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Original Research

Decline in LDL-C control in patients with dyslipidemia treated with PCSK9-inhibitors: The role of obesity in LDL-C target achievement

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KEYWORDS
Lipid-lowering therapy;
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Atherosclerotic cardiovascular disease;
Overweight;
Dyslipidemia

BACKGROUND: Proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9-Is: alirocumab and evolocumab) have improved dyslipidemia management in patients with high cardiovascular risk. However, some patients fail to reach low-density lipoprotein cholesterol (LDL-C) targets.

OBJECTIVE: To evaluate factors influencing PCSK9-I therapy effectiveness.

METHODS: A retrospective study (2018-2023) analyzed adults treated with a PCSK9-I for at least 6 months with heterozygous familial hypercholesterolemia (He-FH) in primary prevention, dyslipidemia in secondary prevention, or diabetes with associated complications. Clinical, anthropometric data and lipid profiles were collected at baseline and after 6, 12, 24, and 36 months. The primary outcome was LDL-C target achievement according to European Society of Cardiology/European Atherosclerosis Society guidelines.

RESULTS: Among 180 patients, approximately 45% achieved the LDL-C target. Patients with overweight and obesity showed significantly lower LDL-C reductions compared to normal-weight patients. Those reductions for overweight patients were 47.8%, 50.0%, and 44.0%, and for obese patients were 25.6%, 29.4%, and 28.6%, whereas normal-weight patients achieved reductions of 54.5% ($P = .021$), 62.5% ($P = .024$), and 65.4% ($P = .024$), respectively. Multivariate analysis confirmed these findings (odds ratio [OR]: 0.18, 95% CI, 0.06-0.53, $P = .002$) and highlighted that He-FH was associated with lower likelihood of achieving LDL-C targets (OR: 0.35, 95% CI, 0.15-0.82, $P = .015$). Conversely, patients with coronary artery disease (CAD) were more likely to reach LDL-C targets (OR: 4.54, 95% CI, 1.98-10.41, $P < .0001$). Concomitant oral lipid-lowering therapy was linked to a higher probability of achieving LDL-C targets compared to PCSK9-I monotherapy (OR: 14.5, 95% CI 2.26-92.9, $P = .005$).

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CONCLUSION: Overweight, He-FH, CAD, and concomitant oral lipid-lowering therapy could influence the achievement of LDL-C target in patients treated with PCSK9-Is.

Introduction

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death globally, and dyslipidemia is recognized as a significant contributing risk factor.[1]

In recent decades, lipid-lowering therapies have significantly advanced, evolving from initial statin treatments to more sophisticated and targeted approaches.[2] Recently, monoclonal antibodies that inhibit proprotein convertase subtilisin/kexin type 9 (PCSK9), such as alirocumab and evolocumab, have significantly improved the treatment of hypercholesterolemia, providing an effective therapeutic option for patients with high to very high cardiovascular risk.[3] PCSK9 inhibitors (PCSK9-Is) act by blocking PCSK9 interaction with the low-density lipoprotein (LDL) receptor, enhancing the latter expression on hepatocytes and leading to a significant reduction in circulating LDL-cholesterol (LDL-C) levels.[3] According to the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) guidelines, PCSK9-Is are recommended for patients in secondary prevention who do not achieve LDL-C targets despite maximum tolerated statin and ezetimibe therapy. They are also indicated for very-high-risk primary prevention patients with familial hypercholesterolemia (FH) and another major risk factor, while their use may be considered in very-high-risk primary prevention patients without FH.[4] Despite the proven clinical efficacy of PCSK9-Is in reducing LDL-C and improving cardiovascular outcomes, some patients fail to reach LDL-C targets recommended by international guidelines.[4,5] The clinical benefits of LDL-C lowering are directly proportional to both the absolute LDL-C level achieved and the magnitude of LDL-C reduction.[6,7] This highlights the importance of attaining guideline-recommended LDL-C targets to optimize cardiovascular risk reduction.

Alirocumab and evolocumab have demonstrated robust and sustained efficacy in lowering LDL-C levels over time.[3] In contrast, evidence regarding another PCSK9-I, bococizumab, suggests that its LDL-C control may decline over time due to the development of antidrug antibodies, which ultimately led to the discontinuation of its clinical development.[8,9]

Beyond drug-specific factors, several studies reported that nutritional and hormonal status could impact circulating PCSK9 levels. For instance, PCSK9 concentrations are significantly reduced by glucagon, growth hormone,[10,11] whereas they are increased in the presence of hepatic fat accumulation and have been associated with the presence and severity of steatosis.[12] Emerging evidence also links higher PCSK9 levels with obesity, reinforcing the interplay between metabolic dysfunction and lipid regulation.[13-15] Particularly, the latter condition could also actively influence metabolic and physiological processes, potentially altering pharmacokinetic and pharmacodynamic properties of biological drugs.[16] Moreover, although no studies have specifically investigated this phenomenon for PCSK9-Is, Zamboni et al[16] highlighted that chronic low-grade inflammation associated with obesity may affect drug response and lipid metabolism in anticancer agents, suggesting a potential impact on other pharmacological treatments. Therefore, while PCSK9-Is are well-known for their strong LDL-C lowering effects, the variability in treatment response raises unresolved questions.[17] Given this knowledge, it remains unclear whether weight-related risk factors might really affect the efficacy of PCSK9-Is and, to date, no evidence reports accurately specific factors that could influence the responses to PCSK9-Is.

Therefore, our study aimed to investigate the impact of overweight and obesity, and other contributing factors on the effectiveness of PCSK9-I therapy, and how these factors influence the achievement of LDL-C targets.

Materials and methods

We conducted a retrospective cohort study including adult patients followed by section of the Lipid Clinic of IRCCS Policlinic San Martino Hospital, University of Genoa, Italy, treated with a PCSK9-I between January 2018 and September 2023.

Inclusion criteria were set as follows:

- Patients aged $\leq$ 80 years undergoing treatment with a PCSK9-I, diagnosed with heterozygous (He)-FH in primary prevention.
- Patients aged $\leq$ 80 years in secondary prevention with He-FH, presumed polygenic hypercholesterolemia, or mixed dyslipidemia, and patients with diabetes with at least 1 complication (ie, retinopathy or nephropathy).

Patients with dyslipidemia who were not receiving PCSK9-I therapy, as well as those who had initiated PCSK9-I therapy but lacked follow-up lipid profiles, were excluded from the study.

All included subjects underwent a comprehensive medical evaluation: demographic characteristics (age, sex), current oral lipid-lowering therapy, anthropometric data (height and weight), blood pressure, and smoking habits were documented. Medical history (including history of ASCVD) and comorbidities were assessed through a comprehensive review of medical charts, hospitalization records, and avail-

able test reports. Diagnosis codes were not used for ascertainment. Coronary artery disease (CAD) was defined as requiring revascularization. Patients with noncritical stenoses that did not warrant revascularization were not included in our dataset unless they had He-FH. In such cases, subclinical atherosclerosis was not classified as ASCVD.

Blood tests were performed at baseline and subsequently at 6, 12, 24, and 36 months in a licensed laboratory, evaluating levels of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG). LDL-C was calculated using the Friedewald formula. At 6, 12, 24, and 36 months, weight was reassessed, and body mass index (BMI) was calculated. In the context of the baseline visit, all patients were receiving on-top tolerated conventional lipid-lowering therapy (ie, statins and/or ezetimibe) and started a PCSK9-I. An off-therapy lipid profile was not available, as they were referred to our center while already on treatment.

Lipid-lowering therapies were categorized as follows: ezetimibe alone, ezetimibe plus low-intensity statin, ezetimibe plus high-intensity statin, fibrate, ezetimibe plus statin plus fibrate, or no other therapies than PCSK9-I.

Recommended targets for LDL-C were defined according to international guidelines for the management of dyslipidemia,[4] with targets of 55 mg/dL and 70 mg/dL, along with at least a 50% reduction from baseline, for patients at very high and high cardiovascular risk, respectively. The primary endpoint was achieving the recommended LDL-C target according to ESC/EAS guidelines at 6, 12, 24, and 36 months. We also evaluated the sustained achievement of the LDL-C target, defined as consistently meeting the recommended LDL-C levels according to ESC/EAS guidelines throughout the 36-month period.

Statistical analysis

Kolmogorov-Smirnov test was used to assess whether the variables followed a normal distribution. Continuous variables were summarized using the median and IQR. Contingency tables were employed to present the frequency and proportion of ordinal and nominal variables within the population. To analyze the relationship between nominal and continuous variables, Pearson's X^2 test and Spearman's rank correlation coefficient were applied. The Bonferroni correction was implemented to account for multiple pairwise comparisons. Logistic regression was conducted to evaluate the influence of various predictors on dichotomous outcomes, providing estimates of odds ratios (ORs) and their CIs. Univariate and multivariate logistic regression was applied to evaluate the achievement of LDL-C target considering age, sex, weight status, smoking habits, diagnosis of FH, arterial hypertension, diabetes, CAD, stroke, peripheral artery disease, PCSK9- I therapy, concomitant oral lipid-lowering therapy, and median follow-up in PCSK9-I therapy, as fixed factors and covariates (the probability value for entering the multivariate model was $P = .20$). Statistical analyses were performed using IBM SPSS Statistics (Version 25.0; SPSS, Inc., 2017, www.spss.com), R (Version 3.4.3; R Foundation for Statistical Computing).

Results

From an initial sample of 207 patients 27 were excluded due to initiating PCSK9-I therapy without follow-up lipid profiles. Consequently, our study population comprised 180 patients, with a median follow-up period of 37.1 months (IQR: 19.6-60.3). Of these, 52.2% were women (n = 94) and the median age was 67 years (IQR: 58-73) with 20.0% (n = 36) being active or former smokers. The median BMI was 26.7 kg/m^2 (IQR: 24-30) with 33.3% of the subjects with normal weight (BMI, 18.5-24.9 kg/m^2) and 41.7% and 25.0% with overweight (BMI, 25-29.9 kg/m^2) and obesity (BMI $\geq$30 kg/m^2), respectively. During the follow-up period, a slight reduction in body weight was observed but not substantial enough to lead to a change in BMI category.

A total of 13 patients were lost to follow-up, including 8 (13.3%) in the normal weight group, 3 (4.0%) in the overweight group, and 2 (4.4%) in the obesity group. No statistically significant differences were observed across BMI groups ($P = .081$).

Among patients included, 56.1% (n = 101) had a diagnosis of He-FH and the most common cardiovascular comorbidities reported were arterial hypertension (n = 77, 42.8%) and CAD (n = 74, 41.1%).

Most patients were treated with alirocumab 150 mg (n = 93, 51.7%), while alirocumab 75 mg and evolocumab 140 mg were administered to 19 (10.6%) and 68 (37.8%) patients, respectively. The most commonly prescribed oral lipid-lowering therapy was ezetimibe (55.9%). Additionally, 29.4% of patients received ezetimibe plus high-intensity statin, 5.6% received ezetimibe plus low-intensity statin, and 1.1% received fibrates. Accordingly, statins were prescribed to 35.0% of patients, and none received statin monotherapy. Thirteen patients (7.3%) received only PCSK9-I without other lipid-lowering therapies. Overall, the LDL-C recommended target was reached by 40.0% (n = 72) at 6 months, 44.0% (n = 66) at 12 months, 47.5% (n = 57) at 24 months, and 45.2% (n = 47) at 36 months.

When stratifying patients according to BMI (Table 1), no significant differences were observed among patients with normal weight (n = 60), overweight (n = 75), and obesity (n = 45), except for the presence of diabetes mellitus ($P = .021$). No significant differences in sex, age, smoke habits, presence of He-FH, cardiovascular comorbidities, PCSK9-I therapy, and concomitant lipid-lowering therapy were reported between the 3 groups. Figure 1 shows a significantly lower reduction in LDL-C in patients with obesity compared to patients with normal weight after 12, 24, and 36 months of PCSK9-I therapy. LDL-C levels and differences from baseline across BMI categories are reported in Table S1.

The recommended LDL-C target was achieved more frequently in subjects with normal weight at 12 months (54.5%,

Table 1. Characteristics of patients stratified according to body mass index.

	Normal weight (BMI 18.5-24.9 kg/m²) (n = 60)	Overweight (BMI 25-29.9 kg/m²) (n = 75)	Obesity (BMI ≥30 kg/m²) (n = 45)	*P*-value
Sex [F/M: n; %]	35 (58.3) 25 (41.7)	35 (46.7) 40 (53.3)	24 (53.3) 21 (46.7)	.397
Median age [years] [IQR]	65 (57 – 73)	69 (59 – 74)	67 (61 – 75)	.302
Active and former smokers	10 (16.6)	19 (25.3)	7 (15.5)	.649
Diagnosis of He-FH	41 (68.3)	39 (52)	21 (46.7)	.055
Cardiovascular comorbidities				
Arterial hypertension	20 (33.3)	33 (44)	24 (53.3)	.118
Diabetes	7 (11.7)	20 (26.7)	15 (33.3)	**.021**
Coronary artery disease	24 (40)	32 (42.7)	18 (40)	.938
Stroke	7 (11.9)	11 (14.7)	5 (11.1)	.821
Peripheral artery disease	7 (11.7)	10 (13.3)	4 (9.1)	.786
LDL-C target				
< 55 mg/dL	46 (76.6)	61 (81.3)	36 (80.0)	.796
< 70 mg/dL	14 (23.4)	14 (18.7)	9 (20.0)	
PCSK9 inhibitors				
Alirocumab 75 mg	4 (6.7)	11 (14.7)	4 (8.9)	.506
Alirocumab 150 mg	35 (58.3)	36 (48)	22 (48.9)	
Evolocumab 140 mg	21 (35)	28 (37.3)	19 (42.2)	
Concomitant oral lipid-lowering therapy				
No other therapies	6 (10)	3 (4.1)	4 (9.1)	.524
Ezetimibe	30 (50)	40 (54.8)	29 (65.9)	
Ezetimibe + low-intensity statin	4 (6.7)	4 (5.5)	2 (4.5)	
Ezetimibe + high-intensity statin	20 (33.3)	23 (31.5)	9 (20.5)	
Fibrate	0 (0)	2 (2.7)	0 (0)	
Ezetimibe + statin + fibrate	0 (0)	1 (1.4)	0 (0)	
Median follow-up in PCSK9 inhibitors therapy [months] [IQR]	35.7 (11.9-59.5)	46.8 (23.9-58.6)	36.4 (24.2-70.9)	.195

Abbreviations: BMI, body mass index; F, female; He-FH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; M, male; PCSK9, proprotein convertase subtilisin/kexin type 9.

Data are shown as absolute value and frequency, and as median and IQR.

Bold values are statistically significant at $P < .05$.

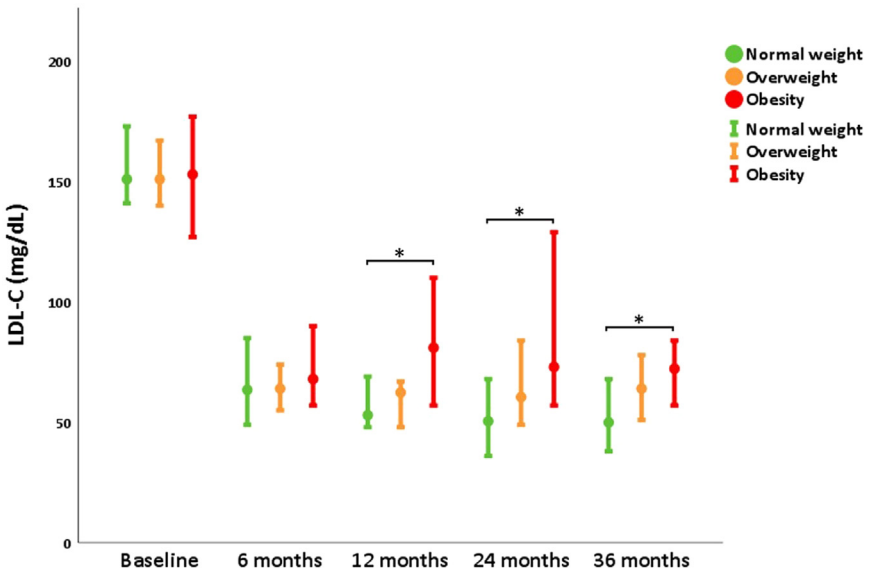

Figure 1. LDL-C levels in patients with normal weight, overweight, and obesity after 6, 12, 24, and 36 months of PCSK9-I therapy. *Statistically significant differences with $P < .05$. Abbreviations: LDL-C, low-density lipoprotein cholesterol; PCSK9-I, proprotein convertase subtilisin/kexin type 9 inhibitor.

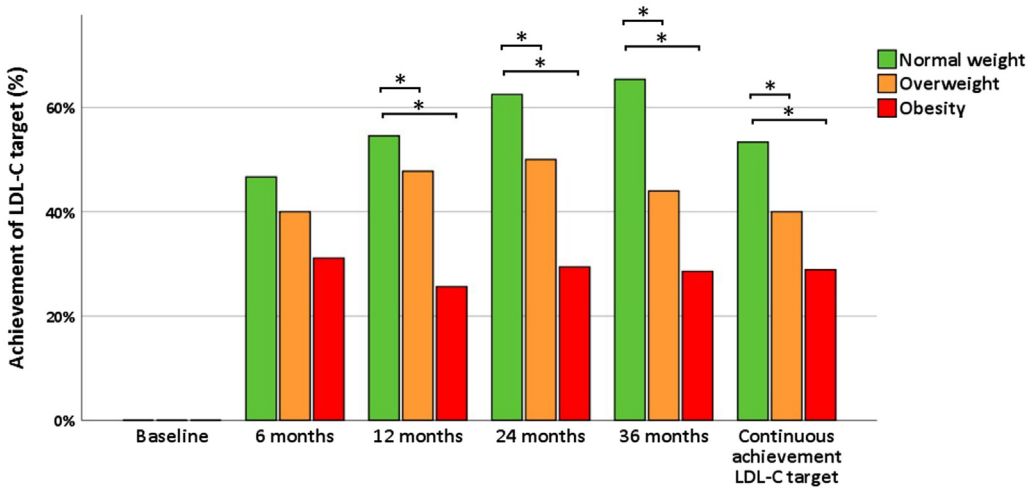

Figure 2. Achievement of recommended LDL-C targets in patients with normal weight, overweight, and obesity. *Statistically significant differences with $P < .05$. Abbreviation: LDL-C, low-density lipoprotein cholesterol.

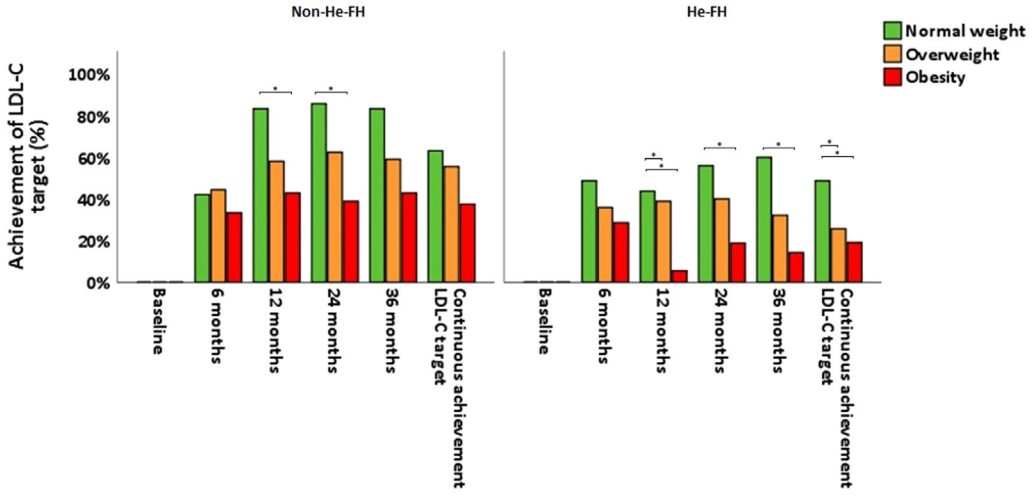

Figure 3. Achievement of recommended LDL-C targets in patients with normal weight, overweight, and obesity and stratified according to He-FH diagnosis. *Statistically significant differences with $P < .05$. Abbreviations: He-FH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol.

$P = .021$), 24 months (62.5%, $P = .024$), and 36 months (65.4%, $P = .024$), compared to those who presented overweight (47.8%, 50.0%, and 44.0%, respectively) or obesity (25.6%, 29.4%, and 28.6%, respectively). The continuous achievement of LDL-C targets over the 36-month follow-up period was also more frequent in patients with normal weight ($P = .039$) (Fig 2).

Focusing on patients with He-FH, LDL-C target was achieved more frequently in patients with normal weight than with overweight and obesity at 12 (43.8% vs 38.9% and 5.6%, $P = .005$ and $P = .010$, respectively), at 24 (44.0% vs 40.0% and 18.8%, $P = .089$ and $P = .018$, respectively), and at 36 (40.0% vs 32.1% and 14.3%, $P = .105$ and $P = .008$, respectively) months, and continuously during the 36-months follow-up period (48.8% vs 25.6% and 19.0%, $P = .033$ and $P = .023$, respectively, Fig 3). Table 2 reports the characteristics of all patients included and categorized based on the diagnosis of He-FH.

In patients with diabetes, LDL-C target was achieved more frequently in patients with normal weight than with obesity at 12 months (60.0% vs 25%, $P = .035$) and more frequently in patients with normal weight compared to patients with overweight and with obesity at 6 (85.7% vs 35.0% and 33.3%, $P = .021$ and $P = .022$, respectively), at 24 (100.0% vs 75.0% and 25.0%, $P = .041$ and $P = .014$, respectively), at 36 months (100.0% vs 60.0% and 25.0%, $P = .020$ and $P = .025$, respectively) and continuously during the 36-months follow-up period (85.7% vs 55.0% and 33.3%, $P = .022$ and $P = .025$, respectively, Fig S1).

Table 3 shows the results of both univariate and multivariate analyses on LDL-C target achievement at 6, 12, 24, and 36 months, as well as continuous achievement over the 36-month follow-up period, considering the main characteristics and risk factors of all included patients.

Patients with overweight had a significantly lower likelihood of achieving LDL-C targets at 36 months (OR: 0.19,

Table 2. Characteristics of all patients included and stratified according to He-FH diagnosis.

	All patients (n = 180)	He-FH (n = 101)	Non-He-FH (n = 79)	*P*-value
Sex [F/M: n; %]	94 (52.2)	59 (58.4)	35 (44.3)	.060
	86 (47.8)	42 (41.6)	44 (55.7)	
Median age [years] [IQR]	67 (58-73)	66 (56-72)	71 (61-76)	**.003**
Median BMI [kg/m^2] [IQR]	26.7 (24.0-30.0)	25.7 (23.5-29.0)	27.6 (25.0-31.2)	**.004**
Normal weight	60 (33.3)	41 (40.6)	19 (24.1)	**.019**
Overweight	75 (41.7)	39 (38.6)	36 (45.6)	.365
Obesity	45 (25.0)	21 (20.8)	24 (30.4)	.166
Active and former smokers	36 (20.0)	17 (16.8)	19 (24.1)	.298
Cardiovascular comorbidities				
Arterial hypertension	77 (42.8)	37 (36.6)	40 (50.6)	.060
Diabetes	42 (23.3)	11 (10.9)	31 (39.2)	**<.0001**
Coronary artery disease	74 (41.1)	28 (27.7)	46 (58.2)	**<.0001**
Stroke	23 (12.8)	8 (8.0)	15 (19.0)	**.029**
Peripheral artery disease	21 (11.7)	7 (7.0)	14 (17.7)	**.027**
PCSK9 inhibitors				
Alirocumab 75 mg	19 (10.6)	7 (6.9)	12 (15.2)	.089
Alirocumab 150 mg	93 (51.7)	49 (48.5)	44 (55.7)	.369
Evolocumab 140 mg	68 (37.8)	45 (44.6)	23 (29.1)	**.034**
Adjunctive lipid-lowering therapy				
No other therapies	13 (7.3)	5 (5.1)	8 (10.1)	.247
Ezetimibe	99 (55.9)	49 (50.0)	50 (63.3)	.068
Ezetimibe + low-intensity statin	10 (5.6)	6 (6.1)	4 (5.1)	1
Ezetimibe + high-intensity statin	52 (29.4)	37 (37.8)	15 (19.0)	**.006**
Fibrate	2 (1.1)	1 (1)	1 (1.3)	1
Ezetimibe + statin + fibrate	1 (0.6)	0 (0)	1 (1.3)	1
Median follow-up in PCSK9 inhibitors therapy [months] [IQR]	37.1 (19.6-60.3)	47.5 (23.8-71.3)	35.2 (11.9-59.7)	**.005**

Abbreviations: BMI, body mass index; F, female; He-FH, heterozygous familial hypercholesterolemia; M, male; PCSK9, proprotein convertase subtilisin/kexin type 9.

Data are shown as absolute value and frequency, and as median and IQR.

Bold values are statistically significant at $P < .05$.

95% CI: 0.05-0.69; $P = .011$) and continuously throughout the 36-months follow-up period (0.28, 95% CI: 0.11–0.70, respectively; $P = .007$) compared to patients with normal weight. Similarly, patients with obesity were significantly less likely to reach LDL-C targets at 12 (OR: 0.13, 95% CI: 0.04-0.41; $P = .001$), 24 (0.14, 95% CI: 0.04–0.52; $P = .004$), and 36 months (0.08, 95% CI: 0.02-0.38; $P = .002$), as well as continuously during the 36-months follow-up (OR: 0.18, 95% CI: 0.06-0.53, respectively; $P = .002$), compared to patients with normal weight (Table 3).

Moreover, patients with He-FH had a significantly lower likelihood of achieving LDL-C targets compared to those without He-FH after 12 months (OR: 0.35 95% CI: 0.15-0.82; $P = .015$, Table 3). Patients with CAD had a significantly higher probability of reaching LDL-C targets compared to those without CAD at 12 (OR: 2.36, 95% CI: 1.05-5.28; $P = .037$), 24 (OR: 5.91, 95% CI: 2.27-15.37; $P < .0001$), and 36 (OR: 8.52, 95% CI: 2.84-25.6; $P < .0001$) months, as well as during the 36-month follow-up period (OR: 4.54, 95% CI: 2.0-10.4; $P < .0001$). Similarly, the presence of peripheral artery disease was associated with a significantly higher probability of reaching LDL-C targets at 36 months (OR: 8.88 95% CI: 1.39-56.84; $P = .021$).

The administration of concomitant on-top lipid-lowering therapy (ie, ezetimibe plus high-intensity statin) was associated with a higher probability of reaching LDL-C targets compared to those without any oral therapy, both after 6 months (OR: 7.51, 95% CI: 1.77-31.92; $P = .006$) and over the 36-month follow-up period (OR: 14.5, 95% CI: 2.26-92.99; $P = .005$). The 12-months therapy with alirocumab 150 mg and evolocumab 140 mg was associated with a lower probability of achieving LDL-C targets compared to therapy with alirocumab 75 mg (OR: 0.13, 95% CI: 0.03-0.58 and 0.20, 95% CI: 0.05-0.92, respectively; $P = .007$ and $P = .038$).

A total of 105 patients (58.3%) were in secondary prevention, while 75 patients (41.7%) were in primary prevention. Table S2 and Table S3 report the logistic regression analysis for patients undergoing PCSK9-I therapy in secondary and primary prevention, respectively. In secondary prevention, patients with obesity had a significantly lower probability of achieving the LDL-C target compared to patients with normal weight after 24 months (OR: 0.16, 95% CI: 0.03-0.89; $P = .036$; Table S2).

Table 3. Logistic regression analysis for all patients included.

	6 months		12 months		24 months		36 months		Continuous achievement of LDL-C target	
	Univariate	Multivariate	Univariate	Multivariate	Univariate	Multivariate	Univariate	Multivariate	Univariate	Multivariate
Sex (female=ref)	1.16 (0.64-2.11)		1.64 (0.86-3.15)	1.36 (0.62-2.99)	1.63 (0.79-3.36)	1.08 (0.42-2.76)	0.97 (0.45-2.11)		1.34 (0.74-2.42)	
Age (+1 y)	1.01 (0.98-1.03)		**1.03 (1.00-1.06)**	1.02 (0.98-1.06)	1.03 (0.99-1.07)	1.00 (0.96-1.05)	1.04 (0.99-1.08)	1.02 (0.97-1.08)	**1.03 (1.00-1.06)**	1.00 (0.96-1.04)
Weight status (normal weight - BMI 18.5-24.9 kg/m² = ref)										
Overweight (BMI 25–29.9 kg/m²)	0.76 (0.38-1.51)	0.68 (0.31-1.46)	0.76 (0.36-1.63)	0.47 (0.20-1.13)	0.60 (0.25-1.47)	0.39 (0.13-1.18)	0.42 (0.16-1.11)	**0.19 (0.05-0.69)**	0.58 (0.29-1.15)	**0.28 (0.11-0.70)**
Obesity (BMI ≥30 kg/m²)	0.52 (0.23-1.16)	0.55 (0.23-1.35)	**0.29 (0.11-0.73)**	**0.13 (0.04-0.41)**	**0.25 (0.89-0.70)**	**0.14 (0.04-0.52)**	**0.21 (0.07-0.67)**	**0.08 (0.02-0.38)**	**0.36 (0.16-0.81)**	**0.18 (0.06 -0.53)**
Smoking habits (non-smoker = ref)	1.09 (0.52-2.29)		1.34 (0.57-3.13)		1.64 (0.61-4.43)	1.38 (0.40-4.72)	1.45 (0.51-4.11)		2.02 (0.97-4.23)	1.03 (0.38-2.76)
Diagnosis of He-FH (no = ref)	0.96 (0.53-1.76)		**0.37 (0.19-0.72)**	**0.35 (0.15-0.82)**	0.52 (0.25-1.08)	0.49 (0.17-1.45)	**0.44 (0.20-0.98)**	0.53 (0.18-1.54)	**0.47 (0.26-0.86)**	0.42 (0.17-1.05)
Arterial hypertension (no = ref)	1.12 (0.61-2.05)		1.71 (0.89-3.29)	1.34 (0.61-2.98)	2.07 (0.99-4.31)		1.93 (0.88-4.25)	1.10 (0.39-3.15)	1.58 (0.87-2.88)	1.32 (0.58-2.97)
Diabetes (no = ref)	1.17 (0.58-2.35)		1.37 (0.64-2.94)		1.26 (0.52-3.03)		1.11 (0.41-3.02)		1.76 (0.88-3.54)	1.96 (0.77-4.97)
Coronary artery disease (no = ref)	1.38 (0.76-2.53)		**3.01 (1.53–5.91)**	**2.36 (1.05-5.28)**	**7.86 (3.42-18.1)**	**5.91 (2.27-15.37)**	**6.56 (2.78–15.5)**	**8.52 (2.84-25.6)**	**4.85 (2.56–9.2)**	**4.54 (1.98-10.41)**
Stroke (no = ref)	2.14 (0.88-5.18)	2.43 (0.92-6.39)	1.49 (0.57-3.91)		0.81 (0.26-2.49)		1.05 (0.33-3.35)		1.32 (0.55-3.18)	
Peripheral artery disease (no = ref)	2.18 (0.87-5.48)	1.99 (0.69-5.71)	2.05 (0.69-6.09)	2.30 (0.65-8.11)	1.74 (0.46-6.49)		4.81 (0.95-24.4)	**8.88 (1.39-56.84)**	2.52 (0.99-6.42)	2.41 (0.73-7.96)
PCSK9 inhibitors (Alirocumab 75 mg = ref)										
Alirocumab 150 mg	0.79 (0.29-2.16)		**0.19 (0.49-0.74)**	**0.13 (0.03-0.58)**	0.69 (0.18-2.63)		0.72 (0.16-3.23)		0.31 (0.31-2.26)	
Evolocumab 140 mg	1.09 (0.39-3.04)		**0.24 (0.59-0.95)**	**0.20 (0.05-0.92)**	1.22 (0.31-4.73)		0.91 (0.20-4.11)		1.62 (0.46-5.67)	
Concomitant oral lipid-lowering therapy (No other therapies = ref)										
Ezetimibe	1.32 (0.34-5.13)	1.52 (0.38-6.13)	>10⁵		>10⁵		>10⁵		2.62 (0.55-12-56)	3.59 (0.62-20.79)
Ezetimibe + low-intensity statin	1.42 (0.22-9.26)	1.68 (0.24-11.62)	>10⁵		>10⁵		>10⁵		2.35 (0.31-17.85)	2.06 (0.19-22.31)
Ezetimibe + high-intensity statin	**6.86 (1.67-28.23)**	**7.51 (1.77-31.92)**	>10⁵		>10⁵		>10⁵		**10.39 (2.07-52.04)**	**14.50 (2.26-92.99)**
Fibrate	0	0	>10⁵						>10⁵	>10⁵
Ezetimibe + statin + fibrate	>10⁵	>10⁵	>10⁵						>10⁵	>10⁵
Median follow-up in PCSK9-I therapy (+ 12 mo)	0.95 (0.82-1.11)		0.96 (0.80-1.15)		1.25 (0.97-1.61)	1.25 (0.89-1.74)	0.96 (0.71-1.31)		1.00 (0.86-1.17)	

Abbreviations: BMI, body mass index; He-FH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; PCSK9-I, proprotein convertase subtilisin/kexin type 9 inhibitor; ref, reference.

Logistic ordinal regression analysis according to the nature of dependent variable analyzed. Data are reported as odd ratio (CI).

Bold values are statistically significant at $P < .05$.

In primary prevention, patients with overweight had a significantly lower probability of achieving the LDL-C target compared to patients with normal weight after 36 months (OR: 0.06, 95% CI: 0.01-0.72; $P = .022$), and continuously during the 36-month follow-up (0.08, 95% CI: 0.01-0.60; $P = .015$; Table S3).

Discussion

In this real-world retrospective study, we investigated the impact of various contributing factors on the effectiveness of PCSK9-I therapy with a particular focus on overweight and obesity. While the powerful LDL-C lowering effects of PCSK9-Is are well-established and have markedly advanced the treatment of hypercholesterolemia, particularly in those at high cardiovascular risk, an important interindividual variability in PCSK9-I response already persists.[17-19]

Our study found that <50% of patients reached the LDL-C target during the 36-month follow-up. This partially aligns with a large multicenter observational study, which reported that about 60% of patients with high and very high ASCVD risk achieved LDL-C targets after a median follow-up of 19 months.[20] Similarly, a recent real-world analysis of 256 patients demonstrated an approximate 60% reduction over a 24-month period.[21] Focusing on patients with FH, a large retrospective cohort study using Italian Medicines Agency (AIFA) monitoring registries in Italy documented real-world effectiveness, with approximately 40% of patients achieving LDL-C target.[22] We believe that achieving LDL-C targets could be improved with the use of new therapies (ie, inclisiran, bempedoic acid), as highlighted by recent evidence,[23] but, in the meantime, optimizing existing therapies through effective combinations remains pivotal. In our cohort, only 29.4% of patients were treated with combination therapy with on-top oral lipid-lowering drugs. This percentage suggests a need for more aggressive treatment strategies. Indeed, a large prospective cohort analysis confirmed that the addition of alirocumab or evolocumab in patients with FH, 93% of whom were already on maximal oral lipid-lowering therapy, significantly reduced LDL-C levels by 60% over a median follow-up of 2.5 years.[19]

To date, it is well known that a healthy diet and lifestyle modification are pivotal to cardiovascular prevention and lipid-lowering therapy,[24-26] as excess body weight is strongly associated with increased risk of ASCVD events and premature death.[24] Our study not only highlights that a significant proportion of patients receiving PCSK9-I therapy presents a condition of overweight and obesity (41.7% and 25.0%, respectively), but also reveals that these patients are less likely to achieve LDL-C targets as compared to patients with normal weight. Notably, early LDL-C lowering at 6 months was comparable across patients with normal weight, overweight, and obesity. Conversely, a progressive reduction of LDL-C control over time was observed in patients with overweight and with obesity.

From a biological point of view, it is well-documented that excessive body weight can alter the pharmacokinetic and pharmacodynamic properties of biological drugs, potentially reducing their efficacy. A recent meta-analysis by Shan et al, has shown that patients with obesity have lower odds of achieving optimal therapeutic responses, particularly with anti-tumor necrosis factor agents.[27] We believe that this could be due to the effects of excessive body weight on drug clearance and volume of distribution.[28]

Moreover, the chronic low-grade inflammation associated with obesity can influence drug response and lipid metabolism through different pathways.[16] This persistent inflammatory state can lead to altered expression of drug-metabolizing enzymes and transporters,[29] although there is no direct evidence that it could reduce the efficacy of lipid-lowering therapies such as PCSK9-Is. However, inflammation may contribute to a more challenging clinical context, potentially diminishing the overall therapeutic response indirectly, particularly in patients with ASCVD risk.[30]

Focusing on PCSK9 levels, it is known that patients with obesity exhibit significantly higher serum levels of PCSK9 compared to those with normal weight.[31] Furthermore, elevated circulating PCSK9 levels increase with hepatic fat accumulation.[12] Despite this, evidence shows that PCSK9-Is effectively lower LDL-C regardless of baseline PCSK9 levels, suggesting that their mechanism of action—blocking the interaction between PCSK9 and LDL receptors—remains effective, independent of circulating PCSK9 concentrations.[32] Nevertheless, further research is warranted to determine whether individuals with elevated PCSK9, such as those with metabolic disorders, may benefit from optimized dosing strategies to maximize long-term therapeutic efficacy.

Recent evidence shows a large variability in terms of PCSK9-I efficacy relative to BMI variation. A meta-analysis conducted by Khan et al reported that patients with normal BMI treated with intensive lipid-lowering treatments may obtain a larger clinical benefit compared with patients with higher BMI.[33] A recent pooled analysis of randomized controlled trials on alirocumab suggested an association between higher BMI and the need for dose escalation. However, after dose adjustment, the overall absolute reductions in LDL-C from baseline to the 12- and 24-week observations were similar across patients with different BMI.[34] We believe that the controlled setting of a randomized trial cannot fully account for the several factors that may influence outcomes in a real-world setting, such as our study, where nonbiological determinants of unmet treatment targets can be highlighted. Thus, it is possible to suggest that other factors, such as insulin resistance, may play a more significant role in influencing the overall response to PCSK9-Is. Insulin resistance, a hallmark characteristic of type 2 diabetes mellitus, is known to contribute to a more atherogenic lipid profile, characterized by elevated TG, increased very low-density lipoprotein levels, reduced HDL-C, and the formation of small, dense LDL particles.[35] In our study, we observed a significantly higher prevalence of diabetes among patients with obesity

and overweight compared to those of normal weight. The reduced efficacy of PCSK9-Is observed in overweight individuals could be linked to the increased expression of PCSK9 promoted by insulin, as documented by Miao et al[36] in an in vivo study. In fact, hyperinsulinemia is a condition strongly associated with obesity and it stimulates PCSK9 expression, further contributing to the degradation of LDL receptors.[37] This leads to a reduced capacity for LDL clearance, potentially requiring a higher PCSK9-I dosage to achieve the desired lipid-lowering effect.[34]

In our study, we found that patients with He-FH had a significantly lower likelihood of achieving LDL-C targets compared to those without He-FH after 12 months. This finding is consistent with existing literature, as documented by Pasta et al[38] who reported that despite significant improvements in lipid profiles, the ESC/EAS recommended LDL-C goals were achieved by only a small number of patients with He-FH treated with a PCSK9-I in addition to the maximum tolerated doses of statins plus ezetimibe.

This could be attributed to the more severe dyslipidemia seen in patients with He-FH, who typically have higher baseline LDL-C levels (LDL-C $\geq$ 190 mg/dL) compared to non-He-FH patients.[39,40] This underlines a persistent unmet need in managing He-FH, as even with advanced therapeutic interventions, achieving optimal LDL-C levels remains challenging. Our analysis did not consider newer therapies (ie, inclisiran, bempedoic acid), although recent studies have shown that their use significantly improves the achievement of LDL-C targets in He-FH patients.[41]

Another interesting finding from our study was that patients with CAD had a significantly higher probability of reaching LDL-C targets compared to those without CAD at 12, 24, and 36 months, as well as throughout the 36-month follow-up period. Probably, this mechanism is likely influenced by an increased perception of illness among CAD patients, which plays a role in enhancing self-efficacy in disease management and medication adherence, as documented by Mobini et al.[42] To note, the more aggressive lipid-lowering strategies typically employed in CAD patients, as recommended by international guidelines,[4] likely contributed to the achievement of LDL-C targets.

We observed a generally low use of oral add-on therapies, such as ezetimibe in combination with high-dose statins in <25% of the PCSK9-I-treated cohort. This limited use likely contributes to the relatively low rates of LDL-C goal attainment observed across all BMI groups. This finding deserves particular emphasis, as it highlights a missed opportunity for therapeutic optimization. It should serve as a call to action to reinforce guideline-based strategies, promoting a more systematic use of combination lipid-lowering therapies. Moreover, we believe that greater attention should also be given to optimizing adherence through lifestyle interventions, including reinforcement of the Mediterranean diet and the use of evidence-based nutraceutical therapies, which may further support LDL-C reduction and improve overall treatment compliance.[25]

The main limitation of this study is the inherent bias associated with retrospective designs. Additionally, all participants were from a single, highly specialized third-level center, which may limit the generalizability of our findings and could induce selection bias. Furthermore, we did not assess potential factors contributing to unusual responsiveness to PCSK9-Is, such as genetic variations in PCSK9 and LDLR,[43] or other genetic variants, which could affect the observed lipid-lowering response.[44,45] Despite these limitations, the relatively large sample size and the use of appropriate analyses adjusted for multiple confounders provide novel clinical insights into the differential lipid-lowering efficacy of PCSK9-Is based on weight status. Future research should investigate the underlying mechanisms linking increased BMI to reduced efficacy of PCSK9-Is and validate our findings through prospective studies.

Conclusion

Our study highlights that while PCSK9-Is are usually successful in lowering LDL-C levels, their efficacy is significantly lower in patients with overweight and obesity. These individuals are less likely to achieve LDL-C targets compared to those with normal weight, highlighting the need for customized lipid-lowering strategies in this subgroup. The reduced long-term effectiveness of PCSK9-Is in patients with overweight or obesity may be influenced by both physiological factors—such as higher volume of distribution and increased PCSK9 levels in insulin-resistant states—and behavioral aspects. Optimizing PCSK9-I therapy for patients with overweight and obesity is crucial, potentially involving adjusted dosing regimens or combination therapies. Future research should further investigate the underlying dynamics to enhance treatment efficacy and improve cardiovascular outcomes in this population. In conclusion, our findings also support a call to action for the broader implementation of tailored oral lipid-lowering strategies in patients with obesity treated with a PCSK9-I, to enhance long-term efficacy and target attainment.

CRediT authorship contribution statement

Elena Formisano: Writing – original draft, Formal analysis, Data curation. **Andrea Vignati:** Data curation. **Almina Bertolini:** Data curation. **Valeria Maria Barreto Spandonari:** Data curation. **Michele Tafuro:** Data curation. **Andrea Pasta:** Writing – original draft, Methodology, Formal analysis, Data curation. **Samir Giuseppe Sukkar:** Writing – review & editing. **Livia Pisciotta:** Writing – review & editing, Supervision, Conceptualization.

Ethical approval

According to the Italian Medicines Agency det. 20/03/2008 on retrospective observational studies on anonymous

data, approval by an ethics committee was not mandatory. Informed consent was obtained. The study was conducted in accordance with the Declaration of Helsinki and its later amendments.

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Declaration of competing interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data availability

Data are available upon request from the corresponding author.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jacl.2025.06.018.

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