




Persistence with long-term PCSK9 inhibitor treatment and its effectiveness in familial hypercholesterolaemia: data from the SAFEHEART study

Rodrigo Alonso ^{1,2*}, Raquel Arroyo-Olivares¹, Ovidio Muñoz-Grijalvo ³, Jose Luis Díaz-Díaz⁴, Juan Sanchez Muñoz-Torrero⁵, Manuel J. Romero⁶, Raimundo de Andrés⁷, Daniel Zambón⁸, María Dolores Mañas⁹, Francisco Fuentes-Jiménez ¹⁰, Rocío Aguado¹¹, Pilar Alvarez-Baños¹², Francisco Arrieta¹³, Pablo Gonzalez-Bustos¹⁴, José Cepeda¹⁵, Mercedes Martin-Ordiales¹⁶, Daniel Mosquera¹⁷, Alfredo Michan¹⁸, Leopoldo Perez de Isla¹⁹, Rosa Argueso²⁰, and Pedro Mata^{1*} on behalf of SAFEHEART investigators

¹Fundación Hipercolesterolemia Familiar, C/General Álvarez de Castro 14, 28010 Madrid, Spain; ²Center for Advanced Metabolic Medicine and Nutrition, Santiago de Chile, Fundación hipercolesterolemia Familiar, Madrid, Spain; ³Department of Internal Medicine, Hospital Virgen del Rocío, Sevilla, Spain; ⁴Department of Internal Medicine, Hospital Abente y Lago, A Coruña, Spain; ⁵Department of Internal Medicine, Hospital San Pedro de Alcántara, Cáceres, Spain; ⁶Department of Internal Medicine, Hospital Infanta Elena, Huelva, Spain; ⁷Department of Internal Medicine, Fundación Jiménez Díaz, Madrid, Spain; ⁸Lipid Unit, Hospital Clinic, Barcelona, Spain; ⁹Department of Internal Medicine, Hospital Universitario, Ciudad Real, Spain; ¹⁰Maimonides Biomedical Research Institute of Cordoba (IMIBIC), University of Cordoba, Reina Sofia University Hospital, CIBEROBn, Córdoba, Spain; ¹¹Department of Endocrinology, Hospital General de León, León, Spain; ¹²Department of Endocrinology, Hospital Universitario de Burgos, Burgos, Spain; ¹³Department of Endocrinology, Hospital Ramón y Cajal, Madrid, Spain; ¹⁴Department of Internal Medicine, Hospital Universitario Virgen de las Nieves, Granada, Spain; ¹⁵Department of Internal Medicine, Hospital Comarcal Vega Baja, Orihuela, Spain; ¹⁶Department of Internal Medicine, Hospital Universitario, Salamanca, Spain; ¹⁷Department of Internal Medicine, Hospital San Pedro, Logroño, Spain; ¹⁸Department of Internal Medicine, Hospital de Jerez, Jerez, Spain; ¹⁹Department of Cardiology, Hospital Clínico San Carlos, IDISSC, Madrid, Spain; and ²⁰Department of Endocrinology, Hospital Universitario Lucus Augusti, Lugo, Spain

Received 24 August 2022; revised 14 November 2022; accepted 16 November 2022; online publish-ahead-of-print 23 November 2022

Aims

Most heterozygous familial hypercholesterolaemia (FH) patients require intensive lipid-lowering therapy (LLT) including PCSK9 inhibitors (PCSK9is) to reach current low-density lipoprotein cholesterol (LDL-C) goals. Persistence with chronic treatment is important to reduce the burden of atherosclerotic cardiovascular disease. We analysed persistence, efficacy, and impact on quality of life (QoL) of PCSK9i in FH patients in clinical practice setting.

Methods and results

Spanish Familial Hypercholesterolaemia Cohort Study (SAFEHEART) is an open, prospective study in genetically defined FH patients in Spain. Patients ≥ 18 years of age ($n = 696$, 46% females) on stable LLT treated with PCSK9i were analysed. Median LDL-C at starting PCSK9i was 145 mg/dL [interquartile range (IQR), 123–177], 3.8 mmol/L (IQR 3.2–4.6). After a median follow up of 3.7 years (IQR 2.3–4.8), 27 patients (4%) discontinued PCSK9i treatment: 5 temporarily (0.7%) and 22 permanently (3.2%). Persistence with PCSK9i was 96.1% in the whole period. Median LDL-C levels and % LDL-C reduction attained after 1 year of treatment and in the last follow-up visit were 63 mg/dL (IQR 43–88), 1.6 mmol/L (IQR 1.1–2.23); 61 mg/dL (IQR 44–82), 1.6 mmol/L (IQR 1.1–2.1); 57.6% (IQR 39.5–69); and 58% (IQR 44–68), respectively. 2016 and 2019 ESC/EAS LDL-C goals were attained by 77 and 48% of patients, respectively, at the last follow-up visit ($P < 0.001$). Mean QoL score increased slightly in the first year and remained stable.

* Corresponding authors. Tel: +34915042206, Emails: rodrigoalonsok@gmail.com; pmata@colesterolfamiliar.org

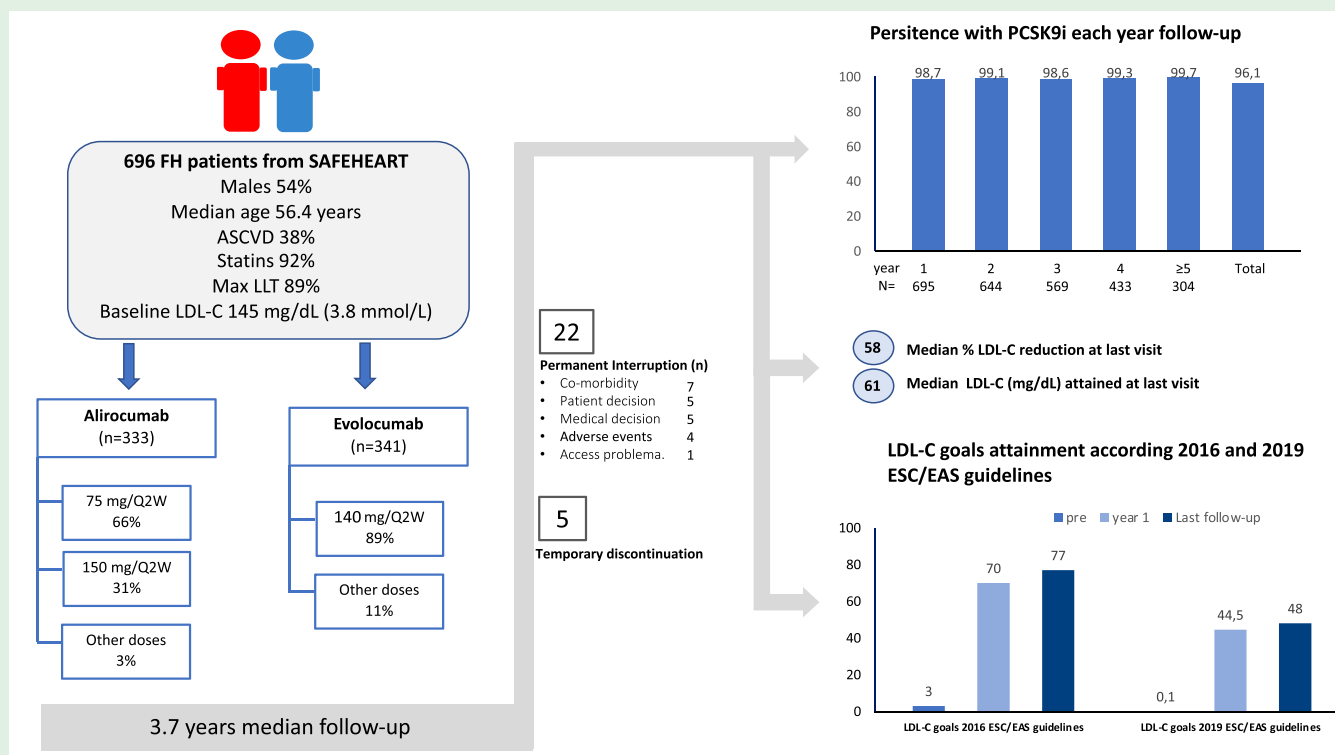
© The Author(s) 2022. Published by Oxford University Press on behalf of the European Society of Cardiology. This is an Open Access article distributed under the terms of the Creative Commons Attribution- Non-Commercial License (<https://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

Conclusion

Long-term persistence with PCSK9i in FH patients is very high, with a good QoL. Effectiveness in LDL-C reduction and LDL-C goal achievement dramatically improved with PCSK9i in this high-risk population in clinical practice setting.

Trial registration

ClinicalTrials.gov number NCT02693548.

Graphical Abstract

Persistence with long-term PCSK9 inhibitors treatment and its effectiveness in familial hypercholesterolaemia.

Keywords

Familial hypercholesterolaemia • Lipid-lowering treatment • Statins • PCSK9 inhibitors • LDL-C targets • Persistence

Introduction

Heterozygous familial hypercholesterolaemia (FH), an autosomal codominant disorder is the most common genetic condition associated with premature atherosclerotic cardiovascular disease (ASCVD).^{1,2} Recent European Guidelines for the management of dyslipidaemias considered FH patients with ASCVD or with the presence of a major cardiovascular risk factor (CVRF) to be at very high risk, and those without CVRF to be at high risk.³ According to this classification, low-density lipoprotein cholesterol (LDL-C) goals are lower than those recommended in the 2016 ESC/EAS guidelines.⁴ For the very high-risk group, an LDL-C < 55 mg/dL (<1.4 mmol/L) and 50% reduction in LDL-C is recommended, and for the high-risk group, LDL-C should be <70 mg/dL (<1.8 mmol/L) and a 50% reduction from baseline.³ To achieve these goals most FH patients require to use high-intensity statins with ezetimibe.¹⁻⁴ However, different studies have shown that <20% of FH patients achieve LDL-C goals despite the use of maximally tolerated high-intensity statins plus ezetimibe in different clinical settings.⁵⁻⁷ The incorporation of PCSK9 inhibitors (PCSK9is) to the treatment of FH has significantly contributed to a better control of patients, since

they produce an additional reduction of LDL-C, up to 60% on top of statins, leading to more patients achieving therapeutic goals.⁸⁻¹¹

Persistence with and adherence to chronic use of lipid-lowering therapies (LLTs) is important to achieve the full effect of medications in LDL-C reduction and recommended LDL-C goals. Outcomes can be affected by how well patients take their medication (adherence), and by how long they take it (persistence). Few studies have analysed the persistence with statin treatment in FH and showed that 30–50% had adherence issues.¹²⁻¹⁴ Regarding PCSK9i, some studies have shown that almost 40% of patients discontinued therapy during the first 6 months of initiation explained in part to cost and access to medication.^{15,16} Studies analysing persistence with PCSK9i treatment in FH in a clinical practice setting for a long term are lacking. On the other hand, although quality of life (QoL) has been analysed in FH patients,¹⁷ data on the impact that an intensive treatment with PCSK9i may have on QoL in FH are scarce.¹⁸

The aim of the present study was to assess persistence with PCSK9i (alirocumab and evolocumab), reasons for non-persistence, as well as to assess effectiveness of PCSK9i, and QoL in those patients who

persisted with therapy in a large cohort of FH patients in a clinical practice setting registered and followed up in the Spanish Familial Hypercholesterolaemia Cohort Study (SAFEHEART) study.

Methods

Patients

The SAFEHEART is an open, multicentre, nation-wide, long-term prospective study of a cohort of subjects with a molecular diagnosis of FH and their affected and non-affected relatives which was initiated in 2004. The design and methodology of the study have been previously described.¹⁹ Individuals are contacted once a year by the coordinating centre using a standardized telephone survey (STS) which asks about LLT patterns and tolerance, changes in lifestyle habits and medications, QoL, and the occurrence of cardiovascular events. Individuals were instructed that in the event of changing or discontinuing the LLT, they should write down the reason and date of interruption and then restart.

Blood analysis during the follow up is performed in local lipid units according to international recommendations and results sent to the coordinating centre. This study included all patients ≥ 18 years old with heterozygous FH who were prescribed a PCSK9i monoclonal antibody (alirocumab or evolocumab) since its approval in Spain in February 2016 until September 2021, and who have been treated at least 6 months with one of them. Patients who participated in randomized clinical trials with PCSK9i before 2016 were excluded from this analysis.

This study was approved by the local ethics committees, and all eligible subjects gave written informed consent.

PCSK9 inhibitor treatment

The choice of the particular PCSK9i and dosing regimen was at the discretion of the medical specialist and was based according to the Spanish National Health System reimbursement regulations for FH patients. In Spain, PCSK9is are delivered directly to the patient by the hospital pharmacy ensuring access to it. During the COVID-19 pandemic, those few patients who could not get their medication from the pharmacy, it was dispatched to their respective homes.

Variables and outcomes

Demographic and clinical variables including age, classic CVRF, physical examination, and LLT were included. LDL-C was estimated by means of the Friedewald formula. Lipid levels at inclusion, at Year 1 of follow up and the most recent lipid profile before the analysis from the last visit follow up were determined using standard techniques and selected for this study. Lipoprotein(a) levels were measured once at inclusion in the study with a turbidimetric method [Quantia Lp(a) 7K00-01] in a centralized laboratory.²⁰ Classification of LLT was defined as previously reported.⁷ The genetic diagnosis and molecular classification of FH were performed as previously described.¹⁹ The SAFEHEART risk equation was estimated in each subject at initiation of PCSK9i and in the last control of follow up.²¹ LDL-C goals were defined and analysed according to the 2016 and 2019 European Dyslipidaemia Guidelines.^{3,4}

Persistence with PCSK9 inhibitor treatment

Through the annual STS, patients were advised to report to the coordinating centre any change in PCSK9i treatment, specifically those related to access, delivery, administration period, dose, and reason for discontinuation. Individual persistence is reported as a dichotomous variable and is collectively determined as the percentage of patients staying on PCSK9i at the end of each year of follow up. A gap of >60 days without administration of PCSK9i during each year follow-up period was considered as discontinuation and thus the end of the persistence period.²²

Quality of life

The EuroQol 5D (EQ-5D) measurement in the Spanish language was used to measure health status perceived by patients at initiation of PCSK9i, and at Year 1 and in the last follow-up visit. The scale measures QoL on a 5-component scale including mobility, self-care, usual activities, pain/discomfort,

and anxiety/depression each one with 5 severity levels.²³ Besides, the EuroQol includes a 100-point score numeric visual analogue scale (EQ-VAS) providing a global assessment of their health being 100 the best and 0 the worst imaginable health. The EQ-VAS was categorized in a qualitative 5-level scale (poor <40 ; fair 41–53; good 54–76; very good 76–80, and excellent >80).²³

Statistical analysis

Statistical analyses were carried out with the STATA program, version 12.0 (Stata Corporation, College Station, TX, USA). Variables were analysed for a normal distribution with the Kolmogorov–Smirnov test. A descriptive analysis was carried out to report the number of cases and percentages for the qualitative variables, and the median and interquartile range (IQR) for the quantitative variables that did not follow a normal distribution. Comparisons of changes before and after initiation of PCSK9i were analysed using the Wilcoxon signed-rank test for quantitative variables and McNemar test for qualitative variables. Comparisons between independent groups were analysed with the Mann–Whitney U test for quantitative variables, and χ^2 test for qualitative variables. The association between PCSK9i treatment and LDL-C goal achievement as well as patient characteristics and CVRF including age, gender, body mass index, tobacco, hypertension, diabetes, LLT background, and LDL-C levels categorized as <130 , 130–159, and ≥ 160 mg/dL (<3.4 , 3.4–4.1, and ≥ 4.1 mmol/L) was first assessed by univariate logistic regression analysis. All significant variables were then included in a multivariable logistic regression analysis. A value of $P < 0.05$ was considered statistically significant.

Results

Over the study period, a total of 696 patients (46% females) from 3759 heterozygous FH individuals registered in the SAFEHEART initiated treatment with PCSK9i, 51% received evolocumab and 49% received alirocumab. Median age at initiation of therapy was 56.4 years (IQR 49–66), 38% had history of ASCVD, and 89% were on maximum tolerated LLT to reduce LDL-C $> 50\%$. Patients carrying-out a null allele variant were 50.4%. Other clinical characteristics before receiving PCSK9i of the individuals are shown in [Table 1](#). No differences in clinical characteristics and risk factors were observed between patients with evolocumab and alirocumab except a higher percentage of hypertension with alirocumab (29 vs. 22% with evolocumab, $P < 0.05$), and slightly higher total cholesterol and LDL-C levels in evolocumab group ($P < 0.05$; see [Supplementary material online, Table S1](#)). Background conventional LLT was statin plus ezetimibe in 503 cases (74.6%), statin monotherapy in 106 cases (17.5%), ezetimibe in 31 cases (4.6%), and no LLT in 34 cases (5.1%). There were no differences in background LLT between patients receiving alirocumab or evolocumab (data not shown). Median LDL-C levels at the initiation of treatment with PCSK9i were 145 mg/dL (IQR 123–177), 3.8 mmol/L (IQR 3.2–4.6). Median follow up was 3.7 years (IQR 2.3–4.8). Only one patient (59 years old female) died during the follow up.

PCSK9 inhibitor dosing, persistence, and switching

During the first year of follow up, there were no changes in PCSK9i. Dosing changes and switching between both PCSK9i from Year 1 to the last follow up are shown in [Supplementary material online, Table S2](#). Nine patients (2.7%) receiving alirocumab switched to evolocumab; 272 (81.4%) patients remained with the same dose and frequency; and 53 (15.9%) patients changed the dose or the frequency of administration. On the other hand, 317 (93.2%) of patients with evolocumab remained with the same dose or frequency of administration; 8 (2.4%) patients were switched to alirocumab, and 14 (4.1%) patients changed the dose or frequency of administration.

During the follow-up period, 27 patients discontinued PCSK9i treatment in at least one occasion for a period >60 days and were

Table 1 Characteristics of patients before receiving PCSK9 inhibitor

N	696
Gender (male)	377 (54)
Employed	406 (58)
University studies	153 (22)
Age, years	56.4 (49–66)
BMI (kg/m ²)	27.5 (24.7–30.5)
ASCVD	266 (38)
Diabetes	46 (7)
Hypertension	181 (26)
Current smoker	101 (14.5)
Null allele variants	351 (50.4)
Maximal tolerated LLT	619 (89)
Maximal combined treatment	518 (74)
Years with statins	22 (16–29)
Years with ezetimibe	14 (9–16)
Total cholesterol	
mg/dL	220 (193–254.5)
mmol/L	5.7 (5.0–6.6)
LDL-C	
mg/dL	145 (123–177)
mmol/L	3.8 (3.2–4.6)
HDL-C	
mg/dL	50 (42–78)
mmol/L	1.3 (1.1–2.0)
Triglycerides	
mg/dL	104 (79–143)
mmol/L	1.2 (0.9–1.6)
Lp(a)	
mg/dL	32 (12–79)
mmol/L	66 (22–168)
SAF-RE—5 years	1.3 (0.6–4.0)

Continuous variables are expressed as median (IQR) and other variables are expressed as number (%).

ASCVD, atherosclerosis cardiovascular disease; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering treatment; Lp(a), lipoprotein (a); SAF-RE, SAFEHEART risk equation.

Table 2 Annual and total (cumulative) persistence to PCSK9 inhibitor during follow up

Follow up	n	Permanent interruption, n (%)	Temporarily interruption, n (%)	Persistent, n (%)
Year 1	696	8 (1.1)	1 (0.1)	687 (98.7)
Year 2	644	6 (0.9)	0	638 (99.1)
Year 3	569	5 (0.9)	3 (0.5)	561 (98.6)
Year 4	433	3 (0.7)	0	430 (99.3)
>Year 5	304	0	1 (0.3)	303 (99.7)
Total	696	22 (3.2)	5 (0.7)	669 (96.1)

considered non-persistent (see [Supplementary material online, Figure S1](#)). In 22 cases, the interruption was permanent, and in 5 patients' discontinuation was temporary and restarted treatment later on during follow up.

Reasons for permanent interruption of treatment (see [Supplementary material online, Table S3](#)) were physician's decision related to efficacy (five cases), adverse event (four cases), patient decision not related with an adverse event (five cases), occurrence of a medical disorder mostly anxiety/depression (seven cases), and difficulties to access to medication (one case). Median time from PCSK9i initiation to permanent interruption was 15 months (IQR 4–33) being earlier in those who presented an adverse event (4.5 months; IQR 2.2–11.3). Of those five cases who discontinued PCSK9i temporarily, two were related to the COVID-19 pandemic, two cases were due to a medical decision, and one case was due to a traffic accident. Median time to temporarily discontinuation was 27 months (IQR 14–39), median duration of PCSK9i discontinuation was 4 months (IQR 3–6), and the median time from restarting PCSK9i to the last visit was 9 months (IQR 5–16). The percentage of cases who persisted with PCSK9i at the end of the follow up was 96.1%. Persistence with inhibitors in each year of follow up is shown in [Table 2](#) and [Figure 1](#). Most of the permanent discontinuations occurred during the first year of treatment.

Differences between persistent ($n = 669$) and non-persistent ($n = 27$) subjects are shown in [Table 3](#). Non-persistent patients had significantly less time of treatment with ezetimibe ($P < 0.05$), were less treated with maximum combined LLT (52 vs. 75%, $P < 0.05$), had higher total cholesterol ($P < 0.001$) and LDL-C ($P < 0.001$), and lower Lp(a) levels ($P < 0.05$) when they started with PCSK9i.

There was no effect of type of mutation in the persistence with PCSK9i.

Low-density lipoprotein cholesterol reduction and low-density lipoprotein cholesterol goal attainment

Median LDL-C level after 1 year of PCSK9i treatment was 63 mg/dL (IQR 43–88), 1.6 mmol/L (IQR 1.1–2.3) and remained constant until the last follow up (61 mg/dL, IQR 44–82; 1.6 mmol/L, IQR 1.1–2.1). Median LDL-C per cent reduction was similar at Year 1 and in the last follow up, 57.6 and 58%, respectively, $P < 0.001$ compared with baseline levels.

A highly significant increase in LDL-C goal attainment was observed at Year 1 and in the last follow up. 2016 ESC/EAS goals were attained by 70 and 77% of individuals at Year 1 and at the last follow up, respectively ($P < 0.001$), whereas 2019 ESC/EAS goals were attained by 44.5 and 48% in the same periods ($P = 0.1$). 2016 and 2019 ESC/EAS guideline goal attainment according to cardiovascular risk of FH patients is shown in [Figure 2](#). A significant increase in 2016 LDL-C goal attainment from Year 1 to the last follow up was observed only in secondary prevention patients.

The effect of PCSK9i was significantly different according to background LLT ($P < 0.001$). Those individuals with statins and ezetimibe reached lower LDL-C levels, and showed higher per cent LDL-C reduction and greater attainment of goals than those with statin or ezetimibe alone (see [Supplementary material online, Figure S2](#) and [Table S4](#)). There were no differences between evolocumab and alirocumab. According to persistence in the last follow-up visit, non-persistent patients had significantly higher LDL-C levels (149 mg/dL, IQR 115–187 vs. 61 mg/dL, IQR 44–82, $P < 0.001$; 3.9 mmol/L, IQR 3.0–4.8 vs. 1.6 mmol/L, IQR 1.1–2.1), less per cent LDL-C reduction (15%, IQR 0–39 vs. 58%, IQR 44–68, $P < 0.001$), and less LDL-C goal attainment ([Table 3](#)).

In multivariate regression analysis, independent predictors for attainment of 2019 LDL-C goals were the use of statins with [OR 25.67, 95%

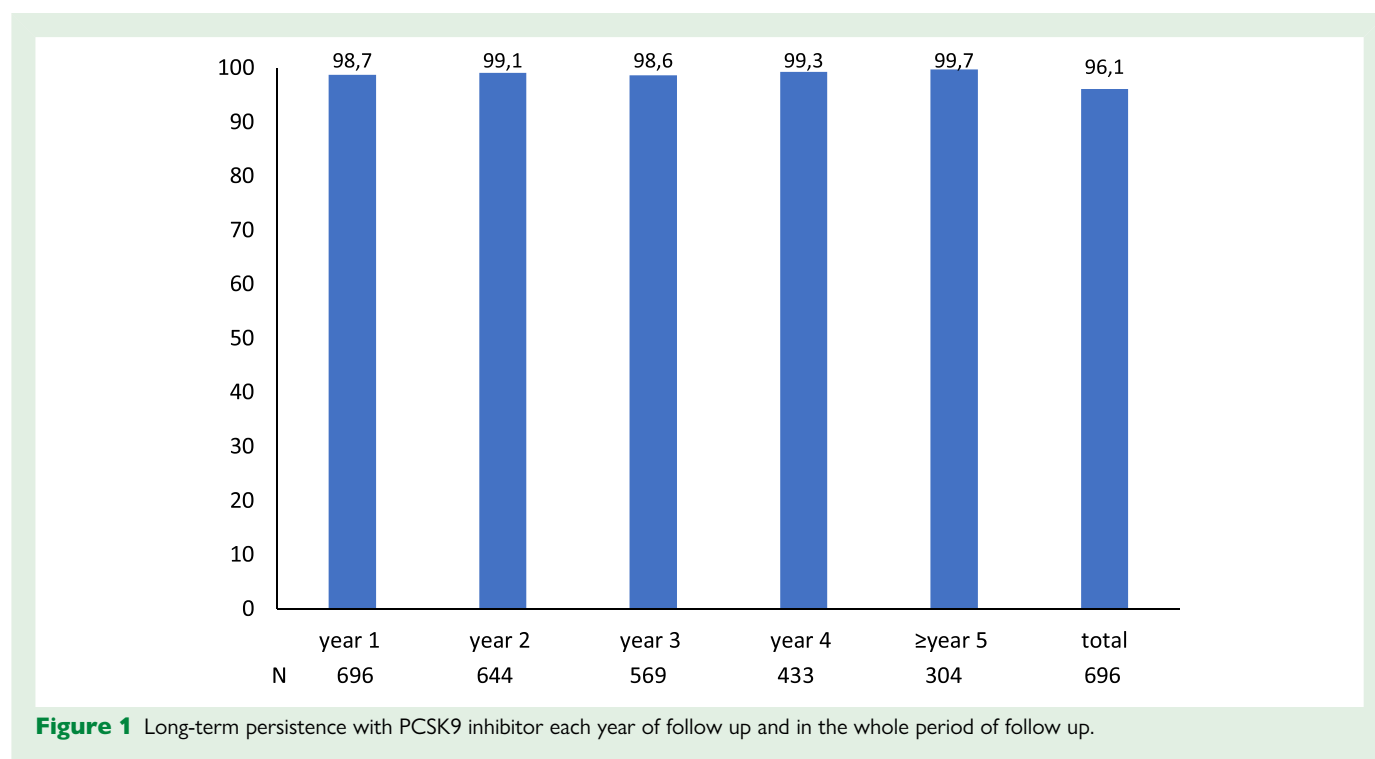


Figure 1 Long-term persistence with PCSK9 inhibitor each year of follow up and in the whole period of follow up.

confidence interval (CI) 3.41–192.9, $P=0.002$] or without (OR 12.87, 95% CI 1.6–99.8, $P=0.014$) ezetimibe. On the other hand, higher LDL-C levels (≥ 160 mg/dL, 4.1 mmol/L) prior to initiation of PCSK9i showed a significant inverse relationship with goal attainment (Table 4, Supplementary material online, Table S5). Goal attainment with PCSK9i according different combinations of significant variables including gender, smoking status, LLT, and LDL-C are shown in Supplementary material online, Table S6. Non-smoking males and females with combined LLT achieved more LDL-C goals compared with smoking males and females with statin monotherapy.

As two different doses of alirocumab were used, a comparison of patients treated with 75 or 150 mg biweekly was performed ($n=188$ and 139, respectively). Patients receiving alirocumab 75 mg every 15 days had significantly lower baseline LDL-C levels and obtained lower percent LDL-C reduction compared with those who received 150 mg every 15 days [137 mg/dL (3.5 mmol/L) vs. 146 mg/dL (3.8 mmol/L), $P<0.05$; and 54 vs. 61%, $P<0.05$, respectively]. However, there were no differences in attainment of 2016 and 2019 goals (data not shown).

Quality of life

Mean EQ-5D index improved from 0.92 ± 0.14 at initiation of PCSK9i to 0.94 ± 0.12 at 1-year follow up ($P<0.001$) and 0.93 ± 0.13 in the last control ($P=0.16$ compared with Year 1). Three dimensions of the EQ-5D (mobility, usual activities, and pain/discomfort) significantly improved ($P<0.001$), and two of them (self-care and anxiety/depression) did not change during the first year of use of inhibitors (see Supplementary material online, Table S7). No changes were observed in the last follow up compared with first year of use, except for the anxiety/depression dimension that increased from 11.3 to 16% ($P<0.001$) between Year 1 and last follow up.

Median EQ-5D score measured as VAS improved slightly but significantly ($P<0.001$) in the first year of follow up and remained stable at the last follow up. A significant reduction in the percentage of cases categorized as fair and good in the VAS scale ($P<0.05$), and an increase in

the excellent category ($P<0.005$) was observed in the first year of follow up with no changes in the last follow up, except a slight reduction in the excellent category.

Discussion

In this prospective multicentre study, we showed that long-term persistence with PCSK9i treatment is very high (96%) in FH patients in a real-life setting, and that persistence is associated with an improvement in LDL-C goal attainment. In this regard, 77% of patients achieved 2016 ESC/EAS LDL-C goals and 48% achieved the more stringent 2019 ESC/EAS goals after a median follow up of 3.7 years. In addition, health-related QoL of this population improved slightly during the first year of starting the inhibitors and remained stable until the last follow up. These results could be important in the prevention of cardiovascular events in FH patients since the sustained absolute LDL-C reduction of 84 mg/dL (2.2 mmol/L) obtained with PCSK9i in the follow up could be translated into a significant reduction of events of at least 40% according CTT collaboration study.²⁴

Persistence with PCSK9 inhibitors

Persistence with and adherence to chronic LLT has been demonstrated to be crucial for the attainment of LDL-C goals and reduction of ASCVD outcomes.²⁵ In the last years, the term persistence has begun to be used to define the time during which a patient continues with the treatment until the interruption. This is different from adherence that reflects how the patient take the medication according the medical prescription.²² To our knowledge, there are no studies analysing persistence with long-term PCSK9i treatment in the FH population. This is an important topic because FH patients require LLT from their diagnosis for the rest of their life to decrease LDL-C burden and to prevent the development of ASCVD.² In this large cohort of FH patients treated in clinical practice setting in different centres, there was a high rate of

Table 3 Characteristics of patients according to their persistence with PCSK9 inhibitor

	Non-persistent (n = 27)	Persistent (n = 669)	P-value
Gender (male)	10 (37)	367 (55)	0.06
Age, years	53 (48–63)	56 (49–66)	0.29
Employed	15 (55.5)	391 (58.5)	0.76
University studies	8 (29.6)	145 (21.7)	0.32
ASCVD	8 (29.6)	258 (38.6)	0.34
Type 2 diabetes	2 (7.4)	44 (6.6)	0.86
Hypertension	9 (33.3)	172 (25.7)	0.37
Current smoker	5 (18.5)	96 (14.3)	0.54
Maximum tolerated LLT	20 (74)	599 (89.5)	<0.05
Maximum combined LLT	14 (52)	504 (75)	<0.05
Years with statins	21 (12–26)	23 (16–30)	0.08
Years with ezetimibe	10 (6–15)	15 (10–17)	<0.005
Null allele variants	11 (40.7)	340 (50.8)	0.3
BMI (kg/m ²)	28 (25.6–33.7)	27 (24.7–30)	0.1
Total cholesterol			
mg/dL	277 (221–327)	218 (192–250)	<0.001
mmol/L	7.2 (5.7–8.5)	5.6 (5.0–6.5)	
LDL-C			
mg/dL	188 (139–231)	144 (122–174)	<0.001
mmol/L	4.9 (3.6–6.0)	3.7 (3.2–4.5)	
HDL-C			
mg/dL	53 (49–64)	50 (42–58)	<0.05
mmol/L	1.4 (1.3–1.7)	1.3 (1.1–1.5)	
Triglycerides			
mg/dL	122 (97–162)	104 (79–141)	<0.05
mmol/L	1.4 (1.1–1.8)	1.2 (0.9–1.6)	
Lp(a)			
mg/dL	12 (7–46)	33 (12–80)	<0.05
mmol/L	22 (11–96)	68 (22–170)	
LDL-C LFU			
mg/dL	149 (115–187)	61 (44–82)	<0.001
mmol/L	3.9 (3.0–4.8)	1.6 (1.1–2.1)	
% LDL-C reduction to LFU	15 (0–39)	58 (44–68)	<0.001
2016 ESC/EAS goals	2 (7.4)	519 (77.5)	<0.001
2019 ESC/EAS goals	1 (3.7)	321 (48)	<0.001
SAF-RE, 5 years	1.58 (0.75–4.38)	1.30 (0.61–3.89)	0.9
SAF-RE, 10 years	3.36 (1.61–9.14)	2.76 (1.30–8.15)	0.9

Quantitative variables are expressed as median (IQR) and other variables are expressed as number (%).

ASCVD, atherosclerosis cardiovascular disease; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LFU, last follow up; LLT, lipid-lowering treatment; SAF-RE, SAFEHEART risk equation.

persistence (~99%) with PCSK9i in every year of follow up and in the whole period of follow up (>95%) than previously reported in other populations. The few cases that discontinued PCSK9i in our study were due to medical decision related to efficacy, adverse events, and patient decisions not related with adverse events or other factors. Permanent discontinuation of PCSK9i in our study was lower (3%) compared with the 15% or premature discontinuation observed in the open-label extension programme with evolocumab in FOURIER-OLE.²⁶ It is important to highlight that during the pandemic, delivery of PCSK9i was sustained by different hospital pharmacies to patients. Previously reports in the non-FH population have shown

that around 30–40% of patients became non-persistent during the first year of treatment, most of them stopping during the first 6 months.^{16,27} Main reasons for discontinuation were related to cost, lack of insurance approval, and perceived adverse events. Recently, Donald *et al.*²⁸ explored retrospectively the persistence rate and reasons for non-persistence to PCSK9i in 477 subjects from one centre during a follow up of 24 months. They found a persistence rate of 94% at Month 3 that diminished to 68% at 24 months. In this study, the main reasons for non-persistence were mainly adverse events and loss of follow up. Although 41% of patients had FH, there is no analysis in this specific group. In the SAFEHEART study, patients have improved LLT in the

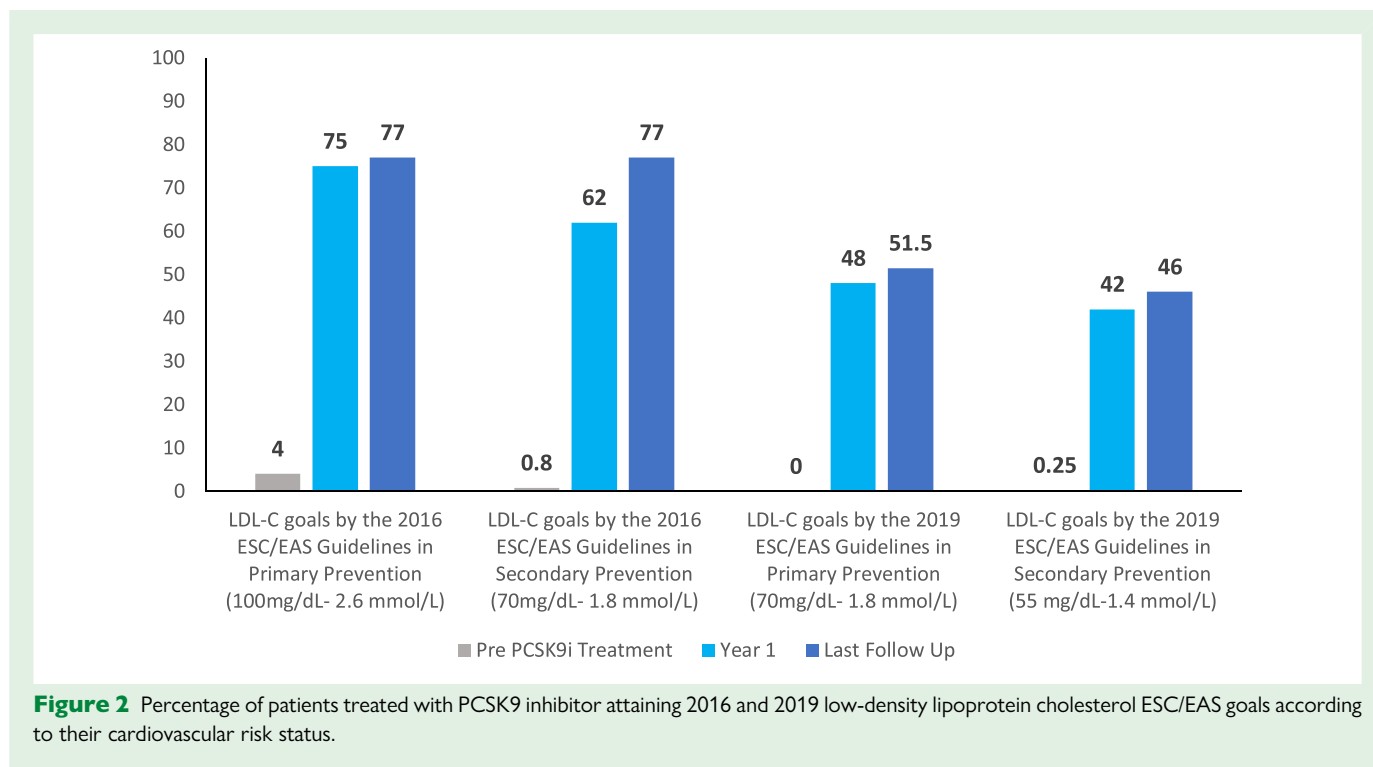


Figure 2 Percentage of patients treated with PCSK9 inhibitor attaining 2016 and 2019 low-density lipoprotein cholesterol ESC/EAS goals according to their cardiovascular risk status.

Table 4 Logistic regression analysis (combined 2019 ESC/EAS low-density lipoprotein cholesterol goal attainment)

Variable	Odds ratio (95% CI)	SE	P-value
Gender (male)	1.31 (0.93–1.86)	0.23	0.118
Hypertension	0.73 (0.51–1.04)	0.13	0.087
ASCVD	0.80 (0.55–1.15)	0.15	0.237
Current smoker	0.38 (0.21–0.69)	0.11	0.002
Background LLT			
Statins + ezetimibe	25.67 (3.41–192.9)	26.42	0.002
Statins	12.87 (1.6–99.8)	13.45	0.014
Ezetimibe	4.06 (0.43–38.06)	4.06	0.219
LDL-C 130–159.9 mg/dL (3.4–4.1 mmol/L)	0.65 (0.43–0.97)	0.13	0.036
LDL-C ≥ 160 mg/dL (≥4.1 mmol/L)	0.27 (0.18–0.41)	0.058	0.0001

ASCVD, atherosclerosis cardiovascular disease; LLT, lipid-lowering therapy; SE, standard error.

last 15 years.⁷ The use of high-intensity statins increased from 40% in 2004 to 75% in 2019; and the use of maximum LLT increased from 51 to 89%, respectively. The permanent contact with patients and families through the standardized annual follow up from the coordinating centre has improved awareness of the disorder and of the importance of maintaining chronic LLT to reduce cardiovascular risk. This is in line with studies that have shown that patient knowledge, patient's beliefs about their condition, and attitude towards LLT are associated with better adherence to treatments.^{29,30}

Low-density lipoprotein cholesterol goal attainment

LDL-C goal attainment is a challenge for clinicians in order to reduce the burden of ASCVD. With the more stringent 2019 European guidelines, most patients at high and very high risk, including those with FH, will require high-intensity statin in combination with non-statin LDL-C-lowering therapies. However, the DA VINCI study, a European cross-sectional study, showed that LLT and LDL-C goal attainment in primary (including FH patients) and secondary prevention were suboptimal.⁸ Most patients were using statin monotherapy, and only 9% were in combination with ezetimibe, explaining the low goal attainment of 54 and 33% for 2016 and 2019 guidelines, respectively. Different studies have also shown that LDL-C goal attainment is very difficult in FH patients despite the use of the combination of high-intensity statin and ezetimibe^{7,31,32} which can be frustrating for patients and their treating physicians. Previous reports of the SAFEHEART have shown a modest increase in the attainment of 2016 ESC/EAS LDL-C goals up to 5% in those FH patients with ASCVD and 10% in those without ASCVD after a median of 5 years follow up, explained by the intensification of conventional LLT at that moment.⁷ Later, with the introduction of PCSK9i, a first report after 2.5 years follow up showed a huge increase in the achievement of 2016 ESC/EAS guidelines LDL-C goals up to 67 and 80%, and 46–50% with 2019 ESC/EAS guidelines.¹¹ In this present and largest study, we confirm major and sustained attainment of LDL-C goals for a longer follow-up period, and that persistent attainment of these goals is higher in those patients already on background LLT, especially statins in combination with ezetimibe. Similar results have been recently shown in FH and non-FH populations from the HEYMANS registry.³³ Our findings show the difficulty in the attainment of LDL-C goals in patients with FH as they usually have higher baseline LDL-C levels, and that the addition of PCSK9i to the combination of statins and ezetimibe could be the best option as in other high-risk populations.^{34,35}

Quality of life in familial hypercholesterolaemia patients treated with PCSK9 inhibitor

Our study showed that patients improved slightly their health-related QoL during the first year of treatment with PCSK9i and that it remained unchanged in the long term, except for the anxiety/depression dimension. Using different tools to measure QoL, previous studies have shown that QoL in FH is similar to their unaffected relatives and the general population.^{17,36,37} However, considering that FH patients require long-term LLT, it is important to determine the impact of treatment in QoL. Previous report of SAFEHEART before the introduction of PCSK9i showed that patients receiving chronic LLT showed better self-perceived health compared with treated unaffected relatives, explained in part by the fact that patients with this high-risk disorder could feel protected against ASCVD.¹⁷ Another study analysing the impact of PCSK9i in QoL in a high cardiovascular risk population showed that most patients treated with PCSK9i had an improvement in health-related QoL.¹⁸ Compared with our results, we can assume that when patients started with PCSK9i, they had a high QoL in part due to chronic conventional LLT, and therefore the impact of PCSK9i was only a slight improvement.

Strengths and limitations

The main strengths of this study is that it is a multicentre nationwide study including a well-defined FH cohort followed up prospectively through a centralized standardized phone interview and interaction with treating physicians. The number of patients included in the analysis and the time of follow up being the longest published to date.

Prescription and changes in PCSK9i treatment was at the discretion of the physician; however, there were no qualitative and quantitative differences between evolocumab and alirocumab groups.

The limitations of this study include the lack of blinding randomization and blood testing in the follow up was not centralized; however, testing was performed in lipid clinics according to national and international standards. Regarding QoL, we cannot compare results with those from enrolment in SAFEHEART, as a different questionnaire was used initially and was not directly comparable with EQ-5D.

Conclusions

Persistence with long-term PCSK9i treatment is very high in FH patients in clinical practice setting with a good health-related QoL. Furthermore, patients receiving PCSK9i on top of statins and ezetimibe vastly increases their LDL-C goal attainment.

Author contributions

R.A.I., R.A.O., O.M.G., J.L.D.D., F.F.J., L.P.I., and P.M. contributed to the concept and design of the work; acquisition, analysis, or interpretation of data. All authors drafted the article and revised critically. All authors approved this version, have participated sufficiently in the work, and have agreed to be accountable for all aspects of work ensuring integrity and accuracy.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology*.

Acknowledgements

The authors thank Ms Teresa Pariente for her hard work managing the familial cascade screening from the beginning of the SAFEHEART registry and all the Spanish Familial Hypercholesterolaemia Foundation for assistance in the recruitment and follow up of participants and to the FH families for their valuable contribution and willingness to participate.

Funding

This study was funded by the Fundación Hipercolesterolemia Familiar; grant G03/181 and FIS PI12/01289 of the Instituto de Salud Carlos III (ISCIII) and grant 08-2008 from the Centro Nacional de Investigaciones Cardiovasculares (CNIC), and supported by an unrestricted grant for the preparation of this manuscript from Amgen.

Conflict of interest: R.A. received honorary fees for talks and advisory boards from Amgen, Sanofi, MSD, Tecnofarma, Abbott, Saval. O.M.G. received honoraria for speaker or researcher activities from Merck Sharp and Dohme, Amgen, and Sanofi. J.L.D.D. received honoraria for speaker or researcher activities from Merck Sharp and Dohme, Amgen, and Sanofi. L.P.I. received honoraria for speaker or researcher activities from Merck Sharp and Dohme, Astra Zeneca, Esteve, Amgen, and Sanofi. P.M. received honoraria for advisory boards and received research grants from Amgen and Sanofi.

Data availability

The data underlying this article cannot be shared publicly due to the privacy of individuals who participated in the study. The data will be shared on reasonable request to the corresponding author.

References

- Watts G, Gidding S, Mata P, Pang J, Sullivan DR, Yamashita S, Raal F, Santos R, Ray K. Familial hypercholesterolemia: evolving knowledge for designing adaptive models of care. *Nat Rev Cardiol* 2020;**17**:360–377.
- Nordestgaard BG, Chapman MJ, Humphries SE, Ginsberg HN, Masana L, Descamps OS, Wiklund O, Hegele RA, Raal FJ, Defesche JC, Wiegman A, Santos RD, Watts GF, Parhofer KG, Hovingh GK, Kovanen PT, Boileau C, Aversa M, Borén J, Bruckert E, Catapano AL, Kuivenhoven JA, Pajukanta P, Ray K, Stalenhoef AF, Stroes E, Taskinen MR, Tybjaerg-Hansen A. For the European Atherosclerosis Society Consensus Panel. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease. *Eur Heart J* 2013;**34**:3478–3490.
- Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, Chapman MJ, De Backer GG, Delgado V, Ference BA, Graham IM, Halliday A, Landmesser U, Mihaylova B, Pedersen TR, Riccardi G, Richter DJ, Sabatine MS, Taskinen MR, Tokgozoglul, Wiklund O; ESC Scientific Document Group. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J* 2020;**41**: 111–188.
- Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H, Hoes AW, Jennings CS, Landmesser U, Pedersen TR, Reiner Ž, Riccardi G, Taskinen MR, Tokgozoglul, Verschuren WMM, Vlachopoulos C, Wood DA, Zamorano JL, Cooney MT; ESC Scientific Document Group. 2016 ESC/EAS guidelines for the management of dyslipidaemias. *Eur Heart J* 2016;**37**:2999–3058.
- Pijlman AH, Huijgen R, Verhagen SN, Imholz BOM, Liem AH, Kastelein JJP, Abbink JJ, Stalenhoef AFH, Visseren FLJ. Evaluation of cholesterol lowering treatment of patients with familial hypercholesterolemia: a large cross sectional study in The Netherlands. *Atherosclerosis* 2010;**209**:189–194.
- Pérez de Isla L, Arroyo-Olivares R, Muñiz-Grijalvo O, Díaz-Díaz JL, Zambón D, Fuentes F, Sánchez Muñoz-Torrero JF, Mediavilla JD, González-Estrada A, Miramontes-González JP, de Andrés R, Mauri M, Mosquera D, Cepeda JM, Suárez L, Barba-Romero MÁ, Argüeso R, Álvarez-Baños P, Michán A, Romero-Jiménez MJ, García-Cruces J, Padró T, Alonso R, Mata P. Long-term effect of 2 intensive statin regimens on treatment and incidence of cardiovascular events in familial hypercholesterolemia: the SAFEHEART study. *J Clin Lipidol* 2019;**13**:989–996.
- Perez de Isla L, Alonso R, Watts GF, Mata N, Saltijeral-Cerezo A, Muñiz O, Fuentes F, Diaz-Diaz JL, de Andrés R, Zambón D, Rubio-Marin P, Barba-Romero MA, Saenz P, Sanchez Muñoz-Torrero JF, Martinez-Faedo C, Miramontes-Gonzalez JP, Badimón L,

- Mata P; SAFEHEART Investigators. Attainment of LDL-cholesterol treatment goals in patients with familial Hypercholesterolemia. 5 years SAFEHEART Registry Follow-up. *J Am Coll Cardiol* 2016;**67**:1278–1285.
8. Ray K, Molemans B, Schoonen WM, Giovas P, Bray S, Kiru G, Murphy J, Banach M, De Servi S, Gaita D, Gouni-Berthold I, Hovingh GK, Jozwiak JJ, Jukema JW, Kiss RG, Kownator S, Iversen HK, Maher V, Masana L, Parkhomenko A, Peeters A, Clifford P, Raslova K, Siotrzonek P, Romeo S, Tousoulis D, Vlachopoulos C, Vrablik M, Catapano AL, Poulter NR; DA VINCI study. EU-wide cross-sectional observational study of lipid-modifying therapy use in secondary and primary care: the DA VINCI study. *Eur J Prev Cardiol* 2021;**28**:1279–1289.
 9. Santos RD, Stein EA, Hovingh GK, Blom DJ, Soran H, Watts GF, López JAG, Bray S, Kurtz CE, Hamer AW, Raal FJ. Long-term evolocumab in patients with familial hypercholesterolemia. *J Am Coll Cardiol* 2020;**75**:565–574.
 10. Farnier M, Hovingh GK, Langslet G, 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.
 11. Alonso R, Muñoz-Grijalvo O, Díaz-Díaz JL, Zambón D, de Andrés R, Arroyo-Olivares R, Fuentes-Jimenez F, Muñoz-Torrero JS, Cepeda J, Aguado R, Alvarez-Baños P, Casañas M, Dieguez M, Mañas MD, Rubio P, Argueso R, Arrieta F, Gonzalez-Bustos P, Perez-Isla L, Mata P; SAFEHEART investigators. Efficacy of PCSK9 inhibitors in the treatment of heterozygous familial hypercholesterolemia: a clinical practice experience. *J Clin Lipidol* 2021;**15**:584–592.
 12. Langslet G, Johansen A, Bogsrud M, Naarverud I, Ristad H, Retterstol K, Holven KB. Thirty percent of children and young adults with familial hypercholesterolemia treated with statins have adherence issues. *Am J Prev Cardiol* 2021;**6**:100180.
 13. Casula M, Scotti L, Tragni E, Merlino L, Corrao G, Catapano AL. Drug treatment and adherence of subjects <40 years with diagnosis of heterozygous familial hypercholesterolemia. *Atherosclerosis* 2016;**254**:172–178.
 14. Benson G, Witt DR, van Wormer JJ, Campbell SM, Sillah A, Hayes SN, Lui M, Gulati M. Medication adherence, cascade screening, and lifestyle patterns among women with hypercholesterolemia: results from the Women Heart Survey. *J Clin Lipidol* 2016;**10**:937–943.
 15. Bradley C, Shrader P, Sanchez R, Peterson E, Navar AM. The patient journey with proprotein convertase subtilisin/kexin type 9 inhibitors in community practice. *J Clin Lipidol* 2019;**13**:725–734.
 16. Hines DM, Rane P, Patel J, Harrison DJ, Wade RL. Treatment patterns and patient characteristics among early initiators of PCSK9 inhibitors. *Vasc Health Risk Manag* 2018;**12**:409–418.
 17. Mata N, Alonso R, Banegas JR, Zambón D, Brea A, Mata P. Quality of life in a cohort of familial hypercholesterolemia patients from the south of Europe. *Eur J Public Health* 2014;**24**:221–225.
 18. Cesaro A, Gragnano F, Fimiani F, Moscarella E, Diana V, Parigianno I, Concilio C, Natale F, Limongelli G, Bossoni E, Calabrò P. Impact of PCSK9 inhibitors on the quality of life of patients at high cardiovascular risk. *Eur J Prev Cardiol* 2020;**27**:556–558.
 19. Mata N, Alonso R, Badimón L, Padró T, Fuentes F, Muñoz O, Perez-Jiménez F, López-Miranda J, Díaz JL, Vidal JJ, Barba A, Piedecausa M, Sanchez JF, Irigoyen L, Guallar E, Ordovas JM, Mata P. Clinical characteristics and evaluation of LDL-cholesterol treatment of the Spanish Familial Hypercholesterolemia Longitudinal Cohort Study (SAFEHEART). *Lipids Health Dis* 2011;**10**:94.
 20. Alonso R, Andres E, Mata N, Fuentes-Jiménez F, Badimón L, López-Miranda J, Padró T, Muñoz O, Díaz-Díaz JL, Mauri M, Ordovas JM, Mata P, SAFEHEART investigators. Lipoprotein(a) levels in familial hypercholesterolemia: an important predictor of cardiovascular disease independent of the type of LDL receptor mutation. *J Am Coll Cardiol* 2014;**63**:1982–1989.
 21. Pérez de Isla L, Alonso R, Mata N, Fernández-Pérez C, Muñoz O, Díaz-Díaz JL, Saltijeral A, Fuentes-Jiménez F, de Andrés R, Zambón D, Piedecausa M, Cepeda JM, Mauri M, Galiana J, Brea Á, Sanchez Muñoz-Torrero JF, Padró T, Argueso R, Miramontes-González JP, Badimón L, Santos RD, Watts GF, Mata P. Predicting cardiovascular events in familial hypercholesterolemia: the SAFEHEART registry (Spanish Familial Hypercholesterolemia Cohort Study). *Circulation* 2017;**135**:2133–2144.
 22. Cramer JA, Roy A, Burrell A, Fairchild CJ, Fuldeore MJ, Ollendorf DA, Wong PK. Medication compliance and persistence: terminology and definitions. *Value Health* 2008;**11**:44–47.
 23. Dyer MT, Goldsmith KA, Sharples LA, Buxton MJ. A review of health utilities using the EQ-5D in studies of cardiovascular disease. *Health Qual Life Outcomes* 2010;**8**:13.
 24. Ference B, Cannon CP, Landmesser U, Lüscher TF, Catapano A, Ray K. Reduction of low density lipoprotein-cholesterol and cardiovascular events with proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors and statins: an analysis of FOURIER, SPIRE, and the Cholesterol Treatment Trialist Collaboration. *Eur Heart J* 2018;**39**:2540–2545.
 25. Rodriguez F, Maron D, Knowles J, Virani S, Lin S, Heidenreich P. Association of statin adherence with mortality in patients with atherosclerotic cardiovascular disease. *JAMA Cardiol* 2019;**4**:206–213.
 26. O'Donoghue M, Giuliano R, Wiviott S, Atar D, Keech A, Kuder J, Im K, Murphy SA, Flores-Arredondo JH, López AG, Elliot-DAvey M, Wang B, Monsalvo ML, Abbasi S, Sabatine MS. Long-term evolocumab in patients with established atherosclerotic cardiovascular disease. *Circulation* 2022;**146**:1109–1119.
 27. Bradley CK, Shrader P, Sanchez RJ, Peterson ED, Navar AM. The patient journey with proprotein convertase subtilisin/kexin type 9 inhibitors in community practice. *J Clin Lipidol* 2019;**13**:725–734.
 28. Donald DR, Reynolds VW, Hall N, DeClercq J, Choi L. Exploring rates of PCSK9 inhibitor persistence and reasons for treatment non-persistence in an integrated specialty pharmacy model. *J Clin Lipidol* 2022;**16**:315–324.
 29. Horne R, Weinman J. Patients' beliefs about prescribed medicines and their role in adherence to treatment in chronic physical illness. *J Psychosom Res* 1999;**47**:555–567.
 30. Senior V, Marteau T, Weinman J, on behalf of the Genetic Risk Assessment for FH Trial (GRAFT) Study Group. Self-reported adherence to cholesterol-lowering medication in patients with familial hypercholesterolaemia: the role of illness perception. *Cardiovasc Drugs Ther* 2004;**18**:475–481.
 31. Bogsrud MP, Græsdal A, Johansen D, Langslet G, Hovland A, Arnesen KE, Mundal LJ, Retterstol K, Wium C, Holven KB. LDL-cholesterol goal achievement, cardiovascular disease, and attributed risk of Lp(a) in a large cohort of predominantly genetically verified familial hypercholesterolemia. *J Clin Lipidol* 2019;**13**:279–286.
 32. Vrablik M, Raslova K, Vohnout B, Blaha V, Satny M, Kyselak O, Vlacova M, Urbanek R, Maskova J, Soska V, Freiberg T. Real life LDL-C goals achievement in patients with heterozygous familial hypercholesterolemia in the Czech Republic and Slovakia: results of the PLANET registry. *Atherosclerosis* 2018;**277**:355–361.
 33. Ray K, Dhalwani N, Sibartie M, Bridges I, Ebennichler C, Perrone-Filardi P, Villa G, Vogt A, Bruckert E. Low-density lipoprotein cholesterol levels exceed the recommended European threshold for PCSK9i initiation: lessons from the HEYMANS study. *Eur Heart J Qual Care Clin Outcomes* 2022;**8**:447–460.
 34. Banach M, López-Sendon JL, Aversa M, Cariou B, Loy M, Manvelian G, Batsu I, Poulouin Y, Gaudet D. Treatment adherence and effect of concurrent statin intensity on the efficacy and safety of alirocumab in a real-life setting: results from ODYSSEY APPRISE. *Arch Med Sci* 2021;**18**:285–292.
 35. Landmesser U, McGinniss J, Steg PG, Bhatt D, Bittner VA, Diaz R, Dilic M, Goodman SG, Jukema JW, Loy M, Pećin I, Pordy R, Poulsen SH, Szarek M, White HD, Schwartz GG; ODYSSEY OUTCOMES Investigators. Achievement of ESC/EAS LDL-C treatment goals after an acute coronary syndrome with statin and alirocumab. *Eur J Prev Cardiol* 2022;**29**:1842–1851.
 36. Hollman G, Gullberg M, Ek AC, Eriksson M, Olsson AG. Quality of life in patients with familial hypercholesterolaemia. *J Intern Med* 2002;**251**:331–337.
 37. Hyttinen L, Kekalainen P, Vuorio AF, Sintonen H, Strandberg TE. Health-related quality of life in elderly patients with familial hypercholesterolemia. *Int J Technol Assess Health Care* 2008;**24**:228–234.