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LDL-cholesterol lowering and clinical outcomes in hypercholesterolemic subjects with and without a familial hypercholesterolemia phenotype: Analysis from the secondary prevention 4S trial

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ABSTRACT

Background and aims: Trial evidence for the benefits of cholesterol-lowering is limited for familial hypercholesterolemia (FH) patients, since they have not been the focus of large outcome trials. We assess statin use in coronary artery disease (CAD) subjects with low-density lipoprotein cholesterol (LDL-C) ≥4.9 mmol/L with or without an FH phenotype.

Methods: The 4S trial randomized hypercholesterolemic CAD patients to simvastatin or placebo. We first stratified participants into baseline LDL-C <4.9 and ≥ 4.9 mmol/L; next, based on the DLCN criteria for FH, the latter group was stratified into four subgroups by presence of none, one or both of "premature CAD" and "family history of CAD". Participants having both are defined as having an FH phenotype.

Results: 2267 and 2164 participants had LDL-C <4.9 and ≥ 4.9 mmol/L, respectively. Mortality endpoints and major coronary events (MCE) were significantly reduced with simvastatin *versus* placebo in both groups over 5.4 years, but the latter derived greater absolute risk reductions (ARR) (4.1–4.3% for mortality endpoints, *versus* 2.5–2.8%).

LDL-C reductions were similar among the 4 subgroups with levels ≥4.9 mmol/L. Participants with FH phenotype (n = 152) appeared to derive greater relative benefits with simvastatin than the other three subgroups (all-cause death: 84% relative risk reduction, $p = 0.046$; MCE: 55% reduction, $p = 0.0297$); statistical interaction was non-significant. Participants with FH phenotype derived greater ARR than any other group with simvastatin *versus* placebo (all-cause mortality: 6.6% ARR; MCE 13.2%; *versus* 3.8% and 8.3%, respectively, among participants with LDL-C ≥4.9 mmol/L but without features suggestive of FH).

Conclusions: The FH phenotype appeared to be associated with greater clinical benefits from a given magnitude of LDL-C reduction as compared to individuals without FH phenotype.

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1. Introduction

Low-density lipoprotein cholesterol (LDL-C) is a causal factor for coronary artery disease (CAD), with risk being linked to the cumulative exposure to this lipoprotein over a lifetime [1]. This concept of lifetime exposure is of particular relevance for individuals with familial hypercholesterolaemia (FH), since they exhibit high circulating LDL-C concentrations from birth [2,3]. This is supported by studies which show that, within any stratum of LDL-C, risk of CAD is increased in those with FH mutations compared with non-carriers [3]. Individuals with FH, therefore, are at greatly increased risk of early CAD, often in their 30s and 40s [2,4], and, due to the autosomal dominant inheritance of the genetic defect, are also likely to have first-degree relatives affected by cardiovascular disease. Since the disorder is relatively common [5], identification and prompt treatment of FH is now recognized as a global imperative [6,7]. Statins are used as first-line treatment since diet is insufficient to control LDL-C in FH [2]. These drugs have been shown to reduce risk of cardiovascular disease in a wide range of individuals and benefit appears to be proportional to the absolute drop in LDL-C and the duration of treatment [8]. However, patients with FH have not been the focus of large-scale lipid-lowering outcome trials, and therefore robust evidence of cardiovascular benefit in this patient group has not been available. However, an encouraging decline in the rate of cardiovascular events in this condition has been observed since the introduction of statins [9]; and in more severe cases of FH (homozygous FH) evaluation of event rates shows an association with statin therapy [10].

A previous analysis from the WOSCOPS (West of Scotland Coronary Prevention Study) primary prevention trial in patients with LDL-C >4.9 mmol/L provided clear evidence of benefit of statins in this severe hypercholesterolemic group [11], including significant reductions in the risk of CAD and major adverse cardiovascular events, with extended benefit on mortality endpoints over the long-term (20 years). These patients had an FH phenotype based on LDL-C levels [12], but there was insufficient ancillary information (genetic analysis, family history of CAD) to characterize these individuals as potentially having FH.

To explore this concept further, we undertook a *post-hoc* analysis from the 4S (Scandinavian Simvastatin Survival Study) secondary prevention trial, in which high LDL-C was an entry criterion, with a significant proportion of individuals having an LDL-C ≥4.9 mmol/L [13]. Unlike WOSCOPS, in 4S all had CAD, including some with early CAD, and medical history among first-degree family members was also available. The aim was to compare the benefit of lipid-lowering with statins in a secondary prevention setting for those with LDL-C ≥4.9 mmol/L with or without an FH phenotype, and assess if those with FH phenotype derived additional benefit.

2. Materials and methods

2.1. Patients

A full description of the 4S trial has been published elsewhere [13,14]. Briefly, 4S recruited men and women, 30–75 years of age, with established CAD (defined as [i] history of typical exertional angina lasting ≥3 months with documented coronary atherosclerosis/myocardial ischemia, or [ii] acute myocardial infarction ≥6 months before entry in the trial); as an entry criterion; participants had to have primary hypercholesterolaemia with a total fasting cholesterol between 5.5 and 8.0 mmol/L (after a period of 8 weeks of dietary modification) and were not receiving lipid modification therapy; participants with secondary hypercholesterolaemia and those with triglycerides >2.5 mmol/L were excluded [13,14]. A total of 4444 participants were randomized to simvastatin 20 mg/day (n = 2221) or placebo (n = 2223); participants taking simvastatin had their dose increased to 40 mg/day (37% of cases) if LDL-C was >5.2 mmol/L at the 3 or 6-month visit as per the study protocol [13,14]. Median follow-up was 5.4 years [13].

2.2. Identification of FH phenotype

In the present analysis, participants in the 4S trial were initially stratified based on their LDL-C levels at baseline into those with LDL-C <4.9 mmol/L and those with LDL-C ≥4.9 mmol/L (this latter group is referred to as primary severe hypercholesterolaemia, PSH) (Fig. 1A and B) (13 participants from the original cohort were excluded because they lacked data on LDL-C at baseline). We then applied the Dutch Lipid Clinic Network (DLCN) diagnostic criteria for FH to the group of participants with PSH [2]. This classification considers a set of five criteria including family history of CAD, patient's clinical history of premature CAD, physical examination (tendon xanthomas, arcus cornealis before age 45), LDL-C levels, and DNA analysis. For the purpose of the present analysis, premature CAD was defined as having an age <55 years for men or <60 years for women at study entry, as age at diagnosis of CAD was not recorded. No information was available on physical signs related to FH, and there was no genetic testing undertaken. As the age of diagnosis of CAD among first-degree relatives was not recorded, we restricted our definition of a family history of CAD to siblings only. The rationale being that siblings were more likely to be near the age of the participants at the time of study entry, thus making it more likely that the family history of first-degree members had a genetic basis. In contrast, a family history of CAD in parents would be more frequently enriched by age and potentially a constellation of different cardiovascular risk factors.

Based on these criteria, participants with LDL-C ≥4.9 mmol/L (PSH) were stratified into four groups (Fig. 1A), namely: (i) participants not having either premature CAD or family history of CAD; (ii) participants not having premature CAD but having family history of CAD; (iii) participants having premature CAD but not having family history of CAD; and (iv) participants having both premature CAD and family history of CAD; participants in the last group were defined as having an "FH phenotype" for the purpose of this analysis. The number of patients in each group and those allocated to simvastatin or placebo is shown in Fig. 1B.

2.3. Endpoints

Endpoints included all-cause death, cardiovascular death, coronary heart disease death, and major coronary events (MCE). In line with the definitions in the original 4S trial, MCE were defined as the composite of (first occurrence) coronary artery disease death, definite or probable hospital-verified non-fatal acute myocardial infarction, resuscitated cardiac arrest, and definite silent myocardial infarction verified by electrocardiogram [13].

2.4. Statistical analysis

Data are shown as absolute and relative frequencies for categorical variables, and as mean ± standard deviation or median and interquartile range, as appropriate, for quantitative parameters. The effect of therapy (simvastatin *versus* placebo) is reported as a hazard ratio and 95% confidence interval with corresponding *p* values, estimated by Cox regression with treatment allocation (simvastatin or placebo) as the only covariate in the case of groups with and without LDL-C ≥4.9 mmol/L. The effect of therapy in the additional four groups with LDL-C ≥4.9 mmol/L stratified based on features suggestive of FH phenotype were additionally adjusted for baseline characteristics (including age, sex, history of hypertension and diabetes, smoking status, prior myocardial infarction, revascularization and transient ischemic attack, claudication, blood pressure [systolic and diastolic], and parents with history of CAD) and concomitant medication at baseline (including aspirin, beta-blockers, calcium-antagonists, isosorbide, thiazide, warfarin and fish oil). To assess whether the effect of study medication was consistent across the groups prespecified in this analysis, the *p*-value from the treatment by subgroup interaction term is reported where appropriate.

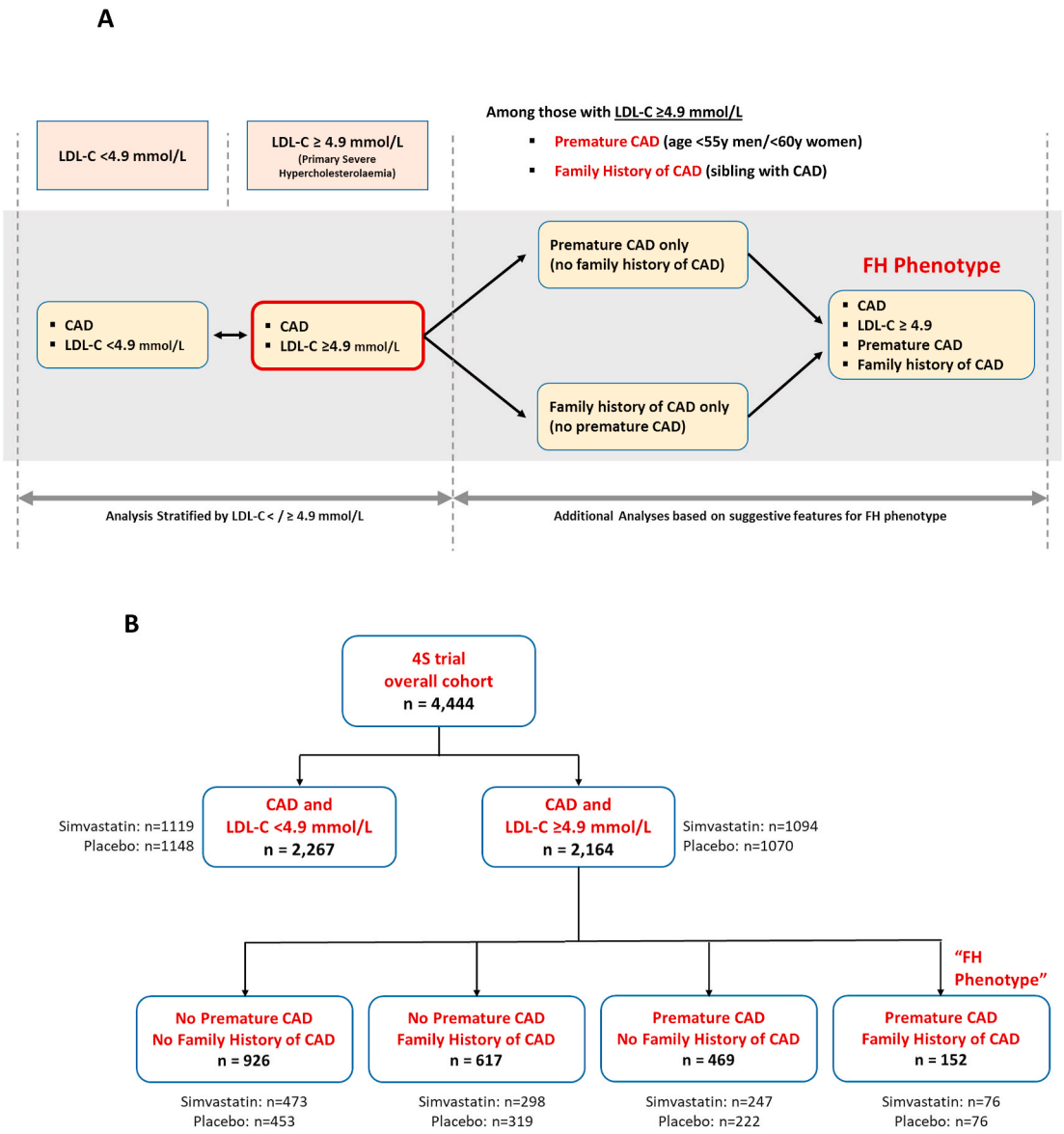


Fig. 1. Stratification of participants by LDL-cholesterol 4.9 mmol/L at baseline and, among those with LDL-C ≥4.9 mmol/L, by features suggestive of a familial hypercholesterolaemia phenotype.
4S, Scandinavian Simvastatin Survival Study; CAD, coronary artery disease; FH, familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol.

Absolute risk reductions (ARR) were calculated from the event rates in each treatment arm. Tests were 2-sided and statistical significance was defined as $p < 0.05$. The statistical analyses were performed using R.

3. Results

3.1. Analysis stratified by LDL-C <4.9 or ≥4.9 mmol/L at baseline

A total of 2267 and 2164 participants had LDL-C levels <4.9 and ≥ 4.9 mmol/L, respectively (Fig. 1B). The characteristics of participants at baseline stratified by LDL-C status are shown in Table 1. Mean age was 58 years and around 80% were men. Prior myocardial infarction was the most frequent CAD qualifying event for inclusion into the trial (approx. 80% of patients). About one-fourth of participants were hypertensive, and <5% had diabetes. Overall, the characteristics of participants were well matched between simvastatin and placebo arms and within each strata of LDL-C <4.9 and ≥ 4.9 mmol/L (Table 1).

For the groups stratified by LDL-C, lipid levels at baseline and during follow-up are shown in Table 1 and Supplemental Table 1. Mean LDL-C levels at baseline differed by around 1 mmol/L between those with an LDL-C <4.9 and ≥ 4.9 mmol/L (4.4 and 5.4 mmol/L, respectively). Lipid levels were well matched between simvastatin and placebo arms at baseline within each LDL-C strata. During follow-up, treatment with simvastatin, compared with placebo, significantly reduced the levels of total cholesterol, LDL-C and triglycerides and increased high-density lipoprotein cholesterol levels, both in absolute and percentage terms (all $p < 0.0001$, Supplemental Table 1). Relative to placebo, simvastatin led to similar percentage reductions in LDL-C levels from baseline of around 38% at year 1 and 34–35% at year 5, but there was a greater absolute placebo-corrected reduction among those with LDL-C ≥4.9 mmol/L (2.05 mmol/L) compared to those with LDL-C <4.9 mmoL/l (1.66 mmol/L).

In the placebo arm, the proportion of individuals dying from any cause, cardiovascular causes or coronary deaths, or suffering a MCE were higher by 2.7%, 2.3%, 1.8% and 1.0%, respectively, among those with an LDL-C ≥4.9 mmol/L *versus* those with LDL-C <4.9 mmoL/l. The effect of simvastatin, compared with placebo, on mortality and cardiovascular outcomes over 5.4 years in the overall cohort and stratified by

Table 1
Characteristics of participants at baseline stratified by LDL-C 4.9 mmol/L at baseline.

	LDL-C <4.9 mmol/L at baseline		LDL-C ≥4.9 mmol/L at baseline	
	n = 2267		n = 2164	
	Simvastatin	Placebo	Simvastatin	Placebo
	n = 1119	n = 1148	n = 1094	n = 1070
Age (years)	58.7 ± 7.0	58.3 ± 7.0	58.5 ± 7.4	58.9 ± 6.9
Men, n (%)	934 (83.5%)	956 (83.3%)	873 (79.8%)	844 (78.9%)
Hypertension, n (%)	285 (25.5%)	314 (27.4%)	286 (26.1%)	275 (25.7%)
Diabetes mellitus, n (%)	53 (4.7%)	52 (4.5%)	52 (4.8%)	44 (4.1%)
Smoking status	–	–	–	–
Never smoker, n (%)	273 (24.4%)	270 (23.5%)	282 (25.8%)	290 (27.1%)
Ex-smoker, n (%)	596 (53.3%)	563 (49.0%)	520 (47.5%)	500 (46.7%)
Current smoker, n (%)	250 (22.3%)	315 (27.4%)	292 (26.7%)	280 (26.2%)
Myocardial infarction, n (%)	887 (79.3%)	921 (80.2%)	869 (79.4%)	843 (78.8%)
Coronary revascularization (CABG/PTCA), n (%)	74 (6.6%)	84 (7.3%)	113 (10.3%)	67 (6.3%)
CABG, n (%)	66 (5.9%)	76 (6.6%)	98 (9.0%)	58 (5.4%)
PTCA, n (%)	9 (0.8%)	11 (1.0%)	15 (1.4%)	9 (0.8%)
Transient ischemic attack[a], n (%)	17 (1.5%)	25 (2.2%)	24 (2.2%)	26 (2.4%)
Claudication, n (%)	59 (5.3%)	62 (5.4%)	71 (6.5%)	62 (5.8%)
Body Mass Index (kg/m^2)	25.9 ± 3.4	26.1 ± 3.4	26.0 ± 3.4	25.9 ± 3.2
Systolic blood pressure (mmHg)	139.4 ± 19.7	139.0 ± 19.8	137.6 ± 19.6	139.3 ± 19.4
Diastolic blood pressure (mmHg)	83.4 ± 9.6	83.7 ± 9.3	83.0 ± 9.3	83.6 ± 9.6
Heart rate (bpm)	63.7 ± 10.1	64.2 ± 10.1	63.8 ± 10.1	64.1 ± 10.0
Medication	–	–	–	–
Aspirin, n (%)	413 (36.9%)	443 (38.6%)	408 (37.3%)	371 (34.7%)
Beta-blocker, n (%)	630 (56.3%)	655 (57.1%)	623 (56.9%)	610 (57.0%)
Calcium antagonists, n (%)	355 (31.7%)	356 (31.0%)	353 (32.3%)	311 (29.1%)
Isosorbide mono/dinitrate, n (%)	355 (31.7%)	377 (32.8%)	326 (29.8%)	348 (32.5%)
Thiazides, n (%)	68 (6.1%)	70 (6.1%)	82 (7.5%)	68 (6.4%)
Warfarin, n (%)	12 (1.1%)	35 (3.0%)	17 (1.6%)	16 (1.5%)
Fish oil, n (%)	127 (11.3%)	128 (11.1%)	155 (14.2%)	164 (15.3%)
Lipid levels	–	–	–	–
Total cholesterol (mmol/L)	6.24 ± 0.42	6.27 ± 0.42	7.25 ± 0.44	7.26 ± 0.45
LDL-cholesterol (mmol/L)	4.35 ± 0.37	4.36 ± 0.37	5.42 ± 0.40	5.43 ± 0.41
HDL-cholesterol (mmol/L)	1.23 ± 0.32	1.22 ± 0.32	1.13 ± 0.25	1.15 ± 0.26
Triglycerides (mmol/L)	1.40 (1.05, 1.75)	1.42 (1.1, 1.85)	1.50 (1.20, 1.85)	1.45 (1.15, 1.85)

Data shown as mean ± standard deviation or median (interquartile range), as appropriate, for quantitative parameters.
CABG, coronary artery bypass graft; CAD, coronary artery disease; HDL, high-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; PTCA, percutaneous transluminal coronary angioplasty.
[a] History of completed stroke was an exclusion criterion in 4S trial.

LDL-C <4.9 or ≥4.9 mmol/L, is shown in Fig. 2A and B and Supplemental Table 2. All mortality endpoints and MCE were significantly reduced with simvastatin compared to placebo in the overall cohort and in analysis stratified by LDL-C level, including a relative risk reduction (RRR) of 35%, 40% and 47% in all-cause, cardiovascular and coronary death, respectively, and 35% in MCE, in the group of patients with LDL-C ≥4.9 mmol/L. There was no statistical interaction between LDL-C group and clinical benefit (interaction *p*-values all >0.4). Participants with LDL-C ≥4.9 mmol/L at baseline exhibited greater ARR with simvastatin *versus* placebo (4.1%–4.3% for mortality endpoints, *versus* 2.5%–2.8% among those with LDL-C <4.9 mmol/L at baseline) (Fig. 2B and Supplemental Table 2). Despite these greater absolute reductions in risk, the residual risk of adverse outcomes among simvastatin-treated patients remained higher among patients with LDL-C ≥4.9 mmol/L *versus* LDL-C <4.9 mmoL/l (0.9% higher for all-cause mortality, 0.7% higher for cardiovascular deaths, and 0.3% higher for both coronary death and MCE).

3.2. Analysis stratified by features suggestive of FH phenotype

Participants with an LDL-C ≥4.9 mmol/L were further stratified into 4 subgroups based on the presence of features suggestive of FH phenotype, as shown in Fig. 1. A total of 152 participants had the "FH phenotype" (LDL-C ≥4.9 mmol/L with premature CAD and family history of CAD); this corresponded to 1 in 29 (3.45%) of the whole trial cohort.

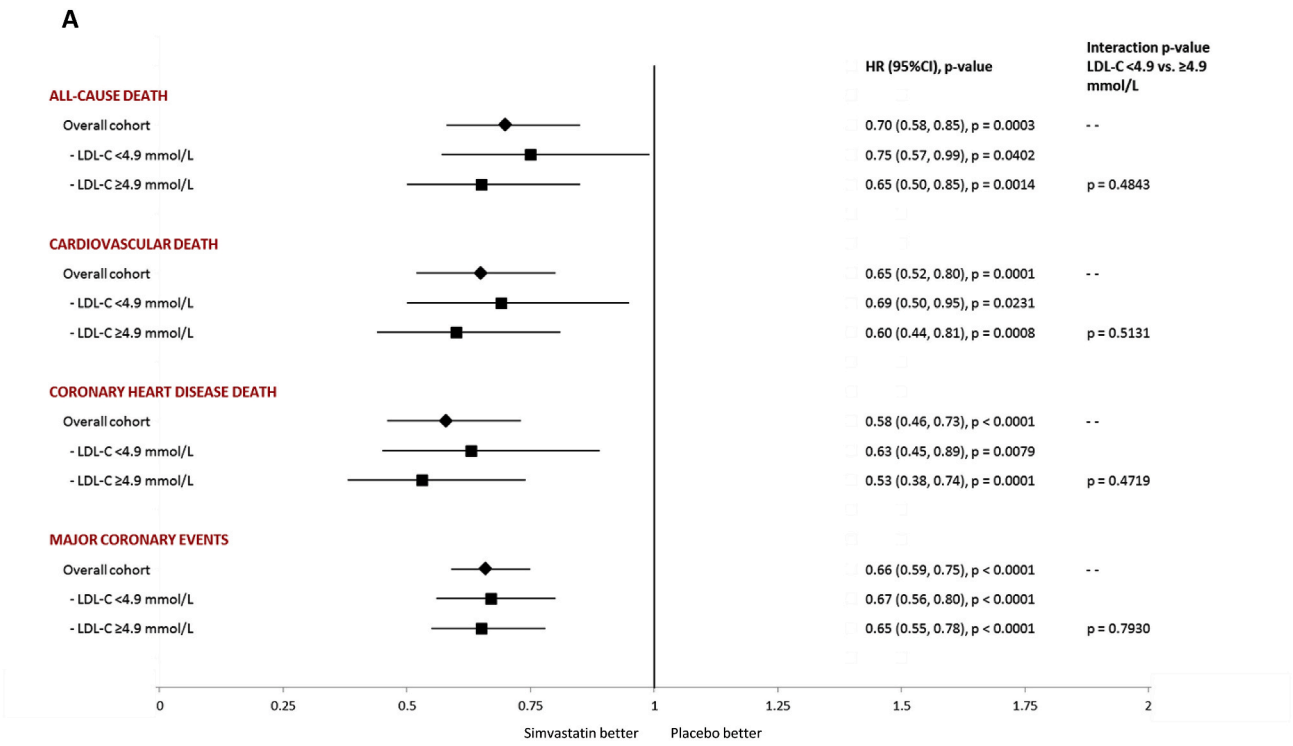
The characteristics of participants at baseline for each subgroup are shown in Table 2. As otherwise expected, the subgroups having premature CAD were younger (mean age approx. 50 years, *versus* 62 years in the subgroups without premature CAD); they also included a higher proportion of smokers. The proportion of women was higher in the subgroup with a FH phenotype (38%, *versus* 15% in the subgroup not having any feature of FH phenotype). Within each of the four subgroups, the characteristics of participants were well matched between simvastatin and placebo overall (Table 2).

Lipid levels at baseline and during follow-up, stratified by features suggestive of the FH phenotype, are shown in Table 2 and Supplemental Table 3, respectively. Of interest, mean LDL-C levels were similar in all four subgroups at baseline (in the range 5.4–5.5 mmol/L) (Table 2). Accounting for the effect of placebo, treatment with simvastatin led to 35.5%–38.5% reduction in LDL-C levels from baseline to year 1 and 31.4%–36.4% at year 5 (1.95–2.08 mmol/L absolute reductions at 1 year and 1.69 to 1.98 at 5 years) (Supplemental Table 3).

The effect of simvastatin, compared with placebo, on mortality and cardiovascular outcomes stratified by features suggestive of an FH phenotype is shown in Fig. 3A and B and Supplemental Table 4. Participants with an FH phenotype tended to derive greater relative benefits including a significant 84% RRR in all-cause death ($p = 0.046$) and 55% RRR in MCE ($p = 0.0297$) with simvastatin compared to those without it (Fig. 3A). However, tests for interaction among groups were not significant for any endpoint studied. Participants with the FH phenotype derived greater ARR with simvastatin *versus* placebo than any other subgroup, including a 6.6% ARR for all-cause mortality and a 13.2% ARR for MCE (e.g. *versus* 3.8% and 8.3% ARR, respectively, in participants with LDL-C ≥4.9 mmol/L but without any feature suggestive of FH) (Fig. 3B and Supplemental Table 4).

4. Discussion

4S was a landmark study that established the importance of cholesterol reduction in patients with existing CAD. The present analysis provides further insight into those individuals in the trial with primary severe hypercholesteroaemia (LDL-C ≥4.9 mmol/L) and, more specifically, those with phenotypic characteristics of FH. First, among the placebo-treated population with established CAD, those with baseline LDL-C ≥4.9 mmol/L had an approximately 2% excess risk of fatal



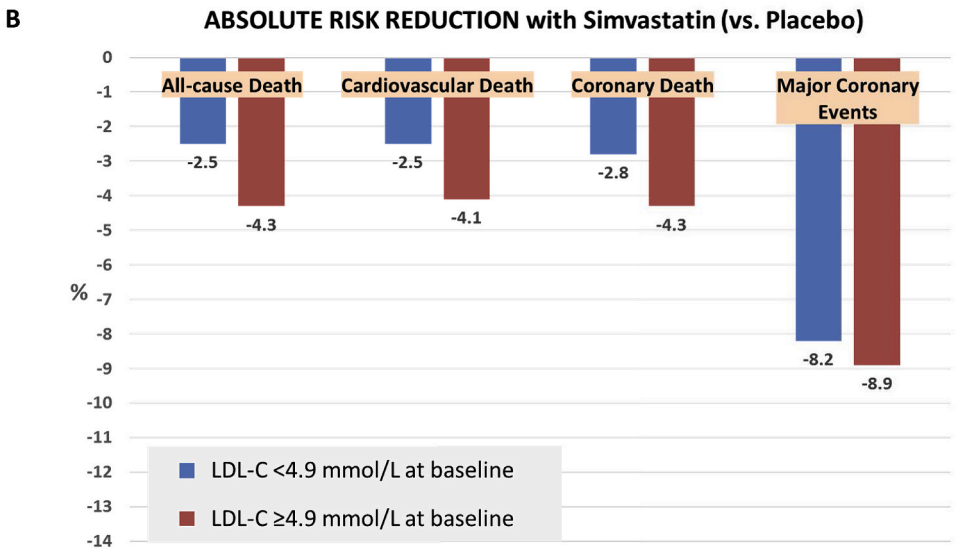


Fig. 2. Relative risk (A) and absolute risk (B) of outcomes at the end of the study associated with simvastatin, compared to placebo, stratified by LDL-cholesterol 4.9 mmol/L.
CI, confidence intervals; LDL-C, low-density lipoprotein cholesterol; HR, hazard ratio.

outcomes and MCE compared with those with LDL-C <4.9 mmol/L, during the course of the trial. The demographic characteristics of those with LDL-C <4.9 or ≥4.9 mmol/L (in the placebo group) were broadly similar except for the fact that those with an LDL-C ≥4.9 mmol/L had about a 1.07 mmol/L higher baseline LDL-C and a 0.76 mmol/L difference at 5 years.

Second, we observed that individuals with CAD and elevated LDL-C ≥4.9 mmol/L derived similar relative reductions in mortality outcomes compared to individuals with LDL-C <4.9 mmol/L but greater absolute benefits in terms of all-cause mortality (4.3% *vs* 2.5%), cardiovascular death (4.1% *vs* 2.5%), coronary death (4.3% *vs* 2.8%) and MCE (8.9% *vs* 8.2%). Although we found no evidence of formal statistically significant interactions among populations stratified by baseline LDL-C, the numerically greater RRR of approximately 10% for mortality outcomes with simvastatin may reflect the 0.62 mmol/L greater LDL-C lowering at 1 year, which was maintained through to 5 years (0.61 mmol/L at year 5), consistent with the hypothesis that the proportional reductions in risk correlate with the absolute difference in LDL-C over time [1,8]. Despite LDL-C lowering with statins, event rates were higher among those with starting levels of LDL-C ≥4.9 mmol/L than those with starting levels <4.9 mmol/L, reinforcing both the importance of LDL-C to risk but also potentially the need for earlier lipid-lowering interventions.

Third, among those with LDL-C ≥4.9 mmol/L, we divided the cohort into 4 subgroups to assess treatment effects separately in those with and

Table 2
Characteristics of participants at baseline stratified by features suggestive of a familial hypercholesterolaemia phenotype.

	LDL-C ≥4.9 mmol/L at baseline							
	No premature CAD No family history of CAD		No premature CAD Family history of CAD		Premature CAD No family history of CAD		FH phenotype	
	Simvastatin	Placebo	Simvastatin	Placebo	Simvastatin	Placebo	Simvastatin	Placebo
	n = 473	n = 453	n = 298	n = 319	n = 247	n = 222	n = 76	n = 76
Age (years)	62.0 ± 4.0	62.1 ± 3.9	63.0 ± 3.8	62.5 ± 3.8	48.8 ± 5.4	49.6 ± 4.9	51.3 ± 5.1	51.9 ± 5.8
Men, n (%)	401 (84.8%)	386 (85.2%)	225 (75.5%)	233 (73.0%)	199 (80.6%)	179 (80.6%)	48 (63.2%)	46 (60.5%)
Hypertension, n (%)	145 (30.7%)	105 (23.2%)	78 (26.2%)	98 (30.7%)	46 (18.6%)	49 (22.1%)	17 (22.4%)	23 (30.3%)
Diabetes mellitus, n (%)	28 (5.9%)	16 (3.5%)	15 (5.0%)	17 (5.3%)	5 (2.0%)	9 (4.1%)	4 (5.3%)	2 (2.6%)
Smoking status, n (%)	–	–	–	–	–	–	–	–
Never smoker, n (%)	133 (28.1%)	128 (28.3%)	95 (31.9%)	99 (31.0%)	37 (15.0%)	40 (18.0%)	17 (22.4%)	23 (30.3%)
Ex-smoker, n (%)	222 (46.9%)	225 (49.7%)	140 (47.0%)	153 (48.0%)	127 (51.4%)	96 (43.2%)	31 (40.8%)	26 (34.2%)
Current smoker, n (%)	118 (24.9%)	100 (22.1%)	63 (21.1%)	67 (21.0%)	83 (33.6%)	86 (38.7%)	28 (36.8%)	27 (35.5%)
Myocardial infarction, n (%)	392 (82.9)	356 (78.6%)	227 (76.2%)	256 (80.3%)	195 (78.9%)	180 (81.1%)	55 (72.4%)	51 (67.1%)
Coronary revascularization), n (%)	52 (11.0%)	27 (6.0%)	35 (11.7%)	19 (6.0%)	22 (8.9%)	15 (6.8%)	4 (5.3%)	6 (7.9%)
CABG, n (%)	47 (9.9%)	26 (5.7%)	32 (10.7%)	17 (5.3%)	16 (6.5%)	11 (5.0%)	3 (3.9%)	4 (5.3%)
PTCA, n (%)	5 (1.1%)	1 (0.2%)	3 (1.0%)	2 (0.6%)	6 (2.4%)	4 (1.8%)	1 (1.3%)	2 (2.6%)
Transient ischemic attack[a], n (%)	12 (2.5%)	9 (2.0%)	10 (3.4%)	13 (4.1%)	2 (0.8%)	4 (1.8%)	0 (0.0%)	0 (0.0%)
Claudication, n (%)	40 (8.5%)	27 (6.0%)	18 (6.0%)	23 (7.2%)	9 (3.6%)	7 (3.2%)	4 (5.3%)	5 (6.3%)
Body Mass Index (kg/m^2)	25.9 ± 3.1	25.7 ± 2.9	25.6 ± 2.9	25.8 ± 3.4	26.7 ± 4.3	26.2 ± 3.2	25.9 ± 3.0	26.3 ± 3.4
Systolic blood pressure (mmHg)	139.7 ± 19.9	140.1 ± 18.6	142.1 ± 20.0	144.1 ± 20.5	130.2 ± 16.5	131.4 ± 17.3	131.7 ± 17.0	137.9 ± 17.7
Diastolic blood pressure (mmHg)	83.6 ± 9.4	83.6 ± 9.0	82.9 ± 9.1	83.7 ± 10.1	82.6 ± 9.5	83.4 ± 9.9	81.5 ± 8.7	84.1 ± 9.7
Heart rate (bpm)	63.7 ± 10.1	64.2 ± 9.9	64.1 ± 10.6	63.7 ± 9.2	63.6 ± 9.6	64.2 ± 11.1	64.2 ± 10.6	64.8 ± 10.3
Medication	–	–	–	–	–	–	–	–
Aspirin, n (%)	186 (39.3%)	157 (34.7%)	99 (33.2%)	97 (30.4%)	99 (40.1%)	86 (38.7%)	24 (31.6%)	31 (40.8%)
Beta-blocker, n (%)	262 (55.4%)	257 (56.7%)	170 (57.0%)	183 (57.4%)	141 (57.1%)	125 (56.3%)	50 (65.8%)	45 (59.2%)
Calcium antagonists, n (%)	162 (34.2%)	123 (27.2%)	98 (32.9%)	102 (32.0%)	67 (27.1%)	56 (25.2%)	26 (34.2%)	30 (39.5%)
Isosorbide mono/dinitrate, n (%)	133 (28.1%)	130 (28.7%)	107 (35.9%)	132 (41.4%)	54 (21.9%)	60 (27.0%)	32 (42.1%)	26 (34.2%)
Thiazides, n (%)	41 (8.7%)	26 (5.7%)	22 (7.4%)	23 (7.2%)	11 (4.5%)	12 (5.4%)	8 (10.5%)	7 (9.2%)
Warfarin, n (%)	4 (0.8%)	5 (1.1%)	7 (2.3%)	6 (1.9%)	4 (1.6%)	5 (2.3%)	2 (2.6%)	0 (0.0%)
Fish oil, n (%)	67 (14.2%)	67 (14.8%)	46 (15.4%)	57 (17.9%)	36 (14.6%)	30 (13.5%)	6 (7.9%)	10 (13.2%)
Parents with history of CAD, n (%)	188 (39.7%)	195 (43.0%)	155 (52.0%)	156 (48.9%)	131 (53.0%)	127 (57.2%)	55 (72.4%)	48 (63.2%)
Lipid levels								
Total cholesterol (mmol/L)	7.23 ± 0.44	7.25 ± 0.45	7.25 ± 0.45	7.22 ± 0.49	7.26 ± 0.42	7.28 ± 0.41	7.36 ± 0.51	7.43 ± 0.44
LDL-cholesterol (mmol/L)	5.42 ± 0.38	5.43 ± 0.41	5.42 ± 0.41	5.39 ± 0.43	5.41 ± 0.40	5.45 ± 0.37	5.49 ± 0.47	5.52 ± 0.39
HDL-cholesterol (mmol/L)	1.13 ± 0.26	1.15 ± 0.25	1.16 ± 0.25	1.16 ± 0.27	1.10 ± 0.24	1.12 ± 0.23	1.15 ± 0.25	1.22 ± 0.28
Triglycerides (mmol/L)	1.40 (1.15, 1.75)	1.45 (1.15, 1.75)	1.40 (1.20, 1.80)	1.45 (1.15, 1.80)	1.60 (1.30, 1.90)	1.55 (1.15, 1.95)	1.55 (1.25, 1.90)	1.50 (1.10, 1.90)

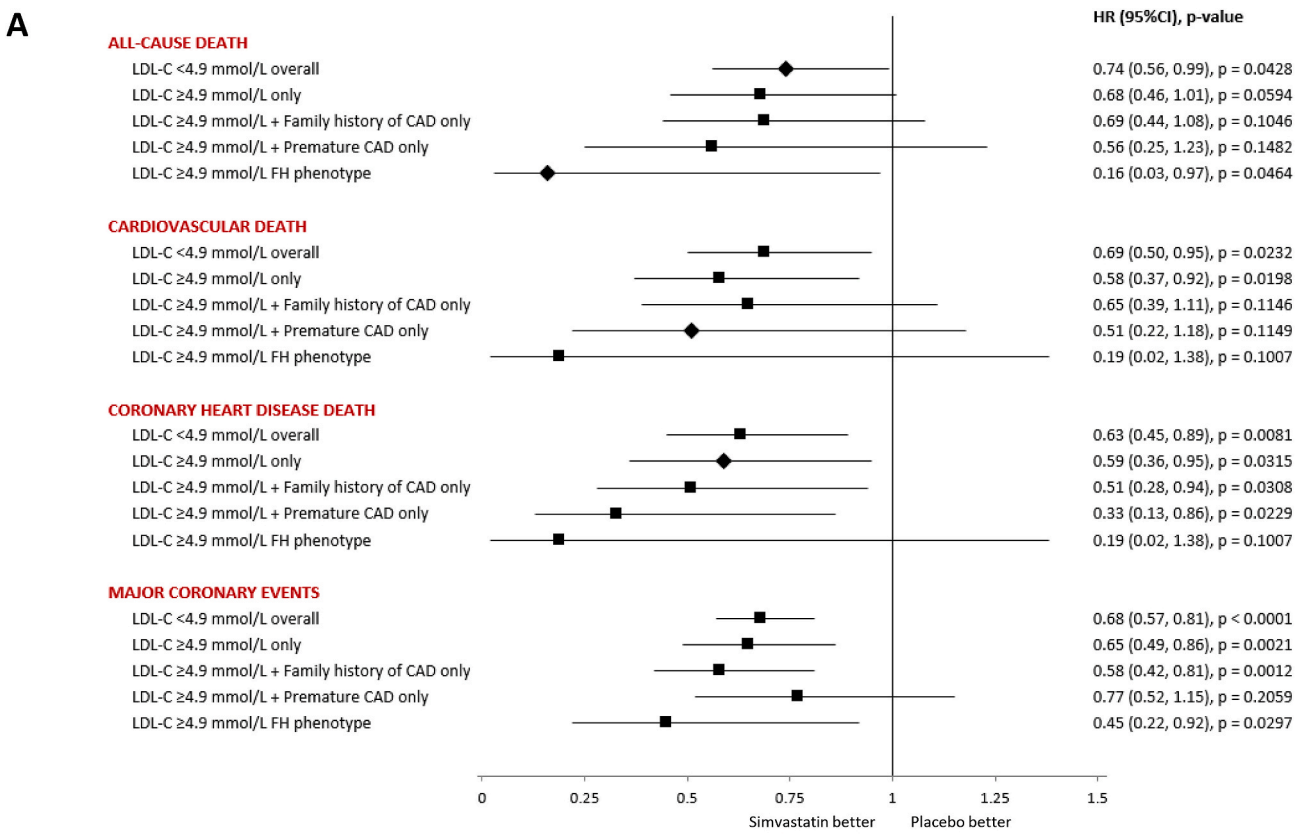
Data shown as mean ± standard deviation or median (interquartile range), as appropriate, for quantitative parameters. FH phenotype: family history of CAD and premature CAD.

CABG, coronary artery bypass graft; CAD, coronary artery disease; FH: familial hypercholesterolaemia; HDL, high-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty.

[a] History of completed stroke was an exclusion criterion in 4S trial.

without potential genetic vulnerability to CAD and/or LDL-C, as judged by proxy measures such as family history and early onset of CAD. This approach identified 1 in 29 (3.45%) individuals of the whole trial cohort as having an FH phenotype; this is consistent with the prevalence of FH among people with CAD reported from large meta-analyses [5,15], supporting the construct validity for the definition of FH phenotype used in these analyses. We observed that baseline LDL-C were similar across the four aforementioned subgroups, ranging from 5.41 to 5.49 mmol/L. At 1 year, the percentage reduction in LDL-C with simvastatin was similar across subgroups with placebo-corrected LDL-C reductions ranging from 35.5% to 38.5% and placebo-corrected absolute differences in LDL-C ranging from between 1.95 and 2.05 mmol/L, and at 5 years the placebo-corrected LDL-C from 1.69 to 1.98 mmol/L between statin and placebo within each of the 4 subgroups. Hence, the effect of simvastatin on LDL-C differences over 5 years was broadly similar across the four subgroups. When we assessed the effect of simvastatin on the four endpoints of interest, the reduction in risk of mortality outcomes and MCE tended to be numerically greater among those with an FH phenotype, with statistically significant reductions in mortality of 84% and MCE of 55%, *vs* 31%–44% and 23%–42% reductions among those with LDL-C ≥4.9 mmol/L but without FH phenotype. It should be noted however that formal tests of statistical interaction between the four subgroups were not significant. Among those defined as FH phenotype, similar reductions in LDL-C over 5 years resulted in greater ARR for all-cause mortality of 6.6% and MCE of 13.2%, *vs* 3.7%–4.6% and 6.6%–10.3%, respectively, among those with LDL-C ≥4.9 mmol/L without FH phenotype.

The observation that although the absolute event rates among the placebo groups were similar among individuals with an LDL-C ≥4.9 mmol/L, for those with or without the FH phenotype, but under statin treated conditions those with an FH phenotype derived greater relative and absolute benefit, may have practical implications. In particular, the presence of premature CAD and a first-degree relative with a history of CAD, in an individual with LDL-C ≥4.9 mmol/L, may identify a group of individuals with a greater vulnerability to LDL-C and, by contrast, a group who may derive greater benefit from LDL-C reduction. If this hypothesis is true, then efforts to improve early detection of these patients and initiate lipid-lowering therapy become even more important.



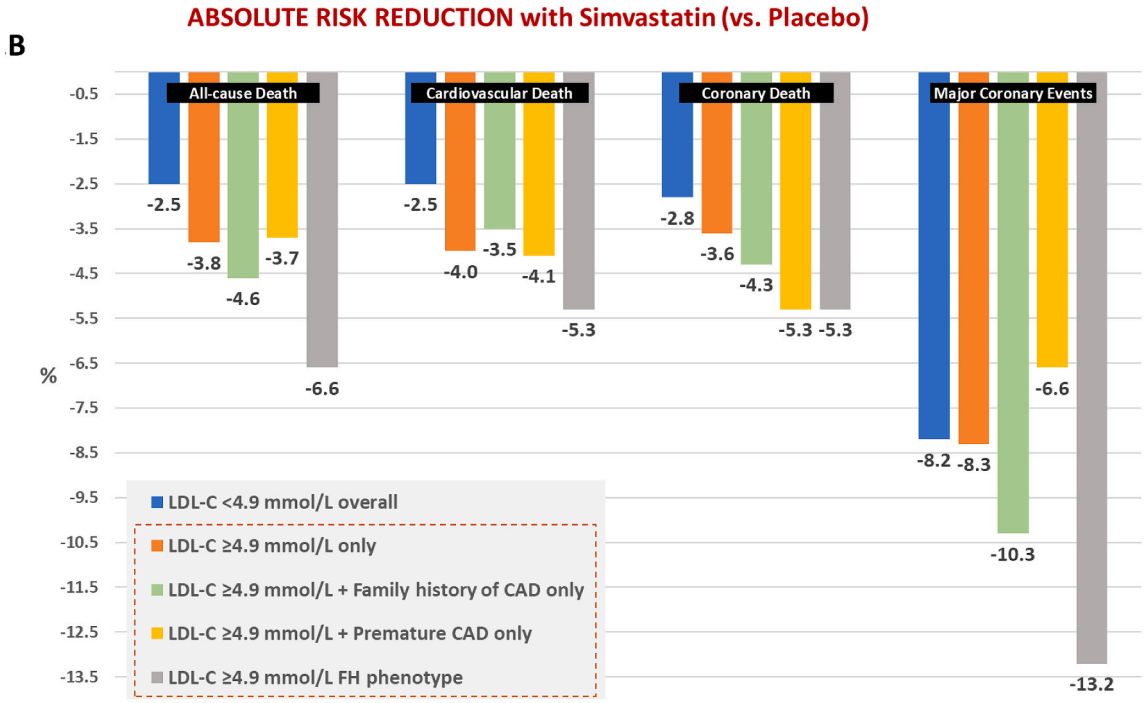


Fig. 3. Relative risk (A) and absolute risk (B) of outcomes at the end of the study associated with simvastatin, compared to placebo, stratified by features suggestive of a familial hypercholesterolaemia phenotype.
CAD, coronary artery disease; CI, confidence intervals; FH, familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol. HR, hazard ratio.

Whilst considerable benefit was observed with moderate intensity statin therapy in this study for those with an FH phenotype, most guidelines recommend intensification of statin treatment and/or the addition of other lipid-lowering therapies such as ezetimibe or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors for FH patients, based on extrapolation from other trial populations that additional risk reductions could be derived from further LDL-C reduction [8,16–18], and where they are more likely to have the greatest cost-effective impact.

Most guidelines have suggested that lower LDL-C levels are more desirable at a population level [10], but these lower goals are harder to achieve with monotherapy, particularly for individuals with FH, meaning that multiple drugs may be needed, with the potential for inconvenience, adherence issues related to polypharmacy and/or higher costs. As most patients with FH are detected late [19], there is a logical suggestion that, as many years of exposure have been missed, LDL-C lowering should be more aggressive at the point of diagnosis. However, the potential for differential benefit from LDL-C lowering among those with the FH phenotype may be an important consideration when it comes to determining optimal strategies for prescribing new, potentially more expensive but powerful treatments to further reduce LDL-C in FH patients. If detection of cases of FH were to occur earlier, then even modest reductions sustained over longer periods of time might translate into large benefits [1,20]. This is supported by studies suggesting that children with FH, if started even on moderate intensity statins, had lower risk of cardiovascular disease or progression of CAD in comparison to their parents who were index cases and diagnosed later in life [1,21]. This despite the fact that although LDL-C levels were lowered, they were not normalised. Our data are consistent with these findings and may provide additional insights. In addition to the obvious benefit of starting lipid-lowering treatment early in FH, if these individuals derive greater benefit from LDL-C lowering, then if the diagnosis of FH is made early, simple generic oral agents (such as statins) may be enough for many patients without the need for multiple therapies or more expensive drugs (such as PCSK9 inhibitors) in most or all individuals, with add-on therapy being reserved for more severe cases. This would assist in moving the public health focus towards detection of FH rather than implementation of polypharmacy when diagnosis is made late in life.

Several limitations in the present study should be considered. The present study is a *post-hoc* analysis of a randomized trial, and these analyses were not prespecified in the original statistical analysis plan. Nevertheless, we prespecified these analyses prior to data analysis alongside similar analyses we conducted within a primary prevention study [11]. As age of diagnosis of CAD among participants was not recorded in the original trial, the age at study entry was used to define premature CAD, which is a conservative estimate for the FH phenotype group; therefore, some patients with actual premature CAD may have been allocated to the non-premature subgroup if they had CAD before the age of 55/60 years in men/women, but were older at the time of study entry. This may have likely led to an underestimation of the differential effect between groups with and without premature CAD. In the same way, it may be possible that some patients in the group with LDL-C $\geq$4.9 mmol/L and premature CAD but without history of CAD in the family could also have FH, and this could potentially underestimate the results by diluting the effect between the groups. Therefore, all things considered, it may mean that the benefits we have found in the FH phenotype subgroup compared to the study subgroups without premature CAD or without history of CAD in the family could potentially be even greater than those reported. In this sense, our results represent a conservative approach/estimates. Stratifying the group with LDL-C $\geq$4.9 mmol/L into multiple subgroups reduced the potential power of the analyses and in particular the FH phenotype group. Although we found statistical evidence of large benefits, the confidence intervals are wide. That said, using alternative definitions such as the American Heart Association (AHA) criteria of LDL-C $\geq$190 mg/dL and family history in order to reduce the number of subgroups would not have offered additional insights given the observed separate and joint contributions of both a personal history of premature CAD and family history in this specific study (Supplemental Table 4). Data from prior statian trials, as collated by the Cholesterol Trialist Collaboration (CTT) [22], suggest that moderate LDL-C lowering with simvastatin 20–40 mg may not be expected to reduce all-cause mortality to the extent (84% RRR) we have found in our analysis; this may reflect a more extreme value than expected based upon the reduced sample size for the FH phenotype group and wide confidence intervals; nevertheless, outcome reduction was statistically significant and it must be noted that the CTT and prior statin trials did not go out to the extremes of LDL-C studied in this subgroup in our analysis. The findings in our study should be considered hypothesis-generating. That said, given that nowadays it would be unethical to conduct a placebo-controlled trial in FH, we are reliant on the type of analyses we have conducted in historical studies.

In conclusion, in individuals with CAD, those with an LDL-C $\geq$4.9 mmol/L and FH phenotype appear to associate greater relative and absolute benefits from LDL-C reduction than individuals with LDL-C $\geq$4.9 mmol/L without FH phenotype from the same magnitude of LDL-C lowering.

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CRediT authorship contribution statement

Antonio J. Vallejo-Vaz: Conceptualization, Methodology, Data curation, Formal analysis, Visualization, Writing - original draft, Writing - review & editing. **Chris J. Packard:** Conceptualization, Writing - original draft, Writing - review & editing. **Brian A. Ference:** Conceptualization, Writing - review & editing. **Raul D. Santos:** Conceptualization, Writing - review & editing. **John J.P. Kastelein:** Conceptualization, Writing - review & editing. **Evan A. Stein:** Conceptualization, Writing - review & editing. **Alberico L. Catapano:** Conceptualization, Writing - review & editing. **Terje R. Pedersen:** Methodology, Writing - review & editing. **Gerald F. Watts:** Conceptualization, Writing - review & editing. **Kausik K. Ray:** Conceptualization, Methodology, Visualization, Writing - original draft, Writing - review & editing.

Declaration of competing interest

Dr Vallejo-Vaz reports honoraria for lectures from Amgen, Mylan, and Akcea; personal fees for consultancy from Bayer; and participation in research grants to Imperial College London from Pfizer, Amgen, MSD, Sanofi, Regeneron, and Daiichi-Sankyo; all outside the submitted work. Dr Packard reports honoraria from Amgen, Daiichi-Sankyo, DalCor, and MSD; all ouside the submitted work. Dr Ference reports research grants and/or honoraria for lectures, consulting and/or advisory board membership, from Merck, Novartis, Amgen, Regeneron, Sanofi, Pfizer, Eli Lilly, Novo Nordisk, The Medicines Co, Mylan, Daiichi-Sankyo, Alnylam, Esperion Therapeutics, Ionis Pharmaceuticals, Silence Therapeutics, dalCOR, CiVi Pharma, KrKa Phamaceuticals, Medtronic, American College of Cardiology, European Atherosclerosis Society, and European Society of Cardiology; outside the submitted work. Dr Santos reports honoraria related to consulting, research and/or speaker activities from Ache, Amgen, Astra Zeneca, Esperion, EMS, Kowa, Novo-Nordisk, Merck, MSD, Pfizer, PTC, and Sanofi/Regeneron. Dr Kastelein reports consulting fees and honoraria for lectures from Astra Zeneca, CSL-Behring, Daichii-Sankyo, Esperion, Genentech, Menarini, Novartis, Novo Nordisk, Pfizer, and Regeneron. Dr Stein has received fees for consulting from Gemphire, CymaBay, and AstraZeneca; has received expert witness fees from Amgen; and is a founder and CEO of LIB Therapeutics. Dr Catapano reports grants, consulting fees and/or

honoraria and delivering lectures from Aegerion, Abbot, Akcea, Amgen, BMS, Eli Lilly, Genzyme, Kowa, Merck, Novartis, Pfizer, Recordati, Roche, Sanofi, and Sigma-Tau; all outside the submitted work. Dr Pedersen has received honoraria from Amgen and Merck for consulting and speaking. Dr Watts reports grants, advisory board and lecture fees from Amgen, Sanofi, Regneron, Arrowhead, and Kowa. Dr Ray reports personal fees for consultancy from AbbVie, Amgen, AstraZeneca, Sanofi, Regeneron, Merck Sharp & Dohme, Pfizer, Resverlogix, Akcea, Boehringer Ingelheim, Novo Nordisk, Takeda, Kowa, Algorithm, Cipla, Cerenis, Dr Reddys, Lilly, Zuellig Pharma, Bayer, Daiichi-Sankyo, The Medicines Company, and Esperion, and research grant support from Pfizer, Amgen, Sanofi, Regeneron, and Merck Sharp & Dohme.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2021.01.003.

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