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Effectiveness of the low-density lipoprotein cholesterol goals in secondary cardiovascular prevention

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Abstract

Background: The effectiveness of statin treatment to reduce coronary events and mortality has been hardly examined considering goals of LDL-C. We aimed to analyse such association in secondary cardiovascular prevention.

Methods: Retrospective cohort analysis of electronic health records from the SIDIAP database, Catalonia-Spain. Recruitment period was from 2006 to 2017 and study period finished at the end of 2018. We included 54,175 people aged ≥35 years in cardiovascular secondary prevention starting statin treatment. We analysed the association of achieved LDL-C goals after statin initiation with coronary heart disease and all-cause mortality.

Results: Mean age was 69 years and 20,146 (37.2%) were women. Coronary heart disease occurred in 5687 (10.5%) participants, and 10,676 (19.7%) persons passed away. Median follow-up lasted 5.7 years (interquartile range, 3.4–8.1). The coronary heart disease HRs (95% CI) for the LDL-C goals of 70–100, <70–55 and <55 mg/dL were .86 (.81–.92), .83 (.76–.9) and .8 (.72–.88), respectively. They were .89 (.83–.96) in the group with 30%–40% reduction and .86 (.8–.93) in the groups with 40%–50% and ≥50% reduction. We observed no association with mortality. We observed no relevant differences by sex or age.

Maria Garcia-Gil and Lia Alves-Cabratosa contributed equally to this work and share first authorship.

Conclusions: This population-level retrospective analysis of real-world data observed that treatment with statins is effective to achieve certain LDL-C goals and CHD reduction. The lack of significant difference between LDL-C goals needs confirmation in additional studies with real-world data. The LDL-C target should consider the magnitude of the decrease in coronary events.

KEYWORDS

cardiovascular disease, electronic health records, low-density lipoprotein cholesterol goals, real-world data, secondary cardiovascular prevention, statins

1 | INTRODUCTION

The Guidelines on the management of blood cholesterol to mitigate cardiovascular risk agree on the crucial role of the reduction of low-density lipoprotein-cholesterol (LDL-C) levels to lower the number of recurrent events after a first cardiovascular episode.[1–3] However, their recommendations on how to manage LDL-C levels differ. The European guidelines recommend an LDL-C reduction of at least 50% from baseline and an LDL-C goal of <55 mg/dL for patients in secondary prevention.[1] The guidelines from the USA for these patients consider initial intensive treatment with statins also aiming to at least 50% reduction in the LDL-C levels and further treatment with ezetimibe/PCSK9 inhibitors if the levels remain ≥70 mg/dL.[2] The NICE guidelines recommend initiation of intensive statin treatment aiming to a minimum of 40% reduction in the non-HDL levels.[3]

Target goals, therefore, vary amongst the Guidelines, and several questions remain unanswered. The main evidence to advocate for unlimited lowering of the LDL-C levels stems from Mendelian randomization studies,[4,5] several meta-analyses[6–8] and posterior clinical trials[9–11] The trials examined populations in primary or secondary cardiovascular prevention and compared people treated with lipid-lowering medications versus controls and more intensive versus moderate statin regimes or proxies for such treatments. But most of them did not examine specific goals by design.[12] Their results reflect the difficulty to discern if the lower incidence of cardiovascular events in the treated groups could be attributed to the very low LDL-C goals, the individual response to fixed doses of statins,[13] individual compliance to treatment,[14] or the pretreatment LDL-C levels.[12,13,15,16] Moreover, the studies with intensive statin treatments suggested that some of the objectives lead to higher risk of side effects[17] and lower adherence to treatment.[12] Finally, analyses from the real-world setting are scarce; we found only an observational study that showed a lack of additional benefit with the reduction of LDL-C levels below 70 mg/dL in secondary prevention.[18]

We need more evidence at a population level from studies specifically designed to assess the value of reaching certain LDL-C goals. Our study aimed to examine the effectiveness of statin treatment initiation in groups defined by goals of achieved LDL-C levels and percentage of LDL-C decrease regarding the occurrence of coronary events and all-cause mortality in a stable secondary prevention population.

2 | METHODS

2.1 | Data source

We analysed medical records from the Information System for the Development of Research in Primary Care (SIDIAP). This database contains pseudonymised records of over 8 million people since 2006, with 5.8 million people active in June 2021 (around 75% of the Catalan population). SIDIAP data are representative of the general population living in Catalonia in terms of age, sex and geographic distribution.[19] Its validity has been specifically documented for cardiovascular risk factors and diseases.[20] The records include information on sociodemographic data, clinical diagnoses, referral and hospital discharge information, laboratory tests and medications, which have been used in previous epidemiological analyses.[21,22] The database is updated every 6 months and the current median follow-up time of the population is 15.5 years.

2.2 | Study design and population

We performed a retrospective population-based cohort study. The study population encompassed individuals aged 35 or older; who started LDL-C lowering treatment with statins: statin new users (defined with a first record of simvastatin, pravastatin, lovastatin, fluvastatin, rosuvastatin, or atorvastatin invoicing); and had previous cardiovascular disease (CVD: acute myocardial infarction, angina, revascularization procedures, stroke, or peripheral artery

disease). Individuals with only one invoice for statins during the enrollment period were excluded, as were those with no recorded LDL-C values either before (pre-LDL-C) or after (post LDL-C) the first statin invoice.

Participants were enrolled from 2006 to 2017 but considered for analysis from 2007 to 2017 to ensure at least 1 year without taking statins before entry date; entry date was that of the first statin invoice and the index date was the date of exposure, defined by achieved LDL-C levels. Censoring occurred at the date of the first coronary event of interest, death, transfer out of SIDIAP coverage, or end of the study period, December 31, 2018.

The exposure was defined as the first stabilised measurement of post LDL-C levels observed after the first statin invoice and before the occurrence of the outcome (Figure S1). We considered the records of stabilised post LDL-C after 2 months; the estimation of the changing points was based on the results from E-Divisive methods (Figure S1).

The categories of post LDL-C were defined according to previous and current established guidelines by goal attainment and percentage of reduction.[2,3,23–25] For LDL-C goal attainment in secondary prevention, they were ≥100 mg/dL, 70–<100 mg/dL, 55–<70 mg/dL, <55 mg/dL; and for the percentage of LDL-C reduction they were <30%, 30%–<40%, 40%–<50% and ≥50%.

The primary outcomes were CHD (coronary heart disease; a composite of acute myocardial infarction and angina) and all-cause mortality. During follow-up, CHD was identified from SIDIAP codes in both primary care (ICD-10-CM) and hospital discharge records (ICD-9). The CHD codes in SIDIAP have been previously validated.[20] We also considered the occurrence of statin adverse effects (diabetes mellitus, cancer, and stroke) as secondary outcomes.

The following covariates were considered before the entry date for adjustment: age (years); sex; high-risk alcohol intake (yes/no); smoking (yes/no); diabetes (yes/no) or record of antidiabetic drug use; hypertension (yes/no) or record of antihypertensive drug use; record of other drugs use: systemic corticosteroids, antithrombotics, psychoanaleptics, psycholeptics, anti-inflammatory and oral contraceptive drugs, non-statin lipid-lowering therapy (LLT); dyslipidaemia (yes/no); triglycerides; high-density lipoprotein cholesterol; obesity (yes/no), defined as BMI >30 kg/m^2; MEDEA index (socioeconomic index); LDL-C before statin treatment (pre LDL-C), defined as the first record before the first statin invoice; and other comorbidities (yes/no): chronic kidney disease (CKD), atrial fibrillation, chronic obstructive pulmonary disease (COPD), asthma, rheumatoid arthritis, lupus, gout, endocrine and metabolic disorders, heart failure, and cancer.

Adherence to treatment was calculated according to the medication possession ratio (MPR): number of days of statin supply during six consecutive months, divided by 183 days. Finally, information about cardiovascular severity was addressed examining the presence of polyvascular, recent, and progressive CVD. Polyvascular CVD was considered if more than one vascular bed was affected; recent CVD, if the last hospitalisation was less than a year from the index date (beginning of the follow-up); and progressive CVD if more than one hospitalisations were counted.

2.3 | Statistical analysis

Categorical variables were expressed as percentages, and continuous variables as mean (SD) or median [quartiles]. Raw incidence rates and 95% confidence intervals were calculated. The hazard ratios (HR) for targeted LDL-C objectives and percentage of LDL-C reduction were calculated for outcome events using Cox proportional hazard regression models adjusted for potential confounders, which were selected using the Akaike Information Criteria (AIC). The proportionality of hazards assumption was tested. We also performed stratified analysis by sex and age, considering a threshold at 75 years.

Two sensitivity analyses were also performed. In the first, the models included only people with MPR >80%; in the second, the models included people with CHD as the only criterion for cohort entry. Statistical analysis used R-software.

2.4 | Ethics approval

Ethics approval was obtained from the IDIAP Jordi Gol ethics committee (P16/185) and all procedures were in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

3 | RESULTS

From 2006 through 2017, we analysed the SIDIAP records of 54,175 people, as shown in the flowchart (Figure 1). Median (interquartile range; IQR) follow-up was 5.7 (3.4–8.1); it decreased slightly with lowering post-LDL-C goals, and inversely to the increase in the percentage of LDL reduction. There were 1906 (3.5%) participants lost to follow-up due to transfer out of the SIDIAP database.

Overall, the study population had a median (IQR) age of 69 (60–78) years and included 20,146 (37.2%) women. Regarding the outcomes, CHD occurred in 5687 (10.5%) people and 10,676 (19.7%) persons passed away. The mean (SD) values of pre and post LDL-C were 137.1 (30.5) and 86.3 (28.6), respectively.

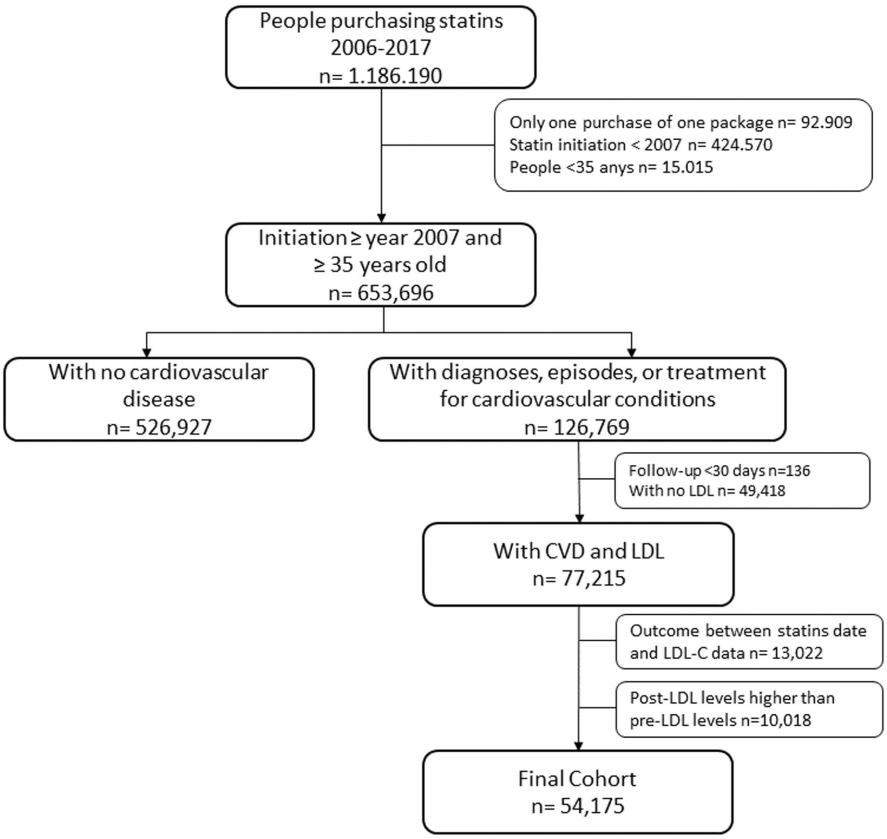

FIGURE 1 Study flowchart.

The main baseline characteristics by categories of post LDL-C levels and percentage of LDL-C reduction are shown in Tables 1 and 2, respectively. Regarding post LDL-C values, 47,800 (88%) participants did not reach the <55 mg/dL goals (Table 1). The analysis by percentage of LDL-C reduction showed that 41,260 (76.2%) participants did not reach the >50% reduction goal (Table 2).

The percentage of LDL-C reduction by categories of post LDL-C goals presented coherent results (Table 1). The proportion of participants with a percentage of LDL-C reduction <30% lowered as the post LDL-C goals decreased; the opposite occurred in the category with an LDL-C reduction ≥50%.

The baseline characteristics by percentage of LDL-C reduction are shown in Table 2. The proportion of participants with MPR >80% increased with incremental percentage of LDL-C reduction. The proportion of people with previous CHD increased with higher percentage of LDL-C reduction, as did the proportion (of people) with factors associated with severe CVD. The baseline characteristics by sex and age are presented as Supporting information (Tables S1–S8). The women were older than the men were and had slightly higher HDL-C levels, a higher percentage of them were non-smokers, had hypertension, dyslipidaemia and previous stroke; a lower percentage of them had CHD compared to men. The characteristics by age showed that the older population included a higher proportion of women and people with cardiovascular conditions (hypertension, atrial fibrillation, heart failure, stroke, polyvascular CVD and lower percentage of people with previous CHD and recent CVD) than participants <75 years of age. A slightly higher percentage of the older people were treated with simvastatin, and a lower percentage with atorvastatin. The incidence of CHD increased with lowering post LDL-C goals and increasing percentage of reduction. The mortality incidence also increased as the post-LDL goals decreased; however, no differences were observed by percentage of LDL-C reduction (Table 3). The unadjusted HRs for both CHD and mortality are shown in Table S9. The adjusted HR (95% CI) of CHD in the category with LDL-goals <100–70 was .86 (.81–.92), and it was .80 (.72–.88) in the category with LDL goals <55 mg/dL (Table 3). The figures by 1 mmol/L of LDC-C levels could be approximated to −10.0% and 11.8% decrease, respectively, in CHD events. Concerning the percentage of LDL-C reduction, the HRs were .89 (.83–.96) in the group with 30%–40% of reduction and .86 (.80–.92) in the rest of the categories. This could be approximated to a 7%–9% decrease in the CHD incidence by 1 mmol/L of LDL reduction. The HRs for mortality showed no clear trend or relevant association. Figures S2–S5 show the survival curves adjusted using the HRs of the Cox

TABLE 1 Baseline characteristics by categories of post LDL-C levels.

Variable		<55 mg/dL ($n=6375$)	55–<70 mg/dL ($n=9527$)	70–<100 mg/dL ($n=22,703$)	≥100 mg/dL ($n=15,570$)	*p*-Values
Age, median (IQR), years		71 [62, 79]	70 [61, 78]	69 [61, 78]	68 [59, 77]	<.001
Women		1752 (27)	2961 (31)	8485 (37)	6948 (45)	<.001
Pre LDL-C, mg/dL	Median [IQR]	108 [90, 127]	124 [107, 141]	136 [119, 154]	155 [138, 172]	<.001
	Mean (SD)	109 (28)	124 (26)	137 (26)	156 (27)	<.001
Post LDL-C, mg/dL	Median [IQR]	47 [40, 51]	63 [59, 66]	83 [76, 91]	116 [107, 131]	<.001
	Mean (SD)	45 (8)	63 (4)	84 (9)	122 (20)	<.001
Post LDL reduction, %	<30	324 (5)	865 (9)	5857 (26)	11,468 (74)	<.001
	30–39	335 (5)	1248 (13)	6407 (28)	2921 (19)	
	40–49	885 (14)	2784 (29)	7102 (31)	1064 (7)	
	≥50	4831 (76)	4630 (49)	3337 (15)	117 (1)	
Triglyceride	Median [IQR]	126 [90, 180]	119 [89, 164]	117 [88, 160]	122 [92, 164]	<.001
HDL-C	Median [IQR]	45 [38, 54]	48 [40, 57]	49 [41, 59]	51 [43, 61]	<.001
Obesity		1853 (29)	2542 (27)	5383 (24)	3299 (21)	<.001
Smoking	No	3151 (50)	4949 (52)	12,585 (56)	8830 (57)	<.001
	Yes	1217 (19)	1814 (19)	4362 (19)	3411 (22)	
	Ex	1961 (31)	2698 (29)	5615 (25)	3212 (21)	
Hypertension		4538 (71)	6405 (67)	15,026 (66)	9639 (62)	<.001
Atrial fibrillation		737 (12)	984 (10)	2257 (10)	1535 (10)	<.001
Dyslipidaemia		1930 (30)	3299 (35)	9986 (44)	8975 (58)	<.001
CKD		719 (11)	853 (9)	1827 (8)	979 (6)	<.001
Diabetes		2938 (46)	3333 (35)	5990 (26)	3193 (21)	<.001
Previous CVD						
Heart failure		824 (13)	1030 (11)	2024 (9)	1101 (7)	<.001
CHD		2820 (44)	3990 (42)	7772 (34)	4141 (27)	<.001
Stroke		2144 (34)	3077 (32)	7382 (33)	4904 (31)	.017
Number of hospitalisations due to CVD						<.001
	1	1304 (20)	2159 (23)	6691 (29)	6139 (39)	
	2–4[a]	2742 (43)	4259 (45)	10,609 (47)	7304 (47)	
	>5[a]	2329 (37)	3109 (33)	5403 (24)	2127 (14)	
Recent CVD		4944 (78)	6988 (73)	14,367 (63)	7773 (50)	<.001
Polyvascular		708 (11)	851 (9)	1735 (8)	908 (6)	<.001
Statins						
Simvastatin		1826 (29)	3762 (39)	12,471 (55)	10,035 (64)	<.001
Lovastatin		2 (0)	11 (0)	70 (0)	102 (1)	<.001
Pravastatin		78 (1)	186 (2)	1004 (4)	1358 (9)	<.001
Fluvastatin		25 (0)	55 (1)	220 (1)	218 (1)	<.001
Atorvastatin		4291 (67)	5293 (56)	8562 (38)	3632 (23)	<.001

(Continues)

TABLE 1 (Continued)

Variable	<55 mg/dL (*n* = 6375)	55–<70 mg/dL (*n* = 9527)	70–<100 mg/dL (*n* = 22,703)	≥100 mg/dL (*n* = 15,570)	*p*-Values
Rosuvastatin	162 (3)	254 (3)	474 (2)	279 (2)	<.001
Pitavastatin	35 (1)	50 (1)	99 (0)	72 (0)	.568
Non-statin LLT	593 (9)	553 (6)	1090 (5)	657 (4)	<.001
MPR	100 [67, 117]	100 [67, 117]	100 [67, 100]	67 [33, 100]	<.001
MPR >80%	4755 (75)	7033 (74)	15,463 (68)	7217 (46)	<.001

Note: Units are *n* (%) unless otherwise specified. HDL-C missings: 956 (1.8%). Triglyceride missings: 1107 (2.0%). SI conversion factors: to convert cholesterol to mmol/L, multiply values by .0259.

Abbreviations: CHD, coronary heart disease; CKD, chronic kidney disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; LLT, lipid-lowering treatment; MPR, medication possession ratio.

[a]Progressive cardiovascular disease.

models. Additionally, we specified the residual risk, that is, the risk that remains in patients treated with current recommended care[26]: Table S10 shows the HRs (95% CI) of all the variables in the models for CHD and all-cause mortality. The analysis of statins adverse effects showed no association of post LDL-C levels or percentage of LDL-C reduction with diabetes, cancer, or stroke (Table 4). The relative hazard of the category with achieved LDL-C <55 mg/dL showed a non-significant 8% increase in the risk of diabetes (HR of 1.08, 95% CI: .92–1.28).

The analysis by sex showed higher incidences of CHD in men than in women (Tables S11 and S12). The mortality incidences were similar, although we observed a steeper increase in women when considering post LDL-C goals. The HRs for CHD were similar to the overall population and significant in men but lost significance in women; for mortality, they were similar to the overall population. The adverse effects showed no relevant differences from the overall population (Tables S4 and S5).

The subdivision by age (Tables S15–S18) appeared to show a more protective association of achieved LDL-C with CHD in the older subgroup (≥75-year-olds) in all categories. Importantly, there were no differences between the categories of achieved LDL-C goals.

A further subdivision by age for each sex showed that both men and women appeared to have a more protective association of achieved LDL-C with CHD in the older subgroups. In the younger subgroups, such association was weaker and only significant in men. Of note, the associations did not differ by categories of achieved LDL-C goals.

Finally, the sensitivity analyses (considering only participants with MPR >.8, and only CHD in the inclusion criteria) were in line with the results for the overall population (data not shown).

4 | DISCUSSION

This study with real-world data and 5.7 years of follow-up analysed the association of achieved LDL-C levels and percentage of LDL-C reduction with the risk of CHD and overall mortality in a large cohort of statin new users with previous CVD. Our results showed that treatment with statins associated with the achievement of certain LDL-C goals and lower risk of CHD. We observed an increasing although non-significant trend in the percentage of reduction of CHD events with lowering LDL-C goals. The risk reduction was 14%, 17%, and 20% in the 70 to <100 mg/dL, 55 to <70 mg/dL and <55 mg/dL categories of achieved LDL-C, respectively. In this retrospective observational study, the magnitude of the association was in the lower range of the variety found in previous clinical trials (Table 5). Additionally, the overlapping 95% CIs precluded confirmation of significant differences between categories of achieved LDL-C goals—the initial hypothesis. Regarding the percentage of LDL-C reduction, we found that the CHD risk decreased by 11%–14% in all the analysed categories, also with overlapping 95% CI. The stratified analyses by sex and age did not show differences between categories of achieved LDL-C goals either. Finally, we observed no significant association of the LDL-C goals with statins adverse effects.

We observed no association of the categories by post LDL-C goals or percentage of LDL-C reduction with mortality. Previous reports showed discrepancy in this regard, likely owing to the differences in the definition of exposure (LDL-C reduction of 1 mmol/L,[27] pre-and achieved LDL-C levels in trials,[28,29] statin versus control studies,[7] more intensive versus less intensive statin treatment analyses[6,16]) and in the definition of mortality, which varies depending on the cause. In general, most studies reported no association, in line with the findings in our analysis.

TABLE 2 Baseline characteristics by percentage groups of LDL-C reduction.

Variable		<30% (*n* = 18,514)	30%–<40% (*n* = 10,911)	40%–<50% (*n* = 11,835)	≥50% (*n* = 12,915)	*p*-Values
Age, median (IQR), years		69 [60, 78]	69 [61, 77]	69 [60, 78]	69 [60, 78]	<.001
Women		7537 (41)	4223 (39)	4236 (36)	4150 (32)	<.001
Pre LDL-C, mg/dL	Median [IQR]	131 [111, 151]	136 [118, 155]	140 [122, 159]	142 [122, 162]	<.001
	Mean (SD)	131 (31)	137 (29)	141 (29)	143 (31)	<.001
Post LDL-C, mg/dL	Median [IQR]	108 [90, 126]	88 [76, 101]	77 [66, 88]	60 [49, 70]	<.001
	Mean (SD)	109 (28)	89 (19)	78 (17)	60 (16)	<.001
Triglyceride	Median [IQR]	116 [87, 160]	117 [88, 160]	119 [89, 163]	127 [95, 175]	<.001
HDL-C	Median [IQR]	50 [42, 60]	50 [42, 59]	49 [41, 58]	48 [40, 56]	<.001
Obesity		4213 (23)	2535 (23)	2957 (25)	3372 (26)	<.001
Smoking	No	10,435 (57)	6050 (56)	6519 (55)	6511 (51)	<.001
	Yes	3710 (20)	2110 (19)	2315 (20)	2669 (21)	
	Ex	4216 (23)	2685 (25)	2933 (25)	3652 (28)	
Hypertension		12,003 (65)	7281 (67)	7824 (66)	8500 (66)	.006
Atrial fibrillation		2161 (12)	1057 (10)	1110 (9)	1185 (9)	<.001
Dyslipidaemia		8677 (47)	4913 (45)	5141 (43)	5459 (42)	<.001
CKD		1466 (8)	856 (8)	991 (8)	1065 (8)	.346
Diabetes		5056 (27)	2889 (26)	3310 (28)	4199 (33)	<.001
Previous CVD						
Heart failure		1596 (9)	930 (9)	1117 (9)	1336 (10)	<.001
CHD		5289 (29)	3483 (32)	4299 (36)	5652 (44)	<.001
Stroke		6102 (33)	3503 (32)	3746 (32)	4156 (32)	.102
Number of hospitalisations due to CVD						<.001
	1	6532 (35)	3543 (32)	3364 (28)	2854 (22)	
	2–4[a]	9027 (49)	5056 (46)	5311 (45)	5520 (43)	
	>5[a]	2955 (16)	2312 (21)	3160 (27)	4541 (35)	
Recent CVD		9267 (50)	6540 (60)	8113 (69)	10,152 (79)	<.001
Polyvascular		1400 (8)	809 (7)	946 (8)	1047 (8)	.116
Statins						
Simvastatin		11,380 (61)	6730 (62)	5933 (50)	4051 (31)	<.001
Lovastatin		117 (1)	40 (0)	23 (0)	5 (0)	<.001
Pravastatin		1634 (9)	540 (5)	299 (3)	153 (1)	<.001
Fluvastatin		275 (1)	109 (1)	91 (1)	43 (0)	<.001
Atorvastatin		4832 (26)	3345 (31)	5263 (44)	8338 (65)	<.001
Rosuvastatin		312 (2)	184 (2)	283 (2)	390 (3)	<.001
Pitavastatin		91 (0)	60 (1)	51 (0)	54 (0)	.427
Non-statin LLT		1011 (5)	558 (5)	552 (5)	772 (6)	<.001
MPR		67 [33, 100]	100 [67, 100]	100 [67, 117]	100 [67, 117]	<.001
MPR >80%		8845 (48)	7400 (68)	8613 (73)	9610 (74)	<.001

Note: Figures are *n* (%) unless otherwise specified. HDL-C missings: 956 (1.8%). Triglyceride missings: 1107 (2.0%). SI conversion factors: to convert cholesterol to mmol/L, multiply values by .0259.

Abbreviations: CHD indicates coronary heart disease; CKD, chronic kidney disease; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; LLT, lipid-lowering treatment; MPR, medication possession ratio.

[a]Progressive cardiovascular disease.

TABLE 3 Incidence rates (per 1000 person-years) and adjusted hazard ratios (95% CI) for CHD and all-cause mortality. Overall population.

Post LDL-C Goals				% LDL-CReduction			
	Incidence rates	HR (CI 95%)	*p*-Values		Incidence rates	HR (CI 95%)	*p*-Values
CHD				CHD			
<55 mg/dL	23.61 (21.87, 25.45)	.8 (.72–.88)	<.001	≥50%	22.52 (21.37, 23.72)	.86 (.8–.92)	<.001
55–<70 mg/dL	22.16 (20.85, 23.55)	.83 (.76–.9)	<.001	40%–<50%	19.47 (18.40, 20.58)	.86 (.8–.93)	<.001
70–<100 mg/dL	18.80 (18.05, 19.58)	.86 (.81–.92)	<.001	30%–<40%	18.09 (17.04, 19.19)	.89 (.83–.96)	.002
≥100 mg/dL	17.14 (16.32, 18.00)	1		<30%	17.93 (17.13, 18.75)	1	
Mortality				Mortality			
<55 mg/dL	43.46 (41.18, 45.84)	1.1 (1.02–1.19)	.014	≥50%	33.69 (32.34, 35.09)	1.03 (.97–1.08)	.351
55–<70 mg/dL	36.00 (34.38, 37.68)	1.01 (.95–1.07)	.789	40%–<50%	32.44 (31.10, 33.82)	.94 (.89–1)	.032
70–<100 mg/dL	32.84 (31.88, 33.83)	.99 (.95–1.04)	.763	30%–<40%	31.95 (30.60, 33.35)	.93 (.88–.98)	.011
≥100 mg/dL	30.77 (29.69, 31.87)	1		<30%	35.60 (34.51, 36.72)	1	

Note: CHD adjusted models: (1) Model 1 post-LDL goal: previous LDL-c, age, sex, socioeconomic status, progressive CHD, polivascular CVD, atrial fibrillation, Metabolic diseases, rheumatoid arthritis, chronic obstructive pulmonary disease, dyslipidemia, previous CVD, diabetes, baseline treatments (antidiabetics, cardiac therapy, antihypertensives), previous HDL-c and Non-statin LLT. (2) Model 2 post-LDL reduction: previous LDL-c, age, sex, socioeconomic status, progressive CHD, polivascular CVD, atrial fibrillation, Metabolic diseases, rheumatoid arthritis, chronic obstructive pulmonary disease, heart failure, dyslipidemia, previous CVD, diabetes, baseline treatments (antidiabetics, cardiac therapy, antihypertensives), previous HDL-c and non-statin LLT. Mortality adjusted models: (3) Model 3 post-LDL goal: previous LDL-c, age, sex, socioeconomic status, smoking, progressive CHD, polivascular CVD, atrial fibrillation, chronic kidney disease, rheumatoid arthritis, asthma, chronic obstructive pulmonary disease, hepatic disease, obesity, dyslipidemia, heart failure, cancer, previous CVD, diabetes, baseline treatments (antidiabetics, cardiac therapy, antihypertensives, antithrombotics, systemic corticosteroids, anti-inflammatories, psychoanaleptics, psycholeptics), previous triglyceride, previous HDL-c and Non-statin LLT. (4) Model 4 post-LDL reduction: previous LDL-c, age, sex, socioeconomic status, smoking, progressive CHD, polivascular CVD, atrial fibrillation, chronic kidney disease, rheumatoid arthritis, asthma, chronic obstructive pulmonary disease, hepatic disease, obesity, dyslipidemia, heart failure, cancer, previous CVD, diabetes, baseline treatments (antidiabetics, cardiac therapy, antihypertensives, antithrombotics, systemic corticosteroids, anti-inflammatories, psychoanaleptics, psycholeptics), previous triglyceride, previous HDL-c and non-statin LLT.

Abbreviations: CHD indicates coronary heart disease; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering treatment.

The recommendations on goals of LDL-C levels and percentage of LDL-C reduction stated in the guidelines originated from estimations carried out in meta-analyses of clinical trials.[6–8] These meta-analyses calculated a 21%–22% decrease in major vascular events per 1 mmol/L decrease in LDL-C levels, and a 23%–26% reduction in major coronary events (also per 1 mmol/L decrease in LDL-C).[6–8] These figures were a weighted mean summarising all the trials, but the percentage of reduction amongst trials varied (including non-significant results), likely due to different study populations, outcomes, and achieved LDL-C levels, which ranged from approximately 77 to 104 mg/dL.[6–8] Posterior clinical trials aimed at further reducing the LDL-C levels. The achieved LDL-C levels ranged from 36.7 to 66.0 mg/dL and the percentage of decrease in the outcome by 1 mmol/L of LDL-C reduction varied from 12% to 31% (Table 5).[9–11] In our study, we observed a 14%, 17% and 20% decrease in the categories with achieved LDL-C levels of 70 to <100, 55 to 70 mg/dL and < 55 mg/dL, which could be approximated to a 10.0%, 10.6% and 11.8% reduction of CHD events per 1 mmol/L of LDL-C decrease, respectively. However, the 95% CIs overlapped, that is, the reduction was similar in the categories considered.

Importantly, neither the initial trials included in the meta-analyses nor the more recent trials for further reduction of the LDL-C levels were specifically designed to test the effectiveness of achieving particular goals. To our knowledge, only two analyses considered prespecified categories of LDL-C goals.[29,30] A secondary analysis of the FOURIER trial found similar risk reduction to ours (15%) in a category with targeted LDL-C of 19 to 50 mg/dL; but reported no significant reduction in the categories with higher achieved LDL-C, of 50 to 101 mg/dL (the reference category was that with targeted LDL-C levels 101 mg/dL or over). Another secondary analysis, of the IMPROVE-IT trial, reported a 17% reduction of risk in the category with achieved LDL-C levels 50 to 69 mg/dL—the reference category being LDL-C levels over 70 mg/dL. In line with our results, they found no significant differences with the rest of the categories considered (the confidence intervals of the estimates overlapped).[29,31] The Task Force authoring the European Guidelines acknowledges the lack of systematic examination of different LDL-C goals in RCTs, and the limitations of some of the evidence sources. They also mention the need to obtain results with different approaches, including clinical observations and epidemiology.[1] We performed a population-level analysis of real

TABLE 4 Adverse effects incidence rates (per 1000 person-years) and hazard ratios (95% CI). Overall population.

Post-LDL Goals				% LDL Reduction			
	Incidence rates	HR (CI 95%)	*p*-Values		Incidence rates	HR (CI 95%)	*p*-Values
Diabetes Mellitus				Diabetes Mellitus			
<55 mg/dL	15.05 (13.11, 17.20)	1.08 (.92–1.28)	.321	>50%	14.54 (13.40, 15.76)	1.01 (.91–1.13)	.826
<70–55 mg/dL	13.07 (12.24, 13.93)	.96 (.84–1.09)	.516	40%–50%	12.14 (11.13, 13.22)	.86 (.77–.96)	.007
70–100 mg/dL	13.12 (11.84, 14.50)	1.01 (.92–1.1)	.875	30%–40%	13.12 (12.07, 14.24)	.95 (.85–1.05)	.296
>100 mg/dL	13.45 (12.69, 14.24)	1		<30%	13.63 (12.80, 14.49)	1	
Cancer				Cancer			
<55 mg/dL	19.59 (17.92, 21.37)	.97 (.87–1.08)	.593	>50%	17.47 (16.41, 18.57)	.95 (.88–1.03)	.189
<70–55 mg/dL	18.42 (17.16, 19.74)	.93 (.85–1.02)	.117	40%–50%	19.72 (18.59, 20.90)	1.04 (.97–1.12)	.288
70–100 mg/dL	19.43 (18.62, 20.26)	1 (.94–1.07)	.955	30%–40%	19.74 (18.59, 20.95)	1.02 (.95–1.1)	.606
>100 mg/dL	18.85 (17.94, 19.80)	1		<30%	19.34 (18.47, 20.25)	1	
Stroke				Stroke			
<55 mg/dL	4.49 (3.76, 5.32)	.96 (.77–1.2)	.732	>50%	4.62 (4.11, 5.17)	1.1 (.94–1.27)	.224
<70–55 mg/dL	4.80 (4.20, 5.45)	1.06 (.9–1.26)	.479	40%–50%	4.26 (3.78, 4.80)	1 (.86–1.16)	.998
70–100 mg/dL	4.35 (4.00, 4.73)	.98 (.86–1.12)	.826	30%–40%	4.41 (3.90, 4.96)	1.02 (.88–1.19)	.777
>100 mg/dL	4.24 (3.84, 4.68)	1		<30%	4.36 (3.97, 4.77)	1	

Note: Diabetes mellitus adjusted models: (1) Model 1 post-LDL goal: previous LDL-c, age, smoking, recent CVD, progressive CHD, hypertension, chronic kidney disease, obesity, previous CVD, cancer, baseline treatments (antihypertensives, psychoanaleptics, psycholeptics), previous triglyceride and previous HDL-c. (2) Model 2 post-LDL reduction: previous LDL-c, age, smoking, progressive CHD, recent CVD, hypertension, chronic kidney disease, obesity, previous CVD, cancer, baseline treatments (antihypertensives, psychoanaleptics, psycholeptics), previous triglyceride and previous HDL-c. Cancer adjusted models: (3) Model 3 post-LDL goal: previous LDL-c, age, sex, socioeconomic status, smoking, progressive CHD, polyvascular CVD, chronic obstructive pulmonary disease, hepatic disease, previous CVD, baseline treatments (antithrombotic agents, anti-inflammatories, psycholeptics, diuretics). (4) Model 4 post-LDL reduction: previous LDL-c, age, sex, socioeconomic status, smoking, progressive CHD, polyvascular CVD, metabolic disease, chronic obstructive pulmonary disease, hepatic disease, dyslipidemia, previous CVD, baseline treatments (cardiac therapy, antithrombotic agents, anti-inflammatories, psycholeptics, diuretics). Stroke adjusted models: (5) Model 5 post-LDL goal: previous LDL-c, age, sex, socioeconomic status, atrial fibrillation, chronic kidney disease, metabolic diseases, systemic lupus erythematosus, chronic obstructive pulmonary disease, heart failure, previous CVD, diabetes, baseline treatments (antithrombotic agents, systemic corticosteroids, (other) anti-inflammatories, psychoanaleptics, antihypertensives), previous HDL-c and previous triglyceride. (6) Model 6 post-LDL reduction: previous LDL-c, age, sex, socioeconomic status, atrial fibrillation, chronic kidney disease, metabolic diseases, systemic lupus erythematosus, chronic obstructive pulmonary disease, heart failure, previous CVD, diabetes, baseline treatments (antithrombotic agents, systemic corticosteroids, (other) anti-inflammatories, psychoanaleptics, antihypertensives), previous HDL-c and previous triglyceride.

world data that contributes to the examination of LDL-C goals in a context that reflects clinical practice and its features such as patients' comorbidities and treatment compliance or adherence to treatment.

The potential difficulty in achieving the recommended goals in clinical practice is another important consideration. Only 15,902 (29%) and 6375 (12%) out of 54,175 participants in our study reached the post LDL-C goals of <70 mg/dL and <55 mg/dL, respectively; and 12,915 (24%) out of the same total achieved a reduction >50% in LDL-C levels. However, interpretation of these results should consider that our retrospective analysis lasted until 2017 and the LDL-C target <55 mg/dL was only introduced in 2019; it was thus unlikely that statin treatment deliberately sought to lower LDL-C under such target. In this regard, though, posterior studies in patients at high or very high cardiovascular risk described a suboptimal management of dyslipidaemia and suggested solutions to improve it. These include earlier use of combination therapies and personalised stepwise approaches.[32] Communication between doctor and patient would benefit from established targets to monitor statin treatment in clinical practice.

4.1 | Strengths and Limitations

The interpretation of our findings should consider its strengths and limitations. An important strength of this analysis was the availability of real-world data to build a large cohort of statin new users in secondary cardiovascular prevention, which confers high representativeness and thus external validity. The analysis of data from electronic health records also reflects what is actually occurring in clinical practice, real conditions, and are a complement to the results obtained from the more controlled conditions of other study designs. Another strength was the robustness of our results, supported by the sensitivity analyses that included only population with a MPR >80% and population with history of only CHD. On the other hand, cohort studies include a follow-up period along time, but their observational

TABLE 5 Summary of previous trials on the effect of lipid-lowering medications on cardiovascular endpoints.

Study	Population and intervention	Achieved LDL-C levels (mg/dL)	HR (95% CI)	Endpoint decrease by 1 mmol/L of LDL-C reduction—reported or estimated
IMPROVE-IT Cannon et al. 2015	Secondary prevention. Ezetimibe versus placebo in patients who also received simvastatin.	53.7	Primary endpoint (death from cardiovascular causes, major coronary event, or nonfatal stroke): .936 (.89–.99)	Primary endpoint (death from cardiovascular causes, major coronary event, or nonfatal stroke): 15.3%
			Myocardial infarction: .87 (.80–.95)	Myocardial infarction: 31.0%
ODYSSEY Schwartz et al. 2018	Secondary prevention. Alirocumab versus placebo in people receiving high doses of statins.	66.0	Primary endpoint (cardiovascular diseases): .85 (.78–.93)	Primary endpoint (cardiovascular diseases): 15.0%
			Coronary heart disease: .88 (.81–.95)	Coronary heart disease: 12.0%
FOURIER Sabatine et al. 2017	Secondary prevention. Evolocumab versus placebo in people receiving statins.	36.7	Primary endpoint (cardiovascular conditions and procedures): .85 (.79–.92)	Primary endpoint (cardiovascular conditions and procedures): 15.8%
			Myocardial infarction: .73 (.65–.82)	Myocardial infarction: 28.4%

nature precludes inference of causality and can only express association. Residual confounding can never be totally ruled out in this type of analyses, although we adjusted the associations of LDL-C with CHD and all-cause mortality by a number of factors to account for this. The variables of adjustment included three proxies for severity and pre-LDL levels. To further account for the pre-LDL-C levels, we also examined their interaction with the magnitude of LDL-C reduction, which was non-significant. Future studies could examine if additional compounds such as insulin resistance, diet, or exercise would improve the CHD prediction. The study time should also be considered when interpreting our results, because some new drugs, like glucose-lowering medications, could modulate the observed associations. However, it is more likely that such new drugs may modulate the lowering of LDL-C than they might the relation of achieved LDL-C goals with CHD. Future studies to elucidate this point would be of interest, along with the comparison between people with and without diabetes. Finally, we examined some of the main adverse effects but not all of them; we did not analyse the incidence of acute liver disease and myopathy due to plausible underreporting, which may yield some inaccuracies in the results.[33]

4.2 | Implications

Our analysis of real-world data showed the benefit when treating people in secondary cardiovascular risk prevention with statins. We observed a non-significant trend towards a reduction of CHD events with lowering goals of achieved LDL-C levels. More analyses with real-world data specifically designed to analyse prespecified LDL-C goals are needed, to provide further information on the magnitude of the effect of statin treatment in clinical practice.

5 | CONCLUSIONS

In conclusion, we observed that treatment with statins is effective to achieve certain LDL-C goals and CHD reduction. Our results call for caution when establishing the magnitude of CHD risk reduction by statin treatment under a certain LDL-C target. Further studies with real-world data could help determine the extent of the benefit in clinical practice when targeting specific LDL-C goals.

AUTHOR CONTRIBUTIONS

MGG, LAC, RML and RR designed the research; OC, JB, ET, LZ acquired, curated and analysed the data. MGG, LAC, RML, AP, FRA, GDA, EG and RR performed the research; all authors contributed to interpret the data; MGG and LAC wrote the manuscript; OC, JB, RML, AP, FRA, ET, LZP, GDA, EG and RR reviewed and offered edits where appropriate to manuscript drafts. All authors approved the final version.

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CONFLICT OF INTEREST STATEMENT

The authors report no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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