Coronary artery event-free or resilient familial hypercholesterolemia: what's in a name?

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Purpose of review
Familial hypercholesterolemia (FH) is an autosomal semi-dominant condition, characterized by excessive circulating low-density lipoprotein cholesterol (LDL-C) from birth that substantially accelerates the onset and progression of atherosclerotic cardiovascular disease (ASCVD), classically coronary artery disease (CAD). Elevated plasma LDL-C integrated over time is unequivocally the major determinant of ASCVD in heterozygous FH (HeFH); however, the wide variation in incidence and progression of ASCVD suggests a role for a wide spectrum of risk modifiers. We reviewed recent evidence describing the features of an ASCVD-free entity referred to as resilient FH among patients with HeFH.

Recent findings
Compared with nonresilient FH patients, resilient patients are more likely to be female, and have a lower prevalence of ASCVD comorbidities, higher levels of HDL-C and larger HDL particles, as well as a lower level of lipoprotein(a). A lower SAFEHEART risk score is also an independent predictor of resilient FH. Gene expression studies also demonstrate that resilient FH patients are associated with a less atherogenic gene expression profile in relation to HDL metabolism and immune responses, as reflected by higher expression of *ABCA1* and *ABCG1,* and lower expression of *STAT2* and *STAT3,* respectively.

Summary
A group of HeFH patients, referred as resilient FH, can survive to advance ages without experiencing any ASCVD events. Several key contributors to the event-fee CAD in HeFH patients have been identified. This could not only improve risk stratification and management for FH but also be of major importance for the general population in primary and secondary prevention. However, resilient FH remains an under-investigated area and requires further research.

Keywords
ASCVD event-free familial hypercholesterolemia, familial hypercholesterolemia, HDL-C, LDL-C, resilient familial hypercholesterolemia

INTRODUCTION

Familial hypercholesterolemia (FH) is an autosomal semi-dominant inherited condition, characterized by markedly elevated low-density lipoprotein cholesterol (LDL-C) from birth due to decreased hepatic LDL clearance [1▪]. The prevalence of heterozygous FH (HeFH) is approximately one in 300 among the general population, making HeFH as one of the most prevalent monogenic disorders [2]. The constant exposure to elevated levels of LDL-C makes FH patients susceptible to the development of atherosclerotic cardiovascular disease (ASCVD) [3]. Although the LDL-C burden over time is the primary determinant of ASCVD risk in HeFH, there is marked heterogeneity in risk, even among those with comparable LDL-C values and carrying the same genetic mutation [3]. Moreover, some FH patients develop ASCVD events despite receiving maximum lipid-lowering treatment (LLT), whereas some do not experience coronary events despite having markedly elevated levels of LDL-C or receiving LLT late in life [4]. Other risk modifiers, such as genetic, clinical and environmental factors, may have a role

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Curr Opin Endocrinol Diabetes Obes 2025, 32:45–51
DOI:10.1097/MED.0000000000000874

KEY POINTS

- Resilient familial hypercholesterolemia (FH) refers to a group of patients with heterozygous FH (HeFH) who survive to advanced age without experiencing an atherosclerotic cardiovascular disease (ASCVD) event.
- Resilient FH patients are more likely to be female, have fewer ASCVD comorbidities, lower plasma lipoprotein (a) concentration, and a greater prevalence of larger high-density lipoprotein (HDL) particles.
- A low SAFEHEART risk score is an independent predictor of resilient FH.
- Resilient FH patients are associated with a less atherogenic gene expression profile related to HDL metabolism (higher expression of *ABCA1* and *ABCG1*) and immune responses (lower expression of *STAT2* and *STAT3*).

in explaining the susceptibility of FH patients to ASCVD [5]. Characterizing patients particularly resistant to ASCVD among those with FH could help to identify protective factors that may allow greater reassurance about prognosis and offered less intensive and costly therapies. In the present review, we discuss the existent evidence concerning the characteristics and determinants of resilient or event-free FH.

Search strategy

A search of original publications in Google Scholar and PubMed was employed, using the following key terms: 'FH', 'elderly patients', 'atherosclerotic cardiovascular disease', 'cardiovascular disease', 'resilient FH', 'resistant FH', 'resistant to CVD', 'resistance to ASCVD', and 'CVD-event free' either alone or in combination.

Atherosclerotic cardiovascular disease risk in heterozygous familial hypercholesterolemia

Population studies have shown an increased prevalence of ASCVD in FH patients [1▪]. In an analysis of real-world data from a retrospective Spanish cohort [6], the incidence of ASCVD was estimated as 14.9/1000 person-years, among patients with the FH phenotype; however, the corresponding values for normolipidemic individuals were 7.1/1000 person-years. FH phenotype was shown to be associated with a seven-fold higher risk of ASCVD among those younger than 35 years [6]. Analyses of pooled data from 6 large US cohorts showed that coronary heart disease (CHD) risk was accelerated in individuals with the FH phenotype (LDL-C $\geq$190 mg/dl) by 10–20 years and 20–30 years in men and women, respectively [7]. Another analysis of 5518 genotyped FH patients from the Norwegian Cause of Death Registry showed that total CVD mortality was significantly higher in FH patients compared with the general population under 70 years [8▪▪]. The mortality was markedly high in young individuals aged 20–39 years (Fig. 1). However, there were no significant differences in total CVD mortality in those older above 70 years compared to the general population. These findings suggest that a subset of older subjects with FH do not develop ASCVD during their lifetime, pointing to potential protective factors.

Atherosclerotic cardiovascular disease risk stratification in familial hypercholesterolemia

The heterogeneity in incidence and progression of ASCVD events in HeFH has led to the development of risk prediction models, such as the SAFEHEART-RE (Spanish Familial Hypercholesterolemia Cohort Study Risk Equation) and the FH Risk Score, to enhance the precision and apportion the best use of resources to care (for example new LDL-C-lowering treatments) [9▪,10]. The SAFEHEART-RE incorporates age, gender, hypertension, obesity, smoking, history of ASCVD and levels of LDL-C and lipoprotein(a) [Lp(a)] to predict ASCVD in adult patients with genetically defined FH [9▪]. This algorithm has been validated using data from French Registry of Familial Hypercholesterolemia (REFERCHOL), showing a better CVD prediction in FH patients than classical risk equations, such as the Framingham risk equation and the American College of Cardiology/American Heart Association ASCVD Pooled Cohort Risk Equations [11]. Despite this risk prediction model has shown a promising value in predicting ASCVD in genetically diagnosed FH, its application to phenotypic FH in primary care appears to be limited [12]. Whether there are other markers or predictors explaining the susceptibility of FH patients to ASCVD, particularly in those older event-free FH patients, remains to be demonstrated.

Resilient or atherosclerotic cardiovascular disease event-free familial hypercholesterolemia

While there is no consensus definition of resilient FH, it is generally described as absence of previous clinical ASCVD manifestation in older subjects with a genetic or clinical diagnosis of FH [13,14▪▪,15▪,16▪▪,17▪,18▪]. Table 1 summarizes the characteristics of patients with resilient FH and

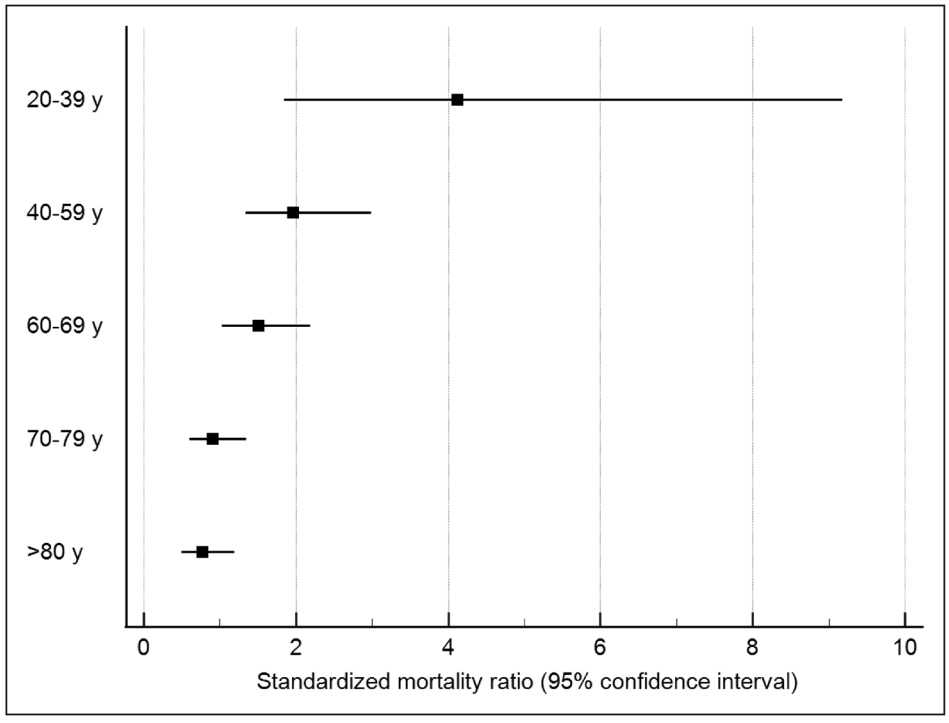

FIGURE 1. Standardized mortality ratio (SMR) for cardiovascular disease (CVD) death by different age categories of patients with heterozygous familial hypercholesterolemia (HeFH) in a Norwegian Cause of Death Registry [8▪▪].

associated determinants. These studies are described and discussed in more detail below [13,14▪▪,15▪,16▪▪,17▪,18▪]. The text below also refers to a control group of nonresilient FH individuals with previous clinical ASCVD manifestation or development of one event and same threshold of age employed in the definition of resilient FH in each corresponding study.

In a cross-sectional analysis from the Hipercol Brasil cascade screening program that included 198 genetically diagnosed FH aged ≥60 years [13], Coutinho *et al.* found that resilient FH individuals were more likely to be female, nonsmokers, had lower prevalence of family history of early ASCVD, lesser use of high intensity LLT and shorter LLT duration, as well as higher plasma level of HDL-C. The relative lower use and shorter duration of LLT in patients with resilient FH may reflect more intensive LLT treatment in the nonresilient FH group following an ASCVD event.

In analyses of 930 case–control follow-up of genetically diagnosed FH patients aged ≥65 years from the SAFEHHEART registry [14▪▪], Perez de Isla *et al.* reported that younger age, female gender, absence of hypertension, a defective *LDLR* mutation, higher plasma level of high-density lipoprotein cholesterol (HDL-C) and lower plasma Lp(a) concentration were independently predictive of resilience FH. In a further model excluding those predictor variables in the SAFEHEART-RF, a higher level of HDL-C and lower 10-year score in SAFEHEART-RE were also independently predictive of resilience FH. Area under curves were 0.635 [95% confidence interval (CI) 0.599–0.672] and 0.873 (95% CI 0.849–0.898) for SAFEHEART-RE and HDL-C, respectively.

In another report [15▪], Perez de Isla *et al.* et al further examined the predictors of resilience FH in 248 octogenarian patients with FH (≥80 years) enrolled in the SAFEHEART study; most of whom initiated on statins treatment at approximately the age of 60 years. They found that resilient FH individuals were more likely to be female, had higher plasma levels of LDL-C and HDL-C, lower plasma level of Lp (a) and a low score in SAFEHEART-RE compared to nonresilient FH group. The higher level of LDL-C present in patients with resilient FH may relate to the use of more potent LDL-lowering therapies in the nonresilient FH group following an ASCVD event. Further multiple regression analysis showed that only a low score in SAFEHEART-RE was independently associated with resilience FH (relative risk 0.639; 95% CI 0.559–0.730).

In a study of 83 patients aged ≥65 years with definite FH diagnosis based on genetic testing ($n = 80$) or a Dutch Lipid Clinic Network (DLCN) score >8 ($n = 3$) [16▪▪], Melnes *et al.* found that resilient FH patients had significantly higher levels of extra-large- and large HDL particles, and higher concentration of total apolipoprotein A-I and

Table 1. Summary of studies that have identified the characteristics of resilient FH patients

Study	Study design	Study population (*n*)	Definition and number of resilient FH	Age at treatment initiation[b]	Years on treatment[b]	Main findings[a]
Coutinho *et al.*[13] (2021)	Cross-sectional	198 genetically diagnosed Female: 128 (63%)	≥60 years old without clinical ASCVD n = 117 (59%)	56 (48- 61)/51.0 (46–60)	10 (5.2–18)/ 14 (7.5–21)	Resilient FH patients were more likely to be female, nonsmoker, had higher prevalence of family history of early ASCVD, less use of high intensity LLT and longer LLT duration, as well as higher levels of HDL-C levels
Pérez de Isla *et al.*[14▪▪] (2022)	Case-control	930 genetically diagnosed Female: 570 (61%)	≥65 years old without clinical ASCVD *n* = 579 (62%)	Not reported	12 (4.9–19)/ 12 (4.8–19)	Resilient FH patients were younger, more likely to be female and had lower body mass index and prevalence of null *LDLR* mutation, diabetes and high blood pressure. Plasma levels of HDL-C and Lp (a) were higher and lower, respectively. Younger age, female sex, a defective *LDLR* mutation, absence of hypertension, higher HDL-C, and low Lp (a) were independently associated with resilient-FH. In the model excluding variables employed in the SAFEHEART-RF, high HDL-C levels and lower 10-year SAFEHEART risk score were independently associate with resilient FH.
Pérez de Isla *et al.*[15▪] (2022)	Case-control	248 genetically diagnosed Female: 160 (64%)	≥ 80 years old without clinical ASCVD *n* = 115 (46%)	Not reported	10 (4.9–17)/ 12 (4.8–20)	Resilient FH patients were more likely to be female, had higher levels of LDL-C and HDL-C, lower levels of Lp (a), and a lower prevalence of patients on statins and LLTs. A low 10-year SAFEHEART risk score was the only independent predictor associated with resilient FH.
Melnes *et al.* [16▪▪,17▪] (2022, 2024)	Cross-sectional	80 genetically diagnosed 3 clinically diagnosed (DLCN score >8) Female: 40 (48%)	≥65 years old without clinical ASCVD *n* = 44 (53%)	44 (40–50)/43 (38–48)	26 (20–32)/28 (24–33)	Resilient FH patients had significantly higher concentrations of extra-large- and large-HDL particles, as well as higher expression of ABCA1 and ABCG1 and lower expression of *STAT1* and *STAT3*
Climent *et al.* [18▪] (2024)	Retrospective	2148 clinically diagnosed (DLCN score ≥3) Female: 1173 (55%)	≥70 years old without clinical ASCVD *n* = 1583 (74%)	Not reported	Not reported	Resilient FH patients were younger, more likely to be female, had fewer comorbidities (hypertension, type 2 diabetes and/or active smoking), higher levels of HDL-C and lower levels of Lp(a) Lp(a) and the presence of at least three cardiovascular risk factors were independently associated with ASCVD

ASCVD, atherosclerosis cardiovascular disease; DLCN, Dutch Lipid Clinic Network; FH, familial hypercholesterolemia; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering treatment; Lp(a), lipoprotein (a); SAFEHEART-RE, Spanish Familial Hypercholesterolemia Cohort Study Risk Equation).

[a]Non-resilient FH group as a comparator and is defined as FH patients with a history of clinical ASCVD event in respect of same threshold of age employed in the definition of resilient FH patients in each study.

[b]Resilient vs. nonresilient FH expressed as median (interquartile range).

cholesterol in HDL and larger HDL_2 particles than nonresilient FH patients, as measured by nuclear magnetic resonance spectroscopy. Gene expression studies also found higher expression of *ABCA1* and *ABCG1*, and lower expression of *STAT2* and *STAT3* in resilient FH patients compared with nonresilient FH group [17▪]. As discussed later, these findings generally suggest that resilient FH patients had a less atherogenic gene expression profile in relation to HDL metabolism and immune responses.

In a recent study of 2148 clinically diagnosed HeFH patients (age $\geq$ 70 years and DLCN score $\geq$3; 74% without ASCVD) from the Spanish Atherosclerosis Society Dyslipidemia Registry [18▪], Climent *et al.* found that resilient FH patients were mostly female and presented with fewer comorbidities (such as hypertension, type 2 diabetes and/or active smoking). They also had a more favourable lipid profile with elevated HDL-C and decreased Lp(a) levels with respect to nonresilient FH group. In a multivariate analysis, Lp(a) and the presence of $\geq$3 risk factors (male sex, hypertension, type 2 diabetes, obesity and active smoking) were associated with the presence of ASCVD.

Interpretation of findings: mechanisms of cardioprotection

The findings from the aforementioned studies in patients with resilient FH collectively show that differences in gender, comorbidities, HDL subfractions, plasma Lp(a) concentration, and gene expression related to the HDL metabolism and immune system could contribute to the susceptibility of FH patients to ASCVD.

Epidemiological studies in unselected populations showed gender differences in ASCVD events [19,20]. In the general population and some FH cohorts, the prevalence of ASCVD events is consistently reported to be lower in women than men [10,19,20,21▪]. Endogenous exposure to oestrogen has been suggested as an explanation for cardioprotection in women. Oestrogen has several pleiotropic effects on the cardiovascular system. These include reduction in atherosclerotic plaque burden, improvement in endothelial function and decreasing inflammatory responses [22]. However, current data suggest that a cardiovascular protective effect may still apply to older postmenopausal women with FH. The precise reason for this is unclear.

Compelling evidence suggests that HDL protects against the development of ASCVD. This may relate to the antioxidant and anti-inflammatory properties of HDL that protect against endothelial dysfunction [23]. However, the atheroprotective functions of HDL can be attributed to the number and size of HDL particles, and biochemical characteristics including their lipid and protein components; evidence suggests larger HDL particles are more cardioprotective than smaller ones [24▪]. This is consistent with the findings of Melnes *et al.* that resilient FH patients had higher concentrations of the larger HDL particles [16▪▪], with increased gene expression of *ABCA1* and *ABCG1*, membrane transporter that regulate HDL metabolism and cholesterol efflux capacity, and hence reverse cholesterol transport pathway [17▪].

The prevalence of elevated Lp(a) may be as high as 30–50% in patients with HeFH, which may in part be related to LDL receptor deficiency [25▪,26]. Several studies have identified elevated plasma Lp(a) concentration as a predictor of ASCVD in FH patients [27,28]. Lp(a) promotes atherosclerosis by inducing atherothrombosis and specifically via adverse effects on endothelial function, oxidative stress and plaque inflammation and stability [25▪,29]. This is in line with the current data showing in FH that low Lp(a) levels are consistently present in patients with resilient compared to nonresilient FH [14▪▪,15▪,18▪].

Immune responses and inflammation are key elements in the development of ASCVD. Transmigration of oxidized LDLs into the arterial wall initiates immune and inflammatory responses in the subendothelial space, resulting in upregulation of monocyte adhesion, transmigration, and foam cell formation [30▪]. As reviewed earlier, lower expression of genes involved in immune response was found in resilient FH patients compared with nonresilient FH patients [17▪], indicating less immune and inflammatory activation in resilient FH.

LIMITATIONS AND RESEARCH GAPS

Identifying possible cardioprotective factors in resilient FH is important in ASCVD risk stratification and design of preventive treatments. However, this remains an under-investigated area, with very few studies systematically evaluating the full spectrum associated with the absence of ASCVD events in FH patients [14▪▪,15▪,16▪▪,17▪,18▪]. None of these studies were of a prospective design, implying difficulty in arriving at firm conclusions. Resilient FH also remains an ambiguous term in respect of threshold of age employed in the definition (see Table 1). As discussed earlier, Masana *et al.* found that the excessive risk of ASCVD was mitigated above the age of 75 years [6], in agreement with the other study in FH [31]. Hence, we consider the resilient FH is best defined with respect to event-free CAD above the age of 70 years. Current data are also restricted to Hispanics and Caucasian populations. Whether the

findings reported also apply to other ethnicities remains to be confirmed. It is noteworthy that the highest prevalence of FH was observed among Africans and the lowest among Asians [2,32].

Clinical and research implications

Identification of resilient FH patients may provide clinicians a better insight to understand factors or determinants of event-free CAD and associated cardioprotective mechanisms. This is important for improving clinical practice and care, as well as better allocating resources, which may guide on which patients need more or less intensive cholesterol-lowering treatments. It is noteworthy that most of patients with FH do not meet guideline-recommended LDL-cholesterol treatment targets [1▪]. Hence, treatment of elevated LDL-cholesterol remains the cornerstone of FH management. Optimization of modifiable risk factors (hypertension, type 2 diabetes, obesity and active smoking) via lifestyle modifications should be considered for a more holistic ASCVD prevention and management in FH. Elevated Lp(a) is also a critical risk factor for ASCVD in FH. Current guidelines recommend that Lp(a) levels should be measured in every patient with FH for ASCVD risk assessment [25▪,33▪,34]. Although several promising new treatments are currently being trialled, there are no medications that robustly lower elevated Lp(a) levels [25▪]. There is also evidence indicating altered HDL metabolism and function in FH [35–37]. Dysregulation of HDL metabolism may result from hepatic secretion of TG-rich lipoproteins and remodelling of HDL particles, leading to the formation of smaller, more atherogenic HDL particles. HDL-microRNA, such as miR-486 and miR-92, may also contribute to ASCVD risk in FH [38]. Other HDL-associated factors, such as the efflux of cellular cholesterol to HDL, and the antioxidant and anti-inflammatory properties of HDL, are also reported to be lower, leading to further increase cardiovascular risk in FH [35–37]. However, a kinetic study using stable isotope has shown concomitant increased production and catabolism of HDL particles in FH, reflecting a rapid HDL turnover; a possible compensatory mechanism against ASCVD in FH [39]. The cardioprotective role of HDL in FH is unclear that merits further investigation. Whether addition of HDL particle size to risk prediction models can improve the performance in predicting ASCVD in HeFH patients merits investigation. Further research is also required for elucidating the role of chronic inflammation and immune responses which may help better understanding of the pathophysiology of ASCVD in FH and developing potential treatments for FH. Several genetic factors related to vascular inflammation, plaque stabilization, and cholesterol efflux that contribute to cardioprotection in FH have been described. These include rs1061170 variant of the complement factor H (CFH) gene [40], rs12526453 of the phosphatase and actin regulator 1 (PHACTR1) gene [41], R219K polymorphism of ABCA1 gene [42], and rs1250229-T variant of the fibronectin gene [43]. Emerging evidence also demonstrate that genetic variants in clonal hematopoiesis of indeterminate potential (CHIP) may play a role in aging-related ASCVD [44]. The relative frequency of such gene variants in patients with and without resilient FH patients requires further investigation. Identification of gene variants shown to be potentially cardioprotective may lead to the discovery of new therapeutic targets for the treatment of FH.

CONCLUSION

A subset of FH patients, referred as resilient FH, can survive to an advanced age without experiencing any ASCVD events. Current knowledge suggest that they are more likely to be female, have fewer ASCVD comorbidities, lower Lp(a) levels, and exhibit larger HDL particles and as well as reduced immune-mediated vascular inflammation compared with HeFH patients with an ASCVD event. Identification of these contributors could not only improve risk stratification and management for FH, but may be of major importance for the general population in primary and secondary prevention.

Acknowledgements

None.

Financial support and sponsorship

No relevant financial support concerning the article.

Conflicts of interest

G.F.W. has received honoraria for lectures, advisory boards or research grants from Amgen Inc., Arrowhead, AstraZeneca, Esperion, Kowa, Novartis, Regeneron, and Sanofi. S.S.T.Z., D.C.C. and P.M. do not declare any conflict of interest.

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