteries disease were excluded as well as other non-ischemic heart diseases such as heart failure of non-ischemic origin, valvular heart disease, or post-cardiac surgery.

For each patient, data were collected on clinical history and evaluations at the start of the CR program. These included age, sex, Body Mass Index (BMI), risk factors (arterial hypertension, diabetes mellitus, smoking, dyslipidemia), Blood Pressure (BP), Heart Rate (HR), and Left Ventricular Ejection Fraction (LVEF). Biochemical data from the recent ACS/CCS hospitalization were considered as baseline values and they were repeated at the end of CR. In particular, we collected creatinine, fasting glucose, total cholesterol, High Density Lipoprotein – HDL – cholesterol).

Furthermore, pharmacological therapies (focusing on beta-blockers, LLT, antiplatelets, and antihypertensives) taken by the patients at the end of CR were collected as well as changes in LLT that occurred during the CR. High-intensity statins were rosuvastatin or atorvastatin, irrespective of the dose.

The Glomerular Filtration Rate (GFR) was calculated using the MDRD (Modification on Diet in Renal Disease) formula, with Chronic Kidney Disease (CKD) defined as a GFR <60 mL/min. Overweight/obesity was defined as a BMI >25 kg/m^2.

Friedewald's formula was applied to calculate LDL cholesterol: Total cholesterol - [HDL cholesterol + (TG/5)]. For patients with TG levels above 400 mg/dL, direct LDL cholesterol was measured.

Data were extracted from electronic hospital records. The study protocol complies with the Declaration of Helsinki and was approved by the Ethics Committee of the institution and all participants provided informed written consent after being advised about the nature and purpose of the study.

2.2. Identification of patients with extreme cardiovascular risk

Extreme CV risk patients were identified following the definitions proposed in 2022 [10]. These are: (i) SCORE >20 % (primary prevention); (ii) ACS with recurrent vascular events within two years; (iii) ACS with peripheral or polyvascular disease; (iv) ACS with multivessel coronary artery disease; (v) ACS with familial hypercholesterolemia; and (vi) ACS with diabetes plus other risk factors (e.g., lipoprotein(a), C-reactive protein, or CKD) [10].

In the present analysis, definition 1 was not considered because it refers to primary prevention, whereas definitions 5 and 6 were not used because the required data (familial hypercholesterolemia, lipoprotein(a) and C-reactive protein) were not available. Patients meeting the criteria 2, 3, or 4 were classified as having extreme CV risk.

Regarding definition 2, previous CV events were defined as: (i) ACS; (ii) prior coronary revascularization (percutaneous intervention or coronary artery bypass grafting), whether elective or urgent; (iii) stroke or transient ischemic attack; (iv) prior revascularization for peripheral artery disease (thromboendarterectomy or stent placement) in the lower limbs or carotid arteries; and (v) acute lower limb events (ischemia, arterial occlusion, or artery-to-artery embolization). Lacunar infarcts or positive imaging findings for cerebrovascular events (e.g., ischemic areas on CT or MRI) were excluded unless associated with concurrent neurological symptoms, as dating these events was impossible without symptomatic onset.

Peripheral or polyvascular disease (definition 3) was identified as previous neurological (stroke and/or TIA and/or previous carotid revascularization and/or known carotid atherosclerotic plaque >50 %) or lower limbs events (acute lower limb events and/or known atherosclerotic plaques >50 % in the lower limb arteries and/or previous lower limb revascularization).

Three vessels CAD (definition 4) was identified as the presence of atherosclerotic involvement in right coronary artery and left main or left descending artery plus the circumflex artery.

2.3. Outcomes definitions

Since all enrolled patients had a recent ACS/CCS hospitalization, they were all classified as having at least a very high CV risk. So, their LDL targets were considered <70 mg/dL for patients concluding CR before August 2019, <55 mg/dL after this date and <40 mg/dL for extreme CV risk subjects.

When PCSK9-i became available on Italian market, the drug regulatory agency initially allowed the possibility to prescribe them to an LDL>100 mg/dL. In June 2022 this level was set down to >70 mg/dL. So, some patients, fall within a “grey zone”, meaning that their LDL cholesterol was not at target but their therapies could not be enhanced. The “grey zone” prevalence was also evaluated and it was defined as a patient with an LDL cholesterol between 56 and 99 from 2017 to June 2022 and between 56 and 69 after that date [13].

2.4. Cardiac rehabilitation program

The CR training program consisted of 25 working-day sessions over 5 weeks in an outpatient setting, tailored for high-intensity rehabilitation services and low-intensity clinical support.

The core activity was daily aerobic exercise, comprising 45 min of resistance training on a cycle ergometer and 45 min of bodyweight exercises, with 15 min of rest between them.

The intensity of the physical activity was tailored to each patient's functional capacity and tolerance and was progressively increased throughout the program. A multidisciplinary team led by a cardiologist, nurses and physiotherapists supervised the program. Patients also received psychological support to manage emotional responses and improve patients' engagement and a dietary consultation to encourage lifestyle and dietary changes.

2.5. Statistical analysis

Categorical variables were expressed as percentages, while continuous variables were reported as mean ± standard deviation. Differences between the two time points (T0 and T1) were calculated using the Paired Samples T-test.

To calculate the yearly prevalence of patients achieving the LDL cholesterol target, the number of such patients was related to the total number of patients in the study each year. The same method was applied to determine the prevalence of the "grey zone", extreme CV risk and the proportion of extreme-risk patients achieving LDL cholesterol targets annually.

Associations between variables were estimated using Pearson's coefficient. Associated factors were used as covariates in a multivariable logistic regression model with LDL cholesterol target achievement as the dependent variable.

IBM SPSS Statistics Version 26.0 (Armonk, NY: IBM Corp) software was used for the statistical analysis and a p-value ≤ 0.05 was considered statistically significant.

3. Results

3.1. Population characteristics

Table 1 presents the characteristics of the 940 patients evaluated. They had a mean age of 66.9 ± 10.6 years and were mainly male (82.9 %). The main CV risk factor was dyslipidemia (75.2 %) followed by hypertension (67.9 %) and overweight/obesity (57.4 %) while 26.2 % of the patients were active smokers and 20.5 % were diabetic.

Regarding previous CV history, 33.6 % of the patients had a previous coronary revascularization, of whom 26.1 % underwent percutaneous angioplasty and 2.2 % bypass grafting, while 5.4 % had both type of procedures. Atrial Fibrillation (both persistent and paroxysmal) affected 7.2 % of the patients, 8.8 % had a known lower limbs Peripheral Artery Disease (PAD) and 9.1 % had a previous stroke or transient ischemic attack or a carotid plaque >50 %.

At index hospitalization for ACS or CCS left main was critically affected by atherosclerotic process in 5.5 % of the subjects, while 63.4 % had a critical plaque in left descending artery, 34.1 % at circumflex level and 38.5 % in the right coronary artery. Overall, 5.2 % of the subjects had a three vessels disease.

Systolic and diastolic BP significantly decreased during CR (systolic BP: from 124.7 ± 16.5 to 115.4 ± 11.3 mmHg; Diastolic BP: from 74.3 ± 9.2 to 66.8 ± 8.6 mmHg; $p < 0.001$ for both comparison) while LVEF significantly increased (from 53.4 ± 8.4 to 55.5 ± 7.6 %, $p < 0.001$)

Regarding biochemical data, creatinine and glucose did not change significantly during CR while mean LDL cholesterol decreased from 107.3 ± 39.3 mg/dL (data from recent ACS/CCS hospitalization) to 64.5 ± 24.6 mg/dL (data from end of CR biochemical analysis) with a p-value <0.001. Average time from index hospitalization to CR conclusion was 9.6 ± 0.5 weeks.

At the end of CR, 72.5 % of the subjects were treated with antihypertensive drug of whom 69.0 % were angiotensin converting enzyme inhibitors or angiotensin receptor blockers. 82.0 % were treated with B-blockers and 87.6 % with antiplatelets.

More specifically, regarding LLT, 88.0 % of the subjects were take high-intensity statins associated in 38.1 % of the cases with ezetimibe. PCSK9-is were used only in 4.6 % (evolocumab 1.4 %, alirocumab 1.6 % and inclisiran 1.6 %) and bempedoic acid in 0.9 % of the cases.

During the CR program 9.5 % of the subjects had an increase in statin dose, while 1.5 % had a dose reduction (due to statin associated muscle symptoms). Moreover, 3.1 % of the subjects initiated a PCSK9–I and 0.6 % initiated bempedoic acid.

Table 1
Population characteristics at beginning (T0) and end (T1) of cardiac rehabilitation.

VARIABLE	T0	T1	p-value
Demographic variable			
Number	940	940	–
Age (years)	66.9 ± 10.6	–	–
Men, n (%)	779 (82.9 %)	–	–
Cardiovascular risk factor			
Body Mass Index (kg/m2)	27.0 ± 4.2	26.9 ± 3.9	0.749
Overweight/Obesity, n (%)	540 (57.4 %)	536 (57.0 %)	0.852
Dyslipidaemia, n (%)	707 (75.2 %)	–	–
Diabetes, n (%)	193 (20.5 %)	–	–
Arterial hypertension, n (%)	638 (67.9 %)	–	–
Active smokers, n (%)	246 (26.2 %)	–	–
Familiar history of early cardiovascular events, n (%)	430 (45.7 %)	–	–
Extreme CV risk, n (%)	280 (29.8 %)	–	–
Previous cardiovascular and non-cardiovascular diseases			
Chronic Kidney Disease, n (%)	137 (14.6 %)	–	–
Atrial Fibrillation, n (%)	68 (7.2 %)	–	–
Peripheral artery disease, n (%)	83 (8.8 %)	–	–
Previous stroke or transient ischemic attack or carotid plaque >50 %, n (%)	85 (9.1 %)	–	–
Prior revascularization, n (%)	316 (33.6 %)	–	–
● Percutaneous, n (%)	245 (26.1 %)		
● Surgical, n (%)	21 (2.2 %)		
● Both, n (%)	51 (5.4 %)		
Index event coronary angiography			
Critical left main, n (%)	52 (5.5 %)	–	–
Critical left descending artery, n (%)	596 (63.4 %)	–	–
Critical circumflex, n (%)	321 (34.1 %)	–	–
Critical right coronary artery, n (%)	362 (38.5 %)	–	–
Three vessels disease, n (%)	49 (5.2 %)	–	–
Haemodynamic variables			
Systolic Blood Pressure (mmHg)	124.7 ± 16.5	115.4 ± 11.3	<0.001
Diastolic Blood Pressure (mmHg)	74.3 ± 9.2	66.8 ± 8.6	<0.001
Heart Rate (bpm)	65.8 ± 8.2	62.3 ± 7.5	0.327
Left Ventricular Ejection Fraction (%)	53.5 ± 8.4	55.5 ± 7.6	<0.001
Biochemical data			
Creatinine (mg/dL)	1.04 ± 0.40	1.05 ± 0.44	0.261
Glucose (mg/dL)	107.6 ± 33.2	108.5 ± 25.4	0.707
Total cholesterol (mg/dL)	175.9 ± 43.1	132.2 ± 30.8	<0.001
HDL cholesterol (mg/dL)	42.9 ± 11.1	44.3 ± 11.6	<0.001
Triglycerides (mg/dL)	133.1 ± 66.1	114.9 ± 77.3	<0.001
LDL cholesterol (mg/dL)	107.3 ± 39.3	64.5 ± 24.6	<0.001

(continued on next page)

Table 1 (*continued*)

VARIABLE	T0	T1	p-value
LDL cholesterol at target, n (%)	–	499 (53.1 %)	–
LDL cholesterol "Grey zone", n (%)	–	288 (30.6 %)	–
Cardiovascular drug therapies			
Antihypertensives, n (%)	–	691 (72.5 %)	–
Calcium antagonists, n (%)	–	67 (7.1 %)	–
Diuretics, n (%)	–	58 (6.2 %)	–
ACE-I/ARBs, n (%)	–	649 (69.0 %)	–
Beta-Blockers, n (%)	–	771 (82.0 %)	–
Antiplatelets, n (%)	–	823 (87.6 %)	–
High intensity statins, n (%)	–	827 (88.0 %)	–
Ezetimibe, n (%)	–	358 (38.1 %)	–
PCSK9-inhibitors, n (%)	–	43 (4.6 %)	–
● Evolocumab, n (%)		13 (1.4 %)	
● Alirocumab, n (%)		15 (1.6 %)	
● Inclisiran, n (%)		15 (1.6 %)	
Bempedoic acid, n (%)	–	8 (0.9 %)	–
Change in lipid lowering therapies done during the cardiac rehabilitation program			
Increase in statin dose	–	90 (9.5 %)	–
Decrease in statin dose	–	15 (1.5 %)	–
Initiation of PCSK9-i	–	30 (3.1 %)	–
Initiation of bempedoic acid	–	6 (0.6 %)	–

Continuous variables are reported as mean ± standard deviation while categorical ones are reported as number and percentages.
Abbreviations: LDL = Low Density Lipoprotein; HDL = High Density Lipoprotein; ACE-I = Angiotensin Converting Enzyme Inhibitors; ARB = Angiotensin Receptor Blockers; PCSK9 = Proprotein Convertase Subtilisin/Kexin type 9.

3.2. LDL cholesterol target achievement

Overall, 53.1 % of patients achieved the LDL cholesterol target. When data were analysed on annual basis (Fig. 1), we found a progressive increase in LDL target achievement from 2012 2018, when the rate peaked at 72.8 %. A decline was observed after the publication of the 2019 ESC guidelines, which lowered the target, and it took two years to return to significant achievement levels (75.7–78.8 % in 2022 and 2023).

The overall prevalence of patients classified as having extreme cardiovascular (CV) risk is 29.8 % with a progressive increase over years (Fig. 2). This figure also illustrates the prevalence of patients within this subgroup who achieved the LDL cholesterol target of <40 mg/dL. Despite a positive trend, the number of extreme CV risk patients that reach their target **remained suboptimal** (acme 32.0 % in 2022).

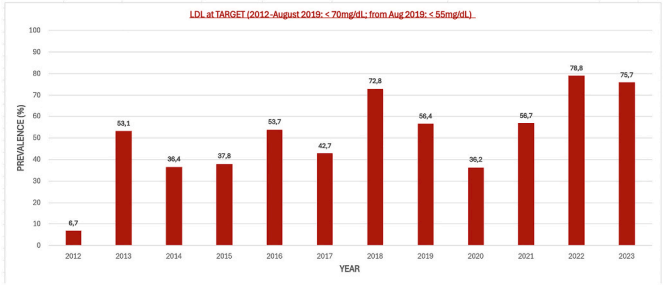

Fig. 1. Prevalence of patients who achieved LDL cholesterol targets.

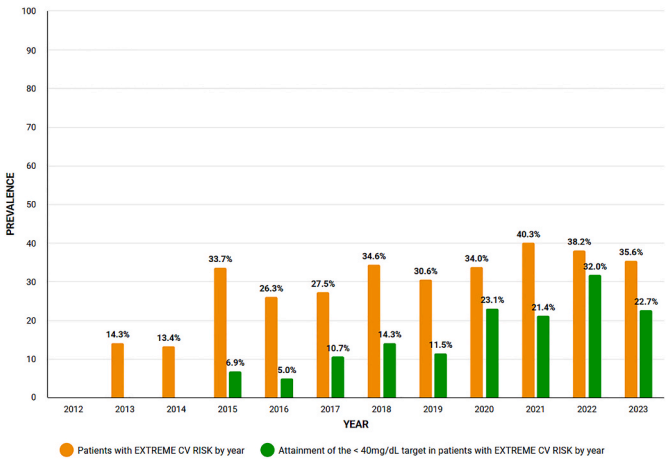

Fig. 2. Prevalence of patients with extreme CV risk in the study population (in orange) and the corresponding prevalence of LDL cholesterol targets achievement (in green). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Supplementary Fig. 1 illustrates the prevalence of the "grey zone", defined as patients who were not at target but did not meet criteria for additional therapeutic interventions beyond first-line treatments according to Italian prescription rules. After the reduction of prescription threshold to 70 mg/dL, in June 2022, the proportion of patients in this category progressively decreased till 18.4 % in 2023.

3.3. Lipid lowering therapies over years

Fig. 3 shows CR discharge LLT on a yearly base. While the approach in 2012 was mainly based on statins monotherapy, in the following years (especially after 2019), the use of combination therapy (with ezetimibe) progressively increases (56.0 % in 2020, 60.7 % in 2021, 67.5 % in 2022 and 73.9 % in 2023).

PCSK9-i uses progressively increase, although rarely as monotherapy (1.2 % in 2021, 2.7 % in 2022 and 2.8 % in 2023) and, more often, in combination with statins/ezetimibe (acme 7.9 % in 2022) or only with statins (acme 3.6 % in 2022). Finally, bempedoic acid was always used in association with statins and ezetimibe in 2.7 % of cases in 2022 and 4.2 % in 2023.

Patients that achieved their LDL cholesterol target had a more intensive LLT with higher use of statin/ezetimibe combination, PCSK9–I and bempedoic acid (Supplementary Fig. 2, $p < 0.05$ for every year excluded 2012 and 2014).

3.4. Correlations and regression analysis

The achievement of LDL cholesterol target values was significantly associated in univariate analysis with male sex ($r = 0.12$; $p < 0.0001$), PAD ($r = -0.12$; $p < 0.0001$), baseline LDL cholesterol ($r = -0.26$; $p < 0.0001$), glucose ($r = 0.12$; $p = 0.0008$), statins ($r = 0.13$; $p < 0.0001$) and PCSK9-i use ($r = 0.07$; $p < 0.0001$).

However, at multivariate logistic regression model with LDL cholesterol target achievement as the dependent variable, none of the covariates (age, sex, PAD, baseline LDL cholesterol, glucose, statins and PCSK9-i use) remained a significant association.

4. Discussion

The main finding of our study highlights significant advancements in achieving the LDL cholesterol targets outlined in the 2019 guidelines for

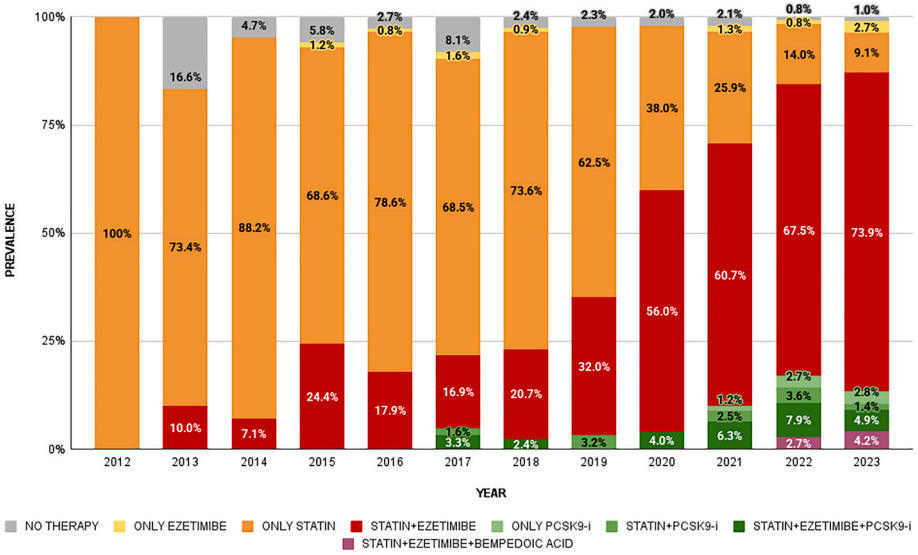

Fig. 3. Distribution of lipid lowering drugs by years at cardiac rehabilitation discharge.

dyslipidemia management. Overall, LDL cholesterol targets were met in 53.1 % of cases, a marked improvement compared to previous report. Importantly, this significant prevalence of LDL cholesterol target achievement is not mainly determined by the exercise performed during the CR program but by the therapeutic optimization and intensification that can be strongly done during such a program. In fact, a significant decrease was found between baseline LDL cholesterol values (collected during the index hospitalization that led to the CR program) and the final one (collected few days before the end of the CR program). The final LDL cholesterol target achievement resulted both from LLT started or intensified at the index hospitalization and the further optimization performed during the CR program. This optimization regarded statin dose increase (9.5 %), PCSK9-i initiation (3.1 %) and bempedoic acid initiation (0.6 %).

In particular, this prevalence is very high if compared with the two already cited large observational studies DA VINCI and SANTORINI [4, 5] in which only 18.0 and 18.3 % respectively, of patients with a previous CV event reached the 55 mg/dL target.

Results of these two studies could also reflect the relatively short interval between the studies and the release of the 2019 ESC dyslipidemia guidelines (1 and 2 years, respectively). A recent publication reported on a further 1-year follow-up of the SANTORINI study [14]. LLT was increased 33 % of the patients with a significant increase in combination therapy (from 25.6 % to 37.9 %). A further decrease in mean LDL cholesterol was observed (from 93 to 77 mg/dL) determining an achievement of respective target that increase from 21.2 to 30.9 %. These values were higher in patients receiving combination LLT (39.4 %) compared with those on monotherapy (25.5 %).

Our data could be compared with the Italian cohort sub-analysis of the SANTORINI study [15]. Italian centers enrolled 1977 patients of which 1531 were at very high CV risk. The LDL cholesterol target achievement rate of these patients was 19.9 % and 34.1 % of the patients had no LLT, 33.1 % took a statin monotherapy and 32.7 % had a combination LLT in which PCSK9–I were used in 8.4 % of the cases. In the Italian cohort, a lower use of statin monotherapy and moderate intensity statins was reported, alongside higher use of PCSK9-i and any other combination LLT.

The 1-year follow-up data of the Italian cohort were recently published [16], showing that untreated patients decreased dramatically (from 32 % to 2.1 %) with a positive trend toward an increase in combination LLT use (from 33.8 % to 55.5 %). This changes determined an LDL cholesterol decreased from 97 to 74 mg/dL with the proportion of patients achieving their LDL cholesterol target increased from 20.8 % to 35.0 %.

Also recently, the JET-LDL register, published in 2024, examined 1095 ACS patients undergoing percutaneous coronary intervention. An LDL cholesterol target achievement of 62 % was reported at 1 month after discharge [17]. An improvement in LLT was noted compared with the previously cited studies: 98.1 % of subjects were treated with statins, 60.1 % with statins plus ezetimibe, and 8.5 % with PCSK9-i. In comparison, only 42 % of DA VINCI participants took high-intensity statins, 9 % used ezetimibe, and only 1 % received a PCSK9-i. In the SANTORINI study, conducted one year later, statin–ezetimibe combinations were used in 17.5 % of subjects, and PCSK9-i in 4.7 %.

Also in our study we observed a progressive increase in LLT intensity with a progressive increase over years of statin-ezetimibe combination, PCSK9–I and bempedoic acid use with higher prevalence in patients reaching their targets.

Studies based on patients undergoing CR yield significantly higher results, although populations were smaller. In 163 patients undergoing a CR program, LDL cholesterol target achievement was 59 % [9], similar to the 53 % rate in the SwissPR registry (875 patients) [8].

A recent meta-analysis also showed that CR participants had a significantly greater decrease in LDL cholesterol than non-CR patients (−9 mg/dL) although the included studies spanned from 1979 to 2022, during which LLT practices significantly changed [18].

Notably, the percentage reported in our study represents an average across all years included (2012–2023), with substantial differences between the firsts and the later years. In 2012, only 6.7 % of patients achieved LDL targets despite the more lenient standards of the time, suggesting limited prioritization of cholesterol management within the cardiology community. Over subsequent years, significant improvement was observed, peaking at 72.8 % in 2018. This was followed by a decline in 2019 (56.4 %) and 2020 (36.2 %) driven by the release of updated ESC guidelines that set stricter LDL cholesterol targets. The initial decrease underscores the delay in clinical practice adaptation to the new standards. Since 2020, success rates have steadily improved, reaching 78.8 % in 2022 and 75.7 % in 2023. These results likely reflect an increase in physicians' awareness, in time dedicated to dyslipidaemia management and of the time from guidelines release, facilitating acceptance of the new targets. Furthermore, also the presence of new available LLT, PCSK9-i and bempedoic acid, supported clinicians in helping patients achieve targets and increase disease awareness for both clinicians and patients.

As highlighted in our study, current LLT predominantly relies on high-intensity statins with a strong trend for ezetimibe use, mainly in

single-pill combinations. Regarding PCSK9-i we showed a progressive increase since their approval in 2017, although they are still used only in 4.6 % among the study population. A further increase could be expected in the coming years due to new formulation (e.g. alirocumab 300 mg monthly and inclisiran) and by prescription rule simplification. Beyond the already mentioned reduction in prescription cut-off (from 100 to 70 mg/dL), a further simplification was recently introduced in Italy, shifting PCSK9 antibody distribution from hospitals to community pharmacies. This change began in April 2024 but is currently active only in a few Italian regions, limiting our ability to evaluate its impact on PCSK9-i prescription rates and secondary prevention outcomes.

However, most patients were on statins/ezetimibe combination, confirming that these treatments represent foundational approach by which most patients of the patients can achieve their LDL targets.

Another important point concerns extreme CV risk patients. Within the heterogeneous group of secondary prevention patients, a subgroup will experience recurrent CV events despite optimal medical treatment and achievement of therapeutic targets. These patients are classified as "extreme CV risk" and correctly identifying them could enable treatment intensification with the attempt of reducing the occurrence of recurrent CV events [19,20]. Our data showed that they are far from infrequent since near 35–40 % of ACS/CCS patients attending to a CR program are included in this risk category. Their LDL target is < 40 mg/dL, yet we found that only 32.0 % in 2022 and 22.7 % in 2023 achieved this threshold. Several factors likely contribute to this suboptimal result, including insufficient clinician awareness, difficulty adopting new definitions, and barriers to LLT prescription. In Italy, extreme CV risk patients historically faced the same restrictive PCSK9-i prescribing criteria as very high CV risk patients. For instance, extreme CV risk patients with LDL levels between 41 and 69 mg/dL do not meet their <40 mg/dL target but are ineligible for PCSK9 inhibitors.

We also attempted to identify factors influencing LDL target achievement. In univariate analysis, male sex, absence of PAD, higher glucose levels, lower baseline LDL cholesterol, and statin and PCSK9-i use were associated with target achievement. The negative association with PAD likely reflects that PAD is included in the definition of extreme CV risk, which automatically lowers the LDL target to 40 mg/dL and therefore makes achievement more difficult.

However, in multivariate analysis none of the previously variables remain significantly associated, suggesting that other determinants—likely environmental factors such as local LLT prescription rules, physician inertia, and patient compliance—play a substantial role.

Finally, in the Italian prescribing context, a "grey zone" exist: patients who don't reach their LDL cholesterol target but remain ineligible for PCSK9-i due to regulatory restrictions [13]. In fact, PCSK9-i could be prescribed only for patients with LDL cholesterol >100 mg/dL (till June 2022, thereafter if > 70 mg/dL). Consequently, patients with LDL levels between 56 and 99 mg/dL (or between 56 and 69 mg/dL after June 2022) were not at target but their LLT cannot be optimize. After the shift from 100 to 70 mg/dL, a broader access to these treatments was permitted with an improved achievement of LDL targets. In fact, patients falling in the "grey zone" decreased significantly over years and it regards only the 15–18 % of the patients.

Our study presents some limitations, the most important being one the absence of a follow-up regarding LDL cholesterol values that are limited to the one collected at the end of the CR program. This limitation prevents assessment of long-term target maintenance, which is clinically relevant. Moreover, with only two LDL measurements (index hospitalization and end of CR) in a short interval, and without additional follow-up data, it is not possible to determine the time required to reach target levels. Furthermore, we did not collect follow-up data on CV events, which prevents us from demonstrating that LDL target achievement translated into reduced event recurrence. Another limitation is that we collected data on CV therapies only at the end of CR, although we documented LLT changes. We recorded drug classes but not specific doses; for example, we noted how many patients were taking high-intensity statins (atorvastatin or rosuvastatin) but not how many were on high doses (>40 mg and >20 mg, respectively). We also did not record whether statins and ezetimibe were administered as single-pill combinations or separate pills, although single-pill combinations are known to improve compliance and LDL target achievement [21]. Similarly, we did not collect data on medication adherence, limiting our ability to assess whether poor compliance contributed to failure to achieve LDL targets [22,23]. Finally, our data come from a single centre in Italy, limiting generalizability.

5. Conclusion

In conclusion, our study demonstrates encouraging progress in LDL cholesterol management over the years, driven by increased clinical focus and adherence to updated guidelines. However, barriers such as restrictive prescribing criteria for PCSK9-i and challenges in managing extreme CV risk patients highlight areas that still require improvement to optimize outcomes.

Addressing these limitations in the near future would enable for an even more effective management approach, ultimately improving LDL cholesterol target achievement.

Data availability statement

Data will be available upon request to the corresponding author.

Authors' contributions

Conceptualization: AM, BPD and AL; Methodology: AM, CT, AS and MA; Software: CT and MB; Data acquisition: BPD, MB, AS, MA, GPP, EB, GR, MA, AL and SR; Writing—Original Draft Preparation: BPD, AM and CT; Writing—Review & Editing: BPD, MB, AS, MA, GPP, EB, GR, MA, AL, SR and CG; Visualization: AM, CT and CG; Supervision: AM and CG. All authors have read and agreed to the published version of the manuscript.

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Declaration of competing interest

The authors report no conflict of interest.

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None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2026.104543.

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