TITLE PAGE

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

Running title: LDL-C Lowering for Primary Prevention in LDL-C ≥190

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Word count:

- **Abstract (max. 350):** 347.
- **Clinical Perspective (Q1 and Q2 max. 100 words each):** Q1: 93 words; Q2: 102 words.
- **Main text (max. 5000 words):** 4334.

Figures/Tables (max. 8 in total): 5 figures/3 tables.

References: 31 references.

Date of revision (revision submitted): July, 2017

KEY POINTS

Question: Is the lowering of LDL-cholesterol in the primary prevention of patients with LDL-cholesterol ≥190 mg/dL beneficial?

Findings: in this post-hoc analysis from the WOSCOPS randomised trial of 2560 men with primary elevations of LDL-cholesterol ≥190 mg/dL but without vascular disease, pravastatin (vs. placebo) reduced the risk of coronary heart disease (CHD) by 27% and of major adverse cardiovascular events by 25% over 4.9-years. Randomisation to pravastatin significantly reduced the risk of CHD death (28%), cardiovascular death (25%) and all-cause mortality (18%) over a total of 20-years (extended observational long-term follow-up) among those with LDL-cholesterol ≥190 mg/dL.

Meaning: we provide for the first time evidence from a randomised trial demonstrating the benefit of LDL-cholesterol lowering for the primary prevention of individuals with primary elevations of LDL-cholesterol ≥190 mg/dL.

ABSTRACT

Background: Patients with primary elevations of LDL-C ≥190 mg/dL are at a higher risk of atherosclerotic cardiovascular disease as a result of long-term exposure to markedly elevated LDL-C levels. Therefore, initiation of statin therapy is recommended for these individuals. However, there is a lack of randomised trial evidence supporting these recommendations in primary prevention. In the present analysis we provide hitherto unpublished data on the cardiovascular effects of LDL-C lowering among a primary prevention population with LDL-C ≥190 mg/dL.

Methods: we aimed to assess the benefits of LDL-C lowering on cardiovascular outcomes among individuals with primary elevations of LDL-C ≥190 mg/dL without pre-exiting vascular disease at baseline. We carried out post-hoc analyses from the West Of Scotland Coronary Prevention Study (WOSCOPS) randomised, placebo-controlled trial, and observational post-trial long-term follow-up, after excluding individuals with evidence of vascular disease at baseline. WOSCOPS enrolled 6595 men aged 45-64 years, who were randomised to pravastatin 40 mg/d or placebo. In the present analyses, 5529 participants without evidence of vascular disease were included, stratified by LDL-C levels into those with LDL-C <190 mg/dL (n=2969; mean LDL-C 178±6 mg/dL) and those with LDL-C ≥190 mg/dL (n=2560; mean LDL-C 206±12 mg/dL).

The effect of pravastatin versus placebo on coronary heart disease (CHD) and major adverse cardiovascular events (MACE) were assessed over the 4.9-year randomised-controlled trial phase and on mortality outcomes over a total of 20-years of follow-up.

Results: among 5529 individuals without vascular disease, pravastatin reduced the risk of CHD by 27% (p=0.002) and MACE by 25% (p=0.004) consistently among those with and without LDL-C ≥190 mg/dL (p-interaction >0.9). Among individuals with LDL-C ≥190 mg/dL, pravastatin reduced the risk of CHD by 27% (p=0.033) and MACE by 25% (p=0.037) during the initial trial phase and the risk of CHD death, cardiovascular death and all-cause mortality by 28% (p=0.020), 25% (p=0.009) and 18% (p=0.004), respectively, over a total of 20-years of follow-up.

Conclusions: the present analyses provide robust novel evidence for the short and long-term benefits of lowering LDL-C for the primary prevention of cardiovascular disease among individuals with primary elevations of LDL-C ≥190 mg/dL.

[* Note: Trial Registration: the original WOSCOSP trial was carried out between 1988 and 1995 and so it preceded the formal trial registration era. Nevertheless, the protocol and statistical analysis plan related to the original WOSCOPS trial was pertinently published in an international peer-reviewed journal and can be consulted as follows: *J Clin Epidemiol* 1992;45(8):849-60. The results we are reporting in the present manuscript are post hoc analyses not envisaged in the original protocol; therefore, we provide in the present manuscript a detailed description of the post hoc analyses design, methods and statistical analyses carried out.]

Keywords: lipids and lipoproteins; statin therapy; primary prevention; cardiovascular disease prevention

CLINICAL PERSPECTIVE

1) What is new?

- The present analysis from the WOSCOPS trial reports for the first time new information on over 2500 men with LDL-cholesterol ≥190 mg/dL without pre-existing vascular disease (a group lacking randomised trial evidence for statin therapy) and their subsequent risk of cardiovascular events.
- Individuals with a LDL-Cholesterol ≥190 mg/dL have a 2-fold higher observed risk of major cardiovascular events than would be predicted from a risk calculator.
- We provide compelling novel evidence from a randomised trial supporting the benefit of LDL-cholesterol lowering on cardiovascular events among a primary prevention population with LDL-Cholesterol ≥190 mg/dL.

2) What are the clinical implications?

- The present analysis provides novel supporting evidence from a randomised trial to reinforce current recommendations of initiation of lipid-lowering therapy in the primary prevention of individuals with primary elevations of LDL-C ≥190 mg/dL without the need for risk estimation.
- Although these analyses are post-hoc, this approach is the only one that allows us to address this question currently, since (i) nowadays it would be unethical to perform a placebo-controlled trial in the population with LDL-C ≥190 mg/dL, and (ii) there is no other randomised trial in primary prevention with statins including such a significant proportion of patients with an LDL-C ≥190 mg/dL.

MAIN TEXT

Introduction

Patients with primary elevations of low-density lipoprotein cholesterol (LDL-C) ≥190 mg/dL (to convert values for cholesterol to mmol/L, multiply by 0.02586) are at a higher risk of atherosclerotic cardiovascular disease (ASCVD) as a result of a long-term exposure to markedly elevated LDL-C levels, even in the absence of pre-existing ASCVD (i.e. primary prevention).[1,2] This has been recently further supported by observations from the Cardiovascular Lifetime Risk Pooling Project where these individuals, who were even referred to as "FH phenotype" (eTable 1 in the Supplement), were observed to have an accelerated risk of coronary heart disease (CHD) and ASCVD compared to individuals with "average" levels of LDL-C.[3] As such, initiation of statin therapy (and more recently also of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors to further reduce LDL-C levels) is recommended for individuals with primary elevations of LDL-C ≥190 mg/dL without the need for risk assessment.[1,2,4] However, there is a lack of published randomised trial evidence supporting these recommendations in primary prevention with available evidence extrapolated from the Cholesterol Treatment Trialist (CTT) meta-analyses (where lower LDL-C cut-off points were used and patients with established vascular disease were included in the high LDL-C category).[5,6]

Currently it would be unethical to perform a placebo-controlled trial of LDL-C lowering therapy among individuals with LDL-C ≥190 mg/dL. Nonetheless, we can address this question using data from the West Of Scotland Coronary Prevention Study (WOSCOPS), which aimed to assess the benefits of statin therapy among men with

hypercholesterolaemia and enrolled a significant proportion of patients with LDL-C ≥190 mg/dL (mean LDL-C 192 mg/dL).[7,8] Although WOSCOPS excluded individuals with apparent myocardial infarction (MI), a proportion of participants still had evidence of other vascular diseases at baseline.

In the present analysis, we provide hitherto unpublished data on the cardiovascular effects of LDL-C lowering among a population with primary elevation of LDL-C ≥190 mg/dL after restricting analyses to participants without evidence of vascular disease at baseline. Furthermore, clinical guidelines have differed on whether to recommend percentage reductions in LDL-C or specific LDL-C levels among such patients[1,9,10]. To provide practical insights into desirable reductions in LDL-C among these individuals, we also conducted an observational analysis which assessed the relationship between reductions in LDL-C (in relative or absolute terms) and on-treatment LDL-C levels with subsequent clinical events.

Methods

Randomised trial

Details of the design of WOSCOPS have been described in detail elsewhere.[7,8] Briefly, WOSCOPS enrolled 6595 men aged 45-64 years (mean age 55 years) without evidence of prior MI and with a LDL-C ≥155 mg/dL not receiving lipid lowering therapy (mean LDL-C 192 mg/dL). Patients likely to have an elevated LDL-C due to secondary causes or with LDL-C >232 mg/dL on two fasting lipid measurements during the screening phase were excluded (supplementary eMethods, eFigure 1). Subjects were then randomised (double-blind) to pravastatin 40 mg once daily or placebo. Mean follow-up was 4.9 years (range 3.1-6.1).

To assess a purely primary prevention population the present analyses adopted more rigorous criteria than those used in the main WOSCOPS trial and additionally excluded those

individuals with any evidence of vascular disease at baseline (n=1066) namely, evidence of angina, intermittent claudication, stroke, transient ischemic attack, and minor ECG abnormalities (classified by Minnesota code).[7,8,11] Patients were then stratified by LDL-C levels at baseline into those with LDL-C <190 mg/dL and those with LDL-C ≥190 mg/dL, eFigure 1, eTable 1. The following principal endpoints were considered for the present analysis in order to maximise power (given the smaller sample size resulting from the stricter exclusion criteria and further restricting analysis to approximately half of the remaining individuals, i.e. participants with LDL-C ≥190 mg/dL): (i) the composite of definite or suspected non-fatal MI plus definite or suspected CHD death, hereinafter referred to as CHD (same co-principal endpoint as the original WOSCOPS trial); (ii) the composite of cardiovascular death, non-fatal MI (definite or suspected) and non-fatal stroke (major adverse cardiovascular events [MACE]). Endpoint definitions including definite and suspected coronary events are shown in the supplementary methods. Other outcomes explored include the principal endpoints but restricted to definite-only coronary events, MACE including coronary revascularisation, mortality endpoints (CHD death, cardiovascular death and all-cause mortality), coronary revascularization, and cerebrovascular events (fatal/non-fatal stroke and transient ischemic attack).

Extended observational long-term follow-up

After completion of the randomised trial phase an extended observational follow-up of the WOSCOPS cohort is now ongoing, through linkage to national mortality and electronic hospital discharge records held by the National Health Service for Scotland.[12,13] Further details are available in the supplementary methods, but briefly at 5 years after the initial trial finished approximately one third of individuals originally allocated to pravastatin or

placebo were on statins. In the present analysis we compared long-term mortality outcomes (including deaths from CHD, cardiovascular causes, and any-cause) between those originally randomised to pravastatin compared with placebo among individuals without evidence of vascular disease at baseline stratified by hypercholesterolaemia status.

Ethics

The ethics committees from the University of Glasgow and participating health boards in Scotland approved the original WOSCOPS trial. The corresponding committees from the Glasgow Royal Infirmary and Privacy Advisory Committee of the National Health Service for Scotland approved the extended follow-up study. The participants in each phase of WOSCOPS provided informed consent to partake in the trial and review of their medical records.

Statistical analysis

Effect of statin therapy on outcomes

The effect of therapy (pravastatin vs. placebo) among those with and without LDL-C ≥190 mg/dL was calculated for both the initial trial period and the extended follow-up. Estimates of hazard ratios and 95% confidence intervals with corresponding p-values were obtained by means of Cox proportional-hazards model with randomised therapy as the only covariate. A test for interaction was performed to assess whether the effect of therapy was consistent across the LDL-C strata pre-specified for this analysis. The p-value obtained from the treatment by LDL-C subgroup interaction term was reported. Time-to-event curves were estimated using the Kaplan-Meier method based on the original treatment arm and LDL-C strata. Tests were 2-sided and statistical significance defined as $p<0.05$.

Changes in LDL-C and outcomes

To elucidate the extent to which the magnitude of LDL-C reduction from pravastatin therapy influenced outcomes among those with LDL-C ≥190 mg/dL, observational analyses were performed. Therefore, we assessed changes in LDL-C levels and pravastatin effect during the randomised trial restricted to those subjects with LDL-C ≥190 mg/dL at baseline. The placebo group was taken as the reference category for the models. The relationship between absolute LDL-C fall (mean baseline level minus mean on-treatment value) or percentage LDL-C reduction and risk of events were assessed using multivariable Cox regression models (Wald test) for the different groups (placebo and pravastatin subgroups), accounting for the following covariates: age, smoking, blood pressure, history of hypertension, diabetes mellitus, and body mass index, as previously published.[5,14] LDL-C reductions were modelled as categorical variables based on previous WOSCOPS and CTT publications.[5,6,14] For the assessment of the relative fall in LDL-C, above and below 30% was used (consistent with the perceived average potency of pravastatin 40 mg/day: moderate-intensity statin therapy).[1]

On-treatment LDL-C and outcomes

The relationship between on-treatment LDL-C levels achieved with therapy on the risk of events was studied following similar analyses to those described above. Consistent with previous WOSCOPS analyses,[14] "on-treatment lipid levels" were defined as the mean of all lipid values measured after randomisation until the patient had an event or reached the end of the trial. On-treatment LDL-C analyses excluded individuals with events in the first 6 months of the trial as first on-treatment lipid measurements were at 6 months after randomisation.

Participants with a predicted 10-year ASCVD risk below 7.5% and no diabetes

Finally, we performed additional analyses among participants without an indication of statin therapy based on global cardiovascular risk estimation and who were free from diabetes in whom LDL-C was ≥190 mg/dL (and for comparison below 190 mg/dL), to specifically assess the impact of LDL-C related-cardiovascular risk. To assess global cardiovascular risk we applied the Pooled Cohort Risk Equations[15] to the WOSCOPS cohort who were free from ASCVD and diabetes, restricted to those with a predicted 10-year ASCVD risk below 7.5%. To maximise power we focused on MACE during the 5-year on-trial period and 20-year extended follow-up.

The statistical analyses were performed using SAS v9.2 (SAS Institute Inc., USA).

Results

A total of 5529 patients without prior evidence of vascular disease were included in the present analyses; of these, 2560 individuals had LDL-C ≥190 mg/dL (placebo n=1274; pravastatin n=1286). The baseline characteristics, stratified by presence or absence of LDL-C ≥190 mg/dL, comparing pravastatin to placebo treatment groups are shown in table 1. Overall, patients had a mean age of 55 years and there were no significant differences between placebo and pravastatin treated groups in any of the characteristics.

Lipid levels

LDL-C levels at baseline, 1 year and end of trial, as well as percentage changes from baseline to year 1 and to end of trial, are shown in table 1. Mean (±SD) LDL-C at baseline was 206±12 mg/dL among patients with LDL-C ≥190 mg/dL, and 178±6 mg/dL among those with LDL-C <190 mg/dL. LDL-C levels at year 1 and end of trial were significantly lower among

pravastatin treated subjects compared to placebo across cohorts (p<0.001). The percentage reduction in LDL-C from baseline with pravastatin (accounting for the effect of placebo) among those with and without LDL-C ≥190 mg/dL was of a similar magnitude (approximately 23% at year 1 and 19.5-20% at end of trial), eFigure 2. The effects on other lipids are shown in eTable 2.

Initial trial phase

The effect of pravastatin versus placebo on cardiovascular outcomes over 4.9 years stratified by LDL-C <190 or ≥190 mg/dL is shown in figure 1, table 2 and eTable 3. Overall, both CHD and MACE were reduced in the 5529 patients without vascular disease. Analyses stratified by LDL-C status showed no evidence of heterogeneity between cohorts for the principal endpoints or for the additional outcomes explored (interaction p-value all >0.2) (interaction results did not materially change when using LDL-C as a continuous measure rather than categorical, eTable 4). The corresponding Kaplan-Meier curves are shown in figures 2-3 and eFigures 3-5. Among individuals with LDL-C ≥190 mg/dL, pravastatin significantly reduced the risk of CHD by 27% (p=0.033) with a 25% risk reduction in MACE (p=0.037).

Long-term follow-up

The effect of initial randomisation to pravastatin or placebo on mortality endpoints during a total of 20-years of follow-up (from randomisation to end of extended follow-up) is shown in figure 4, and eFigures 6-8. Overall, amongst all subjects initially allocated to pravastatin CHD death, cardiovascular death and all-cause mortality were significantly reduced by 22%, 17% and 12% respectively (table 2). Long-term risk of CHD death, cardiovascular death and all-cause mortality were significantly reduced by 28%, 25% and 18%, respectively, among

those with LDL-C ≥190 mg/dL originally randomised to pravastatin. The absolute reduction in the risk (ARR) of death at 20 years from CHD, cardiovascular causes and from any-cause was at least two-fold greater among patients with LDL-C ≥190 mg/dL (ARR 2.34%, 3.25% and 5.39%, respectively) compared with those with LDL-C <190 mg/dL (Table 2). Analysis considering specifically the post-trial period only (15-year end of randomised trial to end of extended follow-up period) did not materially change the results (eTable 5).

Change in LDL-C and outcomes

Among individuals with LDL-C ≥190 mg/dL, reduction in LDL-C of greater than 30% or 39 mg/dL (1 mmol/L) were associated with a lower risk of CHD and MACE compared to placebo (figure 5, eTables 6-7). In contrast, those individuals allocated to pravastatin whose LDL-C reduction was less than 30% or 39 mg/dL were not significantly different from placebo. Consistent with earlier publications from WOSCOPS, we did not observe a continuous relationship between lower achieved LDL-C and outcomes (figure 5, eTables 6-8).

Participants with a predicted 10-year ASCVD risk below 7.5% and no diabetes

Using the Pooled Cohort Risk Equations[15] participants were stratified into those free from diabetes and with a 10-year predicted risk of MACE at baseline of <7.5% but with a LDL-C ≥ 190 mg/dl (n=1714), representing 67% of the initial primary prevention cohort with LDL-C ≥ 190 mg/dl (table 3). During the 5-year trial period MACE was significantly reduced to 4.8% among those allocated to pravastatin in contrast to a rate of 7.5% among placebo, representing a 38% reduction in risk (HR 0.62, 95%CI 0.42, 0.92), p=0.018). During the 20-year extended follow up the corresponding rates were 18.76% vs 24.18%, representing a risk reduction of 27% (HR 0.73, 95%CI 0.60, 0.90, p=0.003). There was no evidence of

heterogeneity among those with LDL-C less than 190 mg/dL and a predicted 10-year risk less than 7.5% treated with pravastatin (table 3 and eTable 9).

Discussion

Observational data support the assertion that having a LDL-C ≥190 mg/dL is associated with increased cardiovascular risk, even in the absence of other risk factors.[3] However, current guidelines recognise the paucity of evidence for primary prevention among these individuals and, specifically, the lack of evidence from randomised trials which include only patients with LDL-C ≥190 mg/dL.[1] Instead, indirect evidence derived from the extrapolation of other data is used to support this viewpoint.[1] Indeed, the largest evidence base is derived from the CTT meta-analyses, where a significant reduction in major coronary events and major vascular events per 39 mg/dL reduction in LDL-C with statins were observed across different categories of baseline LDL-C, including those with LDL-C ≥135 mg/dL[5] or with LDL-C >174 mg/dL[6]; but these groups included patients with established vascular disease. Thus, while the primary prevention of adults with primary LDL-C ≥190 mg/dL is identified as one of the groups where the benefit of statin therapy exceeds the risk of adverse events the data currently available from randomised clinical trials are still limited.[1,2]

The present analyses from the WOSCOPS study provide for the first time, evidence from a randomised trial supporting the benefit of LDL-C reduction in the primary prevention of ASCVD in those with LDL-C ≥190 mg/dL. Specifically, we provide three lines of evidence for the benefit of LDL-C lowering with statins in these patients: (i) randomised trial evidence that LDL-C reduction by approximately one quarter with statins reduces the risk of CHD by 27% and of MACE by 25%; (ii) extended follow-up evidence that the early benefits extend to reductions in CHD death by 28%, cardiovascular death by 25%, and all-cause mortality by

18% over 20 years; the greater absolute benefit and smaller numbers needed-to-treat in patients with LDL-C ≥190 mg/dL likely reflect the higher lifetime cardiovascular risk due to the cumulative atherosclerotic burden compared with those with LDL-C <190 mg/dL; (iii) observational data showing that reductions above 30% or 39 mg/dL are associated with lower risk of CHD and MACE compared to placebo. Another consideration of our results is that LDL-C does not appear to be an effect modifier of outcomes at either 5 years or at 20 years of follow-up (all interaction p-values >0.18); in addition, there is not much difference in event rates based on LDL-C cut-off of 190 mg/dL during the initial 5 year trial period. While these data provide support for statin therapy for primary prevention in subject with LDL-C ≥190 mg/dL, the data also provide support for the use of statin therapy for those with LDL-C <190 mg/dL (lower limit for inclusion being 155 mg/dL).

To assess the importance of LDL-C to cardiovascular risk we conducted an analysis among the primary prevention cohort in WOSCOPS who were free from diabetes at baseline and who on the basis of the current Pooled Cohort Risk Equations would be considered at low risk (i.e. 10-year predicted risk below 7.5%) and otherwise would be ineligible for statin therapy (approximately two thirds). Among placebo-treated patients with LDL-C ≥190 mg/dL the observed risk of MACE at 5 years was already 7.5%, i.e. double what would have been predicted using a risk calculator. In comparison, among those with a LDL-C between 155 and 190 mg/dL the 5-year risk of MACE was 5.7% in the placebo group. These data reinforce the notion that among patients with a LDL-C ≥190 mg/dL the observed risk is much greater than would be predicted through a risk calculator, and thus global risk estimation is not necessary. During the 5-year randomised trial period patients with a LDL-C ≥190 mg/dL but with a 10-year predicted risk below 7.5% derived a statistically significant 2.7% ARR in MACE with pravastatin (relative risk reduction 38%).

We studied a primary prevention population with a LDL-C ≥190 mg/dL, also defined by some guidelines as primary severe hypercholesterolaemia[1]. Some have also referred to patients with LDL-C ≥190 mg/dL as FH phenotype[3,4] (eTable 1). However, FH does not have a "gold standard" definition and its prevalence may ultimately depend on the LDL-C threshold and the presence of a pathogenic gene variant.[16,4] Notwithstanding this, individuals with LDL-C ≥190 mg/dL are more likely to have FH by clinical and/or genetic criteria (eTable 1).[9,17-19] However, according to a recent study, only a small proportion of people with severe hypercholesterolaemia in the community have an identifiable FH mutation.[16] In the present study we lacked genetic data and indeed relevant clinical information to help define FH in the WOSCOPS population according to accepted diagnostic criteria;[9] however, the number of individuals who fulfil the strict clinical or genetic criteria for FH in the present analyses is likely to have been small, as WOSCOPS excluded patients with LDL-C >232 mg/dL or with prior MI.[7] Hence, a number of patients with more severe manifestations of FH (in terms of higher LDL-C levels or coronary disease at an earlier age) might have been excluded. Nevertheless, our results are applicable to the broader FH population, based on (i) that there was no heterogeneity in treatment effect between patients with and without LDL-C ≥190 mg/dL, (ii) our observation that individuals with primary elevation of LDL-C ≥190 mg/dL and likely greater lifetime burden from elevated LDL-C derive significant risk reductions from LDL-C lowering, (iii) a number of observational studies that suggest FH patients benefit of statins.[20-23]

The ACC/AHA cholesterol guidelines recommend high-intensity statin therapy for individuals with LDL-C ≥190 mg/dL[1] and whilst the present analyses provide direct evidence for the benefits for approximately a 23% reduction in LDL-C (i.e. a low-intensity statin regimen), there are no trials presently capable of providing similar evidence for the benefit of even

greater percentage reductions or higher intensity statin therapy in this population. Whilst the current paradigm is that lower on-treatment LDL-C levels and/or greater reductions in LDL-C are associated with a lower risk of ASCVD,[24-26] we did not find evidence for a continuous relationship between on-treatment LDL-C and better outcomes, which is consistent with earlier analyses from the overall WOSCOPS cohort.[14] To what degree this reflects studies of pravastatin and its relevance to more contemporary statin use is uncertain. Since the inclusion criteria was an LDL-C of 155-232 mg/dL and the average LDL-C reduction at 1 year was approximately 23%, we did not have the data to validate or refute the current recommendation for a LDL-C target of 100 mg/dL in some guidelines.[9,10]

When LDL-C reductions in the pravastatin group were analysed as a binary trait, the present analyses suggested that those individuals who derived >30% reduction or >39 mg/dL absolute lowering in LDL-C, appeared to derive significant benefit compared to placebo. It should however be recognised that there was considerable overlap in the observed benefits between this group and those achieving lesser reductions on pravastatin. We also need to acknowledge that a fair number of people in the lower effect group never took the treatment or withdrew from treatment. We know that 9% of the original WOSCOPS cohort never took the treatment and about 30% were off treatment by 5 years (no significant difference in the withdrawal rates between pravastatin and placebo arms).[8] Many of these people attended the annual visits and got their lipids assessed because they saw the study doctor and had ECGs recorded. Hence, we cannot say that any trends to differences seen are differences in statin response.

The high baseline LDL-C and the limited potency of pravastatin 40 mg/day limit the extent of the analyses which can be performed in WOSCOPS. Direct evidence for the benefit of even

404 greater reductions in LDL-C among patients with LDL-C ≥190 mg/dL in primary prevention
405 may be inferred indirectly from the recently reported "Studies of PCSK9 Inhibition and the
406 Reduction of Vascular Events" (SPIRE)-2 trial,[27-29] evaluating the efficacy of PCSK9 inhibition
407 with bococizumab in reducing the risk of major cardiovascular events in subjects with LDL-C
408 ≥100 mg/dL despite maximally tolerated statin therapy. With a mean baseline LDL-C level of
409 134 mg/dL and assuming a 50% reduction in LDL-C from intensive-statin therapy it suggests
410 that many participants in the SPIRE-2 trial likely started with untreated LDL-C levels ≥190
411 mg/dL. Therapy with bococizumab led to a reduction in LDL-C levels of around 55% and 40%
412 at 14 and 52 weeks, respectively.[29] Although the trial was prematurely stopped due to the
413 development of high rates of antidrug antibodies and attenuation of the cholesterol
414 lowering effect over time, a significant 21% risk reduction of cardiovascular events was
415 observed in those treated with bococizumab (compared to placebo) after a median follow-
416 up of 12 months, with no significant differences in analyses stratified by the presence or
417 absence of clinical evidence of cardiovascular disease.[29] Of note, the USA National Lipid
418 Association has recently recommended that therapy with PCSK9 inhibitors may be
419 considered to further reduce LDL-C in patients with LDL-C ≥190 mg/dL.[4]

420 A major strength of the present analysis is that it explores a group of higher risk individuals
421 (LDL-C ≥190 mg/dL) specifically highlighted in guidelines, but one in which clinical trial
422 evidence is lacking.[1] Thus, the present results from a randomised trial provide novel
423 information and evidence to support guideline recommendations. Additionally, since high
424 lipid levels like those included in WOSCOPS (LDL-C ≥155 mg/dL) may be present in a
425 significant proportion of the population, the results of the present study may impact on the
426 care of a significant number of patients; for instance, recent surveys from USA have
427 estimated a prevalence of 16%-33% for LDL-C ≥155-160 mg/dL and of 5.6%-10.4% for LDL-C

≥190 mg/dL (depending on the characteristics of the population scrutinised) in the adult population.[30,31] That said, some aspects of the present analyses warrant further discussion. This is an analysis of a subgroup of the overall WOSCOPS cohort which was not pre-specified and, whilst the findings are consistent with the original trial publications,[8,12-14] the present findings remain post-hoc. The lack of statistically significant reductions in additional endpoints in the group with LDL-C ≥190 mg/dL (figure 1) may reflect a limited power resulting from restricting the original sample size. In addition, it should be noted that the LDL-C levels in those with LDL-C <190 mg/dL were still high (mean LDL-C at baseline 178 mg/dL overall; at year 1: 177 and 135 mg/dL in placebo and pravastatin arms, respectively) and not markedly different than in those with LDL-C ≥190 mg/dL (mean LDL-C at baseline 206 mg/dL overall; at year 1: 199 and 157 mg/dL in placebo and pravastatin arms, respectively); as such, the difference in absolute risk reduction between these groups may not have been as wide as could be observed in current populations where mean LDL-C levels (in those with LDL-C <190 mg/dL) are significantly lower.

The extended long-term follow-up reports data among individuals enrolled in the original trial and, although the comparisons provided are for the original randomised groups, it should be recognised that the data from the additional 15 years of follow-up after the original trial was completed are observational and might be confounded by the lack of ongoing information regarding medication use. For instance, those participants with LDL-C ≥190 mg/dL may have been more likely kept on treatment than those with lower LDL-C levels after the completion of the trial. Nevertheless, it provides valuable information on what a period of treatment may confer in terms of long-term risk reduction benefit ("legacy effect" or "reset of the atherosclerotic event clock" based on the original trial). Nevertheless, without excluding the possibility of confounding factors it is not possible to

fully characterize the long-term follow-up estimates as either underestimates or overestimates since it cannot be assumed that the outcomes are only modulated by statin use or non-use. Notwithstanding this, we consider the former is more likely due to the fact that (i) many actively treated patients during the trial phase may have no longer received statin therapy and (ii) the expected increased cross-over in the original placebo arm to statin therapy during follow-up; as such, the results of the extended follow-up may likely underestimate the benefits of longer-term therapy due to reduced differential statin use over time, and so likely the benefit for those ≥190 mg/dL may be larger than that implied by the trial (especially if one were to use a statin regimen of greater potency to that used in WOSCOPS). On the other hand, the high prevalence of smokers in the WOSCOPS population might mean that a similar study today might not show as strong an effect with a statin regimen of similar potency.

Regarding the exploratory analyses evaluating LDL-C change on treatment versus outcome (compared with placebo), it cannot completely rule out the influence of non-compliance to medication. That said, to be included in the analysis men had to attend to have their blood sample taken; many non-compliers did not do so (which is why the achieved LDL-C rose slightly over time). Thus, there is some allowance for non-compliance in the analysis as performed. Finally, the analyses of reductions in LDL-C on pravastatin and outcomes are observational in nature and should be interpreted as such as residual confounding cannot be excluded despite statistical adjustment.

Conclusion

Among men with primary elevations of LDL-C levels ≥190 mg/dL, primary prevention with pravastatin reduced the risk of cardiovascular events. Thus, the present analyses from a

randomised clinical trial provides for the first time evidence for the benefits of LDL-C lowering for the primary prevention of individuals with primary elevations of LDL-C ≥190 mg/dL, which may help reinforce current recommendations for this group of patients.

Funding Sources

The present analyses have been partly funded by a grant from Sanofi to Imperial College London (Medical and Educational Goods and Services Grant, reference number UKME-15-00020). The WOSCOPS trial was originally funded by Bristol-Myers Squibb and Sankyo.

Role of authors and funding source

The present analyses were conceived by KKR and AJVV. MR and IF performed the statistical analyses. CP and IF conducted the original WOSCOPS trial and extended follow-up. KKR and AJVV wrote the draft of the present paper. All authors critically reviewed the manuscript and approved its submission. IF and MR had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Funding organizations had no influence on the design and conduct of the study; collection, management, analyses, and interpretation of the data; preparation, review or approval of the manuscript; or the decision to submit the manuscript for publication.

Disclosure of potential conflicts of interests

Dr. Catapano reports grants and/or personal fees from Merck, Sanofi, Amgen, Pfizer, Mylan, Kowa, Sigma Tau, Astra Zeneca, Recordati, and Doc Generici, outside the submitted work.

Dr. Ford reports grants from Imperial College London, during the conduct of the study, and from Merck, outside the submitted work.

Dr. Kastelein reports personal fees from Regeneron, Sanofi, Amgen, Pfizer, Eli Lilly, Ionis Pharmaceuticals, AstraZeneca, CSL Behring, Cerenis, Esperion, The Medicines Company, Kowa, Affiris, UniQure, Madrigal, Akcea Therapeutics, Staten Biotech, Akarna, Corvidia, and Gemphire, outside the submitted work.

Dr. Packard reports grants and/or personal fees from MSD, Pfizer, Sanofi, and Roche, outside the submitted work.

Dr. Ray reports grants and/or personal fees from Pfizer, MSD, Astra Zeneca, Sanofi, Aegerion, Regeneron, Abbvie, Kowa, Cerenis, Medicines Company, Lilly, Esperion, Amgen, Cipla, and Algorithm, outside the submitted work.

Dr. Robertson reports grants from Imperial College London, during the conduct of the study.

Dr. Vallejo-Vaz has nothing to disclose.

Dr. Watts reports grants and/or personal fees from Sanofi, Amgen, and Regeneron, outside the submitted work.

Previous presentation of the information reported in the manuscript

The work reported in the present manuscript was selected for presentation at the late-breaking science session “Clinical Trials Update – Prevention” during the 2016 European Society of Cardiology (ESC) Congress held in Rome, Italy, 27-31 August, 2016.

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FIGURE LEGENDS

Figure 1. Endpoints during the randomised trial period, overall and stratified by LDL-cholesterol levels at baseline.

Effect of therapy (vs. placebo) shown as hazard ratio (HR) and corresponding 95% confidence interval (95% CI). (*) 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.

Figure 2. Coronary heart disease risk: Kaplan-Meier curves during the randomised trial period stratified by LDL-cholesterol levels at baseline and treatment allocation.

5-year follow-up Kaplan-Meier analysis for coronary heart disease (CHD) endpoint, stratified by LDL-cholesterol 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=104; pravastatin, LDL-C <190 mg/dL: n=75; placebo, LDL-C ≥190 mg/dL: n=107; pravastatin, LDL-C ≥190 mg/dL: n=80. CI: confidence interval. HR: hazard ratio. To convert values for cholesterol to mmol/L, multiply by 0.02586.

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

5-year follow-up Kaplan-Meier analysis for major adverse cardiovascular disease events (MACE) 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=119; pravastatin, LDL-C <190 mg/dL: n=90; placebo, LDL-C ≥190 mg/dL: n=121; pravastatin, LDL-C ≥190 mg/dL: n=93. 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.

Figure 4. Long-term mortality endpoints at 20 years of follow-up, overall and stratified by LDL-cholesterol levels at baseline.

Effect of therapy (vs. placebo) shown as hazard ratio (HR) and corresponding 95% confidence interval (95% CI). CHD: coronary heart disease. LDL-C: low-density lipoprotein cholesterol. To convert values for cholesterol to mmol/L, multiply by 0.02586.

Figure 5. Principal endpoints during the randomised trial period based on different categories of LDL-C levels with pravastatin in subjects with LDL-cholesterol ≥190 mg/dL at baseline.

Effect of therapy (vs. placebo) shown as hazard ratio (HR) and corresponding 95% confidence interval (95% CI). 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. 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 randomisation. 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.

TABLE 1. Characteristics of the participants without vascular disease at enrolment stratified by LDL-cholesterol levels at baseline.

	Participants LDL-C <190 mg/dL		Participants With LDL-C ≥190 mg/dL	
	Placebo	Pravastatin	Placebo	Pravastatin
	n = 1493	n = 1476	n = 1274	n = 1286
Demographics at baseline				
Age (years)	54.8 ± 5.5	55.0 ± 5.6	54.7 ± 5.5	54.8 ± 5.5
Body mass index (kg/m^2)	25.9 ± 3.1	25.8 ± 3.2	25.8 ± 3.1	25.8 ± 3.0
Systolic BP (mmHg)	134.8 ± 16.3	134.6 ± 17.0	135.2 ± 17.1	134.5 ± 17.4
Diastolic BP (mmHg)	83.8 ± 10.2	83.5 ± 10.5	83.8 ± 9.9	83.6 ± 10.4
History of hypertension, n (%)	194 (13.0)	199 (13.5)	164 (12.9)	188 (14.6)
History of diabetes, n (%)	13 (0.9)	12 (0.8)	13 (1.0)	21 (1.6)
Current smoker, n (%)	634 (42.5)	594 (40.2)	563 (44.2)	583 (45.3)
Lipid levels at baseline				
LDL-Cholesterol (mg/dL)	178.5 ± 6.5	178.2 ± 6.7	206.6 ± 12.8	206.7 ± 12.7
Total cholesterol (mg/dL)	258.0 ± 15.3	257.7 ± 15.7	286.6 ± 19.1	286.3 ± 18.9
HDL-Cholesterol (mg/dL)	44.3 ± 9.6	44.7 ± 9.7	44.4 ± 9.6	44.1 ± 8.9
Non-HDL-Cholesterol (mg/dL)	213.8 ± 16.2	213.0 ± 16.5	242.2 ± 19.5	242.3 ± 19.2
Triglycerides (mg/dL)	143.9 (108.5, 194.9)	139.5 (106.3, 190.4)	150.6 (115.1, 197.1)	148.4 (115.1, 192.6)
LDL-Cholesterol levels during the follow-up				
LDL-C Year 1 (mg/dL)	177.8 ± 21.7	135.8 ± 29.2	199.8 ± 26.0	152.7 ± 33.3
LDL-C End of trial (mg/dL)	179.1 ± 24.3	142.9 ± 32.0	199.6 ± 28.7	158.4 ± 35.4
Percentage change from baseline to 1 year	-0.4 ± 11.9	-23.8 ± 16.2	-3.1 ± 11.8	-26.1 ± 15.5
Percentage change from baseline to end of trial	0.4 ± 13.4	-19.8 ± 17.7	-3.2 ± 13.1	-23.3 ± 16.7

Data shown as absolute and relative (%) number of subjects for categorical variables and as mean ± standard deviation or median (interquartile range) for continuous parameters. BP: blood pressure. HDL: high-density lipoprotein. LDL-C: low-density lipoprotein cholesterol. To convert values for cholesterol to mmol/L, multiply by 0.02586. To convert values for triglycerides to mmol/L, multiply by 0.01129.

TABLE 2. Principal and mortality endpoints during the randomised trial period, and long-term mortality endpoints from randomisation to 20 years of follow-up, stratified by LDL-cholesterol levels at baseline.

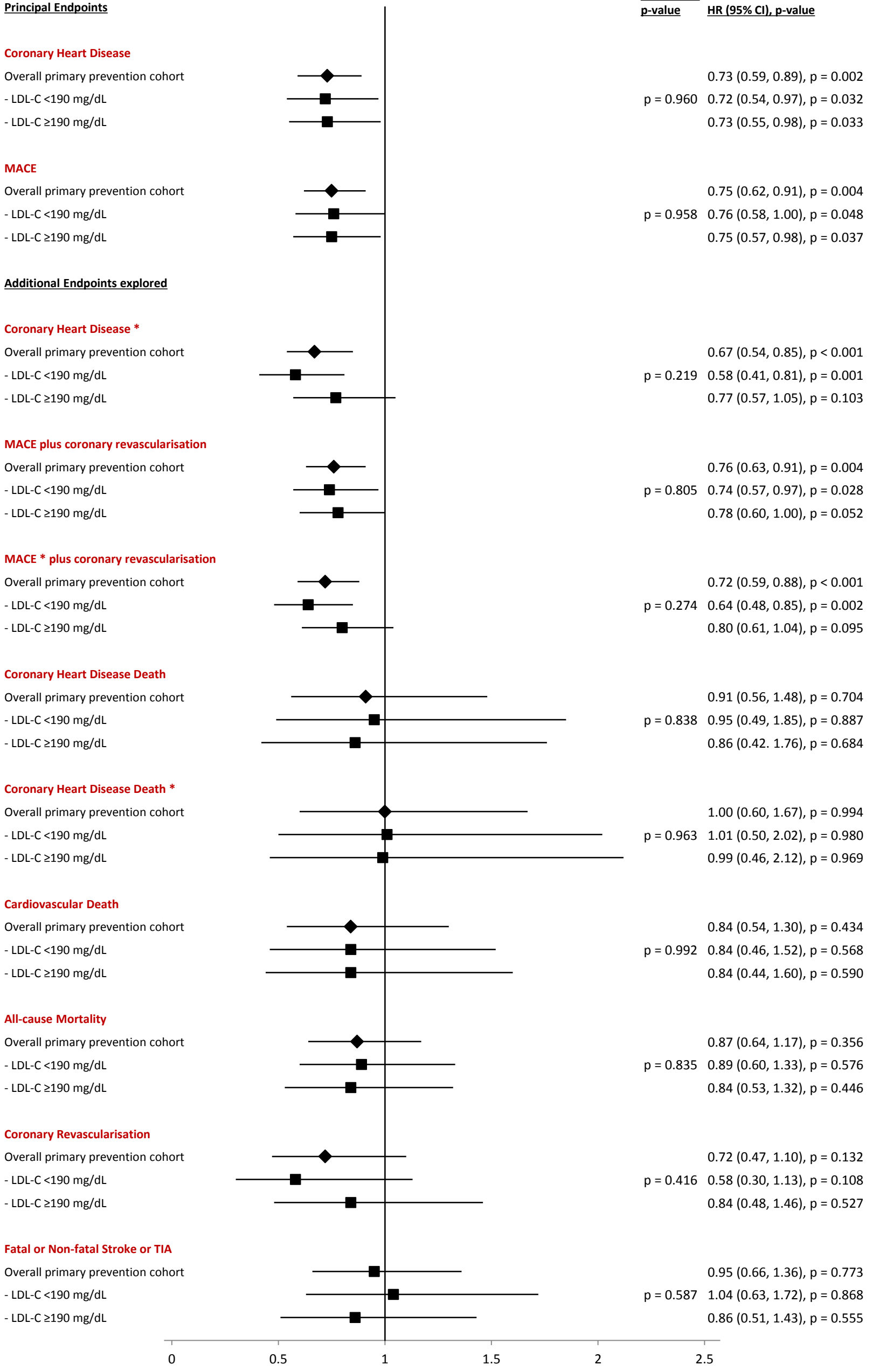
	Overall cohort	Participants with LDL-C <190 mg/dL			Participants With LDL-C ≥190 mg/dL			Interaction p-value between LDL-C grouping at baseline and randomised treatment
	HR (95% CI), p-value	Events [n (%)]		HR (95% CI), p-value	Events [n (%)]		HR (95% CI), p-value	
		Placebo (n=1493)	Pravastatin (n=1476)		Placebo (n=1274)	Pravastatin (n=1286)		
5-year randomised trial								
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
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
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
20-year long-term follow-up								
CHD	0.74 (0.65, 0.84), <0.001	268 (17.95%)	201 (13.62%)	0.73 (0.61, 0.88), <0.001	261 (20.49%)	203 (15.79%)	0.74 (0.61, 0.89), 0.001	0.942
MACE	0.79 (0.71, 0.88), <0.001	383 (25.65%)	306 (20.73%)	0.77 (0.66, 0.89), <0.001	344 (27.00%)	295 (22.94%)	0.81 (0.69, 0.94), 0.007	0.642
CHD death	0.78 (0.64, 0.94), 0.011	115 (7.70%)	96 (6.50%)	0.84 (0.64, 1.10), 0.193	115 (9.03%)	86 (6.69%)	0.72 (0.54, 0.95), 0.020	0.453
Cardiovascular death	0.83 (0.71, 0.96), 0.015	177 (11.86%)	161 (10.91%)	0.91 (0.73, 1.13), 0.382	182 (14.29%)	142 (11.04%)	0.75 (0.60, 0.93), 0.009	0.211
All-cause mortality	0.88 (0.80, 0.96), 0.005	513 (34.36%)	477 (32.32%)	0.93 (0.82, 1.05), 0.247	460 (36.11%)	395 (30.72%)	0.82 (0.72, 0.94), 0.004	0.184

Effect of therapy (vs. placebo) shown as hazard ratios (HR) and corresponding 95% confidence intervals (95% CI) and p value. 5-year randomised trial: from randomisation to end of randomised trial (on-trial period). 20-year long-term follow-up: from randomisation to end of extended follow-up (on-trial plus post-trial periods). Results for the 15-year post-trial period only (from end of randomised trial to end of extended follow-up) did not materially differ from those in the 20-year long-term follow-up and are presented in eTable 5 in supplementary material. 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. See main text and supplementary material for endpoints definitions. To convert values for cholesterol to mmol/L, multiply by 0.02586.

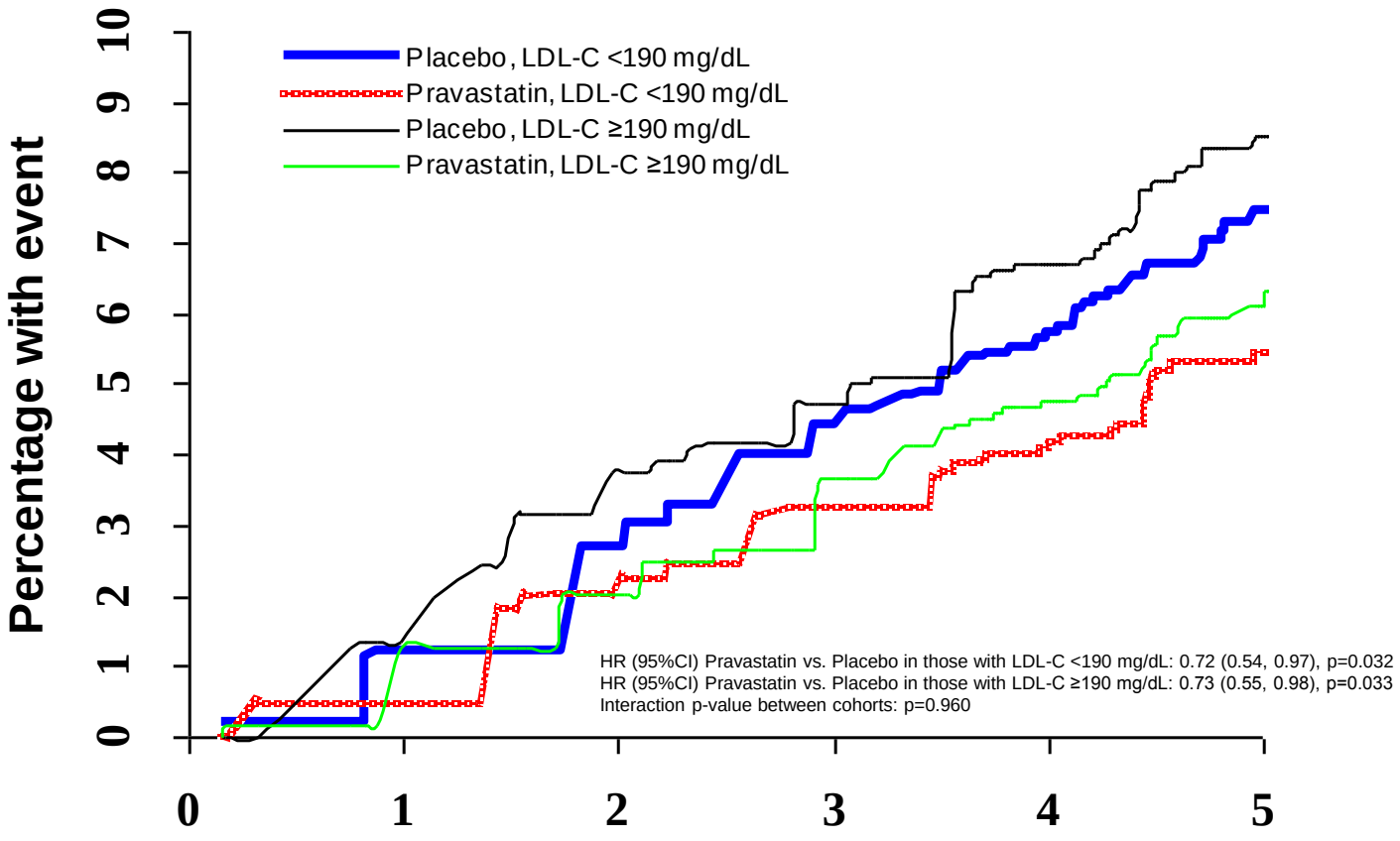
TABLE 3. Risk of major adverse cardiovascular events in the subgroup of patients without diabetes and with a predicted 10-year ASCVD risk* below 7.5% at baseline.

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	
5-year randomised trial period							
MACE	62 (5.7%)	48 (4.5%)	0.79 (0.54, 1.15), 0.21	64 (7.5%)	41 (4.8%)	0.62 (0.42, 0.92), 0.018	0.404
20-year long-term follow-up							
MACE	230 (21.20%)	178 (16.73%)	0.76 (0.62, 0.92), 0.005	207 (24.18%)	161 (18.76%)	0.73 (0.60, 0.90), 0.003	0.832

* ASCVD risk according to the Pooled Cohort Equations risk calculator (ref. 15). Effect of therapy (vs. placebo) shown as hazard ratios (HR) and corresponding 95% confidence intervals (95% CI) and p value. 5-year randomised trial: from randomisation to end of randomised trial (on-trial period). 20-year long-term follow-up: from randomisation to end of extended follow-up (on-trial plus post-trial periods). ASCVD: atherosclerotic cardiovascular 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.


Principal Endpoints
Interaction p-value
HR (95% CI), p-value
Coronary Heart Disease
Overall primary prevention cohort
0.73 (0.59, 0.89), p = 0.002
- LDL-C <190 mg/dL
p = 0.960
0.72 (0.54, 0.97), p = 0.032
- LDL-C ≥190 mg/dL
0.73 (0.55, 0.98), p = 0.033
MACE
Overall primary prevention cohort
0.75 (0.62, 0.91), p = 0.004
- LDL-C <190 mg/dL
p = 0.958
0.76 (0.58, 1.00), p = 0.048
- LDL-C ≥190 mg/dL
0.75 (0.57, 0.98), p = 0.037
Additional Endpoints explored
Coronary Heart Disease *
Overall primary prevention cohort
0.67 (0.54, 0.85), p < 0.001
- LDL-C <190 mg/dL
p = 0.219
0.58 (0.41, 0.81), p = 0.001
- LDL-C ≥190 mg/dL
0.77 (0.57, 1.05), p = 0.103
MACE plus coronary revascularisation
Overall primary prevention cohort
0.76 (0.63, 0.91), p = 0.004
- LDL-C <190 mg/dL
p = 0.805
0.74 (0.57, 0.97), p = 0.028
- LDL-C ≥190 mg/dL
0.78 (0.60, 1.00), p = 0.052
MACE * plus coronary revascularisation
Overall primary prevention cohort
0.72 (0.59, 0.88), p < 0.001
- LDL-C <190 mg/dL
p = 0.274
0.64 (0.48, 0.85), p = 0.002
- LDL-C ≥190 mg/dL
0.80 (0.61, 1.04), p = 0.095
Coronary Heart Disease Death
Overall primary prevention cohort
0.91 (0.56, 1.48), p = 0.704
- LDL-C <190 mg/dL
p = 0.838
0.95 (0.49, 1.85), p = 0.887
- LDL-C ≥190 mg/dL
0.86 (0.42. 1.76), p = 0.684
Coronary Heart Disease Death *
Overall primary prevention cohort
1.00 (0.60, 1.67), p = 0.994
- LDL-C <190 mg/dL
p = 0.963
1.01 (0.50, 2.02), p = 0.980
- LDL-C ≥190 mg/dL
0.99 (0.46, 2.12), p = 0.969
Cardiovascular Death
Overall primary prevention cohort
0.84 (0.54, 1.30), p = 0.434
- LDL-C <190 mg/dL
p = 0.992
0.84 (0.46, 1.52), p = 0.568
- LDL-C ≥190 mg/dL
0.84 (0.44, 1.60), p = 0.590
All-cause Mortality
Overall primary prevention cohort
0.87 (0.64, 1.17), p = 0.356
- LDL-C <190 mg/dL
p = 0.835
0.89 (0.60, 1.33), p = 0.576
- LDL-C ≥190 mg/dL
0.84 (0.53, 1.32), p = 0.446
Coronary Revascularisation
Overall primary prevention cohort
0.72 (0.47, 1.10), p = 0.132
- LDL-C <190 mg/dL
p = 0.416
0.58 (0.30, 1.13), p = 0.108
- LDL-C ≥190 mg/dL
0.84 (0.48, 1.46), p = 0.527
Fatal or Non-fatal Stroke or TIA
Overall primary prevention cohort
0.95 (0.66, 1.36), p = 0.773
- LDL-C <190 mg/dL
p = 0.587
1.04 (0.63, 1.72), p = 0.868
- LDL-C ≥190 mg/dL
0.86 (0.51, 1.43), p = 0.555
0
0.5
1
1.5
2
2.5

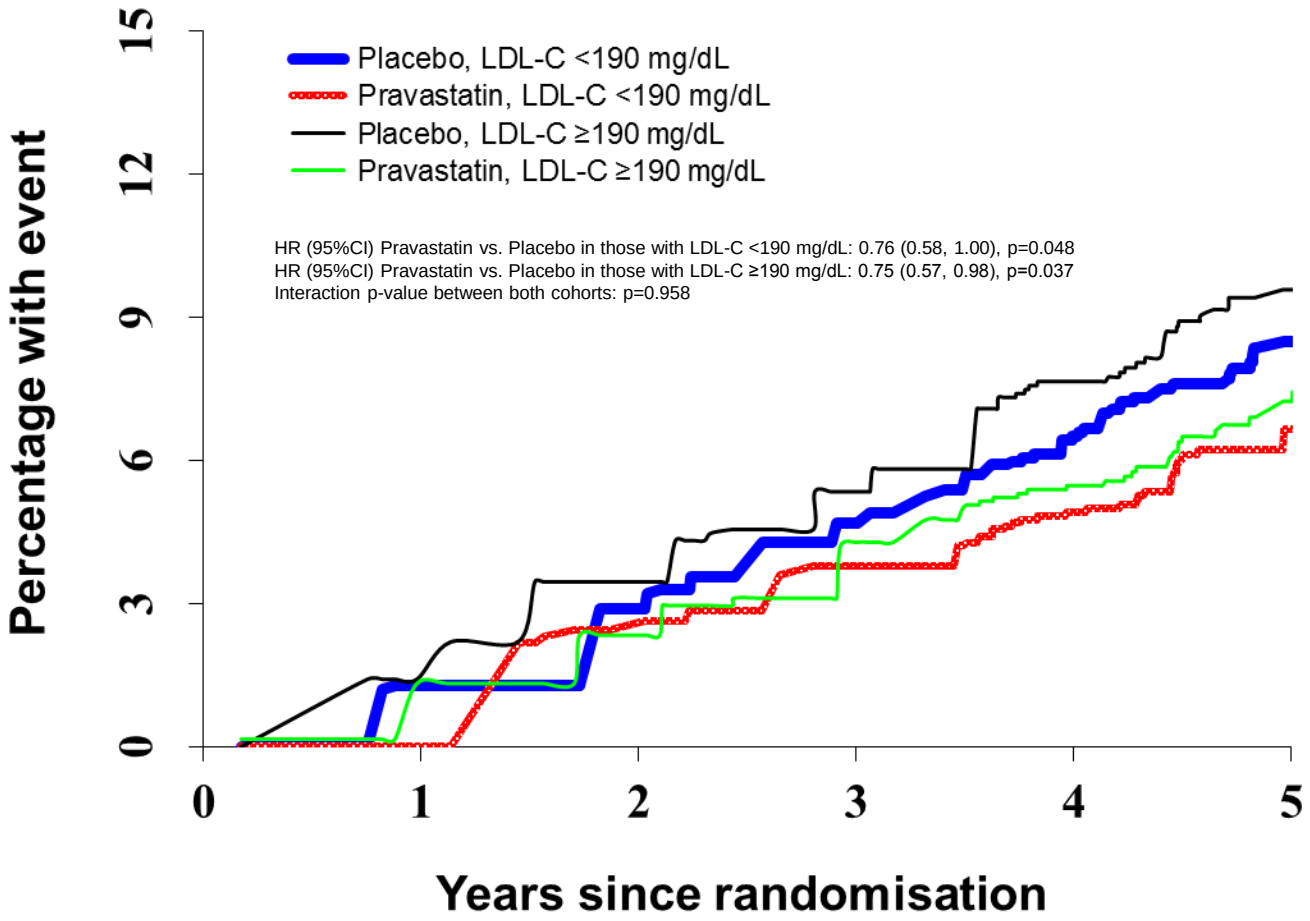
Coronary Heart Disease



Numbers at risk

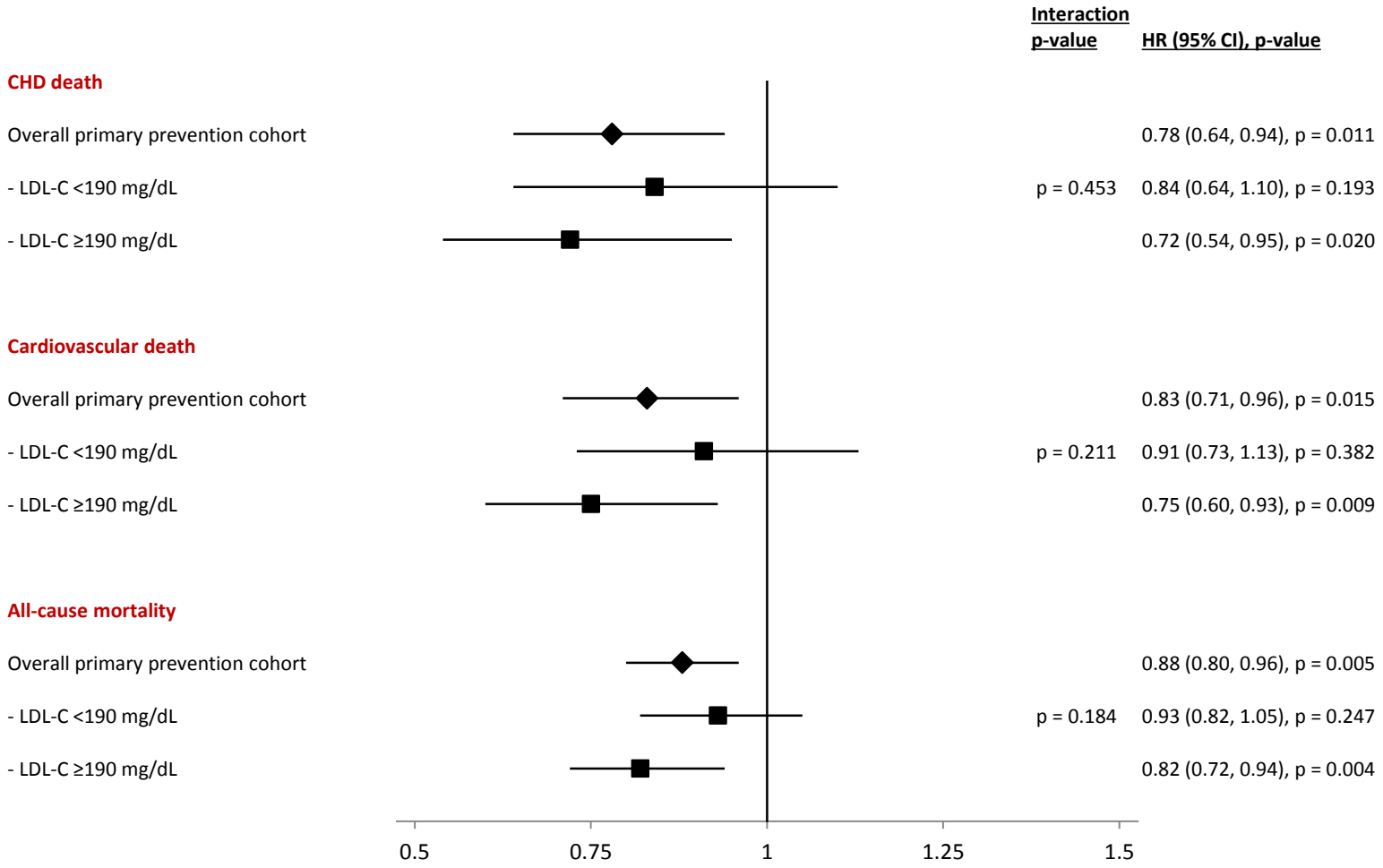
Placebo, LDL-C <190:	1493	1469	1446	1415	1222	564
Pravastatin, LDL-C <190:	1476	1457	1440	1415	1242	591
Placebo, LDL-C ≥190:	1274	1248	1219	1201	1044	478
Pravastatin, LDL-C ≥190:	1286	1267	1253	1231	1088	489

Major Adverse Cardiovascular Events



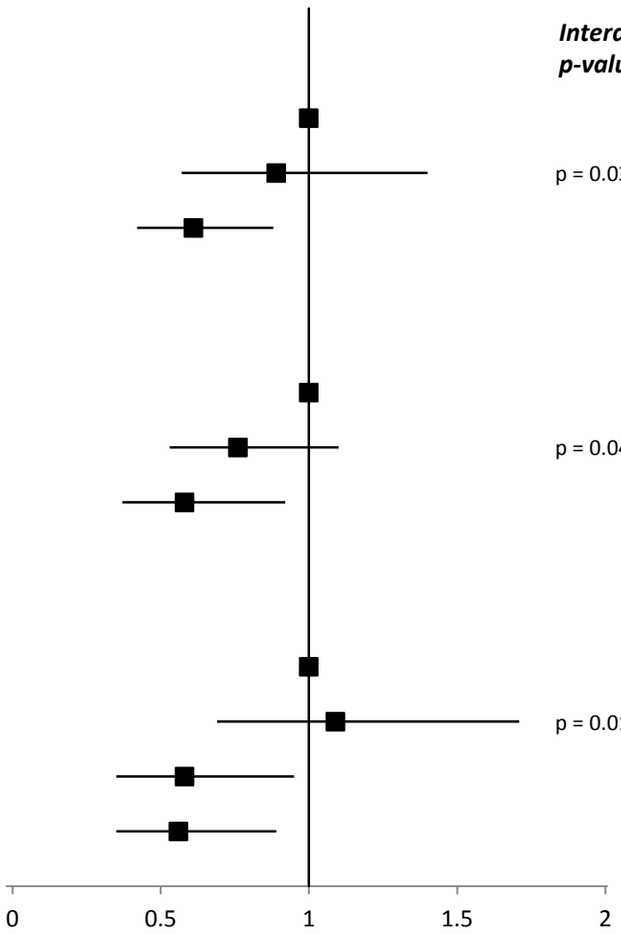
Numbers at risk

Placebo, LDL-C <190:	1493	1468	1444	1413	1216	560
Pravastatin, LDL-C <190:	1476	1453	1435	1409	1235	585
Placebo, LDL-C ≥190:	1274	1246	1217	1194	1036	474
Pravastatin, LDL-C ≥190:	1286	1266	1247	1223	1080	486


Interaction p-value
HR (95% CI), p-value
CHD death
Overall primary prevention cohort
0.78 (0.64, 0.94), p = 0.011
- LDL-C <190 mg/dL
p = 0.453
0.84 (0.64, 1.10), p = 0.193
- LDL-C ≥190 mg/dL
0.72 (0.54, 0.95), p = 0.020
Cardiovascular death
Overall primary prevention cohort
0.83 (0.71, 0.96), p = 0.015
- LDL-C <190 mg/dL
p = 0.211
0.91 (0.73, 1.13), p = 0.382
- LDL-C ≥190 mg/dL
0.75 (0.60, 0.93), p = 0.009
All-cause mortality
Overall primary prevention cohort
0.88 (0.80, 0.96), p = 0.005
- LDL-C <190 mg/dL
p = 0.184
0.93 (0.82, 1.05), p = 0.247
- LDL-C ≥190 mg/dL
0.82 (0.72, 0.94), p = 0.004
0.5
0.75
1
1.25
1.5

Coronary Heart Disease

	Interaction p-value	*HR (95% CI), p-value*
Absolute reduction in LDL-C levels		
Placebo		Ref. group
Absolute fall <39 mg/dL	p = 0.030	0.89 (0.57, 1.40), p = 0.612
Absolute fall ≥39 mg/dL		0.61 (0.42, 0.88), p = 0.008
Relative reduction in LDL-C levels		
Placebo		Ref. group
Percentage reduction <30%	p = 0.047	0.76 (0.53, 1.10), p = 0.148
Percentage reduction ≥30%		0.58 (0.37, 0.92), p = 0.021
On-treatment LDL-C levels		
Placebo		Ref. group
On-treatment ≥174 mg/dL	p = 0.015	1.09 (0.69, 1.71), p = 0.724
On-treatment 145 to <174 mg/dL		0.58 (0.35, 0.95), p = 0.030
On-treatment <145 mg/dL		0.56 (0.35, 0.89), p = 0.014



MACE plus coronary revascularisation

	Interaction p-value	*HR (95% CI), p-value*
Placebo		Ref. group
Absolute fall <39 mg/dL	p = 0.086	0.88 (0.58, 1.32), p = 0.524
Absolute fall ≥39 mg/dL		0.70 (0.51, 0.96), p = 0.027
Placebo		Ref. group
Percentage reduction <30%	p = 0.106	0.80 (0.57, 1.10), p = 0.171
Percentage reduction ≥30%		0.68 (0.46, 1.01), p = 0.054
Placebo		Ref. group
On-treatment ≥174 mg/dL	p = 0.046	1.06 (0.70, 1.60), p = 0.772
On-treatment 145 to <174 mg/dL		0.67 (0.44, 1.02), p = 0.064
On-treatment <145 mg/dL		0.64 (0.43, 0.95), p = 0.027