


Lipoprotein(a), LDL-cholesterol, and hypertension: predictors of the need for aortic valve replacement in familial hypercholesterolaemia

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Aims

Familial hypercholesterolaemia (FH) and elevated lipoprotein(a) [Lp(a)] are inherited disorders associated with premature atherosclerotic cardiovascular disease (ASCVD). Aortic valve stenosis (AVS) is the most prevalent valvular heart disease and low-density lipoprotein cholesterol (LDL-C) and Lp(a) may be involved in its pathobiology. We investigated the frequency and predictors of severe AVS requiring aortic valve replacement (AVR) in molecularly defined patients with FH.

Methods and results

SAFEHEART is a long-term prospective cohort study of a population with FH and non-affected relatives (NAR). We analysed the frequency and predictors of the need for AVR due to AVS in this cohort. Five thousand and twenty-two subjects were enrolled (3712 with FH; 1310 NAR). Fifty patients with FH (1.48%) and 3 NAR (0.27%) required AVR [odds ratio 5.71; 95% confidence interval (CI): 1.78–18.4; $P=0.003$] after a mean follow-up of 7.48 (3.75) years. The incidence of AVR was significantly higher in patients with FH (log-rank 5.93; $P=0.015$). Cox regression analysis demonstrated an association between FH and AVR (hazard ratio: 3.89; 95% CI: 1.20–12.63; $P=0.024$), with older age, previous ASCVD, hypertension, increased LDL-C_{Lp(a)}-years, and elevated Lp(a) being independently predictive of an event.

Conclusion

The need for AVR due to AVS is significantly increased in FH patients, particularly in those who are older and have previous ASCVD, hypertension, increased LDL-C_{Lp(a)}-years and elevated Lp(a). Reduction in LDL-C and Lp(a) together with control of hypertension could retard the progression of AVS in FH, but this needs testing in clinical trials.

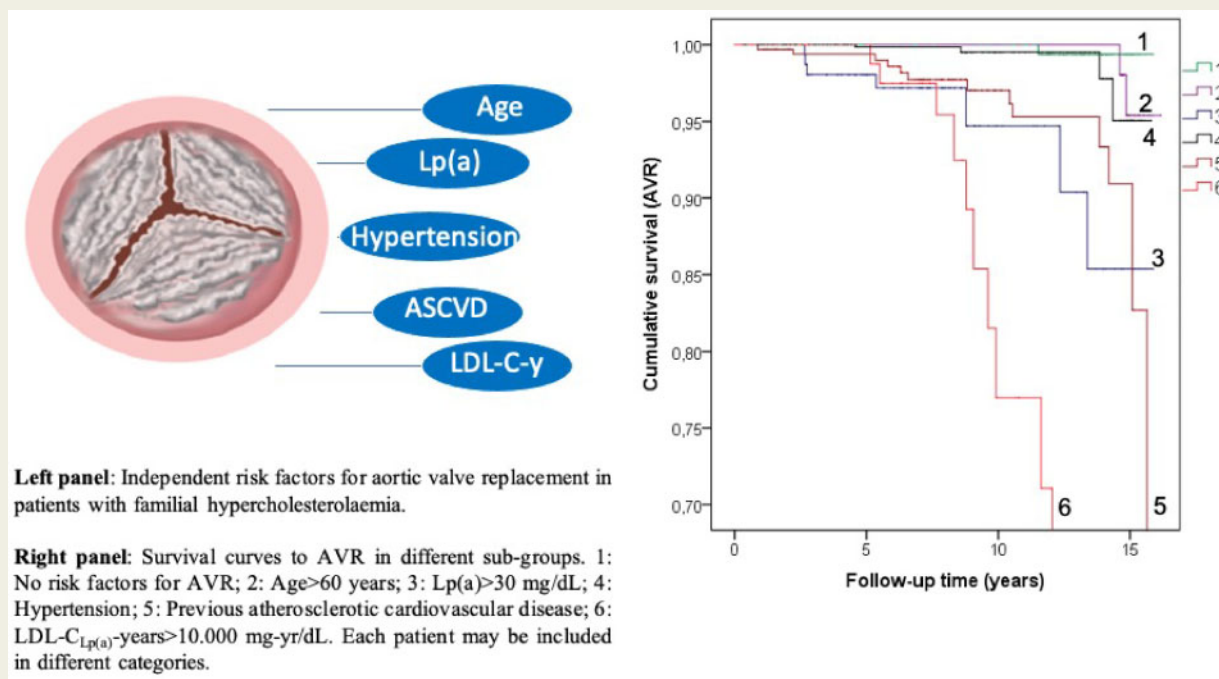
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For the SAFEHEART Investigators (complete list accessible at: <https://www.cholesterolfamilial.org/en/safeheart-study/lipid-clinics-participating-in-the-study/>).

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Graphical abstract



Keywords

Familial hypercholesterolaemia • Aortic valve replacement • Aortic stenosis • Lp(a)

Introduction

Heterozygous familial hypercholesterolaemia (FH) is a co-dominant disorder with an estimated population prevalence of 1 in 250 and the most common inherited cause of premature atherosclerotic cardiovascular disease (ASCVD).¹ Degenerative aortic valve stenosis (AVS) is the most prevalent form of valvular heart disease and the most common indication for surgical or transcatheter aortic valve replacement (TAVR).^{2,3} AVS has been well described in patients with homozygous FH,⁴ but its development and, in particular, its clinical sequelae are less clear in heterozygous FH.

The development of AVS is closely related to atherosclerosis, with common predisposing factors, including hypertension, diabetes, current smoking, and hypercholesterolaemia.^{5–7} Mendelian randomization data testify to causal roles of elevated low-density lipoprotein-cholesterol (LDL-C) and lipoprotein(a) [Lp(a)] in the development of AVS.^{7–10} Accordingly, these lipoproteins may conjointly contribute to the initiation and propagation phases of the AVS that involve lipid infiltration, inflammation, fibrosis, and calcification; this is especially relevant to patients with FH.^{10–12} A major role of Lp(a) and oxidized phospholipids on progression of AVS and need of aortic valve replacement (AVR) has been reported.¹³

Prospective registry data afford the best opportunity to explore the frequency of AVS and need for valvular replacement in patients with FH. We have previously utilized the SAFEHEART (Spanish

Familial Hypercholesterolemia Cohort Study) to demonstrate that elevated Lp(a) is an independent predictor of major adverse cardiac event in patients with pathogenic mutations affecting the LDL receptor pathway and that Lp(a) and FH are independently inherited within families.^{14,15}

In the present study, we investigated the frequency and predictors of the need for AVR due to severe AVS in genetically defined patients with heterozygous FH in the SAFEHEART cohort.

Methods

Design and population

SAFEHEART is a prospective, multi-centre, nationwide cohort study, with long-term protocolized follow-up in a molecularly defined FH population and their non-affected relatives (NAR).¹⁶ The recruitment of families began in 2004 and the end date for reporting events was December 2019. The coordinating centre of the SAFEHEART study managed the follow-up of the patients. The patients were contacted on a yearly basis by using a standardized telephone survey to obtain relevant changes in life habits, medication, and the appearance of cardiovascular events. This study was approved by the ethics committee of the Fundación Jiménez Díaz Hospital in Madrid and all the subjects gave their written informed consent. The objectives of treatment were defined according to the hyperlipidaemia guidelines.¹⁷ These guidelines were used to inform,

educate, and train participating physicians and include patients and families in this registry.

Variables

Demographic and clinical variables, age, classic cardiovascular risk factors, physical examination, and lipid-lowering treatment were included. LDL-C was estimated by means of the Friedewald formula. Baseline (without treatment) LDL-C was estimated.¹⁸ Lp(a) was quantified using an isoform independent assay [Quantia Lp(a) 7K00-01; Tulip Diagnostics, Bambolim, India] and an Architect autoanalyzer C16000 (Abbott Diagnostics, Lake Forest, Illinois) that was calibrated using the International Federation of Clinical Chemistry (IFCC) reference apo(a) standard (IFCC/SRM 2B). Inter-assay variation was <7%.¹⁵ The lipid profile, including Lp(a), was determined in venous blood samples in a centralized laboratory. Adjustment of LDL-C by cholesterol content of Lp(a) [$LDL-C_{Lp(a)} = TC - HDL-C - TG/5 - (Lp(a) \times 0.45)$] that assumed that 45% of Lp(a) mass in mg/dl was cholesterol. LDL-C-year score was calculated as previously described.¹⁹ LDL-CLp(a)-year score was calculated in the same way, using the estimated $LDL-C_{Lp(a)}$ instead of LDL-C.²⁰ LDL-C-year score and LDL-CLp(a)-year score were divided by 100 units to make the results more easily interpretable. The genetic diagnosis of FH was performed as published elsewhere.²¹ Cardiovascular risk was assessed by the SAFEHEART-Risk Equation (SAFEHEART-RE).²² The classification of lipid-lowering therapy was defined as previously reported.²³

Aortic valve replacement was defined as the need for mechanical (surgical or transcatheter replacement) treatment due to severe symptomatic AVS according current guidelines, including an estimated aortic valve area <0.9 cm².^{2,3} Incident AVR during follow-up was present if it occurred after enrolment of the patient in the registry. Patients who underwent AVR due to any other condition different from degenerative AVS were excluded from the analysis. Atherosclerotic cardiovascular disease was defined as the presence of any of the following: (i) myocardial infarction: proved by at least two of the following: classic symptoms, specific electrocardiographic changes, and increased levels of cardiac biomarkers; (ii) angina pectoris: diagnosed as classic symptoms in combination with at least one unequivocal result of one of the following: exercise test, nuclear scintigram, dobutamine stress ultrasound scan, or >70% stenosis on a coronary angiogram; (iii) percutaneous coronary intervention or other invasive coronary procedures as indicated by his/her treating physician; (iv) coronary artery bypass grafting; (v) ischaemic stroke demonstrated by computed tomography or magnetic resonance scanning scan or documented transient ischaemic attack; (vi) peripheral arterial disease: intermittent claudication, which was defined as classic symptoms and at least one positive result of an ankle/arm index <0.9 or stenosis >50% on angiography or ultrasonography or abdominal aortic aneurism; (vii) peripheral arterial revascularization: peripheral artery bypass grafting or percutaneous transluminal angioplasty.

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, the mean and the standard deviation for the quantitative variables that followed a normal distribution and the median and interquartile range for the quantitative variables that did not follow a normal distribution. Comparisons of proportions between the qualitative variables were carried out using the Chi-square test and the binomial test to compare the proportion observed in each treatment group with the value of the total population. The mean comparisons of the quantitative variables were analysed with the Student's *T*-test

for independent data, and the medians comparisons were analysed with the Mann–Whitney *U* test for independent data. Patients with AVR before enrolment were excluded for the survival analysis. Cumulative survival curves were constructed according the Kaplan–Meier method. Log-rank test was used to compare survival curves. Uni- and multivariate Cox regression analyses were used to determine factors predictive of AVR and to elucidate the role of each variable of the SAFEHEART risk equation. Variables with a *P*-value <0.05 in the univariate analysis were included in the multivariate model. A value of *P* < 0.05 was considered statistically significant.

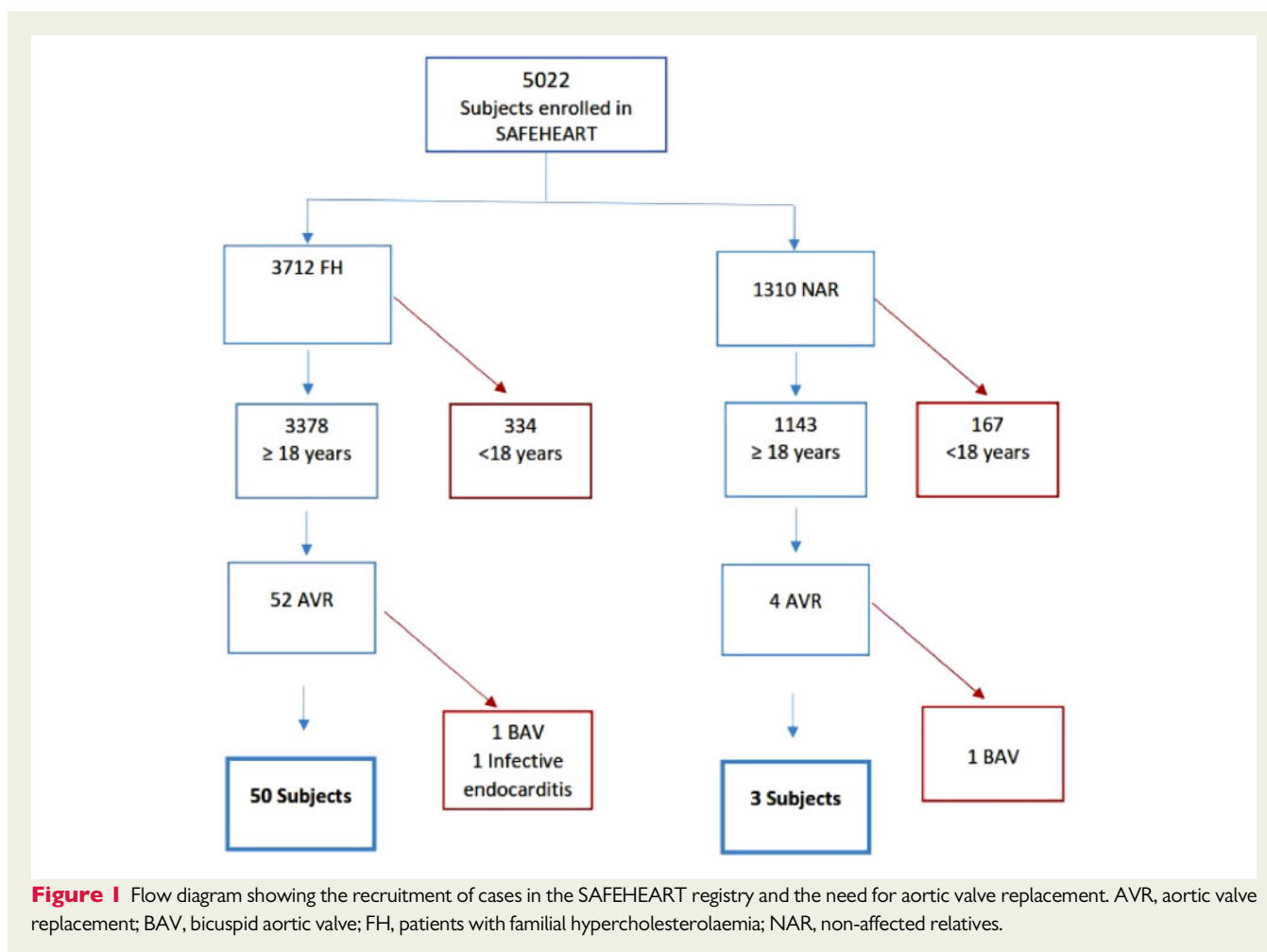
Results

A total of 5022 subjects were enrolled, 3712 with a genetic diagnosis of FH and 1310 NAR (Figure 1). Patients younger than 18 years who underwent AVR due to infective endocarditis or patients with bicuspid aortic valves were excluded. Fifty patients with FH (1.48%) and 3 NAR (0.27%) required AVR [odds ratio 5.71; 95% confidence interval (CI): 1.78–18.4; *P* = 0.003]. Among those, 12 patients with FH and no NAR underwent AVR before enrolment in the registry. Forty-three (86%) and 7 (14%) patients with FH underwent surgical AVR and TAVR, respectively. Two (66.7%) and 1 (33.3%) NAR underwent surgical AVR and TAVR, respectively. Seventeen patients with FH underwent simultaneous AVR and coronary revascularization (15 coronary artery by-pass graft and 2 percutaneous coronary revascularization), all of them having severe AVS and revascularization based on the finding of significant coronary lesions on angiography prior to surgery. The mean follow-up from enrolment into the registry to AVR was 7.48 (3.75) years: 7.49 (3.85) years for patients with FH and 7.46 (3.42) years for NAR. All patients with FH who underwent AVR had a mutation in LDL receptor; none had demonstrable mutation in APO-B or PCSK9.

The characteristics of the cohort are described in Tables 1 and 2. The frequency of AVR in patients with FH, before and after enrolment, was 1.48% and in NAR 0.27%. Patients with FH tended to be younger than their NARs at AVR [67.72 (10.43) vs. 79.33 (5.77) years, *P* = 0.063], but there were only three AVR in among the NAR. ASCVD was more frequent in patients with both FH and AVR than in patients with FH without AVR (64% vs. 14.6%, *P* < 0.001), not being present in any NARs with AVR. Coronary heart disease was also more frequent in patients with FH and AVR than in those with FH without AVR (46% vs. 12.5%, *P* < 0.001). There were no significant differences in the prevalence of LDL receptor null mutations between FH patients with and without AVR (46% vs. 41.8%, respectively; *P* = 0.55).

The prevalence of hypertension was significantly higher in patients with FH and AVR than in those with FH and no AVR: 25 (50%) and 496 (14.90%), respectively (*P* < 0.001). Hypertension was also higher in NAR and AVR compared with NAR without AVR. Plasma Lp(a) concentration, LDL-C-years, and $LDL-C_{Lp(a)}$ -years were significantly higher in patients with FH and AVR than in patients with FH without AVR. Finally, the 10-year cardiovascular risk estimated in patients with FH using the 10-year SAFEHEART-RE was significantly higher in patients with FH and AVR than in patients with FH without AVR: 11.48% (11.2) vs. 3.15% (4.81), respectively (*P* < 0.001).

There were no statistically significant differences among groups in gender, prevalence of null mutations, tobacco smoking, total



cholesterol, and LDL-C. Nevertheless, the levels of HDL-cholesterol and triglycerides were significantly higher in patients with FH without and with AVR, respectively. Furthermore, cholesterol lowering treatment was more intensive in FH patients and AVR than in those without AVR.

Incidence of aortic valve replacement in patients with familial hypercholesterolaemia and non-affected relatives

Figure 2 shows the cumulative survival curves for AVR in patients with FH and NARs during the follow-up period, showing that the incidence of AVR was statistically significantly higher in patients with FH (log-rank 5.93; $P = 0.015$). Cox regression analysis also demonstrated the association between FH and AVR [hazard ratio (HR): 3.89; 95% CI: 1.20–12.63; $P = 0.024$]. Time of risk exposure for patients with FH was 22 036.85 patients-year, with an incidence rate of AVR of 1.7 for 1000 patients-year; time of risk exposure for NAR was 7766.34 patients-year, with an incidence rate of AVR of 0.39 for 1000 patients-year. Hence, the incidence rate of AVR was 4.36 times higher in patients with FH than in NAR.

Factors related to aortic valve replacement in patients with familial hypercholesterolaemia

Table 3 shows the univariate Cox regression analysis results. As can be seen, age, hypertension, body mass index, Lp(a), LDL-C-years, LDL-C_{Lp(a)}-years, and cardiovascular risk estimated by means of the 10-years SAFEHEART-RE were all significantly predictive of the need for AVR during follow-up. Multivariate Cox regression analysis results are shown in Table 4. Age, hypertension, LDL-C_{Lp(a)}-years, and Lp(a) were independently predictive of the need for AVR during follow-up. When Lp(a) was employed in this analysis as a binary variable (threshold of risk > 50 mg/dL), the following were results in the uni- and multivariate analysis, respectively: HR: 4.08; 95% CI: 2.13–7.81; $P < 0.001$ and HR: 2.94; 95% CI: 1.52–5.69; $P = 0.001$. A cut-off point > 30 mg/dL provides the following results in the uni- and multivariate analysis, respectively: HR: 4.75; 95% CI: 2.25–10.10; $P < 0.001$ and HR: 3.85; 95% CI: 1.81–8.19; $P < 0.001$. Survival curves for patients with FH and Lp(a) levels above and below 30 mg/dL, with or without hypertension and LDL-C_{Lp(a)}-years above and below 10.000 mg-year/dL are depicted in Figure 3; Log-rank test P -value was < 0.001 in every case.

Table 1 Characteristics of the patients with familial hypercholesterolaemia (FH) and non-affected relatives (NAR) at enrolment in relation to those who required (AVR+) and did not require (AVR-) aortic valve replacement (AVR)

	FH AVR (+)		FH AVR (-)		NAR AVR (+)		NAR AVR (-)		FH AVR (+) vs. NAR AVR (+)	
	Mean (SD)/n (%)	P-value	Mean (SD)/n (%)	P-value	Mean (SD)/n (%)	P-value	Mean (SD)/n (%)	P-value	Mean (SD)/n (%)	P-value
N	50	—	3326	—	3	—	1140	—	—	—
Female	31 (62.0%)	0.29	1813 (54.5%)	0.29	1 (33.3%)	0.61	597 (52.4%)	0.61	—	0.56
Age at enrolment (years)	64.25 (10.27)	<0.001	45.71 (15.41)	<0.001	75.53 (3.81)	<0.001	42.92 (15.63)	<0.001	—	0.066
Age at AVR (years)	67.72 (10.43)	—	—	—	79.33 (5.77)	—	—	—	—	0.063
AVR before enrolment	12 (24%)	—	—	—	0	—	—	—	—	—
ASCVD	32 (64%)	<0.001	487 (14.6%)	<0.001	0	<0.001	62 (5.4%)	1	—	0.06
CHD	23 (46%)	<0.001	416 (12.5%)	<0.001	0	<0.001	47 (4.1%)	1	—	0.25
Premature familial ASCVD history	25 (56.8%)	0.028	1284 (40.4%)	0.028	2 (66.7%)	0.253	392 (35.1%)	0.253	—	0.739
LDL receptor mutations	50 (100%)	0.012	3014 (90.6%)	0.012	—	—	—	—	—	—
Type 2 diabetes	5 (10%)	0.072	147 (4.4%)	0.072	0 (0%)	0.699	54 (4.7%)	0.699	—	1.0
Hypertension	25 (50%)	<0.001	496 (14.9%)	<0.001	3 (100%)	<0.001	172 (15.1%)	<0.001	—	0.238
Active tobacco smoker	7 (14%)	0.055	863 (25.9%)	0.055	0 (0%)	0.226	374 (32.8%)	0.226	—	1.0
BMI (kg/m ²)	27.84 (4.23)	0.054	26.5 (4.87)	0.054	28.13 (1.76)	0.49	26.14 (4.98)	0.49	—	0.91
10-y SAFEHEART-RE (%)	11.48 (11.2)	<0.001	3.15 (4.81)	<0.001	—	—	—	—	—	—

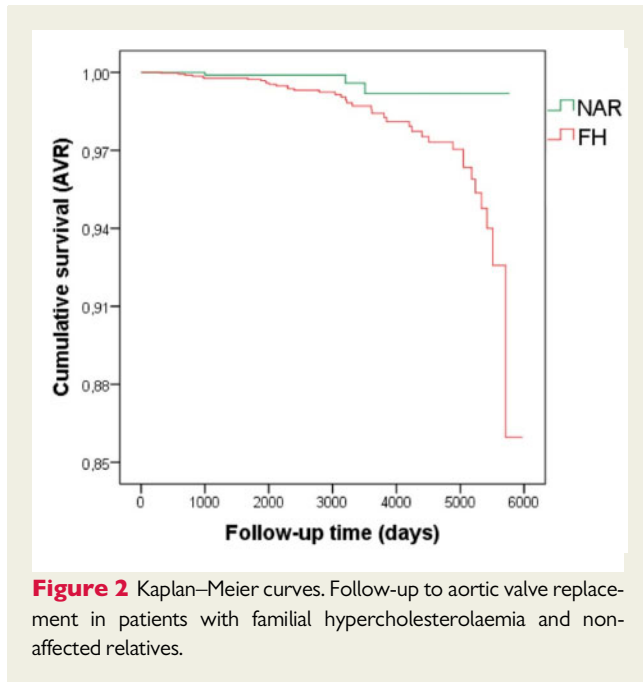
10-y SAFEHEART-RE, 10-year risk estimated by means of the SAFEHEART risk equation, which estimates the likelihood to occur the first one of the following: fatal or non-fatal myocardial infarction, fatal or non-fatal ischaemic stroke, coronary revascularization, peripheral artery revascularization, and cardiovascular death (any death related to cardiovascular disease or derived of cardiovascular therapeutic procedures not described in the previous definitions); ASCVD, cardiovascular disease; AVR, aortic valve replacement; BMI, body mass index; CHD, coronary heart disease; FH, patients with familial hypercholesterolaemia; NAR, non-affected relatives.

Table 2 Lipid-related variables in patients with familial hypercholesterolaemia (FH) and non-affected relatives (NAR) at enrolment in relation to those who required (AVR+) and did not required (AVR-) aortic valve replacement (AVR)

	FH AVR (+)		FH AVR (-)		NAR AVR (+)		NAR AVR (-)		FH AVR (+) vs. NAR AVR (+)	
	n	Mean (SD) or median (IQR)/n (%)	n	Mean (SD) or median (IQR)/n (%)	n	Mean (SD) or median (IQR)/n (%)	n	Mean (SD) or median (IQR)/n (%)	P-value	P-value
n	50	3326	3	1140	—	—	—	—	—	—
Total cholesterol (mg/dL)	252.0 (221.0–297.6)	235.0 (203.0–278.0)	0.038	272.0 (244.0–279.0)	0.038	204.0 (179.0–235.0)	0.043	0.93	0.93	
LDL-C (mg/dL)	186.2 (148.0–233.5)	163.0 (135.0–205.0)	0.019	175.0 (147.5–185.5)	0.019	128.0 (106.0–156.0)	0.14	0.47	0.47	
LDL-C without treatment (estimated) (mg/dL)	266.3 (211.6–335.3)	232.8 (193.1–293.2)	0.002	210.9 (166.8–272.8)	0.002	183.0 (151.6–223.1)	0.14	0.24	0.24	
LDL-C _{lip(a)}	150.8 (116.4–189.4)	149.0 (117.2–189.3)	0.77	171.7 (143.6–177.0)	0.77	114.5 (91.0–141.7)	0.08	0.93	0.93	
HDL-C (mg/dL)	42.8 (35.0–55.0)	49.0 (42.0–58.0)	0.004	71.0 (60.5–72.0)	0.004	53.0 (45.0–63.0)	0.17	0.035	0.035	
TG (mg/dL)	99 (80.3–145.5)	84.6 (64.0–117.7)	0.004	130.0 (110.0–181.0)	0.004	90 (66.0–127.0)	0.15	0.32	0.32	
Lp(a) (mg/dL)	58.5 (25.4–95.6)	23.6 (9.1–55.5)	<0.001	10.0 (8.7–20.2)	<0.001	19.7 (7.0–45.5)	0.6	0.027	0.027	
Lp(a) > 30 mg/dL	36 (72.0%)	1360 (40.9%)	<0.001	1 (33.3%)	<0.001	411 (36.1%)	1	0.21	0.21	
Patients on LLT	48 (96%)	2719 (81.8%)	0.009	2 (66.7%)	0.009	283 (24.8%)	0.156	0.163	0.163	
Patients on maximum LLT	36 (72%)	1781 (53.5%)	0.009	2 (66.7%)	0.009	74 (6.5%)	0.013	1.0	1.0	
Time of statin use (years)	14.13 (7.39)	11.93 (7.27)	0.14	10.5 (7.83)	0.14	3.91 (2.87)	0.36	0.92	0.92	
Time of ezetimibe use (years) ^a	3.91 (2.87)	3.6 (3.04)	0.57	0	0.57	2.6 (2.48)	—	—	—	
LDL-C-years (mg-year/dL)	16 311.24 (14 319.46–21 170.25)	10 281.86 (7583.67–13 682.17)	<0.001	17 099.40 (14 863.25–17 417.12)	<0.001	6741.28 (4551.40–9366.48)	0.005	0.81	0.81	
LDL-C _{lip(a)} -years (mg-year/dL)	14 199.86 (9855.86–17 320.88)	9198.4 (6637.95–12 404.05)	<0.001	15 885.88 (12 152.22–17 385.90)	<0.001	5956.25 (3961.0–8559.78)	0.004	0.55	0.55	

AVR, aortic valve replacement; FH, patients with familial hypercholesterolaemia; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile ranges; LDL-C, low-density lipoprotein cholesterol; LDL-C_{lip(a)}, LDL-C adjusted by content of Lp(a); LLT, lipid-lowering therapy; Lp(a), lipoprotein (a); NAR, non-affected relatives; TG, triglycerides.

^aEstimated in patients on ezetimibe.



When affected family members of index cases with FH were analysed, the multi-variable analysis showed similar results to those using the entire FH population. The independent predictors for AVR in the final multi-variable model of affected family members of index cases with FH were: Age (HR: 1.58; 95% CI: 1.012–1.105; $P = 0.012$), previous ASCVD (HR: 6.49; 95% CI: 2.08–20.28; $P = 0.001$), hypertension (HR: 3.25; 95% CI: 1.17–8.90; $P = 0.023$), Lp(a) mg/dL (HR: 1.014; 95% CI: 1.008–1.02; $P < 0.001$), and LDL-C_{Lp(a)}-years/100 (mg-year/dL) (HR: 1.009; 95% CI: 1.001–1.018; $P = 0.04$).

Discussion

Based on data from a long-term follow-up cohort, we found that heterozygous FH was associated with a markedly increased need for AVR due to severe AVS. Specifically, we observed a 5.71-fold increase in the need for AVR in patients with FH compared with NARs. Increasing age, previous ASCVD, hypertension, higher LDL-C_{Lp(a)}-years, and elevated plasma Lp(a) concentrations were independent predictors of the need for AVR.

The development of AVS is a well-recognized problem to occur in patients with homozygous FH.⁴ This is less common in patients with heterozygous FH. In a recently study, Ten Kate *et al.*⁷ demonstrated increased aortic valve calcification in asymptomatic patients with heterozygous FH compared with controls. In a large Mendelian randomization study, genetic predisposition to high LDL-C was associated with increased risk of aortic valve calcification and AVS.⁸ Furthermore, Mundal *et al.*⁵ reported that increased LDL-C due to FH increases the risk of severe AVS and AVR. Our study extends these findings by using a longer term follow-up period of a real-life cohort and showing the factors predictive of the need for AVR in patients with heterozygous FH. Prospective registry data, such as those from the SAFEHEART study, afford the best opportunity to

Table 3 Cox univariate regression analysis showing variables predictive of aortic valve replacement in patients with familial hypercholesterolaemia

	HR	95% CI	P-value
Age (years)	1.089	1.063–1.12	<0.001
Male	0.56	0.28–1.11	0.095
Premature familial ASCVD history	1.95	0.98–3.86	0.06
Previous ASCVD	16.89	6.93–41.23	<0.001
Diabetes mellitus	3.19	0.97–10.46	0.06
Hypertension	7.48	3.95–14.20	<0.001
BMI (kg/m ²)	1.09	1.027–1.15	0.004
Active smoking	0.64	0.28–1.45	0.28
Total cholesterol (mg/dL)	1.003	0.99–1.007	0.17
LDL-C (mg/dl)	1.003	0.99–1.008	0.17
LDL-C without treatment (estimated) (mg/dL)	1.002	0.99–1.01	0.17
LDL-C _{Lp(a)} (mg/dL)	0.99	0.00–1.004	0.76
HDL-C (mg/dL)	0.97	0.96–1.013	0.33
TG (mg/dL)	1.004	0.94–1.008	0.10
Lp(a) (mg/dL)	1.013	1.009–1.018	<0.001
LDL-C-years (mg-year/dL)/100	1.013	1.009–1.016	<0.001
LDL-C _{Lp(a)} -years (mg-year/dL)/100	1.01	1.006–1.014	<0.001
SAFEHEART-RE 10 years (%)	1.1	1.08–1.13	<0.001

Sample size = 3364 patients.

10-y SAFEHEART-RE, 10-year risk estimated by means of the SAFEHEART risk equation; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); TG, triglycerides.

explore the frequency of AVS and need for valvular replacement in patients with FH. The incidence rate of AVR was 4.36 times higher in patients with FH than in NARs and the average incidence in the present study of AVR in patients with FH was 1.7 cases for 1000 patients-year compared with a corresponding incidence of 7.7-fold for ASCVD.²⁴

We showed that AVS in FH was associated with sustained elevation in plasma LDL-C concentrations, as reflected by LDL-C_{Lp(a)}-years, but also with age, previous ASCVD, hypertension, and elevated Lp(a). Given these five risk predictors, we propose that the use of the SAFEHEART risk equation²² may offer a simple and pragmatic first approach to identify patients with FH at risk of ASCVD and in turn greater predisposition to severe AVS requiring AVR. These five risk factors are important for understanding the pathogenesis of AVS in FH: increasing age is a degenerative biological factor, hypertension a haemodynamic factor, and elevated Lp(a) and LDL-C_{Lp(a)}-years two metabolic factors. All of them were also related to the development of ASCVD. Mendelian randomization data show that elevated LDL-C and Lp(a) both contribute to the development of AVS^{8–10}; this involves lipid infiltration, inflammation, fibrosis, and calcification.^{6,12} A major impact of Lp(a) per se on progression of AVS has been supported by several studies; mechanisms include valvular deposition of oxidized phospholipids, autotaxin-mediated generation of phosphatidic acid, activation of the nuclear factor- κ B inflammatory cascade, and calcification due to induction of alkaline phosphatase.¹² Faster

Table 4 Cox regression multivariate analysis showing variables predictive of aortic valve replacement in patients with familial hypercholesterolaemia

	HR	95% CI	P-value
Age (years)	1.04	1.008–1.076	0.014
Previous ASCVD	6.27	2.32–16.94	<0.001
Hypertension	3.06	1.35–6.92	<0.001
BMI (kg/m ²)	1.03	0.95–1.11	0.45
Lp(a) (mg/dL)	1.015	1.009–1.02	<0.001
LDL-C _{Lp(a)} -years (mg-year/dL)/100	1.009	1.003–1.014	0.003

Sample size = 3364 patients.

BMI, body mass index; HR, hazard ratio; Lp(a), lipoprotein (a).

progression of AVS and need for AVR are directly dependent on elevated Lp(a) and specifically the particle content of oxidized phospholipids.^{12,13} Regrettably, no treatment has shown to be efficacious in reducing progression of aortic stenosis. Nevertheless, a preventive screening based on the SAFEHEART-RE affords an opportunity to explore whether early control of the modifiable risk factors identified in this study may be useful in diminishing progression of AVS in patients with FH. While this needs to be tested in prospective trials with appropriate interventions and imaging endpoints, it is noteworthy that the more advanced stages of AVS may be refractory to interventions targeted at the modifiable risk factors which we have identified.

Furthermore, this crucial role of Lp(a) could explain the limited effectiveness of the cholesterol-lowering therapy on calcific aortic stenosis,^{25–28} given that statins and ezetimibe lower plasma levels of LDL-cholesterol but not Lp(a). Statins may also increase Lp(a),^{26,29} which could in part account for the lack of effect of such an intervention on the progression of AVS.^{27,28} On the other hand, in our study, LDL-C levels were not associated with the need for AVR due to AVS. A potential explanation for this finding is that the estimated LDL-C contains the Lp(a)-cholesterol, which can account for up to 45% of the estimated LDL-C.¹⁰ Consistent with this, in an exploratory analysis of the FOURIER trial, higher Lp(a) levels, but not Lp(a)-corrected LDL-C levels, were associated with a higher risk of cardiovascular events, including aortic valve replacement.³⁰ Specific management of elevated Lp(a) remains a therapeutic challenge. PCSK9 inhibitors and specific therapies that lower Lp(a) are required to address the residual risk attributed of ASCVD and AVS in FH.^{29,31} Recently, profound reductions in Lp(a) levels have been achieved with apo(a) antisense therapy that targets hepatic apo(a) mRNA and safely reduces Lp(a) concentrations by up to 92.4% in patients with and without established cardiovascular disease, at least in shorter term trials.^{32,33} It is noteworthy that patients in the present study who subsequently required AVR were more intensively treated at enrolment. This may be related to a higher pre-treatment LDL-C and the fact that statins and ezetimibe do not lower elevated plasma concentrations of Lp(a).^{27,28} Future studies should assess the relationship between Lp(a) and rates of progression of AVS and the response to specific Lp(a)-lowering therapy.³³

The results of the present study may lead to a new paradigm for managing patients with FH centred on preventing the development

AVS by targeting the total burden (intensity and time of exposition) of LDL-C, elevated Lp(a), and hypertension. Cardiac auscultation in trained hands could be a useful clinical method for screening for AVS, since in the absence of a mid-systolic murmur, significant valvular stenosis is unlikely to be present. If such a heart murmur is detected, the next step should be an echocardiogram to establish the diagnosis, differentiate sclerosis from stenosis, and assess its severity.^{2,3} An early echocardiogram may also be useful to guide the intensity of the cholesterol-lowering treatment according to the detection of aortic sclerosis or stenosis. We consider that it is essential to make the medical practitioners aware of our new findings, which merit inclusion in future management guidelines for patients with FH. An important issue to be discussed would be at what age and with what periodicity should patients with FH have an echocardiogram. We consider that the use of other imaging techniques, such as quantification of aortic valve calcium by computed tomography, should be reserved for patients in whom the detection and quantification of valvular calcification could be used to modify their estimated cardiovascular prognosis.

Study strengths and limitations

Our case-control design allowed comparison of members of the same families who lived in similar conditions (social environment and lifestyle) and differed in respect of the presence or absence of a mutation causative of FH.¹⁶ We also employed the hard endpoint of need of AVR, the only effective treatment for severe AVS based on the established indications.² This endpoint is a particular strength of the present work but had the inherent limitation of a lower number of events in the NAR group. This overcomes limitations such as the need to decide on the definition (anatomic or functional) severe AVS, which can be subject to imprecision.^{2,3} Furthermore, using AVR as an endpoint, as opposed to subclinical aortic valve disease, focuses on the final stage of the disease, and not an early stage that is influenced by diverse factors.^{2,3}

Conclusion

The need for AVR due to severe AVS is significantly increased among patients with heterozygous FH and is particularly driven by increasing age, previous ASCVD, hypertension, elevated LDL-C_{Lp(a)}-years, and elevated Lp(a) concentration. Improved control of hypertension and more potent reduction in Lp(a) and LDL-C could retard the progression of AVS in FH, but this needs testing in clinical trials. Our study lays the basis for future therapeutic strategies for patients with FH, elevated Lp(a), and hypertension aimed at preventing not only ASCVD, but also the progression of AVS.

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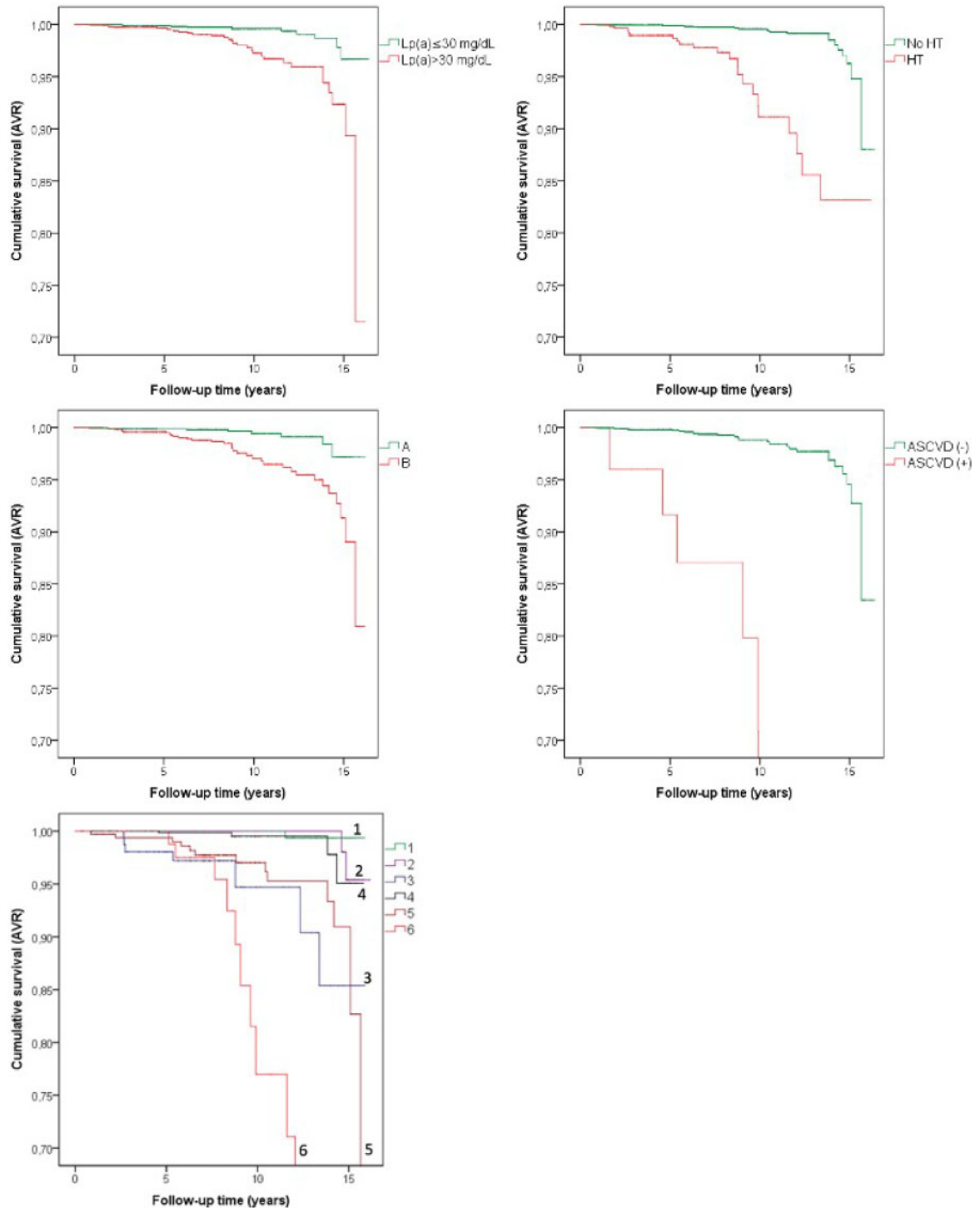


Figure 3 Kaplan–Meier curves. (Top left) Follow-up to aortic valve replacement in patients with FH and Lp(a) \leq or $>$ 30 mg/dL ($n = 1975$ and 1389 , respectively). (Top right) Follow-up to aortic valve replacement in patients with FH without ($n = 2843$) or with hypertension (HT) ($n = 521$). (Middle left) Follow-up to aortic valve replacement in patients with FH and LDL-C_{Lp(a)}-years $\leq 10,000$ (A; $n = 1909$) or $> 10,000$ (B; $n = 1455$) mg-year/dL. (Middle right) Follow-up to aortic valve replacement in patients with FH and no previous atherosclerotic cardiovascular disease ($n = 2845$) or previous ASCVD ($n = 519$). (Bottom) Follow-up to aortic valve replacement in different sub-groups [1: No risk factors for aortic valve replacement ($n = 1210$); 2: Age $>$ 60 years ($n = 874$); 3: Lp(a) $>$ 30 mg/dL ($n = 1389$); 4: Hypertension ($n = 521$); 5: Previous atherosclerotic cardiovascular disease ($n = 519$); 6: LDL-C_{Lp(a)}-years $>$ 10,000 mg-year/dL ($n = 1455$)]. The four first graphs represent mutually exclusive and exhaustive categories. Each patient may be included in different categories in the last graph.

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