ESC European Society of Cardiology

European Journal of Preventive Cardiology
https://doi.org/10.1093/eurjpc/zwab185

FULL RESEARCH PAPER
Lipids & Atherosclerosis

A resilient type of familial hypercholesterolaemia: case–control follow-up of genetically characterized older patients in the SAFEHEART cohort

Leopoldo Pérez de Isla [1,2]*, Gerald F. Watts[3,4], Ovidio Muñiz-Grijalvo [5], Jose Luis Díaz-Díaz[6], Rodrigo Alonso [2,7], Daniel Zambón[8], Francisco Fuentes-Jimenez [9], Marta Mauri [10], Teresa Padró [11], José I. Vidal-Pardo[12], Miguel A. Barba[13], Enrique Ruiz-Pérez[14], Alfredo Michán [15], Juan D. Mediavilla[16], Antonio M. Hernandez [17], Manuel J. Romero-Jimenez [18], Lina Badimon [12], and Pedro Mata[2]*; on behalf of SAFEHEART Investigators†

[1]Cardiology Department, Hospital Clínico San Carlos, IDISSC, Facultad de Medicina, Universidad Complutense, C/Profesor Martín Lagos s/n, 28040 Madrid, Spain; [2]Fundación Hipercolesterolemia Familiar, C/General Alvarez de Castro 14, 28010 Madrid, Spain; [3]School of Medicine, Faculty of Health and Medical Sciences, University of Western Australia, Perth, Western Australia, Australia; [4]Department of Cardiology, Royal Perth Hospital, Lipid Disorders Clinic, Cardiometabolic Services, Perth, Western Australia, Australia; [5]Internal Medicine Department, Hospital Virgen del Rocío, Sevilla, Spain; [6]Internal Medicine Department, Hospital Abente y Lago, A Coruña, Spain; [7]Center for Advanced Metabolic Medicine and Nutrition, Santiago, Chile; [8]Department of Endocrinology, Hospital Clinic, Barcelona, Spain; [9]Lipid and Atherosclerosis Unit, CIBERObn, IMBIC, Hospital Universitario Reina Sofia, Córdoba, Spain; [10]Internal Medicine Department, Hospital de Terrassa, Barcelona, Spain; [11]ICCC Cardiovascular, Institut de Recerca del Hospital Santa Creu i Sant Pau, IIB Santa Pau, Barcelona, Spain; [12]Department of Endocrinology, Hospital Universitario Lucus Augusti, Lugo, Spain; [13]Internal Medicine Department, Complejo Hospitalario Universitario, Albacete, Spain; [14]Department of Endocrinology, Hospital Universitario de Burgos, Burgos, Spain; [15]Internal Medicine Department, Hospital Jerez de la Frontera, Cadiz, Spain; [16]Internal Medicine Department, Hospital Universitario Virgen de las Nieves, Granada, Spain; [17]Department of Endocrinology, Hospital Universitario Virgen de la Arrixaca, Murcia, Spain; and [18]Internal Medicine Department, Hospital Infanta Elena, Huelva, Spain

Received 11 August 2021; revised 8 September 2021; editorial decision 15 October 2021; accepted 19 October 2021

Aims Knowledge of the features of patients with familial hypercholesterolaemia (FH) who are protected from atherosclerotic cardiovascular disease (ASCVD) is important for the clinical and prognostic care of this apparently high-risk condition. Our aim was to investigate the determinant and characteristics of patients with FH who are protected from ASCVD and have normal life expectancy, so-called 'resilient' FH (R-FH).

Methods and results Spanish Familial Hypercholesterolaemia cohort study (SAFEHEART) is an open, multicentre, nation-wide, long-term prospective cohort study in genetically defined patients with heterozygous FH in Spain. Patients in the registry who at the time of analysis were at least 65 years or those who would have reached that age had they not died from an ASCVD event were analysed as a case–control study. Resilient FH was defined as the presence of a pathogenic mutation causative of FH in a patient aged ≥65 years without clinical ASCVD. Nine hundred and thirty registrants with FH met the study criteria. A defective low-density lipoprotein (LDL)-receptor mutation, higher plasma level of high-density lipoprotein cholesterol (HDL-C), younger age, female gender, absence of hypertension, and lower plasma lipoprotein (a) [Lp(a)] concentration were independently predictive of R-FH. In a second model, higher levels of HDL-C and lower 10-year score in SAFEHEART-RE were also independently predictive of R-FH.

Conclusion Resilient FH may be typified as being female and having a defective LDL-receptor mutation, higher levels of plasma HDL-C, lower levels of Lp(a), and an absence of hypertension. The implications of this type of FH for clinical practice guidelines and the value for service design and optional care of FH remains to be established.

Trial registration ClinicalTrials.gov number NCT02693548.

*Corresponding authors. Tel: +34 91 5570071, Email: pmata@colesterolfamiliar.org (P.M.); Tel: +34 91 3323290, Email: leopisla@hotmail.com (L.P.d.l.)
†For the SAFEHEART Investigators (https://www.colesterolfamiliar.org/en/safeheart-study/lipid-clinics-participating-in-the-study/).

Keywords Familial hypercholesterolaemia • Older individuals • Cardiovascular disease • Statins • Lipid-lowering treatment • HDL-cholesterol

Introduction

Heterozygous familial hypercholesterolaemia (FH), an autosomal codominant disorder that is not infrequent in the general population,[1,2] is the most common genetic condition associated with premature atherosclerotic cardiovascular disease (ASCVD). However, there is significant heterogeneity in the onset and progression of ASCVD among individuals with FH[3] that is not adequately accounted for in current clinical practice guidelines.[4,5] Heterogeneity in ASCVD risks has engendered the development of specific ASCVD risk prediction algorithms to improve the precision and cost-effectiveness of care for FH patients.[6] Beyond targeting evidence-informed therapy to higher risk groups, a reciprocal consideration related to variation in risk is that there are patients who will be protected from ASCVD and have normal life expectancy. The clinical features of this, so called, 'resilient' FH has not been adequately considered nor previously investigated in the context of a high-quality registry of patients with genetically defined FH. This knowledge is important to not only improved clinical care and practice, but also to identify a resource of patients for discovery medicine programs.

The aim of the present study was to employ data from the Spanish Familial Hypercholesterolaemia cohort study (SAFEHEART) registry to better define the characteristics and determinants a 'resilient' type of FH.

Methods

Registry population

SAFEHEART is an open, multicentre, nation-wide, long-term prospective cohort study in genetically defined patients with heterozygous FH in Spain; recruitment of subjects from FH families began in 2004.[7] SAFEHEART is a well-established, quality clinical registry on FH that has been well-described over time since inception: full details of the inclusion criteria, clinical and laboratory procedures, genetic testing, definition of ASCVD, follow-up protocols, and development and validation of the SAFEHEART risk equation (SAFEHEART-RE) have been published elsewhere, with material relevant to the present study included in Supplementary material online. Patients with nonsense, frameshift, large rearrangements, or other variants shown *in vitro* to have <2% LDLR activity were considered to be carriers of a null allele variant. Patients with an alteration where LDL receptor (LDLR) activity has been determined to be <80% or when a functional study has not been performed, but the overall *in silico* analysis indicated pathogenicity, were considered to be carriers of a defective allele variant.

Selection of population for study

We selected patients from the registry who at the time of analysis (July 2020) were 65 years of age or older or those who would have been that age if they had not died from a cardiovascular event. Resilient FH (R-FH) was accordingly defined as the presence of a pathogenic mutation causative of FH in a patient without clinical ASCVD and aged ≥65 years; non-R-FH was defined as the presence of a pathogenic mutation causative of FH in a patient with clinical ASCVD and aged ≥65 years or who would have been aged ≥65 years had they not died from an ASCVD event. These patients were followed up and managed as described elsewhere.[6] The analysis was carried out as a control–case study.

Statistical analyses

Statistical analyses were carried out using SPSS version 18.0. 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 for the quantitative variables. Comparisons of proportions between the qualitative variables were carried out using the χ^2 test. The median comparisons were analysed with the Mann–Whitney *U* test for independent data. Univariate and multivariate logistic regression analysis of pooled data at baseline were used to determine factors predictive of R-FH by using the baseline variables. Multivariable analysis was carried out in two ways: In the first model, variables with a *P*-value <0.05 in the univariate analysis were included in the multivariate model except SAFEHEART-RE. In the second model, variables with a *P*-value <0.05 in the univariate analysis were included in the multivariate model except those variables included in the SAFEHEART-RE. Receiver operating characteristic (ROC) curves were constructed to determine the accuracy of the most relevant variables to detect R-FH patients. A value of *P*-value <0.05 was considered statistically significant.

Results

Five thousand two hundred and sixty-two subjects were recruited in the SAFEHEART study at the time of the analysis. Of these, 3589 were 18 years old or older and suffered from molecularly defined FH. From these, we identified 930 patients who were 65 years old or older or would have had this age if a cardiovascular fatal event had not occurred. This subgroup of patients comprised the study group, of which 579 were defined as having R-FH and 351 as having non-R-FH (*Figure 1*). Among those with non-R-FH, the ASCVD (first event) events were distributed as follows: 244 non-fatal acute coronary syndromes (69.5%), 2 fatal acute coronary syndromes (0.6%), 28 coronary artery revascularizations (8.0%), 33 non-fatal strokes (9.4%), 3 fatal stroke (0.9%), 12 peripheral artery revascularizations (3.4%), 16 aortic valve replacements secondary to severe aortic stenosis (4.6%), and 13 cardiovascular deaths (3.7%). Median follow-up cohort time was 8.35 (5.35–11.05) years and median statin treatment time in FH patients was 21.7 (15.9–27.5) years at the end of follow-up (July 2020).

Table 1 shows changes in clinical and biochemical characteristics in the study population between enrolment into the registry and at latest follow-up. There was an overall improvement in ASCVD risk factors, including plasma low-density lipoprotein cholesterol (LDL-C) and triglyceride concentrations. This was reflected by the significant improvement in the 10-year cardiovascular risk estimated by SAFEHEART-RE: 3.1% (1.6–7.2) at enrolment and 2.5% (1.2–6.0) at follow-up ($P < 0.001$). There was also an increase in the incidence of

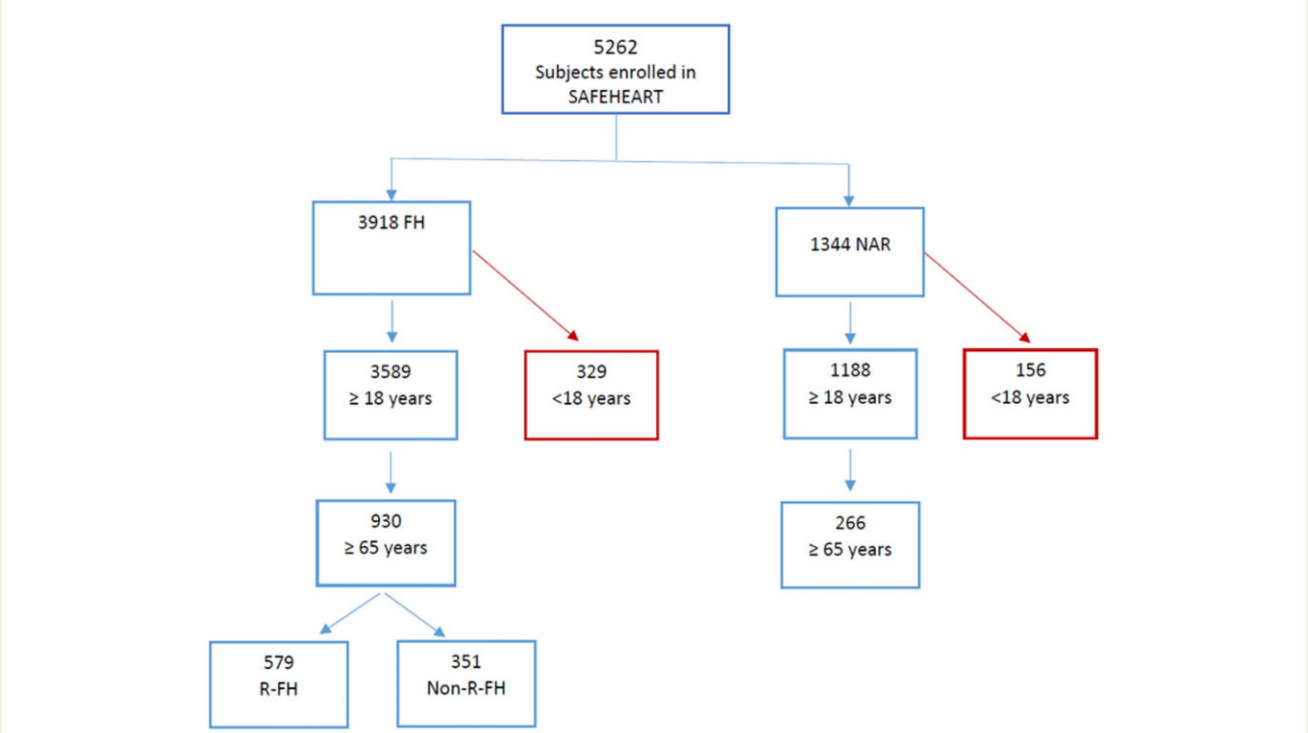


Figure 1 Flow diagram for the study showing recruitment of cases for the present analysis within the SAFEHEART registry. FH, familial hypercholesterolaemia; NAR, non affected relatives; R-FH, resilient familial hypercholesterolaemia.

Table 1 Characteristics at the entry in the SAFEHEART registry and at the end of follow-up period of the study population

	Entry, median (Q1–Q3)/*n* (%)	Follow-up, median (Q1–Q3)/*n* (%)	*P*-value
n	930	930	—
Age (years)	64.2 (59.3–70.8)	73.7 (69.0–80.4)	<0.001
Female gender	570 (61.3%)	535 (57.5%)	0.27
Type 2 diabetes mellitus	99 (10.6%)	145 (15.6%)	<0.001
Hypertension	334 (35.9%)	437 (47.0%)	<0.001
Active tobacco smoker	108 (11.6%)	36 (3.9%)	<0.001
ASCVD	259 (27.8%)	351 (37.7%)	<0.001
BMI (kg/m^2)	27.7 (25.2–30.9)	27.3 (24.6–30.4)	<0.001
Total cholesterol (mg/dL)	232.0 (202.6–268.0)	192.0 (164.0–220.0)	<0.001
LDL-C (mg/dL)	159.0 (135.0–194.1)	116.0 (91.3–140.0)	<0.001
HDL-C (mg/dL)	50.0 (42.0–58.0)	53.0 (44.0–61.0)	<0.001
TG (mg/dL)	95.0 (72.9–127.2)	98.5 (77.0–135.0)	<0.001
Patients on maximum statin	474 (51.0%)	624 (67.1%)	<0.001
Patients on maximum LLT	614 (66.0%)	762 (81.9%)	<0.001
SAFEHEART-RE 10 years (%)	3.1 (1.6–7.2)	2.5 (1.2–6.0)	<0.001

Study population refers to FH patients from the SAFEHEART registry 65 years or older in July 2020.
ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; FH, familial hypercholesterolaemia patient; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering treatment; TG, triglycerides.

Table 2 Baseline characteristics at entry in the SAFEHEART registry of the study population split into resilient familial hypercholesterolaemia patients and non-resilient familial hypercholesterolaemia patients

	R-FH, median (Q1–Q3)/*n* (%)	Non-R-FH, median (Q1–Q3)/*n* (%)	*P*-value
n	579	351	
Age (years)	63.4 (58.3–68.7)	66.2 (61.1–73.4)	<0.001
Female	428 (73.9%)	142 (40.5%)	<0.001
Null mutation	235.0 (40.6%)	167 (47.6%)	0.037
Type 2 diabetes mellitus	49 (8.5%)	50 (14.2%)	0.006
Hypertension	176 (30.4%)	158 (45.0%)	<0.001
Active smoking	70 (12.1%)	38 (10.8%)	0.560
BMI (kg/m^2)	27.5 (24.9–30.8)	28.4 (25.7–31.1)	0.011
Total cholesterol (mg/dL)	235.0 (208.0–272.0)	223.0 (192.0–264.0)	<0.001
LDL-C (mg/dL)	162.0 (138.0–196.0)	153.6 (126.0–190.6)	0.002
HDL-C (mg/dL)	52.0 (44.0–60.0)	46.0 (38.1–54.0)	<0.001
TG (mg/dL)	91.0 (71.0–122.0)	99.0 (78.0–134.0)	0.004
Lp(a) (mg/dL)	24.8 (9.1–57.7)	38.2 (14.9–82.6)	<0.001
LDL-CLp(a)	145.5 (120.0–179.2)	131.7 (100.2–166.9)	<0.001
Patients on maximum statin	253 (43.7%)	221(63.0%)	<0.001
Patients on maximum LLT	348 (60.1%)	266 (75.8%)	<0.001
Years on statins	11.9 (4.9–19.3)	12.4 (4.8–18.9)	0.567
LDL-C-years (mg-yr/dL)/1000	13.8 (11.5–16.6)	13.9 (11.2–17.2)	0.838
LDL-CLp(a)-years (mg-yr/dL)/1000	12.4 (10.1–15.3)	11.8 (8.9–15.1)	0.044
SAFEHEART-RE 10 years (%)	2.3 (1.2–3.4)	9.3 (4.2–17.1)	<0.001

BMI, body mass index; FH, familial hypercholesterolaemia patient; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LDL-CLp(a), LDL-C adjusted by content of Lp(a); LLT, lipid-lowering treatment; R-FH, resilient familial hypercholesterolaemia; TG, triglycerides.

type 2 diabetes mellitus and arterial hypertension, but a reduction in the proportion of people who smoked.

Characteristics of the population with and without resilient familial hypercholesterolaemia

Table 2 shows the baseline characteristics of the population with FH at entry in the registry, divided into patients with and without R-FH. A long list of variables is significantly different between the two groups: R-FH patients were younger, the prevalence of female gender was higher, the prevalence of null LDL-R mutation was lower, as well as the prevalence of diabetes mellitus and high blood pressure, body mass index (BMI) was lower, total cholesterol (TC), LDL-C, triglycerides (TG), lipoprotein (a) [Lp(a)], and LDL-C adjusted by cholesterol content of Lp(a) [LDL-CLp(a)] were lower and high-density lipoprotein cholesterol (HDL-C) level was higher, treatment intensity as assessed by different variables was lower, LDL-CLp(a)-years was lower and, once more, the cardiovascular risk estimated by the 10-year SAFEHEART-RE was lower than in non-R-FH patients. Median LDL-C at entry and at the end of the follow-up in R-FH patients were 162 (138–196) and 120 (99–143) mg/dL, respectively, and in non-R-FH, they were 153.6 (126–190) and 108 (75–133) mg/dL, respectively.

Predictors of resilient familial hypercholesterolaemia (univariate and multivariate analyses)

Table 3 shows the results of the univariate logistic regression analysis showing variables related to resilient FH. Younger age, female gender, defective mutation, absence of diabetes mellitus, absence of hypertension, low BMI, low TC, low LDL-C, high HDL-C, low TG, low Lp(a), low LDL-CLp(a)-years, and low score in SAFEHEART-RE 10 years were statistically significant in the univariate logistic regression analysis. Nevertheless, multivariate analysis (*Table 4*) showed that defective LDL-R mutation [relative risk (RR) 0.672; 95% confidence interval (CI) 0.493–0.916; $P = 0.012$], high level of HDL-C (RR 1.019; 95% CI 1.005–1.033; $P = 0.009$), younger age (RR 0.946; 95% CI 0.927–0.966; $P < 0.001$), female gender (RR 4.172; 95% CI 3.145–5.534; $P < 0.001$), absence of hypertension (RR 0.580; 95% CI 0.413–0.812; $P = 0.002$), and low Lp(a) (RR 0.990; 95% CI 0.987–0.994; $P < 0.001$) were independently associated with R-FH (*Table 4*). In a second model (*Table 5*), excluding those variables included in SAFEHEART-RE, only higher level of HDL-C (RR 1.024; 95% CI 1.008–1.041; $P = 0.003$) and low score in SAFEHEART-RE 10 years (RR 0.651; 95% CI 0.609–0.696; $P < 0.001$) were independently associated with R-FH (*Table 5*). *Figure 2* shows ROC curve for SAFEHEART-RE. Areas under curve were 0.873 (95% CI 0.849–0.898; $P < 0.001$) and 0.635 (95% CI 0.599–0.672; $P < 0.001$) for SAFEHEART-RE and HDL-C, respectively.

Table 3 Logistic regression univariate analysis showing variables related to resilient familial hypercholesterolaemia

	RR	95% CI	*P*-value
Age (years)	0.950	0.934–0.966	<0.001
Female	4.172	3.145–5.534	<0.001
Null mutation	0.753	0.576–0.983	0.037
Diabetes mellitus	0.557	0.366–0.846	0.006
Hypertension	0.533	0.405–0.702	<0.001
BMI (kg/m^2)	0.959	0.932–0.987	0.005
Active smoking	1.133	0.745–1.723	0.560
Total cholesterol (mg/dL)	1.004	1.001–1.006	0.001
LDL-C (mg/dL)	1.003	1.001–1.005	0.012
LDL-CLp(a)	1.005	1.002–1.007	<0.001
HDL-C (mg/dL)	1.040	1.028–1.052	<0.001
TG (mg/dL)	0.996	0.993–0.999	0.003
Lp(a) (mg/dL)	0.993	0.990–0.996	<0.001
Time on statins (years)	1.004	0.986–1.023	0.659
LDL-C-years (mg-yr/dL)/1000	0.999	0.972–1.027	0.955
LDL-CLp(a)-years (mg-yr/dL)/1000	1.023	0.995–1.052	0.112
SAFEHEART-RE 10 years (%)	0.645	0.604–0.689	<0.001

10-y SAFEHEART-RE, 10-year risk estimated by means of the SAFEHEART risk equation; BMI, body mass index; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LDL-CLp(a), LDL-C adjusted by content of Lp(a); Lp(a), lipoprotein (a); RR, relative risk; TG, triglycerides.

Table 4 Logistic regression multivariate analysis showing variables related to resilient familial hypercholesterolaemia (Model 1)

	RR	95% CI	*P*-value
Age (years)	0.946	0.927–0.966	<0.001
Female	5.301	3.776–7.441	<0.001
Null mutation	0.672	0.493–0.916	0.012
Diabetes mellitus	0.713	0.430–1.181	0.189
Hypertension	0.580	0.413–0.812	0.002
BMI (kg/m^2)	0.965	0.932–1.0	0.052
LDL-C (mg/dL)	1.0	0.997–1.003	0.919
HDL-C (mg/dL)	1.019	1.005–1.033	0.009
TG (mg/dL)	1.0	0.996–1.003	0.887
Lp(a) (mg/dL)	0.990	0.987–0.994	<0.001

BMI, body mass index; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); RR, relative risk; TG, triglycerides.

Table 5 Logistic regression multivariate analysis showing variables related to resilient familial hypercholesterolaemia (Model 2)

	RR	95% CI	*P*-value
Null mutation	0.783	0.545–1.124	0.185
Diabetes mellitus	0.627	0.360–1.091	0.099
HDL-C (mg/dL)	1.024	1.008–1.041	0.003
TG (mg/dL)	1.004	1.0–1.007	0.063
SAFEHEART-RE 10 years (%)	0.651	0.609–0.696	<0.001

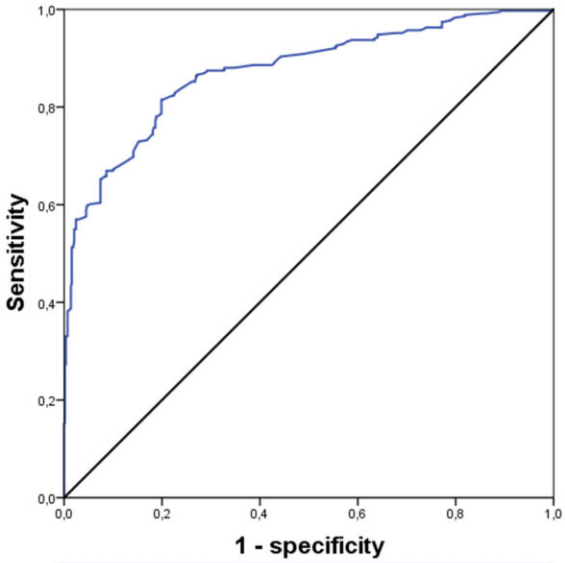
CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; RR, relative risk; TG, triglycerides.

Discussion

We describe the characteristics of a novel phenotype of heterozygous FH patients who we refer to as 'resilient' FH. These genetically diagnosed patients reach 65 years of age without having sustained a clinical ASCVD event. They are typified as female and having a defective LDL-receptor mutation, higher levels of plasma HDL-C, lower levels of Lp(a) and absence of hypertension, or low score using the SAFEHEART risk equation.

In a recently published study by Coutinho *et al.*,[8] 462 genotyped individuals older than 60 years, 198 with FH, and 264 non-FH were analysed. In patients with FH, male sex and age of lipid-lowering treatment (LLT) onset age were independently associated with ASCVD. Lacaze *et al.*[9] suggested that since a polygenic risk score alone does not explain reduced penetrance in a healthy elderly population with FH, environmental factors, adherence to a healthy lifestyle, long-term statin use, and undiscovered rare protective alleles may also have a role in resilence. In our study, patients began to be systematically followed from the moment they were recruited to the SAFEHEART registry but information on the date of initiation of treatment with lipid-lowering treatment prior to inclusion was available. Most of our patients in our study were undertreated according to current recommended guidelines,[4,10] being treated with the available statins in the 90s. In our cohort of patients aged ≥65 years, treatment with statins was started after the age of 40. Despite this, we are showing that there are patients with FH who are resilient to ASCVD. However, we must bear in mind that even if they are resilient, they must be treated optimally as it was done in the study cohort.[11] Furthermore, it is of note that even with optimized statin usage, the prevalent gap between guideline recommended LDL-C goals and their implementation in clinical care requires greater utilization of non-statin drugs in combination with statins for patients at highest risk.[10] This point is even more important as we know that PCSK9 inhibitors have shown similar efficacy and safety throughout a broad range of ages and in both men and women.[12] PCSK9 inhibitors on top of maximum LLT significantly reduced LDL-C levels in men and women patients with FH and improved the achievement of LDL-C targets.[11] Thus, our study has clearer clinical relevance to understand in a large and well-defined cohort which patients with FH may have or may have not a less need for aggressive and expensive treatment because, under optimal treatment, they are resilient to the development of ASCVD events and, conversely, which patients will need the most stringent therapeutic strategy.

Previous studies have shown multiple risk factors for ASCVD in FH, such as type of mutation, sex, HDL-C, Lp(a) levels, and hypertension with many included in the SAFEHEART-RE.[3,6,13] The usefulness of this equation has been recently confirmed in predicting coronary



AUC: 0.873; 95% CI: 0.849 – 0.898; p<0.001.

Cut-off point	Sensitivity	Specificity
1	0.98	0.20
2	0.93	0.44
3	0.87	0.70
4	0.76	0.81

Figure 2 Receiver operating characteristic curve to assess the accuracy of SAFEHEART-RE to detect resilient familial hypercholesterolaemia patients. Bottom: area under curve and sensitivity and specificity for different cut-off points. AUC, area under curve; CI, confidence interval.

artery disease in FH patients without clinical ASCVD.[14] We show that R-FH patients may be predicted with two simple parameters, the SAFEHEART-RE score and HDL-C. Low-density lipoprotein cholesterol was not significant in our multivariable model possibly due to the more intensive LLT used in those patients with an acute cardiovascular event. Women are well known to be protected against ASCVD due to biological aspects related to gender[15,16] and this evidently applies to FH. Our overall findings are supported by a recent smaller and less well-defined study from Canada.[17] An important point to keep in mind is the crucial role of Lp(a). We recommend measuring Lp(a) in every patient with FH owing to it potent prognostic information for ASCVD.[18,19]

Identification of R-FH patients has clinical and social implications. The heterogeneity of the ASCVD risk in FH depends on genetic and environmental factors.[3,6] Patients, carriers of a pathogenic gene variant with an important effect on atherosclerosis can survive to an advanced age without developing clinical ASCVD, even though they were treated with statins late in life. Identification of these FH patients may help clinical management, less-intense LLT use, and better quality of life for the patients.

As a limitation polygenic risk scores were not specifically analysed. Although they are recently being found very informative,[13,20,21] they were out of the scope of the current study. The analysis was carried out as a control–case study and logistic regression analysis was used to analyse not only those ASCVD events occurred during follow-up but also before enrolment in the registry. These results obtained in a Spanish National cohort need validation in other countries worldwide where risk modifiers may differ. The main strength of this study is that it includes the largest number of patients with these characteristics and that they belong to SAFEHEART Cohort, which systematically performs an annual follow-up with a systematized protocol.

Conclusions

We conclude that heterozygous FH patients resilient to the development of cardiovascular disease may be identified with measures regularly employed in clinical practice, included in the SAFEHEART risk algorithm. Our study has implications for precision medicine development programs. The robustness of our approach to the prediction of R-FH needs to be validated in other populations.

Acknowledgements

The authors thank the Spanish Familial Hypercholesterolemia 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 work was supported by Fundación Hipercolesterolemia Familiar; grant G03/181 and FIS PI12/01289 from Instituto de Salud Carlos III (ISCIII), grant 08-2008 Centro Nacional de Investigación Cardiovascular (CNIC).

Conflict of interest: none declared.

References

1. Watts GF, Gidding SS, Mata P, Pang J, Sullivan DR, Yamashita S, Raal FJ, Santos RD, Ray KK. Familial hypercholesterolaemia: evolving knowledge for designing adaptive models of care. *Nat Rev Cardiol* 2020;**17**:360–377.
2. 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, Averna M, Boren J, Bruckert E, Catapano AL, Kuivenhoven JA, Pajukanta P, Ray K, Stalenhoef AFH, Stroes E, Taskinen M-R, Tybjaerg-Hansen A; European Atherosclerosis Society Consensus Panel. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. *Eur Heart J* 2013;**34**:3478–3490.
3. Mata P, Alonso R, Pérez de Isla L. Atherosclerotic cardiovascular disease risk assessment in familial hypercholesterolemia: does one size fit all? *Curr Opin Lipidol* 2018;**29**:445–452.
4. 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, Tokgozoglu LW, Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, Chapman MJ, Backer GGD, Delgado V, Ference BA, Graham IM, Halliday A, Landmesser U, Mihaylova B, Pedersen TR, Riccardi G, Richter DJ, Sabatine MS, Taskinen MR, Tokgozoglu L, 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.
5. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, Ferranti S D, Faiella-Tommasino J, Forman DE, Goldberg R, Heidenreich PA, Hlatky MA, Jones DW, Lloyd-Jones D, Lopez-Pajares N, Ndumele CE, Orringer CE, Peralta CA, Saseen JJ, Smith SC, Sperling L, Virani SS, Yeboah J. 2018 AHA/ACC/

AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the management of blood cholesterol. *J Am Coll Cardiol* 2018;**73**:3168–3209.
6. Pérez De Isla L, Alonso R, Mata N, Fernández-Pérez C, Muñiz O, Díaz-Díaz JL, Saltijeral A, Fuentes-Jiménez F, Andrés RD, 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.
7. Mata N, Alonso R, Badimón L, Padró T, Fuentes F, Muñiz O, Perez-Jiménez F, López-Miranda J, Díaz JL, Vidal JI, 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.
8. Coutinho ER, Miname MH, Rocha VZ, Bittencourt MS, Jannes CE, Tada MT, Lima IR, Filho WS, Chacra AP, Pereira AC, Krieger JE, Santos RD. Familial hypercholesterolemia and cardiovascular disease in older individuals. *Atherosclerosis* 2021;**318**:32–37.
9. Lacaze P, Sebra R, Riaz M, Hooper AJ, Tiller J, Bakshi A, Woods RL, Tonkin AM, Reid CM, Murray AM, Nicholls SJ, Watts GF, Schadt E, McNeil JJ. Familial hypercholesterolemia in a healthy elderly population. *Circ Genomic Precis Med* 2020;**13**:337–339.
10. Ray KK, Molemans B, Schoonen WM, Giovas P, Bray S, Kiru G, Murphy J, Banach M, Servi SD, 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, Siostrzonek P, Romeo S, Tousoulis D, Vlachopoulos C, Vrablik M, Catapano AL, Poulter NR. 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.
11. Alonso R, Muñiz-Grijalvo O, Díaz-Díaz JL, Zambón D, Andrés R D, 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. Efficacy of PCSK9 inhibitors in the treatment of heterozygous familial hypercholesterolemia: a clinical practice experience. *J Clin Lipidol* 2021;S1933-2874(21)00069-6. doi: 10.1016/j.jacl.2021.04.011. Epub ahead of print. PMID: 34052174.
12. Sever P, Gouni-Berthold I, Keech A, Giugliano R, Pedersen TR, Im KAh, Wang H, Knusel B, Sabatine MS, O'Donoghue ML. LDL-cholesterol lowering with evolocumab, and outcomes according to age and sex in patients in the FOURIER Trial. *Eur J Prev Cardiol* 2021;**28**:805–812.
13. Paquette M, Baass A. Predicting cardiovascular disease in familial hypercholesterolemia. *Curr Opin Lipidol* 2018;**29**:299–306.
14. Chiva-Blanch G, Padró T, Alonso R, Crespo J, Perez De Isla L, Mata P, Badimon L. Liquid biopsy of extracellular microvesicles maps coronary calcification and atherosclerotic plaque in asymptomatic patients with familial hypercholesterolemia: a computed tomographic angiography imaging study. *Arterioscler Thromb Vasc Biol* 2019;**39**:945–955.
15. Mendirichaga R, Jacobs AK. Sex differences in ischemic heart disease—the paradox persists. *JAMA Cardiol* 2020;**5**:754.
16. Reynolds HR, Shaw LJ, Min JK, Spertus JA, Chaitman BR, Berman DS, Picard MH, Kwong RY, Bairey-Merz CN, Cyr DD, Lopes RD, Lopez-Sendon JL, Held C, Szwed H, Senior R, Gosselin G, Nair RG, Elghamaz A, Bockeria O, Chen J, Chernyavskiy AM, Bhargava B, Newman JD, Hinic SB, Jaroch J, Hoye A, Berger J, Boden WE, O'Brien SM, Maron DJ, Hochman JS; ISCHEMIA Research Group. Association of sex with severity of coronary artery disease, ischemia, and symptom burden in patients with moderate or severe ischemia: secondary analysis of the ISCHEMIA randomized clinical trial. *JAMA Cardiol* 2020;**5**:773–786.
17. Khoury E, Brisson D, Roy N, Tremblay G, Gaudet D. Identifying markers of cardiovascular event-free survival in familial hypercholesterolemia. *J Clin Med* 2020;**10**:64.
18. Alonso R, Andres E, Mata N, Fuentes-Jiménez F, Badimón L, López-Miranda J, Padró T, Muñiz O, Díaz-Díaz JL, Mauri M, Ordovás JM, Mata P; SAFEHEART Investigators. Lipoprotein(a) levels in familial hypercholesterolemia. *J Am Coll Cardiol* 2014;**63**:1982–1989.
19. Ellis KL, Pérez de Isla L, Alonso R, Fuentes F, Watts GF, Mata P. Value of measuring lipoprotein(a) during cascade testing for familial hypercholesterolemia. *J Am Coll Cardiol* 2019;**73**:1029–1039.
20. Ellis KL, Hooper AJ, Pang J, Chan DC, Burnett JR, Bell DA, Schultz CJ, Moses EK, Watts GF. A genetic risk score predicts coronary artery disease in familial hypercholesterolaemia: enhancing the precision of risk assessment. *Clin Genet* 2020;**97**:257–263.
21. Fahed AC, Wang M, Homburger JR, Patel AP, Bick AG, Neben CL, Lai C, Brockman D, Philippakis A, Ellinor PT, Cassa CA, Lebo M, Ng K, Lander ES, Zhou AY, Kathiresan S, Khera AV. Polygenic background modifies penetrance of monogenic variants for tier 1 genomic conditions. *Nat Commun Nat Res* 2020;**11**:3635.