Journal of Clinical Lipidology (2022) 16, 733–736

Journal of Clinical Lipidology

Predicting resilience in heterozygous familial hypercholesterolaemia: A cohort study of octogenarian patients

Leopoldo Pérez de Isla, MD, PhD, Rodrigo Alonso, MD, PhD, Rosa Argüeso, MD, PhD, Ovidio Muñiz-Grijalvo, MD, PhD, Pilar Álvarez-Baños, MD, Lina Badimón, MD, PhD, Gerald F. Watts, MD, PhD, Pedro Mata, MD, PhD*, on behalf of SAFEHEART Investigators**

Cardiology Department, Hospital Clínico San Carlos, IDISSC, Facultad de Medicina, Universidad Complutense, Madrid, Spain (Dr de Isla); Fundación Hipercolesterolemia Familiar, Madrid, Spain (Drs de Isla, Alonso, and Mata); Center for Advanced Metabolic Medicine and Nutrition, Santiago, Chile (Dr Alonso); Department of Endocrinology, Hospital Universitario Lucus Augusti, Lugo, Spain (Dr Argüeso); Internal Medicine Department, Hospital Virgen del Rocío, Sevilla, Spain (Dr Muñiz-Grijalvo); Department of Endocrinology, Hospital Universitario de Burgos, Burgos, Spain (Dr Álvarez-Baños); ICCC Cardiovascular, Institut de Recerca del Hospital Santa Creu i Sant Pau, IIB Santa Pau, Barcelona, Spain (Dr Badimón); Lipid Disorders Clinic, Department of Cardiology, Royal Perth Hospital, School of Medicine, University of Western Australia, Perth, Australia (Dr Watts)

KEYWORDS
Familial hypercholesterolemia;
Very elderly individuals;
Octogenarian;
Cardiovascular disease;
Lipid-lowering treatment

Abstract: Defining patients with familial hypercholesterolemia (FH) destined not to develop clinical atherosclerotic cardiovascular disease (ASCVD) has significant implications for precision and discovery medicine. We investigated the predictors of resilience to ASCVD in a cohort of 248 octogenarian patients with FH enrolled in the SAFEHEART study. Median age at the time of analysis was 84.7 years (82.3–88.1) and 83.6 years (81.9–86.4) in the octogenarian resilient FH (OR-FH) and octogenarian controls non-resilient FH (OCNoR-FH) groups, respectively (p=0.073); 92 (80.0%) and 68 (51.1%) patients were female in the first compared with the second group (p<0.001). Multivariate logistic regression showed that a low 10-year score in SAFEHEART-Risk Equation was the only independent predictor of OR-FH. Application of this simple and validated risk equation may potentially be useful for predicting patients ultra-resilient to the ASCVD sequelae of FH who may require less intensive use of healthcare resources.

Recognizing patients with familial hypercholesterolemia (FH) who do not develop atherosclerotic cardiovascular disease (ASCVD) is important for the management of this condition, especially in older individuals.[1] Being female, carrying a defective mutation in *LDLR* gene, high HDL-C and low lipoprotein(a) were predictors of resilient FH in patients aged 65 years or more in the SAFEHEART study.[2] There are scarce data, however, on FH patients 80 years old or older without clinical ASCVD. Our aim was to determine

For the SAFEHEART investigators (https://www.colesterolfamiliar.org/en/safeheart-study/lipid-clinics-participating-in-the-study/)

* Corresponding author.
** Corresponding author at: Cardiology Department, Hospital Clínico San Carlos, IDISSC, Facultad de Medicina, Universidad Complutense, C/Profesor Martín Lagos s/n, 28040 Madrid. Spain.
E-mail addresses: leopisla@hotmail.com (L. Pérez de Isla), pmata@colesterolfamiliar.org (P. Mata).

Submitted April 6, 2022. Received in revised form June 21, 2022. Accepted for publication July 11, 2022.

1933-2874/
https://doi.org/10.1016/j.jacl.2022.07.007

Table 1 Baseline characteristics at entry in the SAFEHEART registry of the study population split into octogenarian resilient FH patients (OR-FH) and octogenarian controls non-R-FH patients (OCNoR-FH).

	OR-FH Median (Q1-Q3)/n (%)	OCNoR-FH Median (Q1-Q3)/n (%)	*p*
N	115	133	
Age (years) at inclusion	74.5 (70.4–77.9)	74.5 (71.5–78.8)	0.273
Current age (years)	84.7 (82.3–88.1)	83.6 (81.9–86.4)	0.073
Female	92 (80.0%)	68 (51.1%)	<0.001
Null mutation	45.0 (39.1%)	62 (46.6%)	0.235
Type 2 Diabetes mellitus	10 (8.7%)	19 (14.3%)	0.172
Hypertension	52 (45.2%)	66 (49.6%)	0.488
Active smoking	3 (2.6%)	3 (2.3%)	0.857
BMI (kg/m^2)	28.4 (25.6–31.2)	28.7 (25.9–31.4)	0.629
Total Cholesterol (mg/dl)	233.0 (208.0–270.0)	225.0 (185.0–260.0)	0.014
LDL-C (mg/dl)	160.0 (136.2–202.0)	154.0 (124.0–185.0)	0.051
HDL-C (mg/dl)	52.0 (44.0–59.0)	46.0 (38.0–55.0)	<0.001
TG (mg/dl)	97.0 (76.0–122.0)	98.3 (78.0–131.0)	0.789
Lp(a) (mg/dl)	27.0 (8.3–62.0)	33.6 (15.2–86.7)	0.031
LDL-CLp(a) (mg/dl)	143.6 (114.2–193.9)	133.4 (105.2–166.3)	0.012
Patients on maximum statin	44 (38.3%)	77 (57.9%)	0.002
Patients on maximum LLT	63 (54.8%)	97 (72.9%)	0.003
Years on statins	10.2 (4.9–17.0)	12.4 (4.8–19.9)	0.271
LDL-C-years (mg-yr/dL)/1000	16.1 (13.7–19.3)	15.7 (12.9–19.0)	0.157
LDL-CLp(a)-years (mg-yr/dL)/1000	14.5 (11.7–18.0)	13.4 (10.9–16.5)	0.033
SAFEHEART-RE 10 years (%)	2.4 (1.8–3.9)	9.4 (4.5–17.2)	<0.001

ASCVD: atherosclerotic cardiovascular disease; BMI: Body mass index; FH: familial hypercholesterolemia patient; LDL-CLp(a): LDL-C adjusted by content of Lp(a); LLT: Lipid lowering therapy.

the characteristics and predictors of resilience to ASCVD in a very elderly FH population.

SAFEHEART is a contemporary cohort study in genetically defined patients with FH; the study design, methodology and follow-up have been published elsewhere.[3] Those FH patients who at the time of this analysis were at least 80 years or older free of clinical ASCVD were considered (OR-FH). Those FH patients who at the time of this analysis were at least 80 years or older free of clinical ASCVD were considered (OR-FH). They were compared with a group, considered as octogenarian Controls with non-resilient FH (OCNoR-FH), comprised of octogenarians that developed clinical ASCVD and those who would have been 80 years or older at the moment of the analysis but who previously died from a cardiovascular event. Baseline characteristics at inclusion in the registry included age, cardiovascular risk factors, lipid levels and lipid-lowering therapy (LLT). LDL-C was adjusted for Lp(a) content. Also, the SAFEHEART-risk equation (SAFEHEART-RE) including gender, age, categorized LDL-C and Lp(a) levels, body mass index, presence of hypertension, previous ASCVD and smoking habit, was estimated.[3] ASCDV was defined as the occurrence of one of the following: Fatal or non-fatal myocardial infarction, fatal or non-fatal ischemic stroke, coronary revascularization, peripheral artery revascularization, cardiovascular death (any death related to cardiovascular disease or derived of cardiovascular therapeutic procedures not described in the previous definitions) and need for aortic valve replacement due to severe degenerative aortic stenosis.

Two hundred and forty-eight patients with FH met the study criteria (Table 1). Median age at the time of recruitment was 74.5 years (70.4–77.9) and 74.5 years (71.5–78.8) in OR-FH and OCNoR-FH groups respectively (p=0.273). Median age at the time of analysis was 84.7 years (82.3–88.1) and 83.6 years (81.9–86.4), respectively (p=0.073). Ninety-two (80.0%) and 68 (51.1%) were female patients in OR-FH and OCNoR-FH, respectively (p<0.001). No differences in the type of mutation were observed between the groups (39.1% and 46.6% carried null mutation in ORFH and OCNoFH, respectively p=0.235). Four patients were on hormonal replacement therapy, all of them in the OR-FH group. After univariate analysis (Table 2), logistic regression multivariate analysis showed that only a low 10-year score in SAFEHEART-RE (about four times lower than in OCNoR-FH) (Figure 1) was independently predictive of OR-FH (Table 2).

Among those with OCNoR-FH, the ASCVD (first event) events were distributed as follows: 93 non-fatal acute coronary syndromes (69.9%), 2 coronary artery revascularizations (1.5%), 13 non-fatal strokes (9.8%), 2 fatal stroke (1.5%), 2 peripheral artery revascularizations (1.5%), 8 aortic valve replacements secondary to severe aortic stenosis (6%) and 11 cardiovascular deaths (8.3%). Median follow-up cohort time was 6.46 (3.31–8.99) years.

Two recent studies have analyzed ASCVD in elderly FH patients; however, the number of patients over 80 years, and mean age was much lower than in our study (66 and 74 years, respectively).[4–6] Interestingly, most of patients in our

Table 2 Logistic regression univariate and multivariate analysis showing variables related to octogenarian resilient FH.

	RR	95%CI	*p*
Univariate analysis			
Age (years)	0.964	0.920–1.010	0.964
Female	3.824	2.163–6.758	<0.001
Null mutation	0.736	0.444–1.221	0.236
Diabetes mellitus	0.571	0.254–1.285	0.176
Hypertension	0.838	0.508–1.382	0.488
BMI (Kg/m2)	0.976	0.921–1.034	0.405
Active smoking	1.161	0.230–5.866	0.857
Total cholesterol (mg/dl)	1.006	1.002–1.011	0.005
LDL-C (mg/dl)	1.006	1.001–1.010	0.015
LDL-CLp(a) (mg/dl)	1.007	1.002–1.011	0.004
HDL-C (mg/dl)	1.034	1.012–1.056	0.002
TG (mg/dl)	0.999	0.993–1.004	0.598
Lp(a) (mg/dl)	0.994	0.988–0.999	0.023
Time on statins (years)	0.980	0.946–1.016	0.266
LDL-C-years (mg-yr/dL)/1000	1.049	0.996–1.105	0.069
SAFEHEART-RE 10 years (%)	0.632	0.554–0.721	<0.001
Multivariate analysis			
HDL-C (mg/dl)	1.013	0.986–1.042	0.337
SAFEHEART-RE 10 years (%)	0.639	0.559–0.730	<0.001

10-y SAFEHEART-RE: 10-y risk estimated by means of the SAFEHEART risk equation; ASCVD: cardiovascular disease; HDL-C: high-density lipoprotein cholesterol; RR: Relative risk; BMI: Body mass index; LDL-C: low-density lipoprotein cholesterol; LDL-CLp(a): LDL-C adjusted by content of Lp(a); Lp(a): lipoprotein (a); TG: triglycerides.

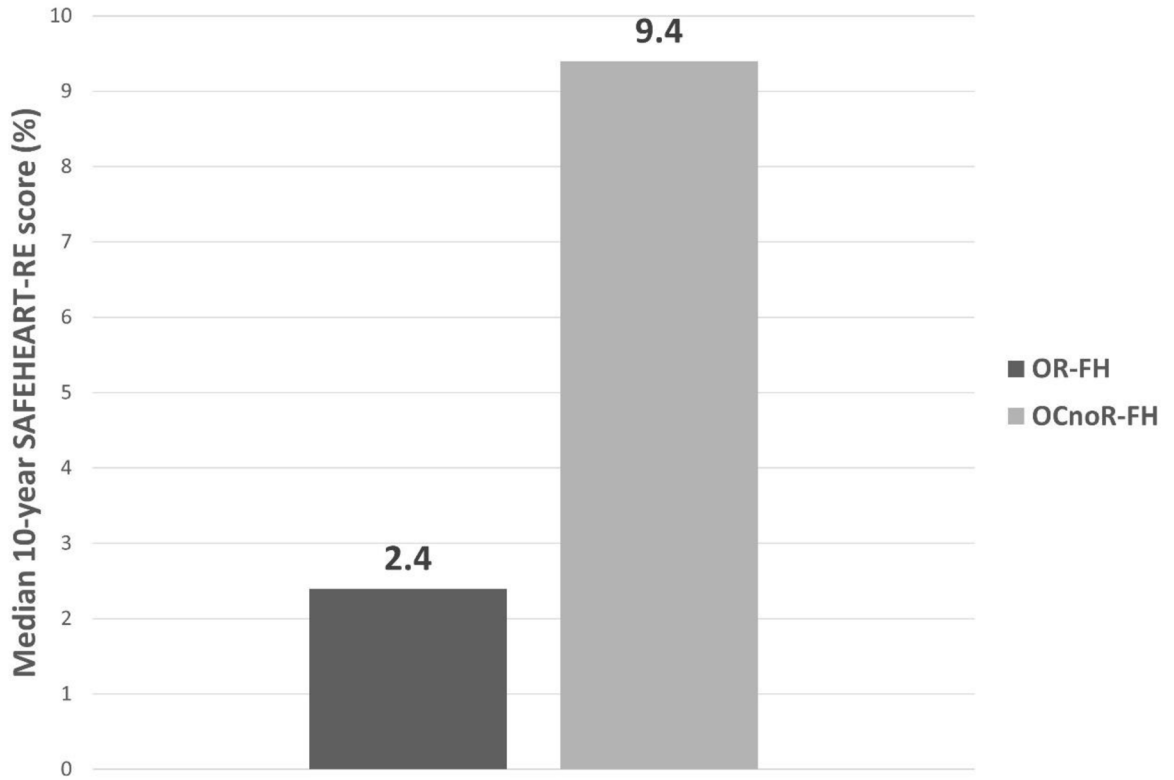

Fig. 1 Median 10-year SAFEHEART risk equation cardiovascular score in octogenarian resilient FH patients (OR-FH) and octogenarian controls non-resilient FH patients (OCNoR-FH).

study have been treated with statins a median of 10–12 years, meaning that they started statin treatment around age 60 years. Despite this late onset, we are showing that there are octogenarian FH patients who are resilient to develop clinical ASCVD. It is important to keep in mind that, although OR-FH patients have not developed clinical atherosclerotic disease, it is very likely that, owing to the presence of elevated LDL-C levels from very early ages in life, they are very likely to have subclinical coronary atherosclerosis.[7]

In this study, we show that resilient FH patients may be identified using the SAFEHEART-RE, that employs ASCVD risk factors that can be readily recorded in routine clinical practice.[3] Our findings may be useful in identifying patients who may be treated less aggressively that recommended by current FH guidelines.[1] Although all resilient patients were on LLT, less than half were receiving high-dose statin therapy and 54.8% were on maximum LLT. Therefore, the identification of OR-FH patients might have clinical and social implications. Risk prediction equations tend to overestimate risk in older individuals and underestimate risk in women.[8] The present analysis refers to an analysis of genetically defined octogenarians with FH, including a high proportion of women, enabled by the unique features of the SAFEHEART study. The higher level of LDL-C present in OR-FH patients is noteworthy and relates, according to the case-control design, to the use of more potent cholesterol-lowering therapies in the OCNoR-FH following an ASCVD event (Table 1), despite length of treatment with statins being similar in both groups. Our results demonstrated that, beyond LDL-C levels, a lower score in SAFEHEART-RE, especially to be female contribute to a reduced risk of ASCVD and cardiovascular events-free survival in FH. These ASCVD-free FH carriers may have protective genetic modifiers or low polygenic risk[9] and healthy lifestyle, modifying FH penetrance. Further genomic evaluation of FH patients that remain unaffected by ASCVD to advances in ages may also provide a new opportunity for novel target discovery for preventive therapies.

In conclusion, we have described a registry subset of people at putatively high genetic risk ASCVD due to FH who survive beyond 80 years without developing clinical ASCVD. These ultra-resilient individuals may be characterised clinically as having a low SAFEHEART-RE score. Further studies of the genetic determinants offering protection against ASCVD[6,9] may lead to the development of new therapies.

Declarations of interest

None.

Contribution Statement

Authors' contributions: L.P.I., R.AL. G.F.W. and P.M. contributed to study design, research, statistical analysis, manuscript writing, and critical review. R.AL., O.M.G., R.AR. P.A.B L.B. L.P.I. G.F.W. and P.M. contributed to study design, patient enrolment, research, manuscript writing, and critical review.

All authors have approved the final article.

Acknowledgment

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).

References

1. Watts GF, Gidding SS, Mata P, et al. Familial hypercholesterolaemia: evolving knowledge for designing adaptive models of care. *Nat Rev Cardiol*. 2020;17(6):360–377. doi:10.1038/s41569-019-0325-8.
2. Pérez de Isla L, Watts G, Muñiz-Grijalvo O, et al. A resilient type of familial hypercholesterolaemia: case-control follow-up of genetically characterized older patients in the SAFEHEART cohort. *Eur J Prev Cardiol*. 2021;Dec 2 zwab(Epub ahead of print). doi:10.1093/eurjpc/zwab185.
3. Pérez De Isla L, Alonso R, Mata N, et al. Predicting cardiovascular events in familial hypercholesterolemia: the SAFEHEART registry (Spanish Familial hypercholesterolemia cohort study). *Circulation*. 2017;135(22):2133–2144. doi:10.1161/CIRCULATIONAHA.116.024541.
4. Coutinho ER, Miname MH, Rocha VZ, et al. Familial hypercholesterolemia and cardiovascular disease in older individuals. *Atherosclerosis*. 2021;318:32–37. doi:10.1016/j.atherosclerosis.2020.12.012.
5. 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(1):64. doi:10.3390/jcm10010064.
6. Lacaze P, Sebra R, Riaz M, et al. Familial hypercholesterolemia in a healthy elderly population. *Circ Genom Precis Med*. 2020;13(4):337–339. doi:10.1161/CIRCGEN.120.002938.
7. Pérez de Isla L, Alonso R, Muñiz-Grijalvo O, et al. Coronary computed tomographic angiography findings and their therapeutic implications in asymptomatic patients with familial hypercholesterolemia. Lessons from the SAFEHEART study. *J Clin Lipidol*. 2018;12(4):948–957. doi:10.1016/j.jacl.2018.04.003.
8. Cooney MT, Dudina A, D'Agostino R, Graham IM. Cardiovascular risk-estimation systems in primary prevention: do they differ? do they make a difference? can we see the future? *Circulation*. 2010;122(3):300–310. doi:10.1161/CIRCULATIONAHA.109.852756.
9. Fahed AC, Wang M, Homburger JR, et al. Polygenic background modifies penetrance of monogenic variants for tier 1 genomic conditions. *Nat Commun*. 2020;11(1):3635. doi:10.1038/s41467-020-17374-3.