LDL-CHOLESTEROL LOWERING FOR THE PRIMARY PREVENTION OF CARDIOVASCULAR DISEASE AMONG MEN WITH PRIMARY ELEVATIONS OF LDL-CHOLESTEROL LEVELS OF 190 mg/dL OR ABOVE

Analyses From the WOSCOPS 5-year Randomised Trial and 20-year Observational Follow-Up

SUPPLEMENTAL MATERIAL

1.- SUPPLEMENTAL METHODS

Participants (men aged 45 to 64) were screened in primary care facilities in the West of Scotland district (after they were identified from doctor´s age/sex registers and invited by mail to attend non-fasting screening clinics).[S1] Fasting lipid levels were measured centrally according to the Lipid Research Clinic's protocol.[S1] Those individuals with a total cholesterol level greater than or equal to 251 mg/dL (6.5 mmol/L) were given dietary advice on cholesterol reduction and invited to return in 4 weeks.[S1] A complete lipoprotein analysis, including low-density lipoprotein cholesterol (LDL-C) levels, were then measured (14 hr fasting sample) during the second and third pre-enrolment screening visits.[S1] Patients who had a LDL-C of 155 mg/dL (4.0 mmol/L) or higher at both screening visits with at least one measurement greater than or equal to 174 mg/dL (4.5 mmol/L) were included. Patients with LDL-C above 232 mg/dL (6.0 mmol/L) on both occasions were excluded. "Baseline lipid levels" were defined as the mean of the values measured at the second and third screening visits. There were no significant differences in lipid levels between the two screening measurements.[S2] Fasting lipid levels were measured at 6-month intervals during the trial follow-up.

Participants included in the study had no evidence of prior myocardial infarction (MI) based on medical history and baseline ECG, though individuals with stable angina not hospitalized within the previous 12 months were eligible in the original trial.[S1] Pre-randomisation exclusion criteria established in the original trial included:[S1] (1) history of treated MI with documented ECG or enzyme changes; (2) angina pectoris requiring hospitalization for treatment or investigation within the previous 12 months (other individuals with positive Rose Questionnaire were not excluded); (3) ECG evidence of disease [Minnesota codes[S3] 1-1, 1-2, 1-3, 4-1, 5-1, 6-4-1, 7-1-1 or 9-6; atrial fibrillation (8-3-1)/flutter (8-3-2), frequent (>1 in 5) ventricular premature beats, second (6-2) or third degree atrioventricular block (6-1) as well as A-V dissociation (8-6)]; (4) hypertension exceeding systolic BP >180 mmHg or diastolic BP >110 mmHg, despite treatment; (5) history of rheumatic heart disease; (6) congenital heart disease; (7) pulmonary heart disease, chronic bronchitis, emphysema or kyphoscoliosis associated with ECG changes codes 2-2, 3-2, 7-2 or 7-3; (8) cardiomegaly, congestive cardiac failure, significant valvular heart disease; (9) other suspected serious physical illness; (10) psychiatric illness (reported by GP); (11) current lipid lowering therapy; (12) biochemical and haematological laboratory exclusions: AST >60 U/L, ALT >70 U/L, Ca (adjusted) <2.1 or >2.7 mmol/L, ALP >430 U/L, protein <57 or >87 g/L, CK >360 U/L, creatinine >155 umol/L, glucose <3.0 or >10.0 mmol/L, MCV <70 or >105 fL, triglycerides >531 mg/dL (>6.0 mmol/L), haemoglobin <10 or >20 g/L, leucocyte count $<2.5x10^9$ or $>17.0x10^9$ cell/L, RBC $<3.7x10^{12}$ or $>7.0x10^{12}$ cell/L, Na <130 or >150 mmol/L, K <3.0 or >5.5 mmol/L, bilirubin >33 umol/L.

As reported previously,[S1] the following endpoints are defined as follows:

Coronary heart disease (CHD) death and non-fatal myocardial infarction (MI):

1) **Definite atherosclerotic CHD death:** either or both of the following categories:
   a) Death certificate with consistent underlying or immediate cause plus one or more of the following:
      i) Preterminal hospitalisation with definite or suspect MI (see below).
      ii) Previous definite angina or suspect or definite MI when no cause other than atherosclerotic CHD could be ascribed as the cause of death.
      iii) Autopsy evidence of acute coronary arterial thrombosis and/or acute MI.
   b) Sudden and unexpected death (requires all 3 characteristics):
      i) Deaths occurring within 1 hour after the onset of severe symptoms or having last been seen without them.
      ii) No known non-atherosclerotic acute or chronic process or event that could have been potentially lethal.
      iii) An "unexpected" death occurs only in a person who is not confined to his home, hospital, or other institution because of illness within 24 hours before death.

2) **Definite non-fatal MI:** any one or more of the following categories using the stated definitions:
      i) Diagnostic ECG at the time of the event.
      ii) Ischaemic cardiac pain and diagnostic enzymes.
      iii) Ischaemic cardiac pain with both equivocal enzymes and equivocal ECG.
      iv) An ECG at the annual visit or at an unscheduled visit is diagnostic for MI while the previous one was not.

3) **Suspect atherosclerotic CHD death**: one or both of the following categories:
    i) Death certificate with consistent underlying or immediate cause but neither adequate preterminal documentation of the event nor previous atherosclerotic CHD diagnosis.
    ii) Rapid and unexpected death (requires all 3 characteristics):
        (1) Death occurring between one and 24 hours after the onset of severe symptoms or having last been seen without them.
        (2) No known non-atherosclerotic acute or chronic process or event that could have been potentially lethal.
        (3) An "unexpected death" occurs only in a person who is not confined to his home, hospital or other institution because of illness within 24 hours before death.

4) **Suspect MI:** any one or more of the following categories using the stated definitions:
    i) Ischaemic cardiac pain, except when infarction is excluded by ECG or enzymes.
    ii) Diagnostic enzymes.
    iii) Equivocal ECG and equivocal enzymes.
    iv) Equivocal ECG alone, provided that it is not based on ST or T-wave changes only.

Cerebrovascular disease:

A single episode of motor paralysis, sensory or speech dysfunction, diplopia or visual disturbance lasting more than 1 hour, or repetitive episodes of a similar nature lasting for 5 min or more.

Extended long-term follow up

Following the final randomised trial visit pravastatin and placebo were withdrawn and patients returned to their primary care physicians. At 5 years after the completion of the randomised trial 38.7% and 35.2% of patients originally allocated to pravastatin and placebo arms, respectively, were taking statins ($p<0.001$)[S4]. No later data on the proportion of individuals taking statin therapy were available for the subsequent years of follow-up.[S4] At approximately 20 years since randomisation (15 years after the completion of the randomised trial) long-term mortality outcomes for the two original study groups (pravastatin and placebo) were compared, through linkage to electronic hospital discharge records held by the National Health Service for Scotland.[S4,S5]

Adverse events

Information on adverse events during the study have been described in detail in previous publications from WOSCOPS.[S5-S8] Briefly, results at 5 years showed that the therapy with pravastatin, compared with placebo, did not unfavourably affect the liver function or produced myopathy;[S6] pravastatin was found to protect from the development of diabetes[S7] and from the risk of hospital admission due to cardiovascular causes without affecting non-cardiovascular hospitalizations;[S8] finally, there was no evidence for an increased risk of incident fatal and non-fatal cancers, death from non-cardiovascular causes, or deaths from suicide or trauma with pravastatin.[S6] Similarly, over the 20-year period of follow-up pravastatin did not adversely affect deaths (cardiovascular, non-cardiovascular, cancer) and hospitalisations (cardiovascular, non-cardiovascular) rates.[S5] Unfortunately, there are no post-trial data on non-serious adverse events.

2.- SUPPLEMENTAL TABLES

- **eTable 1.** Different definitions used in the literature for individuals with a primary elevation in LDL-C ≥190 mg/dL (≥4.91 mmol/L).

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eTable 1. Different definitions used in the literature for individuals with a primary elevation in LDL-C ≥190 mg/dL

Source	Definition / comments	Ref
ACC/AHA 2013 Guidelines on blood cholesterol	□ Primary, severe elevations of LDL-C ≥190 mg/dL. □ This guideline recognizes that individuals ≥21 years of age with primary, severe elevations of LDL-C (≥190 mg/dL) have a high lifetime risk for ASCVD events. □ Additional factors that can contribute to assessment of ASCVD risk (to inform treatment decision making in selected individuals) include primary LDL-C ≥160 mg/dL.	Stone NJ et al, 2014 (Ref. S9)
ACC 2016 Consensus on non-statin therapy for LDL-C lowering	□ It endorses benefit groups from ACC/AHA 2013 Guidelines on blood cholesterol (primary elevations of LDL-C ≥190 mg/dL). □ Patients with ASCVD and primary, severe elevations of LDL-C ≥190 mg/dL have very high risk for future ASCVD events because of their lifetime exposure to markedly elevated LDL-C levels.	Lloyd-Jones DM, et al, 2016 (Ref. S10)
AHA 2015 Scientific Statement on FH	□ Heterozygous FH is diagnosed in the presence of a positive family history of elevated cholesterol or premature CAD and LDL-C ≥190 mg/dL in an adult confirmed on 2 occasions.	Gidding SS et al, 2015 (Ref. S11)
ESC/EAS 2016 Guidelines on dyslipidaemias	□ Subjects with markedly elevated single risk factors, in particular cholesterol >8 mmol/L (>310 mg/dL) (e.g. in familial hypercholesterolaemia) or BP ≥180/110 mmHg, are considered of high risk. □ FH is recommended to be suspected […] in subjects with severely elevated LDL-C [in adults >5 mmol/L (190 mg/dL)]. □ LDL-C levels are considered optimal for testing during childhood to discriminate between FH and non-FH using LDL-C. It is acknowledged that "LDL-C ≥5 mmol/L (190 mg/dL) is most probably FH. In children with a family history of high cholesterol or premature CHD, the cut-off point may be put at ≥4.0 mmol/L (160 mg/dL)".	Catapano AL et al, 2016 (Ref. S12)
Clinical diagnosis criteria of HeFH (e.g. DLCN, Simon-Broome)	□ LDL-C >190 mg/dL: at least possible HeFH. □ LDL-C >190 mg/dL + other clinical features: probable or definite HeFH.	Hoving GK et al, 2013 (Ref. S13)
Perak AM et al, 2016	□ LDL-C levels ≥190 mg/dL defined as FH phenotype. □ Alternative FH phenotype definitions including family history or maximally specific age-based LDL-C criteria decreased the FH phenotype prevalence but did not materially affect CHD risk estimates.	Perak AM et al, 2016 (Ref. S14)
Khera AV et al, 2016	□ Sever hypercholesterolaemia, defined as having a LDL-C level ≥190 mg/dL. □ Primary, severe LDL-C elevation was defined as ≥190 mg/dL, in accordance with cholesterol guidelines (ACC/AHA 2013). □ FH is one cause of severely elevated LDL-C.	Khera AV et al, 2016 (Ref. S15)
Expert Panel of the National Lipid Association	□ PCSK9 inhibitor therapy to be considered for patients with phenotypic FH/LDL-C ≥190 mg/dL, including polygenic hypercholesterolemia, HeFH, and phenotypic homozygous FH	Oriinger CE et al. 2017 (Ref. S16)

ACC: American College of Cardiology. AHA: American Heart Association. ASCVD: atherosclerotic cardiovascular disease. CHD: coronary heart disease. DLCN: Dutch Lipid Clinic Network. FH: familial hypercholesterolaemia. HeFH: heterozygous familial hypercholesterolaemia. LDL-C: low-density lipoprotein cholesterol. To convert values for cholesterol to mmol/L, multiply by 0.02586.

eTable 2. Total Cholesterol, HDL-Cholesterol, Non-HDL-Cholesterol and Triglyceride levels during the randomised trial period stratified by LDL-cholesterol levels at baseline.

	Participants with LDL-C <190 mg/dL					Participants With LDL-C ≥190 mg/dL				
	Placebo		Pravastatin		p-value	Placebo		Pravastatin		p-value
	N	Mean ± SD / Median (IQR)*	N	Mean ± SD / Median (IQR)*		N	Mean ± SD / Median (IQR)*	N	Mean ± SD / Median (IQR)*	
Total Cholesterol										
Baseline (mg/dL)	1493	258.0 ± 15.3	1476	257.7 ± 15.7	0.484	1274	286.6 ± 19.1	1286	286.3 ± 18.9	0.724
Year 1 (mg/dL)	1361	258.7 ± 26.0	1338	213.3 ± 34.7	<0.001	1156	280.0 ± 30.3	1167	229.3 ± 38.0	<0.001
End of trial (mg/dL)	1419	258.7 ± 27.7	1407	219.2 ± 37.3	<0.001	1206	279.0 ± 33.4	1225	235.1 ± 40.4	<0.001
Percentage change from baseline to 1 year	1361	0.3 ± 9.4	1338	-17.1 ± 12.8	<0.001	1156	-2.1 ± 9.4	1167	-19.8 ± 12.5	<0.001
Percentage change from baseline to end of trial	1419	0.4 ± 10.7	1407	-14.9 ± 13.8	<0.001	1206	-2.5 ± 10.7	1225	-17.7 ± 13.5	<0.001
HDL-Cholesterol										
Baseline (mg/dL)	1493	44.3 ± 9.6	1476	44.7 ± 9.7	0.269	1274	44.4 ± 9.6	1286	44.1 ± 8.9	0.409
Year 1 (mg/dL)	1360	45.1 ± 11.1	1338	47.5 ± 11.3	<0.001	1156	44.5 ± 10.1	1167	46.1 ± 10.4	<0.001
Percentage change from baseline to 1 year	1360	2.2 ± 15.1	1338	6.7 ± 14.8	<0.001	1156	1.0 ± 13.3	1167	5.3 ± 14.8	<0.001
Non-HDL-Cholesterol										
Baseline (mg/dL)	1493	213.8 ± 16.2	1476	213.0 ± 16.5	0.187	1274	242.2 ± 19.5	1286	242.3 ± 19.2	0.962
Year 1 (mg/dL)	1360	213.7 ± 26.6	1338	165.8 ± 34.9	<0.001	1156	235.5 ± 30.8	1167	183.2 ± 38.4	<0.001
Percentage change from baseline to 1 year	1360	0.0 ± 11.0	1338	-22.0 ± 15.5	<0.001	1156	-2.6 ± 10.8	1167	-24.3 ± 14.8	<0.001
Triglycerides										
Baseline (mg/dL)	1493	143.9 (108.5, 194.9)	1476	139.5 (106.3, 190.4)	0.113	1274	150.6 (115.1, 197.1)	1286	148.4 (115.1, 192.6)	0.824
Year 1 (mg/dL)	1361	137.3 (101.9, 203.7)	1338	124.0 (88.6, 172.7)	<0.001	1156	146.1 (106.3, 194.9)	1167	128.4 (97.4, 177.1)	<0.001
End of trial (mg/dL)	1419	150.6 (110.7, 208.1)	1407	132.9 (97.4, 186.0)	<0.001	1206	150.6 (110.7, 208.1)	1225	141.7 (106.3, 190.4)	<0.001
Percentage change from baseline to 1 year	1361	4.8 ± 38.3	1338	-5.0 ± 40.6	<0.001	1156	1.5 ± 35.4	1167	-5.3 ± 36.9	<0.001
Percentage change from baseline to end of trial	1419	12.4 ± 44.4	1407	3.5 ± 42.9	<0.001	1206	10.8 ± 47.8	1225	4.4 ± 43.8	<0.001

(*) Data shown as mean ± standard deviation (SD) except for triglycerides at baseline, 1 year and end of trial, where data correspond to median and interquartile range (IQR). HDL-C: high-density lipoprotein cholesterol. Non-HDL-C estimated as total cholesterol minus HDL-C. To convert values for cholesterol to mmol/L, multiply by 0.02586. To convert values for triglycerides to mmol/L, multiply by 0.01129.

eTable 3. Endpoints during the randomised trial period, overall and stratified by LDL-cholesterol levels at baseline.

	Overall	Participants with LDL-C <190 mg/dL			Participants With LDL-C ≥190 mg/dL			Interaction p-value between LDL-C grouping at baseline and randomised treatment
	HR (95% CI), p-value	Events (%)		HR (95% CI), p-value	Events (%)		HR (95% CI), p-value	
		Placebo (n=1493)	Pravastatin (n=1476)		Placebo (n=1274)	Pravastatin (n=1286)		
Principal Endpoints								
CHD	0.73 (0.59, 0.89), 0.002	104 (6.97%)	75 (5.08%)	0.72 (0.54, 0.97), 0.032	107 (8.40%)	80 (6.22%)	0.73 (0.55, 0.98), 0.033	0.960
MACE	0.75 (0.62, 0.91), 0.004	119 (7.97%)	90 (6.10%)	0.76 (0.58, 1.00), 0.048	121 (9.50%)	93 (7.23%)	0.75 (0.57, 0.98), 0.037	0.958
Additional Endpoints explored								
CHD*	0.67 (0.54, 0.85), <0.001	93 (6.23%)	54 (3.66%)	0.58 (0.41, 0.81), 0.001	90 (7.06%)	71 (5.52%)	0.77 (0.57, 1.05), 0.103	0.219
MACE plus coronary revascularisation	0.76 (0.63, 0.91), 0.004	128 (8.57%)	95 (6.44%)	0.74 (0.57, 0.97), 0.028	134 (10.52%)	107 (8.32%)	0.78 (0.60, 1.00), 0.052	0.805
MACE plus coronary revascularisation*	0.72 (0.59, 0.88), <0.001	121 (8.10%)	78 (5.28%)	0.64 (0.48, 0.85), 0.002	121 (9.50%)	99 (7.70%)	0.80 (0.61, 1.04), 0.095	0.274
CHD death	0.91 (0.56, 1.48), 0.704	18 (1.21%)	17 (1.15%)	0.95 (0.49, 1.85), 0.887	16 (1.26%)	14 (1.09%)	0.86 (0.42, 1.76), 0.684	0.838
CHD death*	1.00 (0.60, 1.67), 0.994	16 (1.07%)	16 (1.08%)	1.01 (0.50, 2.02), 0.980	13 (1.02%)	13 (1.01%)	0.99 (0.46, 2.12), 0.969	0.963
Cardiovascular death	0.84 (0.54, 1.30), 0.434	24 (1.61%)	20 (1.36%)	0.84 (0.46, 1.52), 0.568	20 (1.57%)	17 (1.32%)	0.84 (0.44, 1.60), 0.590	0.992
All-cause mortality	0.87 (0.64, 1.17), 0.356	52 (3.48%)	46 (3.12%)	0.89 (0.60, 1.33), 0.576	40 (3.14%)	34 (2.64%)	0.84 (0.53, 1.32), 0.446	0.835
Coronary revascularisation	0.72 (0.47, 1.10), 0.132	24 (1.61%)	14 (0.95%)	0.58 (0.30, 1.13), 0.108	27 (2.12%)	23 (1.79%)	0.84 (0.48, 1.46), 0.527	0.416
Fatal or non-fatal stroke or TIA	0.95 (0.66, 1.36), 0.773	30 (2.01%)	31 (2.10%)	1.04 (0.63, 1.72), 0.868	31 (2.43%)	27 (2.10%)	0.86 (0.51, 1.43), 0.554	0.587

Effect of therapy (vs. placebo) shown as hazard ratio (HR) and corresponding 95% confidence interval (95% CI) and p value. See main text and supplementary material for endpoints definitions. (*) Including coronary events (i.e. non-fatal MI and CHD death) as definite only. CHD: coronary heart disease. LDL-C: low-density lipoprotein cholesterol. MACE: major adverse cardiovascular events, defined as the composite of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke. TIA: transient ischemic attack. To convert values for cholesterol to mmol/L, multiply by 0.02586.

eTable 4. Interaction tests of LDL-cholesterol and treatment for the different endpoints including LDL-cholesterol as categorical (<190 and ≥190 mg/dL) or as a continuous measure for the on-trial, post-trial and full long-term periods.

5-year randomised trial period:

Endpoint	Interaction (LDL above/below 190)	Interaction (LDL continuous)
CHD	0.960	0.862
MACE	0.958	0.650
CHD*	0.219	0.262
MACE plus coronary revascularisation	0.805	0.580
MACE* plus coronary revascularisation	0.274	0.276
CHD death	0.838	0.854
CHD death*	0.963	0.978
Cardiovascular death	0.992	0.721
All-cause mortality	0.835	0.843
Coronary revascularisation	0.416	0.651
Fatal or non-fatal stroke or TIA	0.587	0.380

15-year post-trial period (from end of trial to end of extended follow-up):

Endpoint	Interaction (LDL above/below 190)	Interaction (LDL continuous)
CHD	0.913	0.941
MACE	0.805	0.476
CHD death	0.549	0.767
Cardiovascular death	0.204	0.652
All-cause mortality	0.196	0.114

20-year long-term follow-up period (from randomisation to end of extended follow-up):

Endpoint	Interaction (LDL above/below 190)	Interaction (LDL continuous)
CHD	0.942	0.918
MACE	0.642	0.507
CHD death	0.453	0.874
Cardiovascular death	0.211	0.748
All-cause mortality	0.184	0.136

See main text and supplementary material for endpoints definitions. (*) Including coronary events (i.e. non-fatal MI and CHD death) as definite only. CHD: coronary heart disease. LDL-C: low-density lipoprotein cholesterol. MACE: major adverse cardiovascular events, defined as the composite of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke. TIA: transient ischemic attack. To convert values for cholesterol to mmol/L, multiply by 0.02586.

eTable 5. Endpoints during the extended long-term follow-up, overall and stratified by LDL-cholesterol levels at baseline, presented for the 15-year post-trial period (from end of trial to end of extended follow-up) and for the full 20-year follow-up period (from randomisation to end of extended follow-up).

	Overall cohort	Participants with LDL-C <190 mg/dL			Participants With LDL-C ≥190 mg/dL			Interaction p-value between LDL-C grouping at baseline and randomised treatment
	HR (95% CI), p-value	Events [n (%)]		HR (95% CI), p-value	Events [n (%)]		HR (95% CI), p-value	
		Placebo	Pravastatin		Placebo	Pravastatin		
Post-trial period only (end of trial to end of extended follow-up)								
CHD	0.78 (0.67, 0.90), <0.001	13.99%	11.19%	0.78 (0.63, 0.97), 0.023	16.33%	12.95%	0.77 (0.62, 0.95), 0.014	0.913
MACE	0.80 (0.71, 0.90), <0.001	22.69%	18.58%	0.79 (0.67, 0.93), 0.004	24.50%	20.69%	0.81 (0.68, 0.96), 0.013	0.805
CHD death	0.76 (0.61, 0.93), 0.009	6.80%	5.52%	0.80 (0.60, 1.08), 0.149	8.02%	5.83%	0.71 (0.52, 0.96), 0.024	0.549
Cardiovascular death	0.83 (0.70, 0.98), 0.024	10.62%	9.86%	0.92 (0.73, 1.16), 0.469	13.13%	10.06%	0.74 (0.59, 0.94), 0.012	0.204
All-cause mortality	0.88 (0.80, 0.97), 0.008	32.00%	30.14%	0.93 (0.82, 1.06), 0.290	34.04%	28.83%	0.82 (0.71, 0.95), 0.006	0.196
20-year long-term follow-up (from randomisation to end of extended follow-up)								
CHD	0.74 (0.65, 0.84), <0.001	17.95%	13.62%	0.73 (0.61, 0.88), <0.001	20.49%	15.79%	0.74 (0.61, 0.89), 0.001	0.942
MACE	0.79 (0.71, 0.88), <0.001	25.65%	20.73%	0.77 (0.66, 0.89), <0.001	27.00%	22.94%	0.81 (0.69, 0.94), 0.007	0.642
CHD death	0.78 (0.64, 0.94), 0.011	7.70%	6.50%	0.84 (0.64, 1.10), 0.193	9.03%	6.69%	0.72 (0.54, 0.95), 0.020	0.453
Cardiovascular death	0.83 (0.71, 0.96), 0.015	11.86%	10.91%	0.91 (0.73, 1.13), 0.382	14.29%	11.04%	0.75 (0.60, 0.93), 0.009	0.211
All-cause mortality	0.88 (0.80, 0.96), 0.005	34.36%	32.32%	0.93 (0.82, 1.05), 0.247	36.11%	30.72%	0.82 (0.72, 0.94), 0.004	0.184

Effect of therapy (vs. placebo) shown as hazard ratio (HR) and corresponding 95% confidence interval (95% CI) and p value. See main text and supplementary material for endpoints definitions. CHD: coronary heart disease. LDL-C: low-density lipoprotein cholesterol. MACE: major adverse cardiovascular events, defined as the composite of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke. To convert values for cholesterol to mmol/L, multiply by 0.02586.

eTable 6. Principal endpoints during the randomised trial period in subjects with LDL-cholesterol ≥190 mg/dL allocated to pravastatin.

	CHD				MACE plus coronary revascularisation			
	N	**Events**	**HR (95% CI)*, p-value**	**Overall p-value**	**N**	**Events**	**HR (95% CI)*, p-value**	**Overall p-value**
Placebo	1188	90 (7.58%)	Reference group		1188	111 (9.34%)	Reference group	
absolute LDL-C fall <39 mg/dL	353	24 (6.80%)	0.89 (0.57, 1.40), 0.612	0.030	353	29 (8.22%)	0.88 (0.58, 1.32), 0.524	0.086
absolute LDL-C fall ≥39 mg/dL	856	41 (4.79%)	0.61 (0.42, 0.88), 0.008		856	58 (6.78%)	0.70 (0.51, 0.96), 0.027	
Placebo	1188	90 (7.58%)	Reference group		1188	111 (9.34%)	Reference group	
percentage LDL-C reduction <30%	720	42 (5.83%)	0.76 (0.53, 1.10), 0.148	0.047	720	54 (7.50%)	0.80 (0.57, 1.10), 0.171	0.106
percentage LDL-C reduction ≥30%	489	23 (4.70%)	0.58 (0.37, 0.92), 0.021		489	33 (6.75%)	0.68 (0.46, 1.01), 0.054	
Placebo	1188	90 (7.58%)	Reference group		1188	111 (9.34%)	Reference group	
on treatment LDL-C ≥174 mg/dL	290	24 (8.28%)	1.09 (0.69, 1.71), 0.724	0.015	290	29 (10.00%)	1.06 (0.70, 1.60), 0.772	0.046
on treatment LDL-C 145 to <174 mg/dL	426	19 (4.46%)	0.58 (0.35, 0.95), 0.030		426	27 (6.34%)	0.67 (0.44, 1.02), 0.064	
on treatment LDL-C <145 mg/dL	493	22 (4.46%)	0.56 (0.35, 0.89), 0.014		493	31 (6.29%)	0.64 (0.43, 0.95), 0.027	

Effect of therapy (vs. placebo) shown as hazard ratio (HR) and corresponding 95% confidence interval (95% CI) and p value. Note that MACE plus coronary revascularisation endpoint was used here instead of MACE alone in order to increase the number of events in each stratum and so the power of the analysis in an otherwise restricted sample to those with LDL-C ≥190 mg/dL allocated to pravastatin further stratified in different groups as shown in the table. (*) HRs are adjusted for age, history of hypertension, history of diabetes, smoking status, systolic and diastolic blood pressure, and body mass index. On-treatment LDL-C levels are defined as the mean of all LDL-C values measured after randomisation until the patient had an event or reached the end of the study. On-treatment LDL-C analyses excluded individuals with events in the first 6 months of the trial as first on-treatment LDL-C measurement was at 6 months after randomization. CHD: coronary heart disease. LDL-C: low-density lipoprotein cholesterol. MACE: major adverse cardiovascular events, defined as the composite of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke. To convert values for cholesterol to mmol/L, multiply by 0.02586.

eTable 7. CHD* and MACE* endpoints during the randomised trial period in subjects with LDL-cholesterol ≥190 mg/dL allocated to pravastatin.

	CHD*				MACE* plus coronary revascularisation			
	N	Events	HR (95% CI)†, p-value	Overall p-value	N	Events	HR (95% CI)†, p-value	Overall p-value
Placebo	1188	73 (6.14%)	Reference group		1188	98 (8.25%)	Reference group	
absolute LDL-C fall <39 mg/dL	353	22 (6.23%)	0.98 (0.61, 1.59), 0.946	0.108	353	28 (7.93%)	0.95 (0.62, 1.45), 0.821	0.162
absolute LDL-C fall ≥39 mg/dL	856	36 (4.21%)	0.66 (0.44, 0.98), 0.041		856	53 (6.19%)	0.72 (0.52, 1.01), 0.060	
Placebo	1188	73 (6.14%)	Reference group		1188	98 (8.25%)	Reference group	
percentage LDL-C reduction <30%	720	38 (5.28%)	0.83 (0.56, 1.24), 0.365	0.183	720	51 (7.08%)	0.85 (0.60, 1.19), 0.335	0.228
Percentage LDL-C reduction ≥30%	489	20 (4.09%)	0.64 (0.39, 1.04), 0.074		489	30 (6.13%)	0.71 (0.47, 1.07), 0.101	
Placebo	1188	73 (6.14%)	Reference group		1188	98 (8.25%)	Reference group	
on treatment LDL-C ≥174 mg/dL	290	22 (7.59%)	1.20 (0.74, 1.93), 0.465	0.050	290	28 (9.66%)	1.15 (0.75, 1.76), 0.511	0.072
on treatment LDL-C 145 to <174 mg/dL	426	16 (3.76%)	0.59 (0.34, 1.01), 0.056		426	24 (5.63%)	0.67 (0.43, 1.05), 0.080	
on treatment LDL-C <145 mg/dL	493	20 (4.06%)	0.64 (0.39, 1.04), 0.074		493	29 (5.88%)	0.68 (0.45, 1.04), 0.074	

Effect of therapy (vs. placebo) shown as hazard ratio (HR) and corresponding 95% confidence interval (95% CI) and p value. Note that MACE plus coronary revascularisation endpoint was used here instead of MACE alone in order to increase the number of events in each stratum and so the power of the analysis in an otherwise restricted sample to those with LDL-C ≥190 mg/dL allocated to pravastatin further stratified in different groups as shown in the table. (*) Including coronary events (i.e. non-fatal MI and CHD death) as definite only. (†) HRs are adjusted for age, history of hypertension, history of diabetes, smoking status, systolic and diastolic blood pressure, and body mass index. On-treatment LDL-C levels are defined as the mean of all LDL-C values measured after randomisation until the patient had an event or reached the end of the study. On-treatment LDL-C analyses excluded individuals with events in the first 6 months of the trial as first on-treatment LDL-C measurement was at 6 months after randomization. CHD: coronary heart disease. LDL-C: low-density lipoprotein cholesterol. MACE: major adverse cardiovascular events, defined as the composite of cardiovascular death, non-fatal MI and non-fatal stroke. MI: myocardial infarction. To convert values for cholesterol to mmol/L, multiply by 0.02586.

eTable 8. Mortality endpoints during the randomised trial period in subjects with LDL-cholesterol ≥190 mg/dL allocated to pravastatin.

	CHD death				Cardiovascular death				All-cause mortality			
	N	Events	HR (95% CI)*, p-value	Overall p-value	N	Events	HR (95% CI)*, p-value	Overall p-value	N	Events	HR (95% CI)*, p-value	Overall p-value
Placebo	1188	13 (1.09%)	Reference group		1188	15 (1.26%)	Reference group		1188	32 (2.69%)	Reference group	
Absolute LDL-C fall <39 mg/dL	353	5 (1.42%)	1.32 (0.46, 3.73), 0.606	0.521	353	5 (1.42%)	1.14 (0.41, 3.17), 0.800	0.607	353	11 (3.12%)	1.16 (0.58, 2.31), 0.681	0.375
absolute LDL-C fall ≥39 mg/dL	856	7 (0.82%)	0.68 (0.27, 1.73), 0.422		856	8 (0.93%)	0.69 (0.29, 1.63), 0.397		856	17 (1.99%)	0.71 (0.39, 1.27), 0.248	
Placebo	1188	13 (1.09%)	Reference group		1188	15 (1.26%)	Reference group		1188	32 (2.69%)	Reference group	
percentage LDL-C reduction <30%	720	8 (1.11%)	1.01 (0.41, 2.46), 0.982	0.737	720	8 (1.11%)	0.88 (0.37, 2.09), 0.767	0.821	720	18 (2.50%)	0.94 (0.52, 1.67), 0.821	0.607
percentage LDL-C reduction ≥30%	489	4 (0.82%)	0.65 (0.21, 2.02), 0.460		489	5 (1.02%)	0.73 (0.26, 2.02), 0.538		489	10 (2.04%)	0.69 (0.34, 1.42), 0.319	
Placebo	1188	13 (1.09%)	Reference group		1188	15 (1.26%)	Reference group		1188	32 (2.69%)	Reference group	
on treatment LDL-C ≥174 mg/dL	290	5 (1.72%)	1.57 (0.55, 4.45), 0.399	0.514	290	5 (1.72%)	1.36 (0.49, 3.78), 0.555	0.597	290	9 (3.10%)	1.14 (0.54, 2.41), 0.730	0.656
on treatment LDL-C 145 to <174 mg/dL	426	3 (0.70%)	0.65 (0.18, 2.29), 0.500		426	3 (0.70%)	0.56 (0.16, 1.96), 0.367		426	9 (2.11%)	0.80 (0.38, 1.68), 0.558	
on treatment LDL-C <145 mg/dL	493	4 (0.81%)	0.65 (0.21, 2.00), 0.449		493	5 (1.01%)	0.72 (0.26, 1.99), 0.522		493	10 (2.03%)	0.69 (0.34, 1.41), 0.311	

Effect of therapy (vs. placebo) shown as hazard ratio (HR) and corresponding 95% confidence interval (95% CI) and p value. (*) HR are adjusted for age, history of hypertension, history of diabetes, smoking status, systolic and diastolic blood pressure, and body mass index. On-treatment LDL-C levels are defined as the mean of all LDL-C values measured after randomisation until the patient had an event or reached the end of the study. On-treatment LDL-C analyses excluded individuals with events in the first 6 months of the trial as first on-treatment LDL-C measurement was at 6 months after randomization. CHD: coronary heart disease. LDL-C: low-density lipoprotein cholesterol. To convert values for cholesterol to mmol/L, multiply by 0.02586.

eTable 9. Risk of events during the 20-year long-term follow-up in the subgroup of patients without diabetes and with a predicted 10-year ASCVD risk* below 7.5% at baseline.

Participants with predicted 10-year ASCVD risk <7.5%* and no diabetes	LDL-C <190 mg/dL			LDL-C ≥190 mg/dL			Interaction p-value between LDL-C grouping at baseline and randomised treatment
	Placebo (n=1085)	Pravastatin (n=1064)	HR (95% CI), p-value	Placebo (n=856)	Pravastatin (n=858)	HR (95% CI), p-value	
20-year long-term follow-up							
CHD	161 (14.84%)	123 (13.62%)	0.76 (0.60, 0.96), 0.019	157 (18.34%)	108 (12.59%)	0.65 (0.51, 0.84), <0.001	0.408
CHD death	60 (5.53%)	45 (4.23%)	0.76 (0.51, 1.11), 0.155	58 (6.78%)	42 (4.90%)	0.71 (0.48, 1.05), 0.086	0.816
Cardiovascular death	89 (8.20%)	76 (7.14%)	0.86 (0.63, 1.17), 0.331	83 (9.70%)	67 (7.81%)	0.78 (0.57, 1.08), 0.137	0.699
All-cause mortality	279 (25.71%)	243 (22.84%)	0.87 (0.74, 1.04), 0.126	209 (24.42%)	183 (21.33%)	0.85 (0.70, 1.04), 0.112	0.839

* ASCVD risk according to the Pooled Cohort Equations risk calculator (ref. S17). Effect of therapy (vs. placebo) shown as hazard ratios (HR) and corresponding 95% confidence intervals (95% CI) and p value. 20-year long-term follow-up: from randomisation to end of extended follow-up (on-trial plus post-trial periods). ASCVD: atherosclerotic cardiovascular disease. CHD: coronary heart disease. LDL-C: low-density lipoprotein cholesterol. MACE: major adverse cardiovascular events, defined as the composite of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke. To convert values for cholesterol to mmol/L, multiply by 0.02586.

3.- SUPPLEMENTAL FIGURES

- **eFigure 1.** Screening and selection of participants. WOSCOPS original study and current analyses.

- **eFigure 2.** Low-density lipoprotein cholesterol levels during the randomised trial phase in participants without evidence of vascular disease at enrolment stratified by LDL-cholesterol levels at baseline

- **eFigure 3.** Major adverse cardiovascular events plus coronary revascularisation risk: Kaplan-Meier curves during the randomised trial period stratified by LDL-cholesterol levels at baseline and treatment allocation.

- **eFigure 4**. Coronary heart disease (definite-only coronary events) risk: Kaplan-Meier curves during the randomised trial period stratified by LDL-cholesterol levels at baseline and treatment allocation.

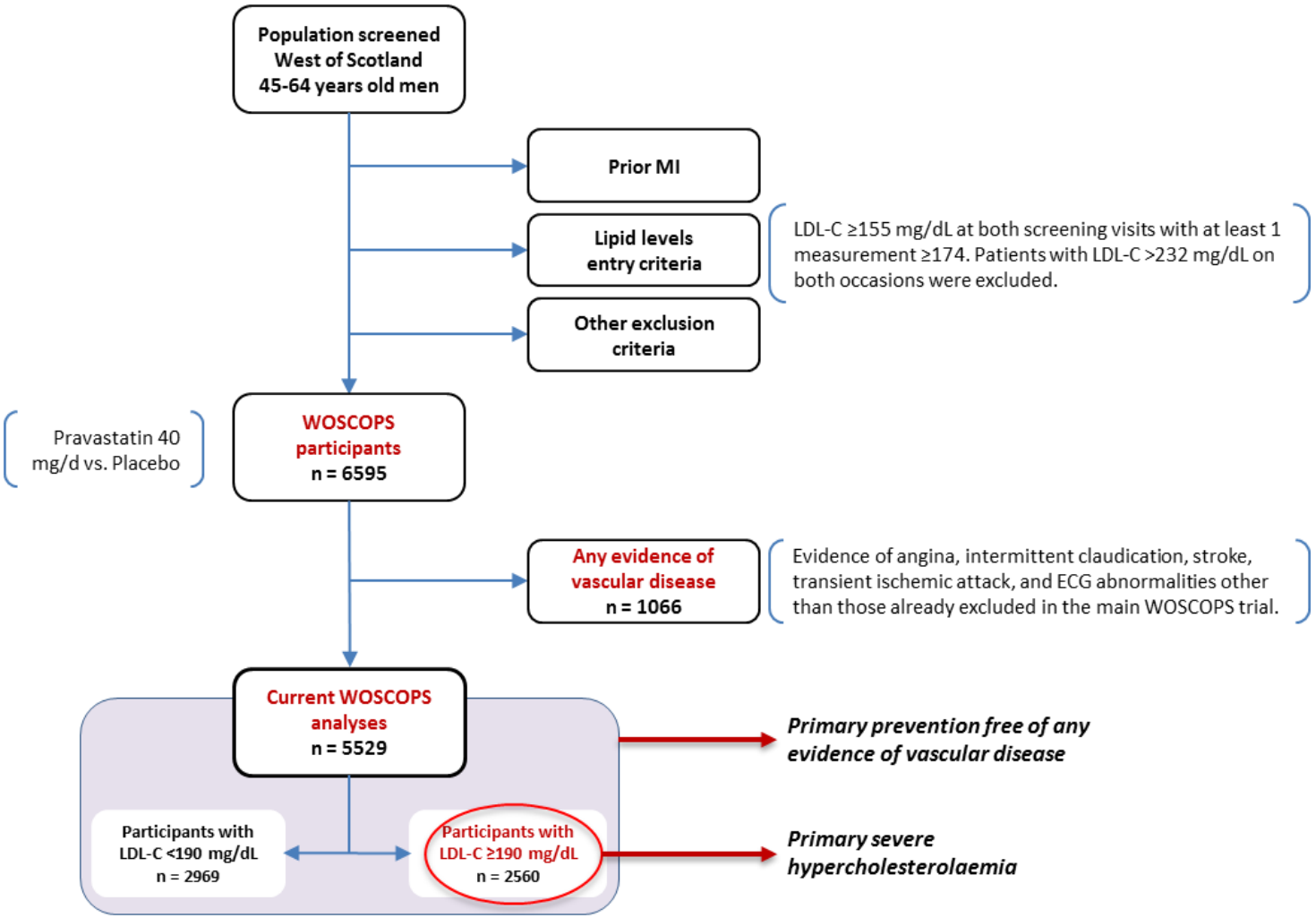
- **eFigure 5.** Major adverse cardiovascular events (including coronary events as definite-only) plus coronary revascularisation risk: Kaplan-Meier curves during the randomised trial period stratified by LDL-cholesterol levels at baseline and treatment allocation.

- **eFigure 6.** Kaplan-Meier curves for long-term (20 years) coronary heart disease death, stratified by LDL-cholesterol levels at baseline and original treatment allocation.

- **eFigure 7.** Kaplan-Meier curves for long-term (20 years) cardiovascular death, stratified by LDL-cholesterol levels at baseline and original treatment allocation.

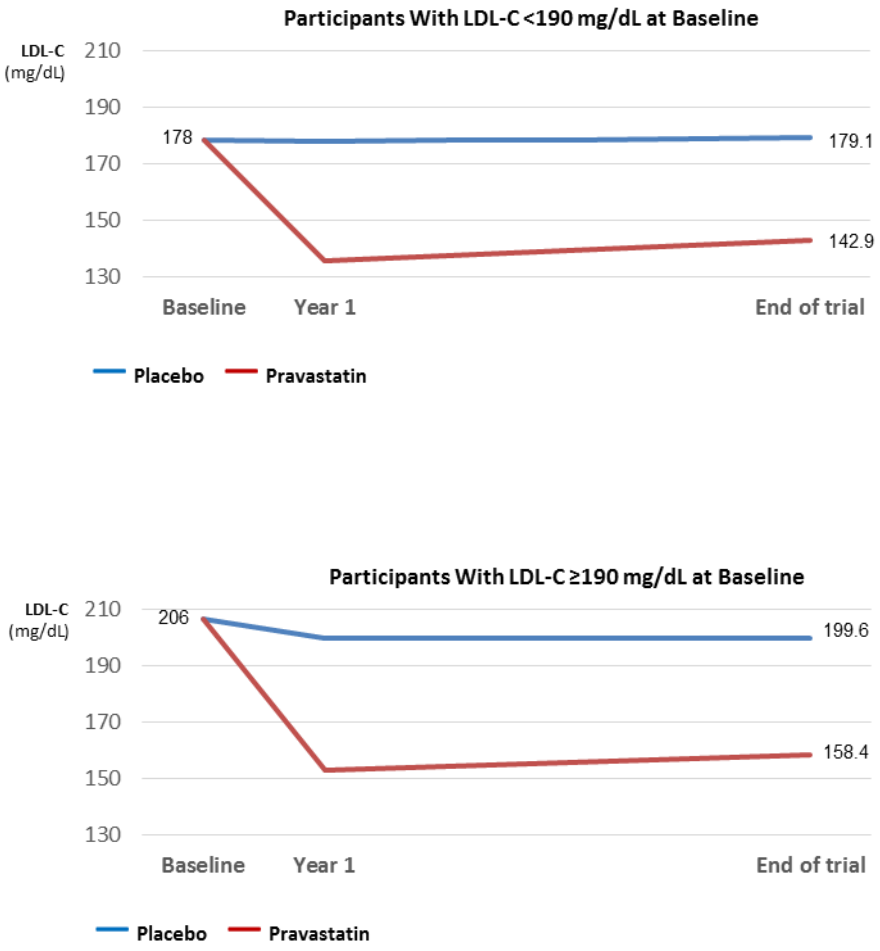
- **eFigure 8.** Kaplan-Meier curves for long-term (20 years) all-cause mortality, stratified by LDL-cholesterol levels at baseline and original treatment allocation.

eFigure 1. Screening and selection of participants. WOSCOPS original study and current analyses.



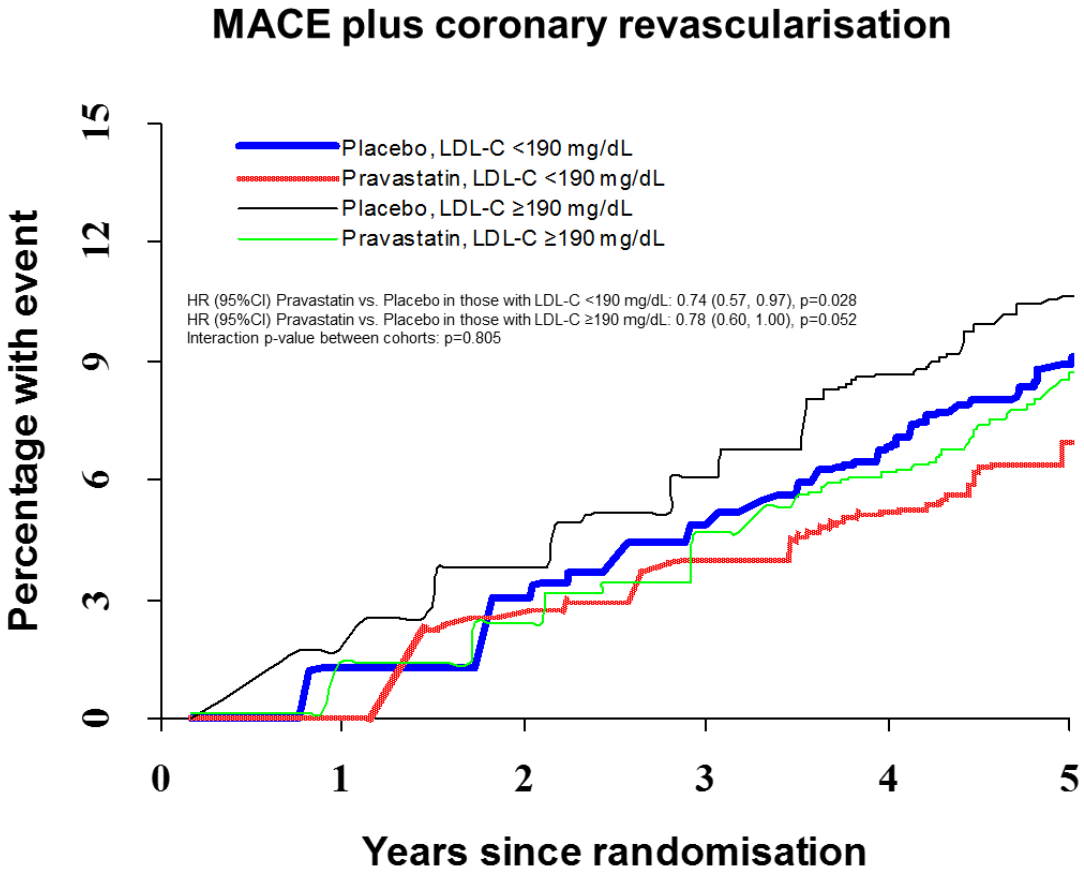
(To convert values for cholesterol to mmol/L, multiply by 0.02586)

eFigure 2. Low-density lipoprotein cholesterol levels during the randomised trial phase in participants without evidence of vascular disease at enrolment stratified by LDL-cholesterol levels at baseline



Comparisons between pravastatin and placebo arms at year 1 and at end of trail in participants with LDL-C <190 mg/dL and in participants with LDL-C ≥190 mg/dL: all p<0.001. LDL-C: low-density lipoprotein cholesterol. To convert values for cholesterol to mmol/L, multiply by 0.02586.

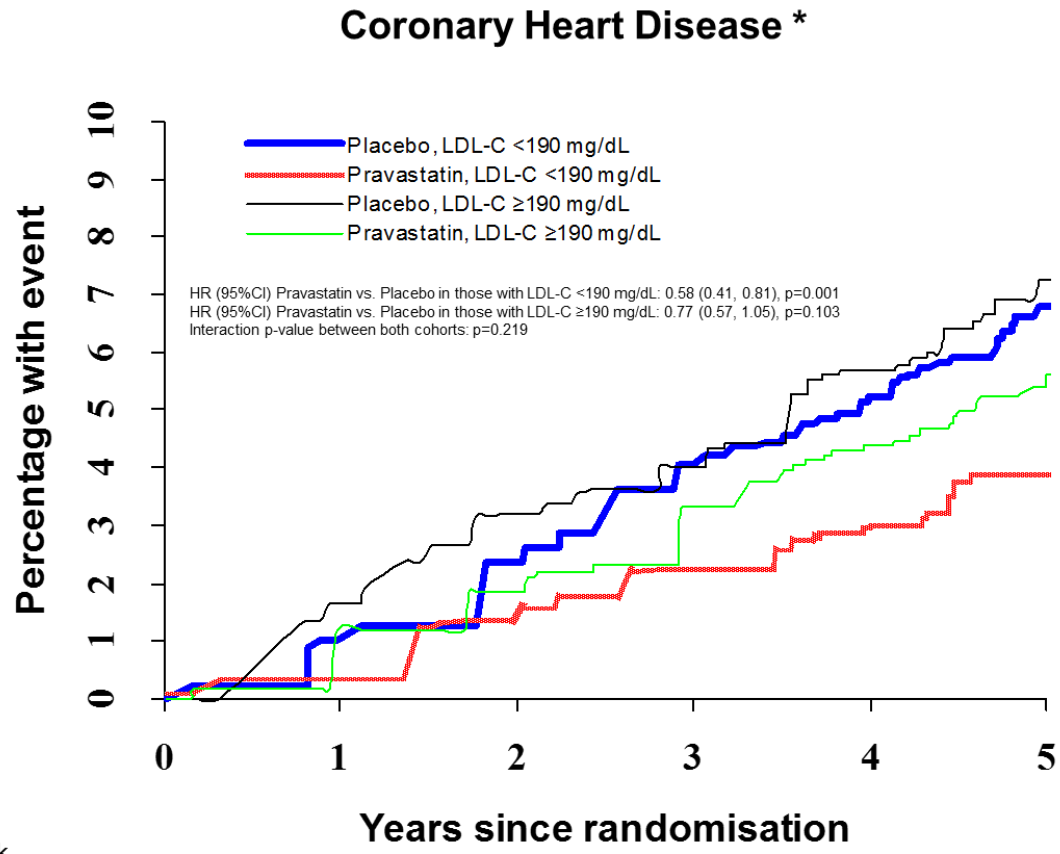
eFigure 3. Major adverse cardiovascular events plus coronary revascularisation risk: Kaplan-Meier curves during the randomised trial period stratified by primary severe hypercholesterolaemia status at baseline and treatment allocation.



Numbers at risk						
Placebo, LDL-C <190:	1493	1467	1442	1410	1211	557
Pravastatin, LDL-C <190:	1476	1452	1434	1406	1231	584
Placebo, LDL-C ≥190:	1274	1242	1210	1182	1025	471
Pravastatin, LDL-C ≥190:	1286	1265	1245	1218	1071	482

5-year follow-up Kaplan-Meier analysis for major adverse cardiovascular disease events (MACE) plus coronary revascularisation endpoint, stratified by LDL-cholesterol levels at baseline (<190 or ≥190 mg/dL) and treatment allocation at randomisation (pravastatin or placebo). Number of events in each group were as follows: placebo, LDL-C <190 mg/dL: n=128; pravastatin, LDL-C <190 mg/dL: n=95; placebo, LDL-C ≥190 mg/dL: n=134; pravastatin, LDL-C ≥190 mg/dL: n=107. MACE: major adverse cardiovascular events, defined as the composite of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke. CI: confidence interval. HR: hazard ratio. To convert values for cholesterol to mmol/L, multiply by 0.02586.

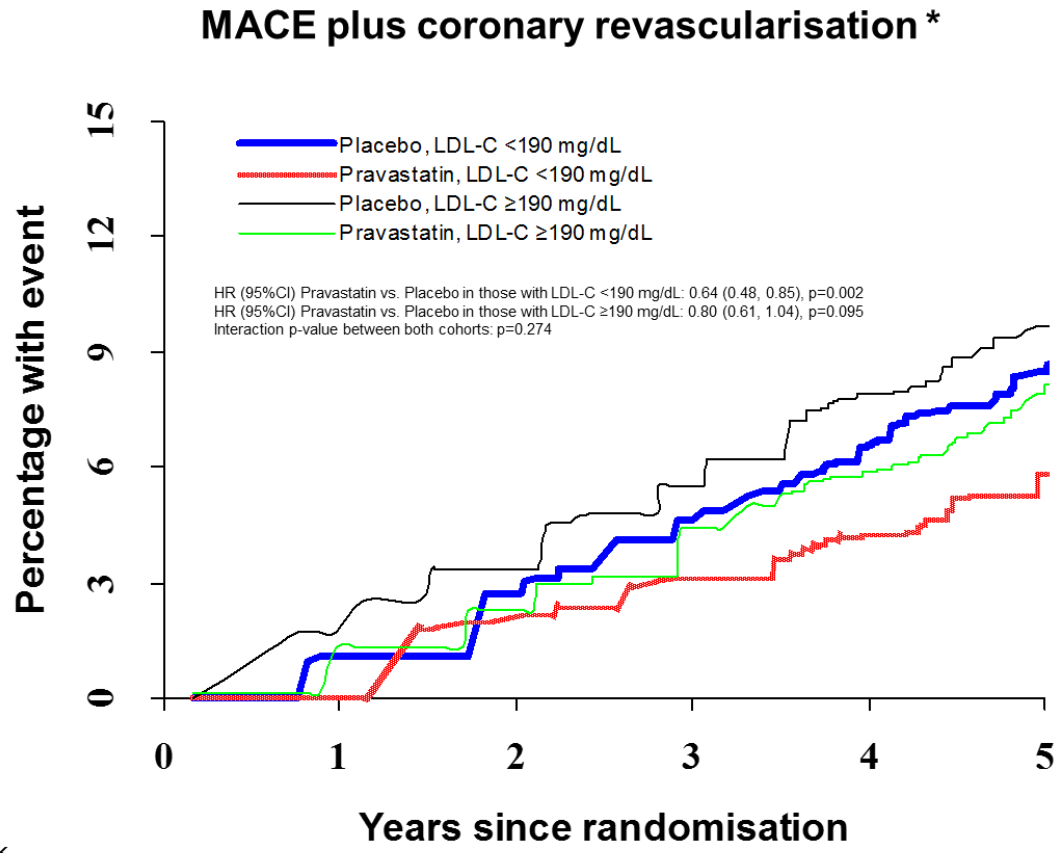
eFigure 4. Coronary heart disease (definite-only coronary events) risk: Kaplan-Meier curves during the randomised trial period stratified by LDL-cholesterol levels at baseline and treatment allocation.



Numbers at risk						
Placebo, LDL-C <190:	1493	1472	1451	1420	1228	567
Pravastatin, LDL-C <190:	1476	1461	1449	1429	1256	603
Placebo, LDL-C ≥190:	1274	1248	1224	1208	1051	480
Pravastatin, LDL-C ≥190:	1286	1268	1256	1234	1092	493

5-year follow-up Kaplan-Meier analysis for coronary heart disease (CHD) endpoint*, stratified by LDL-cholesterol levels at baseline (<190 or ≥190 mg/dL) and treatment allocation at randomisation (pravastatin or placebo). (*) Including coronary events (i.e. non-fatal MI and CHD death) as definite only. Number of events in each group were as follows: placebo, LDL-C <190 mg/dL: n=93; pravastatin, LDL-C <190 mg/dL: n=54; placebo, LDL-C ≥190 mg/dL: n=90; pravastatin, LDL-C ≥190 mg/dL: n=71. CI: confidence interval. HR: hazard ratio. To convert values for cholesterol to mmol/L, multiply by 0.02586.

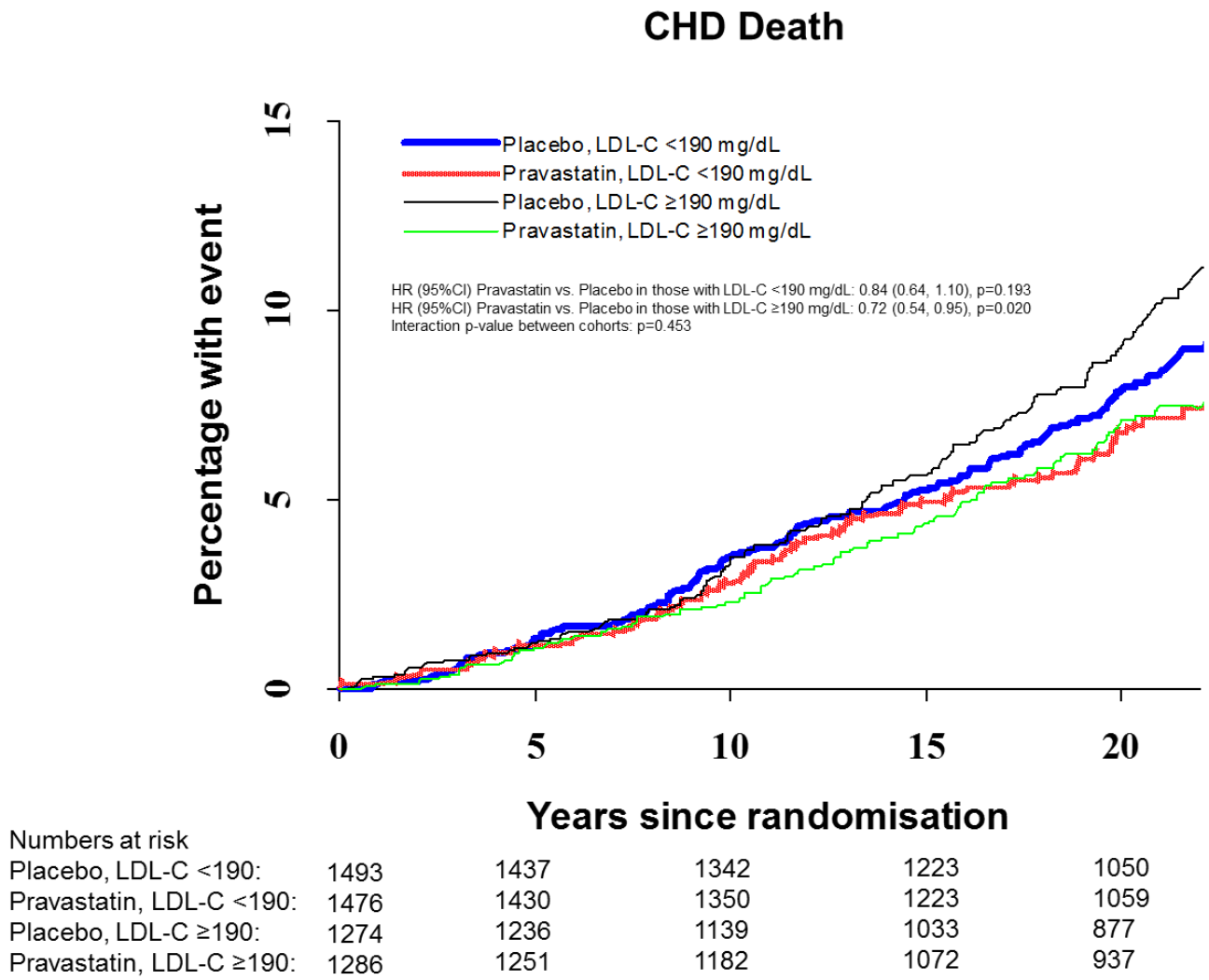
eFigure 5. Major adverse cardiovascular events (including coronary events as definite-only) plus coronary revascularisation risk: Kaplan-Meier curves during the randomised trial period stratified by LDL-cholesterol levels at baseline and treatment allocation.



Numbers at risk						
Placebo, LDL-C <190:	1493	1470	1447	1414	1215	558
Pravastatin, LDL-C <190:	1476	1455	1442	1419	1243	594
Placebo, LDL-C ≥190:	1274	1242	1215	1189	1032	473
Pravastatin, LDL-C ≥190:	1286	1266	1248	1221	1075	486

5-year follow-up Kaplan-Meier analysis for major adverse cardiovascular disease events (MACE) plus coronary revascularisation endpoint*, stratified by LDL-cholesterol levels at baseline (<190 or ≥190 mg/dL) and treatment allocation at randomisation (pravastatin or placebo). (*) Including coronary events (i.e. non-fatal MI and CHD death) as definite only. Number of events in each group were as follows: placebo, LDL-C <190 mg/dL: n=121; pravastatin, LDL-C <190 mg/dL: n=78; placebo, LDL-C ≥190 mg/dL: n=121; pravastatin, LDL-C ≥190 mg/dL: n=99. MACE: major adverse cardiovascular events, defined as the composite of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke. CI: confidence interval. HR: hazard ratio. To convert values for cholesterol to mmol/L, multiply by 0.02586.

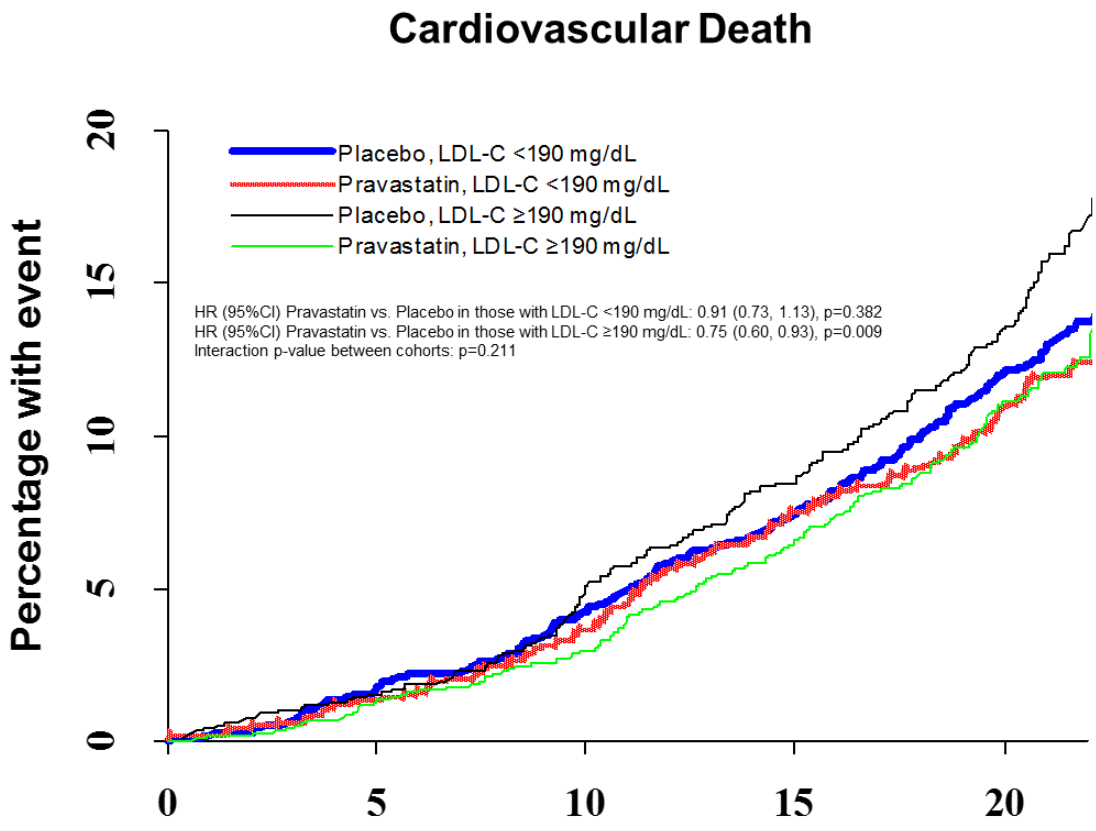
eFigure 6. Kaplan-Meier curves for long-term (20 years) coronary heart disease death, stratified by LDL-cholesterol levels at baseline and original treatment allocation.



Numbers at risk					
Placebo, LDL-C <190:	1493	1437	1342	1223	1050
Pravastatin, LDL-C <190:	1476	1430	1350	1223	1059
Placebo, LDL-C ≥190:	1274	1236	1139	1033	877
Pravastatin, LDL-C ≥190:	1286	1251	1182	1072	937

20-year follow-up Kaplan-Meier analysis for coronary heart disease (CHD) death, stratified by LDL-cholesterol levels at baseline (<190 or ≥190 mg/dL) and original treatment allocation at randomisation (pravastatin or placebo). Number of events in each group were as follows: placebo, LDL-C <190 mg/dL: n=115; pravastatin, LDL-C <190 mg/dL: n=96; placebo, LDL-C ≥190 mg/dL: n=115; pravastatin, LDL-C ≥190 mg/dL: n=86. CI: confidence interval. HR: hazard ratio. To convert values for cholesterol to mmol/L, multiply by 0.02586.

eFigure 7. Kaplan-Meier curves for long-term (20 years) cardiovascular death, stratified by LDL-cholesterol levels at baseline and original treatment allocation.



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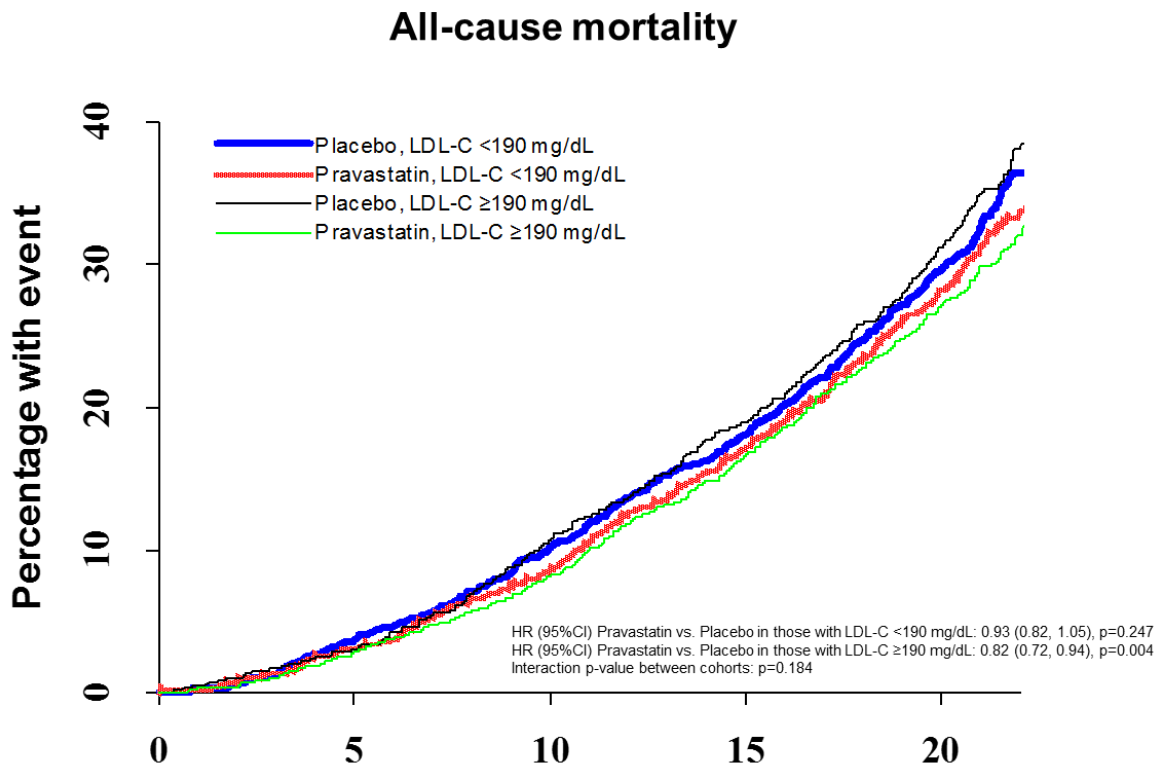
20-year follow-up Kaplan-Meier analysis for cardiovascular death, stratified by LDL-cholesterol levels at baseline (<190 or ≥190 mg/dL) and original treatment allocation at randomisation (pravastatin or placebo). Number of events in each group were as follows: placebo, LDL-C <190 mg/dL: n=177; pravastatin, LDL-C <190 mg/dL: n=161; placebo, LDL-C ≥190 mg/dL: n=182; pravastatin, LDL-C ≥190 mg/dL: n=142. CI: confidence interval. HR: hazard ratio. To convert values for cholesterol to mmol/L, multiply by 0.02586.

eFigure 8. Kaplan-Meier curves for long-term (20 years) all-cause mortality, stratified by LDL-cholesterol levels at baseline and original treatment allocation.



Numbers at risk					
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Pravastatin, LDL-C ≥190:	1286	1251	1182	1072	937

20-year follow-up Kaplan-Meier analysis for all-cause mortality, stratified by LDL-cholesterol levels at baseline (<190 or ≥190 mg/dL) and original treatment allocation at randomisation (pravastatin or placebo). Number of events in each group were as follows: placebo, LDL-C <190 mg/dL: n=513; pravastatin, LDL-C <190 mg/dL: n=477; placebo, LDL-C ≥190 mg/dL: n=460; pravastatin, LDL-C ≥190 mg/dL: n=395. CI: confidence interval. HR: hazard ratio. To convert values for cholesterol to mmol/L, multiply by 0.02586.

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