










ORIGINAL RESEARCH

Real-World Effectiveness of PCSK9 Inhibitors in Reducing LDL-C in Patients With Familial Hypercholesterolemia in Italy: A Retrospective Cohort Study Based on the AIFA Monitoring Registries

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BACKGROUND: Information on the real-world use of proprotein convertase subtilisin kexin 9 inhibitors (PCSK9is) in familial hypercholesterolemia are limited. We evaluated the pattern of prescription and the long-term efficacy of alirocumab and evolocumab in Italian patients with familial hypercholesterolemia in clinical practice.

METHODS AND RESULTS: The data set for analysis was extracted from the PCSK9i Italian Medicines Agency (AIFA) registry and included 2484 patients with heterozygous familial hypercholesterolemia (HeFH) and 62 patients with homozygous familial hypercholesterolemia (HoFH) who were prescribed PCSK9is from February 2017 to December 2021. As the follow-up schedules were not prespecified and could vary, persistence and adherence as well as low-density lipoprotein cholesterol (LDL-C) changes during 2 years of treatment were analyzed in a final cohort of 1299 patients with familial hypercholesterolemia. At baseline, 53.8% of patients with HeFH and 69.4% of patients with HoFH were receiving maximally tolerated lipid-lowering therapies, while 45.9% of patients with HeFH and 30.7% of patients with HoFH reported statin intolerance; mean LDL-C was 197.7 ± 52.3 mg/dL in HeFH and 252.0 ± 106.2 mg/dL in HoFH. The 6-month persistence and adherence to therapy were $>85\%$, and LDL-C reduction reached 58.6% (to 79.7 mg/dL) in HeFH and 57.6% (to 95.1 mg/dL) in HoFH after 24 months of treatment. The European Atherosclerosis Society/European Society of Cardiology LDL-C goals were achieved in 43.3% of patients with HeFH and 37.5% of patients with HoFH.

CONCLUSIONS: PCSK9i prescribed to patients with familial hypercholesterolemia in clinical practice showed LDL-C-lowering efficacy similar to that observed in controlled trials. However, 2 of 5 HeFH cases and 2 of 6 HoFH cases achieved the recommended LDL-C goals. The full achievement of European Atherosclerosis Society/European Society of Cardiology LDL-C goals should require a lower threshold for PCSK9i initiation and a combination of multiple therapies.

Key Words: adherence ■ heterozygous familial hypercholesterolemia ■ homozygous familial hypercholesterolemia ■ LDL cholesterol ■ PCSK9 inhibitors ■ real-world

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CLINICAL PRESPECTIVE

What Is New?

- Data on the real-world efficacy of proprotein convertase subtilisin kexin 9 inhibitor inhibitors (PCSK9is) are limited, but taking advantage of the PCSK9i prescription monitoring registry of the Italian Medicines Agency (AIFA), we confirmed the usefulness of PCSK9is in familial hypercholesterolemia by reporting low-density lipoprotein cholesterol (LDL-C)-lowering results similar to those observed in the clinical trials.
- Despite the marked reduction in LDL-C, a significant proportion of patients with familial hypercholesterolemia still showed LDL-C above the European Atherosclerosis Society/European Society of Cardiology goals, and this was at least partly due to the high LDL-C levels for eligibility to PCSK9i therapy.

What Are the Clinical Implications?

- We showed that the full achievement of European Atherosclerosis Society/European Society of Cardiology LDL-C goals should require a lower threshold for PCSK9i initiation and eventually combination of multiple lipid-lowering therapies.

Nonstandard Abbreviations and Acronyms

AIFA	Italian Medicines Agency
DLCN	Dutch Lipid Clinic Network
FH	familial hypercholesterolemia
HeFH	heterozygous familial hypercholesterolemia
HoFH	homozygous familial hypercholesterolemia
LA	low-density lipoprotein apheresis
LDLR	low-density lipoprotein receptor
LLT	lipid-lowering therapy
ODYSSEY APPRISE	Safety, Tolerability, and Effect of Alirocumab in High Cardiovascular Risk Patients With Severe Hypercholesterolemia Not Adequately Controlled With Conventional Lipid-Modifying Therapies
PCSK9i	proprotein convertase subtilisin kexin 9 inhibitor
wMRs	web platform of monitoring registries

Familial hypercholesterolemia (FH) is the most common genetic disorder of lipid metabolism characterized by elevated plasma concentrations of low-density lipoprotein cholesterol (LDL-C) and a markedly increased risk of premature atherosclerotic cardiovascular disease (ASCVD).^{1,2} It is caused by mutations in the major genes (*LDLR*, *APOB*, and *PCSK9*) controlling the receptor-mediated removal of LDL-C from plasma.^{1,2} FH is inherited as an autosomal codominant trait and most of the patients (1 in 250–300 in the general population) are heterozygotes (HeFH), with only 1 mutated allele. Patients carrying 2 mutated alleles are classified as homozygotes (HoFH) and are much less frequent in the general population (estimated prevalence of 1:160000 to 1:360000¹) but present with the worst LDL-C elevation and ASCVD prognosis.^{1,2}

Statins and ezetimibe are the first-line lipid-lowering therapies (LLTs) in FH.^{1,2} Due to the increased ASCVD risk associated with FH, several guidelines set the goals of treatment at low LDL-C levels.^{2,3} In particular, the recent European guidelines indicated the optimal goal for these patients at LDL-C ≤ 70 mg/dL (< 55 mg/dL in the presence of ASCVD) with $\geq 50\%$ reduction from the level at baseline.² However, real-world data have highlighted that LDL-C levels remain higher than recommended in the vast majority of patients with HeFH under conventional LLT.^{4–9} These difficulties are even greater in HoFH, where the severe impairment of the LDL receptor (LDLR) pathway makes these patients poorly responsive to statins and ezetimibe. Therefore, many of them require LDL apheresis (LA).^{2,10,11}

Proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9is) are monoclonal antibodies able to specifically bind circulating PCSK9 protein, thus blocking its interaction with the LDLR. Therefore, the PCSK9-mediated degradation of LDLR is prevented with the consequent increased availability of the receptor at the cell surface. This enhances the LDLR-mediated removal of LDL particles, thereby decreasing plasma LDL-C concentration. The PCSK9is evolocumab and alirocumab have been proven in randomized clinical trials to be generally well tolerated and effective in HeFH by lowering baseline LDL-C by 50% to 60%.^{12–15} In patients with HoFH, the efficacy of PCSK9i largely depends on the residual LDLR activity, with 25% to 30% LDL-C reduction in patients who were mutation defective and $< 5\%$ in patients who were mutation negative.^{16,17} Considering these results, the use of PCSK9i is recommended for both patients with HeFH and patients with HoFH.^{2,3} However, in many countries the use of these drugs in clinical practice is subject to numerous regulatory limitations.¹⁸ For example, a previous analysis of early adopters of PCSK9i therapy in the United States found that patients treated with PCSK9i had higher cardiovascular risk in terms of LDL-C levels, cardiovascular comorbidities, statin intolerance, and

intensity of LLT compared with patients treated with LLTs other than PCSK9is.¹⁹ As there are remarkable differences in the criteria for access to PCSK9i therapy between countries,²⁰ there is a need to better understand, at the national level, the consequences of recommendations issued for the use of PCSK9is in clinical practice, mainly in patients with high-risk dyslipidemia.

Taking advantage of the availability of the Italian Medicines Agency (AIFA) national registries including data of patients initiating PCSK9i, the present study sought (1) to describe treatment patterns in PCSK9i-eligible patients with FH and (2) to determine the LDL-lowering efficacy and the persistence to therapy in patients with HeFH and HoFH followed in the real-world setting in Italy.

METHODS

Data Source

The data underlying this article were accessed directly from AIFA monitoring registries and no new data set was generated for the present analysis. Therefore, data sharing is not applicable to this article, as registry data are protected by privacy.

This study focuses on a retrospective analysis of patients with HeFH and HoFH treated with alirocumab or evolocumab in Italy, who started treatment between February 2017 and December 2019; treated patients have been observed for a period of 24 months. A cut-off has therefore been imposed on the data collection, on December 31, 2021. The goal was to observe drug effectiveness in reducing the levels of LDL-C every 6 months up to 24 months.

This retrospective analysis was carried out by using data retrieved from the AIFA web platform of monitoring registries (wMRs) recording the prescriptions of PCSK9is in Italy. wMRs are administrative databases designed to monitor in real-world clinical practice the appropriateness of innovative and high-cost drugs in Italy. The use of wMRs in the context of Italian regulatory drug prescription, as well as their technical characteristics, have been described in detail elsewhere.^{21,22} Notably, they allowed the storing and monitoring of clinical characteristics of patients eligible for treatments according to the prespecified reimbursement criteria.

The wMR dedicated to PCSK9is was established immediately after the approval of these medications in Italy,^{23,24} all centers authorized to prescribe alirocumab and evolocumab were obliged to register eligible patients into the PCSK9i wMR to allow drug reimbursement from the National Health Service. According to the AIFA reimbursement criteria,^{25,26} adult patients with HeFH were eligible for PCSK9i therapy on the basis of (1) Dutch Lipid Clinic Network (DLCN) score >8; and (2) LDL-C ≥130 mg/dL (≥100 mg/dL in secondary

prevention) despite treatment with rosuvastatin or atorvastatin at the highest tolerated dose plus ezetimibe or (3) clinically established statin intolerance; in this case, ezetimibe monotherapy was allowed. Moreover, for patients affected by HoFH, the clinical diagnosis was simply required, and evolocumab was the only PCSK9i authorized. Finally, for all patients the following additional criteria were required: (1) age ≤80 years and (2) estimated glomerular filtration rate ≥30 mL/min (according to the Cockcroft–Gault equation).

At patients' registration, the following information was recorded: place of birth, age, sex, history of clinically established ASCVD, presence of major cardiovascular risk factors (smoking, hypertension and type 1 or type 2 diabetes), presence of comorbidities, such as chronic kidney disease (based on estimated glomerular filtration rate), and background LLTs. In addition, for patients eligible for PCSK9is due to FH, the diagnosis was required to be made throughout the application of the DLCN score.² The structure of the DLNC score is reported in [Table S1](#), and a DLCN score value >8 points (definite FH) was mandatory for patients' eligibility.^{23,24} Moreover, in the case of statin intolerance, this condition was required to be diagnosed on the basis of the criteria reported by Banach et al^{27,28} These criteria are detailed in [Table S2](#).

During treatment with PCSK9i, it was allowed to modify or discontinue background LLT. To present analysis, background LLTs were classified according to drug potency, as previously reported.^{9,27} Statin-intolerant and low- to moderate-intensity patients were grouped, as well as those receiving high-intensity and maximally tolerated LLTs.²⁸

Each prescription is entitled to dispense the necessary drug packages to cover 28, 98, or 182 days of treatment. Before every prescription renewal, values of plasma total cholesterol, LDL-C, high-density lipoprotein cholesterol (HDL-C), and triglycerides, as well as information about background LLTs had to be entered into the registry. The registry did not request the recording of adverse events. However, reasons for treatment interruption could be reported but were available only if the end-of-treatment form was filled out by the treating clinician.

According to Italian laws, the monitoring of parameters by registry does not require any informed consent or formal approval from ethical committees. Nevertheless, all included patients did receive information about the purposes of the registry. The study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline.

Patients' Follow-Up Cohorts and Data Assessment

From February 2017 to December 2019, a total of 2484 patients with a diagnosis of HeFH and 62 with a

diagnosis of HoFH were included in the PCSK9i AIFA registry. A cutoff date of December 31, 2021 was imposed for data extraction, so that all patients had at least 2 years of potential follow-up. The prescription of PCSK9is was evaluated at the 6-, 12-, 18- and 24-month time points. Due to the observational nature of the registry, we had to arbitrarily define criteria for data extraction. Indeed, for the 6-month time point observation, the window was set to ± 65 days, which implies that a patient was observed at the 6-month time point (185 days) if a prescription was issued within 120 to 250 days since the treatment initiation; for the 12-month observation, the window was set to ± 75 days; for the 18-month and the 24-month observations, the window was set to ± 80 days. This led to a study cohort comprising a total of 1299 patients (1263 patients with HeFH, 36 patients with HoFH), who were regularly observed across the selected time points. **Figure 1** presents a flowchart, outlining an overview of the cohort selection process. Using standard labeling in longitudinal analyses, these patients were labeled as stayers; conversely, patients not included in the main follow-up analysis due to the fact that the observations fell out of the prespecified time-point windows were labeled as attritors. Because of the above-described data assessment criteria, many patients were described as attritors and this population encompassed a total of 1221 patients with HeFH and 26 patients with HoFH representing, respectively, 49.15% and 41.94% of the patients included in the AIFA registry (**Figure S1**).

In the sensitivity analysis, the right limit of the observation window for each time point was shifted to include the whole period up to the last time point, using a Next Observation Carried Backward approach. In doing so, the measured values were projected backwards to comply with the setup time points (–6, –12, –24 months). By using this strategy, we generated a cohort of 1805 patients (1763 patients with HeFH and 42 patients with HoFH) that have been considered for the sensitivity analysis. The patients who are included in the registry and were not observed in this analysis have at least 1 missing observation during follow-up.

The lipid-lowering effectiveness of PCSK9is was evaluated by estimating the percent reduction of LDL-C at the different time points follow-up. Other outcomes assessed were the proportion of patients with FH achieving individual LDL-C goals according to current guidelines (<55 mg/dL and <70 mg/dL in patients with and without reported ASCVD events, respectively). Changes in the other major lipid parameters, for example, total cholesterol, triglycerides, HDL-C, and non-HDL-C were also estimated. LDL-C values were automatically calculated using the Friedewald's formula²⁹ and those of non-HDL-C by the following formula: total cholesterol (mg/dL) – HDL-C (mg/dL).

Statistical Analysis

Description of parameters at the different time points has been performed using mean values for numerical variables and frequencies for categorical ones. The pairwise significance has been evaluated using ANOVA and tests for proportions, respectively.

A sensitivity analysis was carried out by using variable balancing through a random forest,³⁰ to verify whether baseline characteristics of stayers were substantially comparable to those of attritors, and hence whether missing observation can be assumed to be randomly distributed.

The comparisons across the whole observation period have been made using the Friedman test for numerical variables, and the Cochran–Armitage test for categorical ones. The effect of individual features on the achievement of LDL-C goal has been analyzed using panel data logistic regression with Probit link function with individual random effects. The regressors have all been considered at baseline, except for LLT intensity, which has been considered on the last available information (hence, for the 6-month target, LLT intensity was considered at baseline; for the 12-month target, LLT intensity was considered at the 6-month time point; and so on). Feature selection was performed using a combined approach of clinical knowledge and forward selection. Numerical variables were standardized to avoid singularity issues; in the regression model, LLT max- and high-intensity levels were disaggregated to better understand the impact of LLT on target achievement. LLT intensity reference level was set to max against high and none–low because, at baseline, none–low is highly related to statin intolerance, which could have caused issues in the computation of standard errors.

All statistical analyses were performed using R version 4.0.5³¹ (<http://www.R-project.org/>). The ggplot2 package has been adopted³² (<https://ggplot2.tidyverse.org/>).

RESULTS

Baseline Characteristics of Patients With FH

Baseline characteristics of the whole cohort of patients with FH included in the registry are shown in **Table 1**. In HeFH (n=2484), the mean age was 56.2 ± 12.1 years; 49.1% were men, and the majority were living in the regions of Southern Italy. The FH diagnosis was mostly clinical, with an estimated mean DLCN score of 12.0 points, well within the HeFH category.² Nevertheless, 18.1% of patients were genotyped, showing almost only pathogenic mutations in the *LDLR* gene. Other cardiovascular risk factors were frequent, especially smoking (42.1%) and hypertension (47.2%); 46.3%

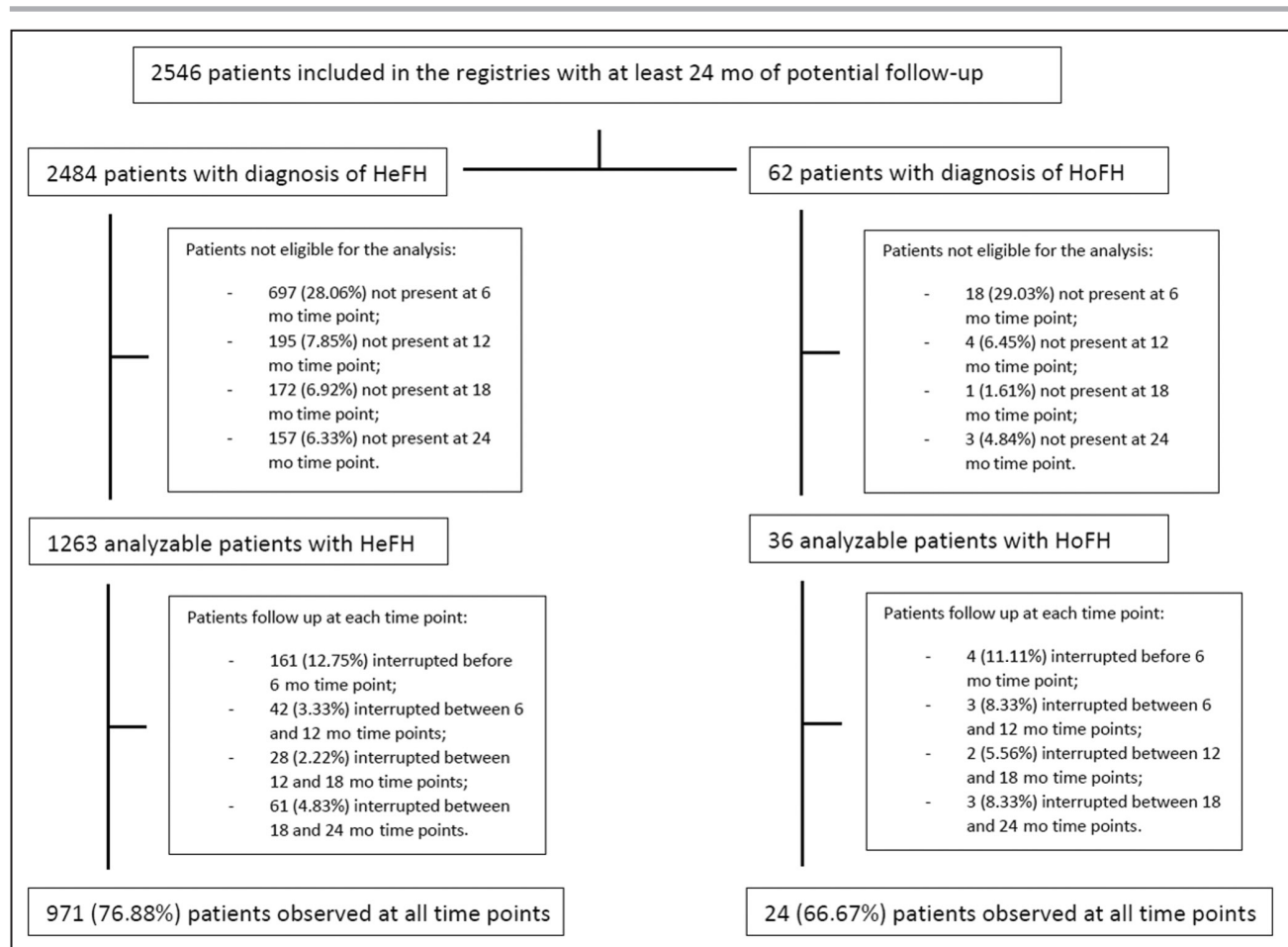


Figure 1. Flowchart of the population selection.

Depicts the criteria used to select patients eligible for the retrospective observational study among those included in the AIFA wMRs registry. Using standard labeling in longitudinal analyses, selected patients were labeled as stayers; conversely, patients not included in the main follow-up analysis due to the fact the observations fell out of the prespecified time-point windows were labeled as attritors. AIFA indicates Italian Medicines Agency; HeFH, heterozygous familial hypercholesterolemia; HoFH, homozygous familial hypercholesterolemia; and wMRs, web platform of monitoring registries.

of patients with HeFH had a history of ASCVD, and a minority (5.4%) showed chronic kidney disease (estimated glomerular filtration rate <30 – 89 mL/min). Among patients with HeFH, only 54.1% were using background therapy with statins, and 45.9% were reported to be statin-intolerant. This subgroup was also in treatment with ezetimibe.^{23,24} Finally, a small group (0.9%) was also receiving LA. Overall, about 53.83% of patients were on high-intensity or maximally tolerated background LLTs.

In the HoFH group ($n=62$), the mean age was lower than in the group with HeFH (48.2 ± 17.8 years), and the proportion of men was higher (58.1%). The regions where most patients were living were those of northern Italy. About 40% of patients with HoFH were genotyped, and the mutations reported were almost exclusively located in the *LDLR* gene (88%). Like patients with HeFH, hypertension and smoking were the most common cardiovascular risk factors (30.7%); one patient with

HoFH (1.61%) reported type 2 diabetes and another chronic kidney disease. Finally, 56.45% of patients with HoFH reported ASCVD events with a prevalent coronary localization. Before starting PCSK9is, 69.35% of HoFH were on high-intensity/maximally tolerated LLTs, and 11.3% were receiving LA. Baseline mean plasma total cholesterol was 279.8 ± 57.8 mg/dL and LDL-C 197.7 ± 52.3 mg/dL in HeFH and 325.1 ± 110.2 mg/dL and 245.6 ± 108.2 mg/dL in HoFH, respectively. In both patient groups, plasma total triglycerides were within normal, borderline-high levels.

Adherence to and Effectiveness of PCSK9i Therapy in HeFH

Among patients with HeFH, 54.3% were prescribed with evolocumab 140 mg every 2 weeks and 45.4% with alirocumab, the most frequently used drug dosage being 75 mg every 2 weeks (26.1%) (Table 1). A

Table 1. Characteristics of Italian Patients With HeFH and HoFH Included in the AIFA PCSK9i Registry

	HeFH (n=2484)	HoFH (n=62)
Characteristics		
Age (y), mean (SD)	56.2 (12.1)	48.2 (17.8)
Male, n (%)	1219 (49.07)	36 (58.06)
Geographic origin, n (%)		
Northern Italy	815 (32.8)	28 (45.16)
Central Italy	475 (19.12)	8 (12.90)
Southern Italy	1194 (48.07)	26 (41.94)
FH diagnosis		
DCLN score, mean (SD)	11.98 (3.44)	15.71 (6.39)
Patients genotyped, n (%)	449 (18.08)	25 (40.32)
<i>LDLR</i> mutation	409 (16.47)	22 (35.48)
<i>APOB</i> mutation	25 (1.01)	3 (4.84)
<i>PCSK9</i> mutation	15 (0.60)	1 (1.61)
Risk factors, n (%)		
Current smoking	411 (16.55)	3 (4.84)
Previous smoking	635 (25.56)	16 (25.81)
Hypertension	1173 (47.22)	19 (30.65)
Diabetes	156 (6.28)	1 (1.61)
Chronic kidney disease	133 (5.35)	1 (1.61)
Mild (eGFR 60–89 mL/min)	94 (3.78)	1 (1.61)
Moderate (eGFR 30–59 mL/min)	39 (1.57)	0 (0.00)
ASCVD, n (%)		
Coronary artery disease	463 (18.64)	28 (45.16)
Cerebrovascular disease	218 (8.78)	3 (4.84)
Peripheral arterial disease	469 (18.88)	4 (6.45)
Prevention, n (%)		
Primary prevention	1489 (59.94)	31 (50.00)
Secondary prevention	995 (40.06)	31 (50.00)
Lipid-lowering therapies, n (%)		
None/low to moderate	1147 (46.17)	19 (30.65)
High/maximal	1337 (53.83)	43 (69.35)
Statins	1314 (54.11)	43 (69.35)
Ezetimibe	2484 (100.0)	62 (100.00)
LA	23 (0.93)	7 (11.29)
Fibrates	35 (1.41)	1 (1.61)
PUFA-N3	85 (3.42)	3 (4.84)
Patients with reported statin intolerance, n (%) [*]	1140 (45.89)	19 (30.65)
Plasma lipids, mg/dL, mean (SD)		
Total cholesterol	279.8 (57.8)	325.1 (110.2)
LDL-C	197.7 (52.3)	245.6 (108.3)
HDL-C	53.4 (13.5)	51.1 (10.4)
Non-HDL-C	226.5 (55.9)	274.1 (108.2)
Total triglycerides	144.1 (74.8)	142.6 (69.0)

(Continued)

Table 1. Continued

	HeFH (n=2484)	HoFH (n=62)
Type and dosages of PCSK9i, n (%)		
Alirocumab 75 mg every 2 wks	647 (26.05)	...
Alirocumab 150 mg every 2 wks	481 (19.36)	...
Evolocumab 140 mg every 2 wks	1348 (54.27)	43 (69.35)
Evolocumab 420 mg once a month	8 (0.32)	19 (30.65)

Data are presented as mean (\pm SD) and number (percentage) as appropriate. *APOB* indicates apolipoprotein B gene; ASCVD, atherosclerotic cardiovascular event; DCLN, Dutch Lipid Clinic Network; eGFR, estimated glomerular filtration rate; FH, familial hypercholesterolemia; HDL-C, high-density lipoprotein cholesterol; HeFH, heterozygous familial hypercholesterolemia; HoFH, homozygous familial hypercholesterolemia; LA, low-density lipoprotein apheresis; LDL-C, low-density lipoprotein cholesterol; *LDLR*, low-density lipoprotein receptor gene; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; *PCSK9*, proprotein convertase subtilisin/kexin type 9 gene; and PUFA-N3, n-3 polyunsaturated fatty acids.

^{*}Statin intolerance was defined according with Italian Medicines Agency definition.²³ eGFR was calculated by using the Modification of Diet in Renal Disease formula.

small group also received evolocumab 420 mg once a month. Patients' disposal is reported in [Table S3](#). Overall, 1263 patients (50.8%) with HeFH have shown a prescription timing compatible with the prespecified criteria for 6-, 12-, 18- and 24-month time-point analysis. Of these, 1102 (87.3%), 1060 (83.9%), 1032 (81.7%), and 971 (76.9%) patients were indeed observed at the 6-, 12-, 18- and 24-month time, respectively, the others having interrupted or suspended the treatment before the expected observation. When a random forest was run to discriminate stayers from attritors, we found that the probability of being a stayer is poorly influenced by baseline features, thus suggesting that no selection bias was introduced (see [Figure S2](#)).

As shown in [Table 2](#), the percentage of patients evaluated at each time point who were classified as persistent is always >80%, and both mean and median adherence to PCSK9i therapy were well above 90% as well as the percentage of high adherence patients.

Plasma lipids after initiation of PCSK9i therapy in HeFH are shown in [Table 3](#). At the 6-month time point, LDL-C levels dropped from baseline by $56.2 \pm 35.2\%$ to 86.6 ± 76.3 mg/dL (95% CI, 82.1–91.1 mg/dL), with a mean absolute reduction of 111.1 mg/dL. A slightly increasing reduction was observed among patients over time; as at the 24-month observation, mean LDL-C was 79.7 ± 45.9 mg/dL (95% CI: 76.8–82.6 mg/dL) generating a reduction of $58.6 \pm 20.5\%$. A similar trend was observed in total and non-HDL-C (*data not shown*). Plasma levels of total triglycerides showed only a small reduction ($\approx 16\%$), while those of HDL-C did not show

Table 2. Adherence and Persistence of HeFH Patients to PCSK9i Treatment at the Different Time Points

Adherence and persistence	6 mo	12 mo	18 mo	24 mo
Persistence	1116 (88.36)	1084 (85.83)	1048 (82.98)	1021 (80.84)
Adherence=100%	480 (43.56)	278 (26.23)	189 (18.31)	104 (10.71)
Adherence ≥80%	1017 (92.29)	1010 (95.28)	992 (96.12)	942 (97.01)
Average adherence, %	94.5	94.1	93.7	93.4
Median adherence, %	98.9	96.3	95.1	94.6

Data are represented as number (percentage). This table represents adherence and persistence to PCSK9i in HeFH at the different time points up to 24 months. Adherence was calculated only for patients observed at the specified time points. HeFH indicates heterozygous familial hypercholesterolemia; and PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor.

appreciable variation during PCSK9i therapy. It is worth mentioning that, after addition of PCSK9i, a decrease in the proportion of patients assuming high/maximal LLTs was observed (Table 3).

The distribution of individual LDL-C values observed at the different time points is described in Figure 2, Panel A. After 6 months of therapy, 70.6% of patients with HeFH presented LDL-C levels below 100 mg/dL and this amount was similar, yet slightly increasing at the different time points. The lowest LDL-C level measured after 6 months of therapy was 4 mg/dL in a patient whose LDL-C decreased by 98.0%. Moreover, at the 6-month time-point observation, 5.4% of patients were classifiable as hyporesponders or nonresponders (<15% LDL-C decrease), while 69.3% showed an LDL-C reduction >50% (Figure 3A).

Overall, the proportion of patients with HeFH who reached the recommended individual goal was 41.9% after 6 months, with a slight increase over time (Table 3). About 60% of patients with HeFH who achieved the therapeutic goal after 6 months of therapy confirmed the same result after 24 months. Conversely, 63.3% of patients who did not achieve the therapeutic goal after 6 months were still above the LDL-C target after 24 months of treatment. The overall flow of patients with HeFH who were at target at the 24-month time point throughout follow-up is depicted in Figure S3A. Notably, a relevant proportion (14.4%) of patients who failed to reach the target after 6 months discontinued treatment before the 24-month time point.

The best predictors of the LDL-C goal achievement across time points were searched by using a

Table 3. Plasma Lipids and Concomitant Background Lipid-Lowering Medications at the Different Time Points in Patients With HeFH Receiving PCSK9i

	Baseline	6 mo	12 mo	18 mo	24 mo	Trend†
Plasma lipids, mg/dL	(n=1263)	(n=1102)	(n=1060)	(n=1032)	(n=971)	
Total cholesterol	279.8 (57.7)	165.2 (80.8)*	158.7 (51.1)*	158.7 (51.1)*	157.8 (50.6)*	0.000*
LDL-C	197.7 (52.5)	86.6 (76.3)*	80.6 (46.2)*	80.5 (45.5)*	79.7 (45.9)*	0.000*
HDL-C	53.7 (13.4)	54.9 (14.3)*	54.7 (14.0)*	54.8 (14.9)*	54.8 (14.1)*	0.000*
Non-HDL-C	226.0 (55.6)	110.3 (78.6)*	104.0 (48.5)*	103.9 (48.3)*	103.0 (48.8)*	0.000*
Total triglycerides	141.7 (70.1)	118.7 (66.4)*	116.8 (60.6)*	117.1 (59.5)*	116.4 (61.9)*	0.000*
Target achievement						
% Reduction of LDL-C from baseline		56.15 (35.2)	58.42 (20.8)	58.46 (20.8)	58.63 (20.5)	
Subjects reaching LDL-C goals, n (%)		462 (41.92)	452 (42.64)	449 (43.51)	420 (43.25)	
Lipid-lowering therapy by intensity, n (%)						
None/low to moderate	554 (43.87)	657 (59.62)*	617 (58.21)*	597 (57.85)*	560 (57.67)*	0.000*
High/maximal	709 (56.13)	445 (40.38)*	443 (41.79)*	435 (42.15)*	411 (42.33)*	0.000*
Fibrates	18 (1.43)	11 (1.00)	12 (1.13)	12 (1.16)	12 (1.24)	0.785
PUFA-N3	44 (3.48)	37 (3.36)	39 (3.68)	44 (4.26)	44 (4.53)	0.284
LA	15 (1.19)	6 (0.54)	5 (0.47)	5 (0.48)	7 (0.72)	0.187

Data are reported as mean (SD). Intensity of lipid-lowering therapies has been classified as reported in the Methods section. Data are reported for the 6-, 12-, 18-, and 24-month time points. Significance indicates comparisons with baseline values in patients reporting values at all time points. HDL-C indicates high-density lipoprotein cholesterol; HeFH, heterozygous familial hypercholesterolemia; LA, low-density lipoprotein apheresis; LDL-C, low-density lipoprotein cholesterol; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; and PUFA-N3, polyunsaturated fatty acids n-3.

*Indicates 99% significance of the difference with baseline values.

†Indicates comparisons with baseline values in patients reporting values at all time points.

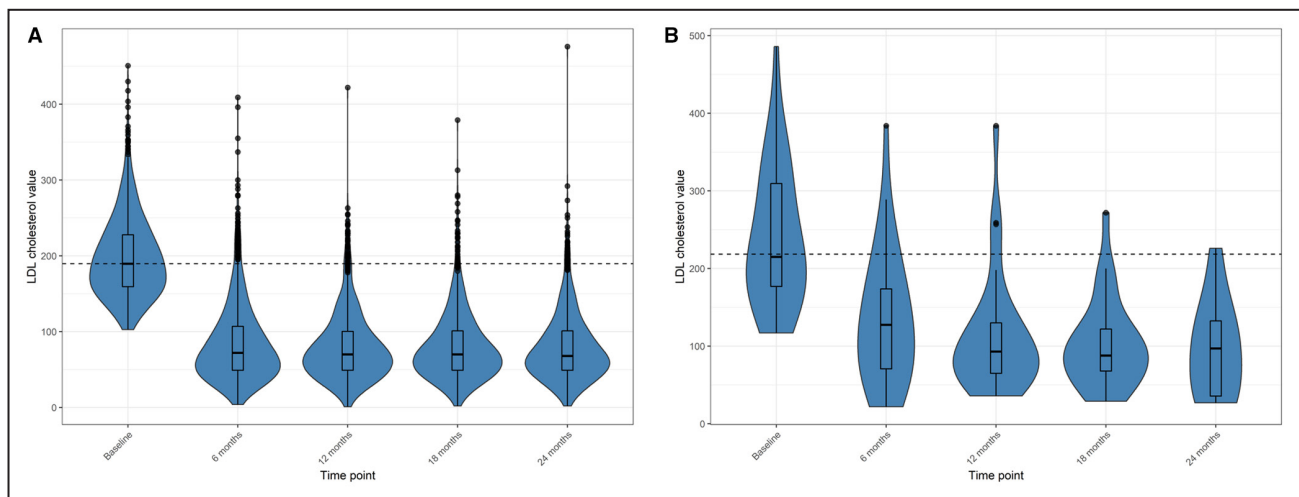


Figure 2. Distribution of individual LDL-C values in patients with HeFH and patients with HoFH receiving PCSK9i at the different time points during treatment.

Data are presented as a violin plot according to the different time points. The dotted line corresponds to the mean value of LDL-C at the first visit. Median values, interquartile ranges, and first and third quartiles are highlighted in the plot. Data are represented for the 6-, 12-, 18-, and 24-month time points in both HeFH and HoFH. LDL-C values are expressed as mg/dL. Individual LDL-C values in HeFH (A), and those in patients with HoFH (B). HeFH indicates heterozygous familial hypercholesterolemia; HoFH, homozygous familial hypercholesterolemia; LDL-C, low-density cholesterol; and PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor.

multivariate logistic analysis with individual random effects, and the results are reported in Table 4. All regressors were those measured at baseline, with the only exception of LLT intensity that was dynamically evaluated; for example, the predictor of target achievement at 12 months was the LLT intensity recorded at 6 months. The probability of LDL-C goals achievement was significantly higher in men and patients with hypertension, while it was lower in patients with

comorbidities, statin intolerance, higher baseline LDL-C, and low potency of background LLTs (all $P < 0.01$).

Adherence to and Effectiveness of PCSK9i Therapy in HoFH

Of the 62 patients entering the registry with the diagnosis of HoFH, 36 (58.1%) showed a prescription schedule compatible with the prespecified criteria for

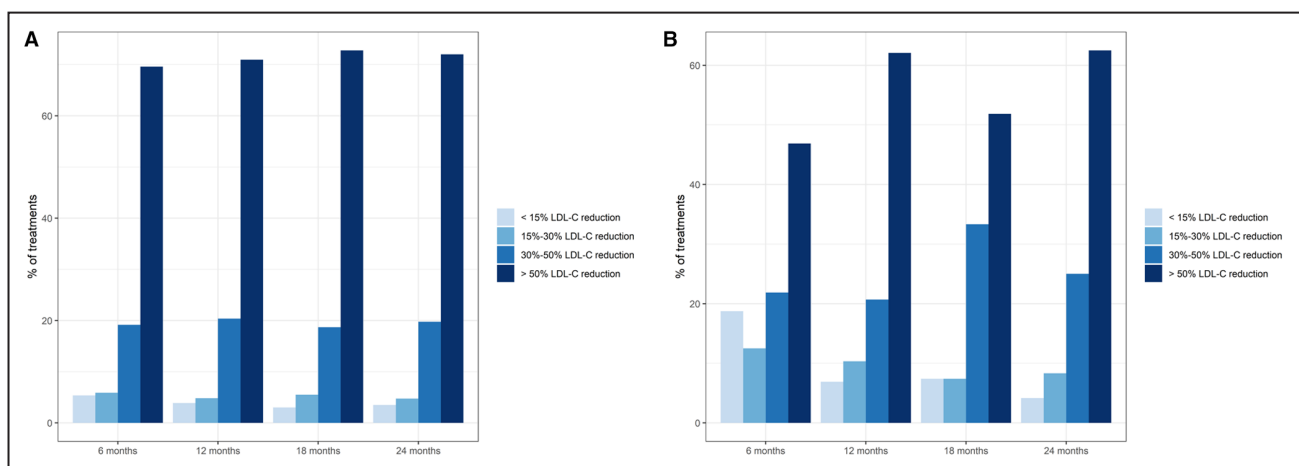


Figure 3. Distribution of categories of percent LDL-C reduction in patients with HeFH and patients with HoFH receiving PCSK9i at the different time points during treatment.

Data are reported as percentage of patients per each time point according to lipid-lowering response to PCSK9i. Categories defined as percent LDL-C reduction from baseline according to 4 groups: <15%, 15% to 30%, 30% to 50%, and >50%. These categories are represented in orange, green, blue, and violet, respectively, and are reported for each time point up to 24 months. Data in patients with HeFH (A) and in patients with HoFH (B). HeFH indicates heterozygous familial hypercholesterolemia; HoFH, homozygous familial hypercholesterolemia; and LDL-C, low-density cholesterol.

Table 4. Predictors for the Attainment of LDL-C Goals in Patients With HeFH Across Time Points

(Intercept)	0.779 (0.224)	0.503–1.208
Sex, male vs female	1.685 (0.095) [†]	1.398–2.030
Age at treatment start	1.025 (0.052)	0.926–1.134
Arterial hypertension, yes vs no	1.665 (0.126) [†]	1.300–2.133
Total number of comorbidities	0.725 (0.086) [†]	0.613–0.858
Diabetes, yes vs no	1.162 (0.207)	0.775–1.742
Normal kidney function, yes vs no	0.919 (0.196)	0.625–1.350
Cardiovascular disease, yes vs no	1.265 (0.146)	0.951–1.683
Statin intolerant, yes vs no	0.623 (0.117) [†]	0.495–0.783
LDL-C	0.565 (0.053) [†]	0.509–0.627
Secondary prevention, yes vs no	0.709 (0.145) [*]	0.534–0.941
LLT intensity, high vs max	0.838 (0.103)	0.685–1.026
LLT intensity, none-low vs max	0.627 (0.101) [†]	0.514–0.764
DLCN score	1.015 (0.047)	0.925–1.113

All variables included in the model are reported in the table. Data are expressed as odds ratio (SD). All regressors were measured at baseline with the only exception of LLT intensity, which is dynamically measured at the previous observation; hence, for instance, the predictor of target achievement at 12 months is LLT intensity at 6 months. DLCN indicates Dutch Lipid Clinic Network; HeFH, heterozygous familial hypercholesterolemia; LDL-C, low density lipoprotein cholesterol; and LLT, lipid-lowering therapy.

^{*}Indicates 95% significance.

[†]Indicates 99% significance of the difference with baseline values.

time-point analysis. Indeed, 32 (88.9%) were observed at 6 months, 29 (80.56%) at 12 months, 27 (75.0%) at 18 months, and 24 (66.7%) after 2 years (Table S3), with the remaining 12 patients suspending or discontinuing the therapy before the expected observation. The majority of the patients with HoFH received evolocumab at a dosage of 140 mg every 2 weeks as recommended. Nevertheless, 30.7% of them started evolocumab at a dosage of 420 mg once a month (Table 1).

The persistence to therapy in HoFH was 75% with a median and mean percentage of treatment adherence both above 90% across the whole follow-up (Table 5). After the prescription of evolocumab, LDL-C levels dropped by 43.9%±29.2% to 133.3±82.8 mg/dL (95% CI, 103.4–163.1 mg/dL) with a mean absolute reduction of 114.7 mg/dL. At the last control, the decrease was more substantial as mean LDL-C was 95.1±60.2 mg/dL (95% CI, 69.7–120.6 mg/dL) (Table 6).

Consistently, total cholesterol and non-HDL-C were similarly reduced (*data not shown*). Surprisingly, a slightly higher proportion of patients were reported to receive no or low-intensity LLTs at the end of follow-up as compared with baseline (Table 6). In addition, fewer patients with HoFH were under LA as compared with the baseline. All together, these observations could be interpreted as a reflection of the fact that the reduction of LDL-C obtained by the addition of PCSK9i could have induced the attending physicians to attenuate the intensity of the therapy.

The distribution of individual LDL-C values observed at the different time points is depicted in Figure 2B. Within the 6-month potential follow-up group of patients, 78.1% of patients with HoFH presented LDL-C <200 mg/dL, and the lowest LDL-C level measured was 22 mg/dL, with a reduction of 92.1% as compared with baseline. The distribution of the percentage reduction of LDL-C during therapy is shown in Table 6. The percentage of responders (>50% LDL-C reduction) was 46.8% of patients after 6 months of therapy and 62.5% after 2 years (Figure 3B). Overall, the achievement of LDL-C targets in patients with HoFH was observed in ≈15% of cases at 6 months, and this value reached 37.5% after 2 years of therapy (Table 6 and Figure 3B). The overall flow of patients with HoFH who were at target at the 24-month time point throughout follow-up is also depicted in Figure S3B. Fourteen patients with HoFH (51.9%) who failed to achieve the therapeutic target after 6 months also fail to reach the target at the 24-month observation; it is noteworthy that 8 of them (29.6%) discontinued treatment before the 24-month time point.

Sensitivity Analysis

Variable balancing showed that baseline characteristics of patients included in the cohort were substantially comparable to those included in the sensitivity analysis (*data not shown*). This step has not been carried out on patients with HoFH because of the reduced numerosity of the data set.

Among patients with HeFH belonging to the sensitivity cohort, 1590 (90.2%), 1542 (87.5%), 1504 (85.3%), and 1405 (76.9%) patients were observed at

Table 5. Adherence and Persistence of Patients With HoFH to PCSK9i Treatment at the Different Time Points

Adherence and persistence	6mo	12mo	18mo	24mo
Persistence	32 (88.89)	30 (83.33)	27 (75.00)	27 (75.00)
Adherence=100%	9 (28.13)	5 (17.24)	2 (7.41)	1 (4.17)
Adherence ≥80%	27 (84.38)	28 (96.55)	25 (92.59)	24 (100.00)
Average adherence, %	92.2	91.1	91.8	92.5
Median adherence, %	95.5	92.0	91.8	92.7

Data are represented as number (percentage). This table represents adherence and persistence to PCSK9i in HoFH at the different time points up to 24 months. Adherence has been calculated only for patients observed at the specified time points. HoFH indicates homozygous familial hypercholesterolemia; and PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor.

Table 6. Plasma Lipids and Concomitant Background Lipid-Lowering Medications at the Different Time Points in Patients With HoFH Receiving PCSK9i

	Baseline	6 mo	12 mo	18 mo	24 mo	Trend [†]
Plasma lipids, mg/dL	(n=36)	(n=32)	(n=29)	(n=27)	(n=24)	
Total cholesterol	328.8 (104.9)	209.3 (82.8) [†]	184.7 (86.5) [†]	175.5 (61.2) [†]	170.5 (66.1) [†]	0.000 [†]
LDL-C	248.0 (105.0)	133.3 (82.8) [†]	113.3 (76.7) [†]	102.5 (56.2) [†]	95.1 (60.2) [†]	0.000 [†]
HDL-C	50.8 (10.7)	51.0 (14.0)	48.6 (16.3)	49.3 (11.1)	50.3 (12.8)	0.343
Non-HDL-C	278.0 (104.5)	158.3 (83.7) [†]	136.1 (79.2) [†]	126.1 (58.1) [†]	120.2 (64.6) [†]	0.000 [†]
Total triglycerides	150.0 (75.8)	126.0 (57.8)	113.8 (46.3) [†]	118.0 (72.7) [†]	125.0 (80.4) *	0.038 *
Target achievement						
% Reduction of LDL-C from baseline		43.89 (29.2)	48.93 (28.8)	53.03 (22.7)	57.55 (25.3)	
Subjects reaching LDL-C goals, n (%)		5 (15.63)	5 (17.24)	8 (29.63)	9 (37.50)	
LLT by intensity, n (%)						
None/low to moderate	10 (27.78)	11 (34.38)	13 (44.83)	13 (48.15) [†]	10 (41.67)	0.139
High/maximal	26 (72.28)	21 (65.62)	16 (55.17)	14 (51.85) [†]	14 (58.33)	0.139
Fibrates	0 (0.00)	0 (0.00)	1 (3.45)	1 (3.70)	1 (4.17)	0.214
PUFA-N3	2 (5.56)	0 (0.00) [†]	1 (3.45)	2 (7.41)	2 (8.33)	0.582
LA	6 (16.67)	1 (6.25)	2 (6.90)	3 (11.11)	3 (12.50)	0.558

Data are reported as mean (SD). Intensity of lipid-lowering therapies has been classified as reported in the Methods section. Data are reported for the 6-, 12-, 18-, and 24-month time points. Significance indicates comparisons with baseline values in patients reporting values at all time points. HDL-C indicates high-density lipoprotein cholesterol; HeFH, heterozygous familial hypercholesterolemia; HoFH, homozygous familial hypercholesterolemia; LA, low-density lipoprotein apheresis; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; and PUFA-N3, polyunsaturated fatty acids n-3.

*Indicates 95% significance.

[†]Indicates 99% significance of the difference with baseline values.

[‡]Indicates comparisons with baseline values in patients reporting values at all time points.

the 6-, 12-, 18-, and 24-month time points, respectively (Table S4). Changes in LDL-C observed in this cohort were very similar to those observed in the main analysis. In particular, at the 6-month time point, LDL-C levels dropped by 56.2±32.3% to 86.0±70.5 mg/dL (95% CI, 82.5–89.5 mg/dL), with a mean absolute reduction of 110.1 mg/dL, and slightly increased at the 24-month observation, where mean LDL-C was 80.3±47.7 mg/dL (95% CI, 77.8–82.8 mg/dL) generating a reduction of 58.3±20.8% (Table S5). Also, the distribution of percentage reduction of LDL-C in the sensitivity cohort was comparable with that obtained in the main analysis (*data not shown*).

As well as for patients with HeFH, the results of sensitivity analysis in HoFH corroborated the results of main analysis in this group. The 2-year persistence to therapy in HoFH was 76% with a median and mean percentage of treatment adherence both >90% across the whole follow-up and high-adherence patients are steadily above 80% (Table S6); a slight change in the pattern of background treatments was observed during follow-up, with a higher rate of patients taking no or low-intensity LLT, at the expense of high- or max-intensity LLTs (Table S7). In this cohort, we detected an LDL-C decrease of 43.5±27.9% to 136.3±81.4 mg/dL (95% CI, 109.5–163.0 mg/dL) with a mean absolute

reduction of 115.7 mg/dL. At the last control, the mean LDL-C was 99.6±59.5 mg/dL (95% CI, 77.0–122.2 mg/dL), corresponding to a decrease of 57.6±23.2% (Table S7).

DISCUSSION

This retrospective, observational study covering the 4-year use in Italy of PCSK9i after their approval in 2017 represents, to the best of our knowledge, the most extensive survey on the use of evolocumab and alirocumab in patients with FH in the real-world setting.

Overall, the characteristics of 2484 patients with HeFH and 62 patients with HoFH included into the AIFA registry well recapitulated the main clinical features of FH usually seen in clinical practice.^{4–9} Although the diagnosis of HeFH was mainly based on clinical criteria, the reported DLCN score (mean 12 points) well reassures that the enrolled patients really had HeFH. Indeed, it has been reported that a DLCN score >8 points predict the presence of FH-causative monogenic mutations in about 90% of Italian patients with clinically suspected FH.^{28,33} Nevertheless, genetic testing was available in about 18% of patients with HeFH and 40% of patients with HoFH. As expected, most patients were carrying a mutation in the *LDLR* gene.^{28,33}

In addition, the pattern of background LLTs was like that reported in other HeFH cohorts, where about 60% of patients were taking highly effective LLTs.⁹ Moreover, 46% of patients with HeFH enrolled into the registry were not receiving LLTs or were prescribed with low-intensity statins or ezetimibe monotherapy, due to statin intolerance. The limited use of high potency LLTs at baseline, together with the eligibility criteria for PCSK9i therapy imposed by the regulatory agency AIFA (see above), may represent the explanation why patients showed the markedly elevated LDL-C concentration at baseline (197.7 mg/dL). Although this value was higher than that reported in clinical trials with PCSK9is involving HeFH,^{12,13} it was comparable with that reported in patients with HeFH included in the ODYSSEY APPRISE (Safety, Tolerability, and Effect of Alirocumab in High Cardiovascular Risk Patients With Severe Hypercholesterolemia Not Adequately Controlled With Conventional Lipid-Modifying Therapies) study,³⁴ a smaller prospective, single-arm study with alirocumab aimed at describing the real-world use of this medication. Overall, these findings strongly suggest that in the initial period of PCSK9i availability in Italy, physicians tended to consider eligible for these drugs patients with HeFH with severe, resistant forms of hypercholesterolemia or without other therapeutic options.

It must be noted that the use of LA in HoFH was significantly lower than that expected.^{35,36} This might have 2 possible explanations. One is that only patients who could not have access to LA were referred for PCSK9i treatment or that in the real world there was a poor attitude of physicians to combine LA with PCSK9is in the management of HoFH. We favor the first explanation given the limited number of lipid centers in Italy able to offer the LA treatment to HoFH and the complexity of this procedure.³⁵ Whatever the reason, patients with HoFH started evolocumab therapy with a baseline LDL-C level of 245.6 ± 108.3 mg/dL. This value is lower than that reported in previous clinical trials evaluating PCSK9is in well-characterized HoFH cohorts.^{16,17} This may raise concerns about the accuracy of HoFH diagnosis in patients included in the registry. Even though almost 40% of patients with HoFH were genotyped, we cannot exclude that patients with more severe manifestations of HeFH (thus clinically overlapping the HoFH phenotype) have been included in this group.

Another interesting observation derived from the present analysis is that persistence and adherence to PCSK9i therapy were remarkably high in real practice. Despite the fact that the scope of AIFA registries is not to provide a systematic collection of data on adverse events and it was impossible to produce a detailed analysis of safety from the present analysis, these data suggest that patients manifest an excellent acceptance of this injectable lipid-modifying treatment. It

must be noted that this is absolutely in line with what has been observed in other studies describing the use of PCSK9is in FH.^{37–39} Furthermore, our data indicate that the addition of PCSK9i therapy produced some changes in the prescription of conventional background LLTs. In fact, the prescription rate of the high-intensity/maximally tolerated LLTs at 12 months decreased from 56% to 42% among HeFH and from 72% to 55% among HoFH. Whether this could reflect the attitude of attending physicians to attenuate the intensity of LLT in the presence of PCSK9is remains a plausible hypothesis, even if it requires further investigations.

Our main analysis demonstrated that in patients with HeFH, the addition of PCSK9is resulted in an overall 56% decrease in LDL-C levels, a benefit that remained consistent also in the sensitivity analysis. This value is comparable with that reported in randomized controlled clinical trials^{12–15} as well as in the 636 HeFH enrolled in the ODYSSEY APPRISE study,³⁴ a nonrandomized trial exploring the real-world use of alirocumab 75 or 150 mg every 2 weeks, reporting a 53.4% LDL-C decrease after 12 weeks. More recently, similar LDL-lowering results were reported in the cohort of the Spanish Familial Hypercholesterolemia Cohort Study where patients with HeFH were followed for a median follow-up of 3.7 years.³⁹ Of note, our analysis showed a large interindividual variability in the real-world response to PCSK9is. The concerns for large interindividual variability in the LDL-C-lowering effects of PCSK9is have already been reported in other studies.^{40–42} Interindividual variation in LDL-C level reduction is also known with statins^{9,27} and has been attributed to demographic, phenotypic, and genetic factors. We can speculate that other potential contributors to the interindividual variability with PCSK9is might include concomitant use of drugs known to influence lipid metabolism, errors in study drug administration or maintenance, and laboratory result discrepancies. However, a more precise identification of these factors is not possible on the basis of the available data.

Despite the marked drop in LDL-C, only 42% of patients with HeFH attained the recommended European Atherosclerosis Society/European Society of Cardiology 2019 individual LDL-C targets (<55 mg/dL in secondary prevention and <70 mg/dL in primary prevention).² This value appears to be significantly lower than that observed in randomized clinical trials where, however, the 2016 European Atherosclerosis Society/European Society of Cardiology targets (<100 mg/dL in primary and $<70\%$ in secondary prevention) were usually considered.^{12–15} Although we cannot exclude that the severity of the underlying *LDLR* defect has a role, the lack of adherence to therapy or a high prevalence of hyporesponders can be excluded in explaining this finding. Therefore, we tend to associate this limited

ability of PCSK9i therapy to bring many patients with HeFH to the LDL-C target because of the high LDL-C levels at the initiation of treatment. In line with this association, baseline LDL-C was the most important negative predictor of target attainment in our HeFH cohort. Nevertheless, present data indicate that, despite their high efficacy, PCSK9is are not the solution for all patients with FH. Indeed, other studies are under way to evaluate the effectiveness of other drugs to optimize treatment in patients with severe HeFH.⁴³

The use of evolocumab in HoFH was associated with a nadir drop of 57.6% in LDL-C concentration, an amount that is much more pronounced than that reported in controlled clinical trials enrolling HoFH.^{16,17} A clear explanation for this discrepancy is not at hand. One possibility might be that patients classified with HoFH not genotyped might have HeFH carrying only 1 mutated allele but showing a very severe LDL-C phenotype. Another possible explanation might be that included patients have biallelic mutations with a moderate impact on LDLR residual functions.

Limitations

The strengths and limitations of our study merit consideration. Our study builds on a nationwide registry in which all patients who were prescribed with PCSK9is in Italy had to be included. The fact that prescriptions covered a large time interval (14 or 26 weeks) made it difficult to establish a systematic follow-up, thus generating potential evaluation biases. This has led to the need to define observational windows, in which the values of interest should be observed for a patient to be included in each time point. On the other hand, this implies that some patients have been discarded from the main analysis because of a prescription timing that was not compatible with the selected time points, thus generating potential follow-up biases. To comply with this difficulty, we decided to conduct a comprehensive sensitivity analysis that has shown that prescription timings are not associated with baseline patient features, which indicates that the results are not supposed to be influenced by missing observations.

Patient persistence and adherence might have been overestimated, as the analysis is focused specifically on patients with consistent prescription timing that were observed regularly across time: a patient who has skipped an observation because of poor adherence was not included in the analysis.

The registries collected a well-defined data set from specialized secondary/tertiary centers with expertise in FH care. In addition, the registries were carefully managed to ensure that the highest-quality data were obtained. Furthermore, physician biases in the choice of background LLT should not have influenced the efficacy data of PCSK9i therapy. Additional limitations of

this registry-based study include the lack of comparative control. In any case, it must be recognized that this collection of data represents the description of the action of these drugs that comes closest to their use in the real world.

CONCLUSIONS

In Italy, due to reimbursement limitations, only the most severe FH patients had access to PCSK9i therapy as demonstrated by high baseline LDL-C levels. The persistence and adherence to this therapy were high, and the prescription of evolocumab and alirocumab resulted in an LDL-C reduction in HeFH (~60%) that was like that seen in controlled clinical trials and higher than that expected in HoFH, probably due to a lower level of diagnostic accuracy in this latter group. Although the real-world data on the use of PCSK9is in Italy confirmed the effectiveness of these drugs to manage LDL-C even in the more severe forms of hypercholesterolemia, ~2 of 5 patients with HeFH and 2 of 6 patients with HoFH reached the LDL-C targets. However, it must be recognized that the generalizability of these findings can be problematic. Indeed, the eligibility criteria for initiation of PCSK9is differ in each country, and in Italy it has been set for FH to a rather restrictive LDL-C threshold (>130 mg/dL). It can be assumed that a lower threshold might have changed that result. Nevertheless, the achievement of European Atherosclerosis Society/European Society of Cardiology LDL-C targets in monogenic hypercholesterolemia remains challenging even with the use of effective drugs such as PCSK9is, highlighting that the optimal LDL-lowering management of these patients would probably require the combination of multiple LLTs.

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Supplemental Material

Tables S1–S7

Figures S1–S3

REFERENCES

- Tokgozoglul L, Kayikcioglu M. Familial hypercholesterolemia: global burden and approaches. *Curr Cardiol Rep*. 2021;23:151. doi: 10.1007/s11886-021-01565-5
- Authors/Task Force Members; ESC Committee for Practice Guidelines (CPG); ESC National Cardiac Societies. ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Atherosclerosis*. 2019;290:140–205. doi: 10.1016/j.atherosclerosis.2019.08.014
- Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, Himmelfarb CD, Khera A, Lloyd-Jones D, McEvoy JW, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;140:e563–e595. doi: 10.1161/CIR.0000000000000677
- Pijlman AH, Huijgen R, Verhagen SN, Imholz BP, Liem AH, Kastelein JJ, Abbink EJ, Stalenhoef AF, Visseren FL. Evaluation of cholesterol lowering treatment of patients with familial hypercholesterolemia: a large cross-sectional study in The Netherlands. *Atherosclerosis*. 2010;209:189–194. doi: 10.1016/j.atherosclerosis.2009.09.014
- Ceska R, Latkovskis G, Ezhov MV, Freiburger T, Lalic K, Mitchenko O, Paragh G, Petrulioniene Z, Pojskic B, Raslova K, et al. The impact of the international cooperation on familial hypercholesterolemia screening and treatment: results from the ScreenPro FH project. *Curr Atheroscler Rep*. 2019;21:36. doi: 10.1007/s11883-019-0797-3
- Bérard E, Bongard V, Haas B, Dallongeville J, Moitry M, Cottel D, Ruidavets JB, Ferrières J. Prevalence and treatment of familial hypercholesterolemia in France. *Can J Cardiol*. 2019;35:744–752. doi: 10.1016/j.cjca.2019.02.013
- Vrablik M, Raslová K, Vohnout B, Blaha V, Satny M, Kyselak O, Vaclova M, Urbanek R, Maskova J, Soska V, et al. Real-life LDL-C treatment goals achievement in patients with heterozygous familial hypercholesterolemia in the Czech Republic and Slovakia: results of the PLANET registry. *Atherosclerosis*. 2018;277:355–361. doi: 10.1016/j.atherosclerosis.2018.08.008
- Rizos CV, Elisaf MS, Skoumas I, Tziomalos K, Kotsis V, Rallidis L, Garoufi A, Athyros VG, Skolidis E, Kolovou G, et al. Characteristics and management of 1093 patients with clinical diagnosis of familial hypercholesterolemia in Greece: data from the Hellenic Familial Hypercholesterolemia Registry (HELLAS-FH). *Atherosclerosis*. 2018;277:308–313. doi: 10.1016/j.atherosclerosis.2018.08.017
- D'Erasmo L, Commodari D, Di Costanzo A, Minicocci I, Polito L, Ceci F, Montali A, Maranghi M, Arca M. Evolving trend in the management of heterozygous familial hypercholesterolemia in Italy: a retrospective, single center, observational study. *Nutr Metab Cardiovasc Dis*. 2020;30:2027–2035. doi: 10.1016/j.numecd.2020.06.028
- Bajaj A, Cuchel M. Homozygous familial hypercholesterolemia: what treatments are on the horizon? *Curr Opin Lipidol*. 2020;31:119–124. doi: 10.1097/MOL.0000000000000677
- D'Erasmo L, Gallo A, Cefalù AB, Di Costanzo A, Saheb S, Giammanco A, Averna M, Buonaiuto A, Iannuzzo G, Fortunato G, et al. Long-term efficacy of lipoprotein apheresis and lomitapide in the treatment of homozygous familial hypercholesterolemia (HoFH): a cross-national retrospective survey. *Orphanet J Rare Dis*. 2021;16:381. doi: 10.1186/s13023-021-01999-8
- Kastelein JJ, Ginsberg HN, Langslet G, Hovingh GK, Ceska R, Dufour R, Blom DJ, Civeira F, Krempf M, Lorenzato C, et al. ODYSSEY FH I and FH II: 78-week results with alirocumab treatment in 735 patients with heterozygous familial hypercholesterolemia. *Eur Heart J*. 2015;36:2996–3003. doi: 10.1093/eurheartj/ehv370
- Raal FJ, Stein EA, Dufour R, Turner T, Civeira F, Burgess L, Langslet G, Scott R, Olsson AG, Sullivan D, et al. PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolemia (RUTHERFORD-2): a randomized, double-blind, placebo-controlled trial. *Lancet*. 2015;385:331–340. doi: 10.1016/S0140-6736(14)61399-4
- Ginsberg HN, Rader DJ, Raal FJ, Guyton JR, Baccara-Dinet MT, Lorenzato C, Pordy R, Stroes E. Efficacy and safety of alirocumab in patients with heterozygous familial hypercholesterolemia and LDL-C of 160 mg/dL or higher. *Cardiovasc Drugs Ther*. 2016;30:473–483. doi: 10.1007/s10557-016-6685-y
- Hovingh GK, Raal FJ, Dent R, Stefanutti C, Descamps O, Masana L, Lira A, Bridges I, Coll B, Sullivan D. Long-term safety, tolerability, and efficacy of evolocumab in patients with heterozygous familial hypercholesterolemia. *J Clin Lipidol*. 2017;11:1448–1457. doi: 10.1016/j.jacl.2017.09.003
- Blom DJ, Harada-Shiba M, Rubba P, Gaudet D, Kastelein JJP, Charnig MJ, Pordy R, Donahue S, Ali S, Dong Y, et al. Efficacy and safety of alirocumab in adults with homozygous familial hypercholesterolemia: the ODYSSEY HoFH trial. *J Am Coll Cardiol*. 2020;76:131–142. doi: 10.1016/j.jacc.2020.05.027
- Raal FJ, Honarpour N, Blom DJ, Hovingh GK, Xu F, Scott R, Wasserman SM, Stein EA; TESLA Investigators. Inhibition of PCSK9 with evolocumab in homozygous familial hypercholesterolemia (TESLA part B): a randomized, double-blind, placebo-controlled trial. *Lancet*. 2015;385:341–350. doi: 10.1016/S0140-6736(14)61374-X
- Hlatky MA, Kazi DS. PCSK9 inhibitors: economics and policy. *J Am Coll Cardiol*. 2017;70:2677–2687. doi: 10.1016/j.jacc.2017.10.001
- Rane PB, Patel J, Harrison DJ, Shepherd J, Leith A, Bailey H, Piercy J. Patient characteristics and real-world treatment patterns among early users of PCSK9 inhibitors. *Am J Cardiovasc Drugs*. 2018;18:103–108. doi: 10.1007/s40256-017-0246-z
- Blais JE, Wei Y, Knapp M, Wong ICK, Wei L, Chan EW. Trends in PCSK9 inhibitor utilization in the United States, Europe, and other countries: an analysis of international sales data. *Am Heart J*. 2022;248:13–20. doi: 10.1016/j.ahj.2022.02.008
- Olimpieri PP, Di Lenarda A, Mammarella F, Gozzo L, Cirilli A, Cuomo M, Gulizia MM, Colivicchi F, Murri G, Gabrielli D, et al. Non-vitamin K antagonist oral anticoagulation agents in patients with atrial fibrillation: insights from Italian monitoring registries. *Int J Cardiol Heart Vasc*. 2020;26:100465. doi: 10.1016/j.ijcha.2019.100465
- Palladini G, Celant S, Milani P, Summa V, Affronti G, Olimpieri PP, Petraglia S, Foli A, Nuvolone M, Merlini G, et al. A nationwide prospective registry of bortezomib-based therapy in light chain (AL) amyloidosis. *Leuk Lymphoma*. 2022;63:205–211. doi: 10.1080/10428194.2021.1971215
- Attivazione web e pubblicazione schede di monitoraggio Registro Praluent (CVD), [aifa.gov](https://www.aifa.gov.it/en/-/attivazione-web-e-pubblicazione-schede-di-monitoraggio-registro-repatha-est), 13 December 2019, Accessed 8 October, 2023. <https://www.aifa.gov.it/en/-/attivazione-web-e-pubblicazione-schede-di-monitoraggio-registro-repatha-est>
- Attivazione web e pubblicazione schede di monitoraggio Registro Praluent (CVD), [aifa.gov](https://www.aifa.gov.it/en/-/attivazione-web-e-pubblicazione-schede-di-monitoraggio-registro-praluent-cvd), 16 April 2022, Accessed 8 October, 2023. <https://www.aifa.gov.it/en/-/attivazione-web-e-pubblicazione-schede-di-monitoraggio-registro-praluent-cvd>
- Modifica Registri di monitoraggio REPATHA E PRALUENT (INIBITORI DI PCSK-9), [aifa.gov](https://www.aifa.gov), 16 June 2022, Accessed 8 October, 2023.

- https://www.aifa.gov.it/documents/20142/961234/Determina_435-2022_Repatha.pdf
26. Modifica Registri di monitoraggio REPATHA E PRALUENT (INIBITORI DI PCSK-9), [aifa.gov](https://www.aifa.gov.it/documents/20142/961234/Determina_434-2022_Praluent.pdf), 16 June 2022, Accessed 8 October, 2023. https://www.aifa.gov.it/documents/20142/961234/Determina_434-2022_Praluent.pdf
 27. D'Erasmio L, Minicocci I, Di Costanzo A, Pigna G, Commodari D, Ceci F, Montali A, Brancato F, Stanca I, Nicolucci A, et al. Clinical implications of monogenic versus polygenic hypercholesterolemia: long-term response to treatment, coronary atherosclerosis burden, and cardiovascular events. *J Am Heart Assoc*. 2021;10:e018932. doi: 10.1161/JAHA.120.018932
 28. Banach M, Mikhailidis DP. Statin intolerance: some practical hints. *Cardiol Clin*. 2018;36:225–231. doi: 10.1016/j.ccl.2017.12.004
 29. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem*. 1972;18:499–502. doi: 10.1093/clinchem/18.6.499
 30. Breiman L. Random forests. *Mach Learn*. 2001;45:5–32. doi: 10.1023/A:1010933404324
 31. R Core Team. *R: A Language and Environment for Statistical Computing*. Vienna: R Foundation for Statistical Computing; 2021. Accessed August 20, 2023. <https://www.R-project.org/>
 32. Wickham H. ggplot2, elegant graphics for data analysis. In: *Use R!* Springer Link; 2016:241–253. doi: 10.1007/978-3-319-24277-4
 33. Casula M, Olmastroni E, Pirillo A, Catapano AL; Members of the LIPIGEN STEERING COMMITTEE; Principal Investigators: Coordinator center; Participant centers; Participant laboratories; Collaborators; Study Central Laboratory and Analysis Group. Evaluation of the performance of Dutch lipid clinic network score in an Italian FH population: the LIPIGEN study. *Atherosclerosis*. 2018;277:413–418. doi: 10.1016/j.atherosclerosis.2018.08.013
 34. Gaudet D, López-Sendón JL, Aversa M, Bigot G, Banach M, Letierce A, Loy M, Samuel R, Manvelian G, Batsu I, et al. Safety and efficacy of alirocumab in a real-life setting: the ODYSSEY APPRISE study. *Eur J Prev Cardiol*. 2022;28:1864–1872. doi: 10.1093/eurjpc/zwaa097
 35. Bertolini S, Calandra S, Arca M, Aversa M, Catapano AL, Tarugi P; Italian Study Group of Homozygous Familial Hypercholesterolemia. Homozygous familial hypercholesterolemia in Italy: clinical and molecular features. *Atherosclerosis*. 2020;312:72–78. doi: 10.1016/j.atherosclerosis.2020.08.027
 36. Pottle A, Thompson G, Barbir M, Bayly G, Cegla J, Cramb R, Dawson T, Eatough R, Kale V, Neuwirth C, et al. Lipoprotein apheresis efficacy, challenges and outcomes: a descriptive analysis from the UK lipoprotein apheresis registry, 1989–2017. *Atherosclerosis*. 2019;290:44–51. doi: 10.1016/j.atherosclerosis.2019.09.006
 37. Guedeney P, Sorrentino S, Giustino G, Chapelle C, Laporte S, Claessen BE, Ollier E, Camaj A, Kalkman DN, Vogel B, et al. Indirect comparison of the efficacy and safety of alirocumab and evolocumab: a systematic review and network meta-analysis. *Eur Heart J Cardiovasc Pharmacother*. 2021;7:225–235. doi: 10.1093/ehjcvp/pvaa024
 38. Farnier M, Hovingh GK, Dufour R, Baccara-Dinet MT, Din-Bell C, Manvelian G, Guyton JR. Long-term safety and efficacy of alirocumab in patients with heterozygous familial hypercholesterolemia: an open-label extension of the ODYSSEY program. *Atherosclerosis*. 2018;278:307–314. doi: 10.1016/j.atherosclerosis.2018.08.036
 39. Alonso R, Arroyo-Olivares R, Muñoz-Grijalvo O, Díaz-Díaz JL, Muñoz-Torrero JS, Romero MJ, de Andrés R, Zambón D, Mañas MD, Fuentes-Jiménez F, et al. Persistence with long-term PCSK9 inhibitor treatment and its effectiveness in familial hypercholesterolemia: data from the SAFEHEART study. *Eur J Prev Cardiol*. 2023;30:320–328. Erratum. 2023;30:370.
 40. Ridker PM, Tardif JC, Amarenco P, Duggan W, Glynn RJ, Jukema JW, Kastelein JJP, Kim AM, Koenig W, Nissen S, et al. Lipid-reduction variability and antidrug-antibody formation with bococizumab. *N Engl J Med*. 2017;376:1517–1526. doi: 10.1056/NEJMoa1614062
 41. Qamar A, Giugliano RP, Keech AC, Kuder JF, Murphy SA, Kurtz CE, Wasserman SM, Sever PS, Pedersen TR, Sabatine MS. Interindividual variation in low-density lipoprotein cholesterol level reduction with evolocumab: an analysis of FOURIER trial data. *JAMA Cardiol*. 2019;4:59–63. doi: 10.1001/jamacardio.2018.4178
 42. Ray KK, Bruckert E, Peronne-Filardi P, Ebenbichler C, Vogt A, Bridges I, Sibartie M, Dhalwani N. Long-term persistence with evolocumab treatment and sustained reductions in LDL-cholesterol levels over 30 months: final results from the European observational HEYMANS study. *Atherosclerosis*. 2023;366:14–21. doi: 10.1016/j.atherosclerosis.2023.01.002
 43. Rosenson RS. Existing and emerging therapies for the treatment of familial hypercholesterolemia. *J Lipid Res*. 2021;62:100060. doi: 10.1016/j.jlr.2021.100060