Baseline and on-statin treatment lipoprotein(a) levels predict cardiovascular events: An individual-patient-data meta-analysis of statin outcome trials

Brief title: Lp(a) and CVD risk in statin outcome trials

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Abstract (300 words)

Background: Elevated lipoprotein(a) [Lp(a)] is a genetic risk factor for cardiovascular disease (CVD) in general population studies, but its contribution to CVD risk in patients with established CVD or on statin therapy is uncertain.

Methods: Patient-level data from seven randomized placebo-controlled statin outcomes trials were collated and harmonized to calculate hazard ratios for CVD, defined as fatal or non-fatal coronary heart disease, stroke, or revascularisation procedures. Hazard ratios for CVD were estimated within each trial across pre-defined Lp(a) groups (15-<30, 30-<50, and ≥50 vs. <15 mg/dL), before pooling estimates using multivariate random-effects meta-analysis.

Findings: Analyses included data for 29069 patients with repeat Lp(a) measurements (mean age 62 years; 28% female; 5751 events during 95576 person-years at risk). Initiation of statin therapy reduced low-density-lipoprotein cholesterol (mean change [95% CI]: -39% [-43, -35]) without a significant change in Lp(a). Associations of baseline and on-statin treatment Lp(a) with CVD risk were approximately linear with increased risk at Lp(a) values ≥30 mg/dL for baseline Lp(a) and ≥50 mg/dL for on-statin Lp(a). Age- and sex-adjusted hazard ratios across Lp(a) groups [referent: Lp(a) <15 mg/dL] were 1·04 (0·91, 1·18), 1·11 (1·00, 1·22), and 1·31 (1·08, 1·58) for baseline Lp(a), and 0·94 (0·81, 1·10), 1·06 (0·94, 1·21), and 1·43 (1·15, 1·76) for on-statin Lp(a). Hazard ratios were virtually identical after further adjustment for prior CVD, diabetes, smoking, systolic blood pressure, low-density-lipoprotein cholesterol, and high-density-lipoprotein cholesterol. The association of on-statin Lp(a) with CVD risk was stronger than for on-placebo Lp(a) (interaction P=0·010) and was more pronounced at younger ages (interaction P=0·008) without effect modification by any other patient-level or study-level characteristics.

Interpretation: In this individual-patient meta-analysis of statin-treated patients, elevated baseline and on-statin Lp(a) showed an independent, approximately linear relationship with CVD risk. This study provides a rationale for testing the Lp(a) lowering hypothesis in CVD outcomes trials.

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Introduction

Lipoprotein(a) [Lp(a)] is a lipoprotein composed of apolipoprotein(a) covalently bound to apolipoprotein B (apoB) of a low-density lipoprotein (LDL) like particle.[1,2] Lp(a) mediates atherogenicity via its LDL moiety that has a similar proportion of cholesterol content as traditional LDL particles. In addition, it induces pro-inflammatory responses[3,4] via accumulation of oxidised phospholipids[5] and potentially exerts pro-thrombotic effects via the plasminogen-like apolipoprotein(a) moiety.[6] In contrast to other major lipoproteins, there is no approved specific therapy to lower circulating plasma levels of Lp(a).

Epidemiologic[7] and genetic[8,9] evidence has accumulated over the last decade showing that elevated Lp(a), driven primarily by the *LPA* gene,[10] is associated with increased risk of coronary heart disease, stroke, peripheral arterial disease, and calcific aortic valve stenosis.[1,2,11] These data have established Lp(a) as a cardiovascular disease (CVD) risk factor, but the bulk of evidence is based on studies involving individuals without prior CVD and without intensive secondary prevention therapies. In contrast, the role of elevated Lp(a) in patients with prior CVD events or on statin therapy and other guideline-recommended therapies is less clear. Prior studies in this patient population yielded inconsistent results, with findings ranging from significant positive associations to null associations such as following acute coronary syndromes (reviewed in reference[2]). In addition, several studies, including JUPITER[12] and AIM-HIGH[13], have shown that elevated Lp(a) remain predictive for CVD risk at LDL-cholesterol (LDL-C) levels <70 mg/dL,[1] but other studies suggest a positive association only when LDL-C is elevated.[14] Furthermore, a major limitation of all post hoc studies reporting Lp(a) levels and outcomes is that they involved only a small number of patients with Lp(a) values above 50 mg/dL and therefore were uniformly underpowered to test the hypothesis that elevated Lp(a) levels are associated with increased CVD risk in the setting of statin therapy or prior history of CVD.

To test this hypothesis with adequate statistical power, we established the Lipoprotein(a) Studies Collaboration, a consortium of patient-level data from placebo-controlled trials of statins with patient-level data on CVD outcomes and Lp(a) measurements at baseline and follow-up (i.e. under statin treatment). We now report the results of this analysis in documenting the associations of baseline and on-treatment Lp(a) with cardiovascular risk.

Methods

Trials included in the meta-analysis

To be eligible in the meta-analysis, randomized placebo-controlled statin trials were required to have assayed Lp(a) concentration at baseline and follow-up, have recorded incidence of CVD outcomes using well-defined criteria, and be willing to share patient data at the individual-level. We included data from AFCAPS, CARDS, 4D, JUPITER, LIPID, MIRACL, and 4S. Their study design, target population, and entry criteria are summarised in **Table 1**; more detailed descriptions of trial designs[15–21] and Lp(a) methodology and data[12,22–26] were previously reported by each trial. Trials not included in the meta-analysis were either not allowed or willing to provide individual-level patient data. Due to contractual agreements on sharing individual patient data, other eligible trials could not be included in the meta-analysis. All contributing trials have obtained ethics approval and patients' informed consent.

Statistical analyses

Analyses were conducted according to a pre-specified analysis plan, developed prior to any combined analyses. Lp(a) values were $\log_e$-transformed. Of 45044 patients enrolled in the seven trials, 15975 (35·5%) patients were excluded because of missing Lp(a) measurements at both baseline and follow-up, leaving 29069 patients for analysis (for CONSORT diagram, please refer to **Supplementary Figure 1**). There were minimal differences in baseline characteristics of patients with or without available Lp(a) measurements (**Supplementary Table 1**). In all trials except 4S, on-statin Lp(a) during follow-up was measured at one time-point. In the 4S trial, on-statin Lp(a) was estimated as the geometric mean of Lp(a) values assessed at up to four distinct time points. Lp(a) values provided in nmol/L were divided by 2·4 (JUPITER), as previously described[27], and those provided in IU/L by 19·07 (4S) to convert them to the common unit of mg/dL. When information on Lp(a) was missing either at baseline (0·5%) or at follow-up (5·5%), their Lp(a) value was mean-imputed from study-specific mixed-effects models which predicted Lp(a) values using fixed effects for assigned treatment, time-in-study, and the interaction of the two variables, plus a random intercept allowed to vary at the patient level.

Because conventional "LDL-C" assays capture cholesterol both in LDL and Lp(a) particles, LDL-C values were corrected for the latter. Lp(a) mass in mg/dL is composed of ~30-45% cholesterol.[28] We used a conservative measurement of the content of Lp(a)-C by multiplying Lp(a) mass (in mg/dL) by 0·30 to derive Lp(a)-cholesterol, and then subtracting this value from the measured LDL-C to obtain corrected LDL-C (LDL-C_{corr}).[28]

The combined CVD endpoint was defined as the occurrence of fatal or non-fatal coronary heart disease, stroke, or any coronary or carotid revascularisation procedures. In analysing on-treatment Lp(a), all CVD events that occurred after randomisation were considered because any change in Lp(a) under statin therapy is anticipated to occur within a short time period (sensitivity analyses omitted the initial period of follow-up).[12]

Associations of Lp(a) with CVD risk were estimated using a two-step approach, with estimates calculated within each study separately before pooling them across studies using multivariate random-effects meta-analysis.[29] Hazard ratios were calculated using Cox proportional hazard regression models which used time-on-study as a timescale, were stratified by trial arm, and compared the pre-specified Lp(a) groups <15 mg/dL, 15-<30 mg/dL, 30-<50 mg/dL, and ≥50 mg/dL. The assumption for the proportionality of hazards was tested using Schoenfeld residuals and was met. The analysis had four inter-related principal aims. First, to evaluate shapes of associations, pooled hazard ratios were calculated over Lp(a) groups and plotted against the pooled geometric mean of Lp(a) concentration within each category.[29] Second, to determine the extent of confounding, hazard ratios were progressively adjusted for age, sex, prior CVD, diabetes, smoking, systolic blood pressure, LDL-C_{corr}, and high-density-lipoprotein-cholesterol ("multivariable adjusted model"). Further adjustment for body-mass index and estimated glomerular filtration rate was employed in the subset of patients, in which these data were available. Third, to investigate whether the predictive value of follow-up Lp(a) differed between patients randomized to statin vs. placebo, interaction models by trial arm were fitted. Fourth, to investigate effect modification by individual-patient and study-level characteristics, formal tests of interaction and meta-regression analyses with these variables were performed. There was little variability within each trial of the proportion of patients with prior CVD and with a history of diabetes at baseline (e.g. secondary vs. primary CVD prevention trials, diabetes as inclusion or exclusion criterion) and hence effect modification by these characteristics was investigated at the study-level instead of at the patient-level. Between-trial heterogeneity was assessed with the I^2 statistic.[30] Analyses were performed using Stata

(version 14·1 MP) and involved two-sided statistical tests and 95% confidence intervals. Principal analyses used a significance level of P<0·05 and subgroup analyses a Bonferroni-corrected significance level of P<0·007 (for seven subgroups).

Role of funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. PW and ST had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Summary of available data

Data on 29069 patients from seven contributing trials were analysed (**Table 2**). At trial entry, mean age was 62 years (SD 8), 8064 were female (28%), 15252 had prior CVD (52%), 5177 had diabetes (18%), 4847 were current smokers (17%), mean systolic blood pressure was 137 mmHg (SD 18), and mean LDL-C_{corr} was 3·30 mmol/L (SD 0·67). Median concentration of Lp(a) at baseline was in low normal range of 11 mg/dL (interquartile range: 5-29). In cross-sectional analyses, baseline Lp(a) concentration was higher in females (+12% [3, 21]), lower in patients with diabetes (-17% [-24, -9]) and unrelated to smoking (+2% [-3, 8]). Furthermore, LDL-C_{corr}, $\log_e$ triglycerides, body-mass index, and systolic blood pressure were associated with a lower and HDL-C with a higher Lp(a) concentration (age-and sex-adjusted differences in Lp(a) per SD: -16% [-23, -8], -12% [-15, -9], -7% [-10, -5], -2% [-5, -0], and +7% [3, 11]). Baseline Lp(a) was not associated with age (-1% [-2, 1] per SD).

A total of 14536 patients were randomized to receive statin therapy (**Table 2**). Initiation of statin therapy reduced LDL-C_{corr} by -39% (95% confidence interval: -43, -35). The effect of statin on Lp(a) concentration was heterogeneous across trials; the pooled percentage change was -0·4% (-7, 7), with three trials showing a mean increase (range +2 to +15%) and four trials showing a mean decrease (range -1 to -13%) in Lp(a). The median concentration of Lp(a) on statin therapy was 11 mg/dL (interquartile range: 5-32). The age- and sex-adjusted correlation between baseline and follow-up $\log_e$ Lp(a) was comparable in the statin arm and the placebo arm (r=0.948 vs. 0.952).

Associations of baseline and on-statin Lp(a) with cardiovascular disease risk

During 95576 person-years at risk (median follow-up 3·0 years [interquartile range: 1·5-5·3]), a total of 5751 CVD events were recorded, of which 2603 occurred in the statin arm (**Table 2**). When patients were grouped by Lp(a) concentration into the categories <15 mg/dL, 15-<30 mg/dL, 30-<50 mg/dL, and ≥50 mg/dL, incidence rates for CVD (95% CI) per 1000 person-years were as follows: 55·3 (53·4-57·3), 56·3 (52·6-60·2), 66·7 (62·0-71·8), and 80·0 (75·3-84·9) for baseline Lp(a), and 49·0 (46·5-51·6), 46·4 (41·6-51·7), 56·2 (50·3-62·8), and 77·2 (71·1-83·8) for on-statin Lp(a).

In analyses adjusted for age and sex only, associations of baseline and on-statin Lp(a) values with the risk of CVD were of positive approximately linear shape, with a possible threshold effect in the group with Lp(a) values of 50 mg/dL or more (**Figure 1**). For baseline Lp(a), the hazard ratios compared to patients with Lp(a) values of <15 mg/dL were 1·04 (0·91, 1·18) with Lp(a) values 15-<30 mg/dL, 1·11 (1·00, 1·22) with Lp(a) values 30-<50 mg/dL, and 1·31 (1·08, 1·58) with Lp(a) values ≥50 mg/dL (**Table 3**). For on-statin Lp(a), corresponding hazard ratios were 0·94 (0·81, 1·10), 1·06 (0·94, 1·21), and 1·43 (1·15, 1·76).

Associations remained robust to additional adjustment for prior CVD, diabetes, smoking, systolic blood pressure, LDL-C_{corr}, and HDL-C concentration (**Figure 1** and **Table 3**). Corresponding hazard ratios were 1·04 (0·91, 1·20), 1·13 (1·02, 1·25), and 1·35 (1·11, 1·66) for baseline Lp(a) and 0·95 (0·82, 1·11), 1·08 (0·95, 1·23), and 1·42 (1·16, 1·74) for on-statin Lp(a). In a sensitivity analysis of patients with information on triglycerides, body-mass index, or estimated glomerular filtration rate, further adjustment for these parameters did not materially change the magnitude of association between Lp(a) measurements and CVD risk (**Supplementary Table 2**). Effect sizes comparable with those in the principal analysis were observed when further categorising the highest Lp(a) group into patients with levels 50-<75 mg/dL and ≥75 mg/dL (**Supplementary Table 3**) and in the on-statin analysis when omitting events that occurred in the initial period between randomization and on-statin measurement of Lp(a) (**Supplementary Table 4**). Trial-specific findings are provided in **Supplementary Table 5**.

Comparative predictive value of on-statin vs. on-placebo Lp(a)

Lp(a) concentration measured during follow-up was more strongly associated with CVD risk in the on-statin arm than in the on-placebo arm (**Figure 2**). In comparison of patients with Lp(a) ≥50 mg/dL with those having Lp(a) <50 mg/dL, the age- and sex-adjusted hazard ratios for CVD were 1·48 (1·23 to 1·78) for on-statin Lp(a) and 1·23 (1·04 to 1·45) for on-placebo Lp(a) (interaction P=0·010). The corresponding multivariable adjusted hazard ratios were 1·47 (1·25 to 1·73) and 1·26 (1·06 to 1·50) (interaction P=0·031). The median time from randomization to Lp(a) repeat was 1.0 years in both trial arms.

Associations according to patient-level and study-level characteristics

There was some heterogeneity between trials in hazard ratios for CVD, most pronounced in the group with a Lp(a) concentrations ≥50 mg/dL. For example, in this group, I^2 values of age- and sex-adjusted hazard ratios were 73% (43, 88) for baseline Lp(a) and 62% (13, 83) for on-statin Lp(a) (**Table 3**). Apart from stronger associations of on-statin Lp(a) with CVD risk at younger age (<60 years vs. 60-<70 years vs. ≥70 years; interaction P=0·008), hazard ratios did not vary significantly across clinically relevant subgroups, such as by sex, smoking, systolic blood pressure, lipid parameters, or body-mass index (**Figure 3**). Furthermore, the magnitude of association was independent of a study's proportion of patients with prior CVD or diabetes, the length of follow-up for clinical events, and the time between study baseline and follow-up on-statin Lp(a) measurement (**Supplementary Figure 2**). Contributing trials employed differing statin interventions, precluding a subgroup analysis by statin type or statin dosage.

Discussion

This well-powered meta-analysis of Lp(a) and CVD events reveals that patients with elevated Lp(a) on statin therapy, primarily with levels of >50 mg/dL, are at a significantly higher risk of CVD. The association with CVD risk was independent of conventional CVD risk factors, as also reflected in the very weak or null cross-sectional correlations of Lp(a) with these risk factors. Importantly, hazard ratios for high Lp(a) at baseline and under statin therapy were of similar magnitude, reflecting that statin therapy may not appreciably affect Lp(a)-mediated risk in patients with elevated Lp(a). Overall, these data suggest that patients with elevated Lp(a), representing ~25% of subjects with prior CVD or statin indication,[1] are at substantial residual risk even under statin therapy. In this patient population, therapies which specifically lower Lp(a) might mitigate Lp(a)-mediated risk. An appropriately designed CVD outcomes trial with

robust Lp(a)-lowering is therefore justified to test the hypothesis that lowering Lp(a) reduces CVD events, independent of statin treatment.

At baseline, Lp(a) levels were weakly associated with demographic and laboratory variables. The most significant but nevertheless weak correlations were inverse with diabetes mellitus and triglycerides. The observation of an inverse association of Lp(a) with incident diabetes has been made previously,[31] and is most pronounced at very low levels of Lp(a) (≤5 mg/dL), which are present in the 10th percentile of the global population.[1,2] It has not been determined if the findings are causal or if there is confounding by reverse causality.[32] Although the underlying mechanisms are not well understood, fasting and post-prandial insulin levels are inversely associated with Lp(a).[33] Lp(a) was weakly correlated with LDL-C, but this relationship became inversely associated after subtracting the estimated cholesterol content in Lp(a) from the laboratory measurement called "LDL-C".[28]

Prior studies evaluating the role of Lp(a) in predicting CVD in patients without CVD, using Lp(a) assays in the modern era that lack limitations of prior assays, have been almost uniformly positive.[7] However, studies in patients with prior CVD or on statin therapy have been mixed, or have suggested the effect is present primarily in patients with elevated LDL-C (reviewed in Tsimikas et al.[2]). A major limitation of all substudies reporting Lp(a) and outcomes has been power. All studies have enrolled patients with Lp(a) levels in the mid to low normal range (10-15 mg/dL, normal <30 mg/dL), as confirmed in the current meta-analysis, thus statistical power to evaluate risk in patients with highly elevated Lp(a) (i.e. >50 mg/dL) was limited. The current study is highly powered with 5751 total events and 2603 events in the statin arms, making it equivalent to, or larger than, most individual randomised controlled cardiovascular outcome trials in the modern era. In contrast to a previous analysis of individual-patient data by O'Donoghue et al,[34] our study afforded higher statistical power because it involved >10 times more CVD events, and hence was able to characterise associations with high Lp(a) concentrations more precisely. Moreover, the present analysis used clinically-relevant Lp(a) categories informed by guideline recommendations, as opposed to trial-specific quintiles.

The current meta-analysis is also highly representative of clinical care in patients treated with statins. First, these studies represent patients who were treated with moderate-high doses of the five major statins used clinically. Second, they reflect the variety of patients treated clinically, including primary prevention, high-risk primary prevention with elevated C-reactive protein or diabetes, secondary prevention, stable coronary artery disease, acute coronary syndromes, patients on dialysis and highly elevated LDL-C in the familial hypercholesterolemia range. Therefore, they broadly reflect patients with high residual risk despite statin treatment, potentially due to other, unmodified risk factors such as elevated Lp(a).

The risk thresholds chosen reflect clinical risk as suggested by epidemiologic and genetic studies. The reference cutoff of <15 mg/dL, reflects roughly the median global level of Lp(a).[35,36] Lp(a) <30 mg/dL represents the usual cutoff in US laboratories that is considered as normal level, and is based on data showing that risk of myocardial infarction starts to accrue at levels above 25-30 mg/dL.[7,37] The range of 30-50 mg/dL was chosen as this is the grey zone between what is considered pathophysiologically relevant and >50 mg/dL is based on what the European Atherosclerosis Society as considered elevated levels at highest risk based on the European population prevalence of 20%.

In this study, elevation of CVD risk became evident at baseline Lp(a) 30 to <50 mg/dL and was further pronounced when Lp(a) levels exceeded 50 mg/dL, including patients treated with statins. The hazard ratios for Lp(a) ≥50 mg/dL are consistent with recent PCSK9 inhibitor

studies in patients with background statin therapy.[38] Additional analyses at even higher Lp(a), i.e. ≥75 mg/dL were limited by low power due to small numbers of patients with Lp(a) levels in this range, but support a graded relationship of Lp(a) with cardiovascular risk. Outcome trials of Lp(a) lowering are likely to include patients with mean baseline Lp(a) substantially >50 mg/dL, therefore, extrapolation to event reduction with Lp(a) lowering from these data may be an underestimate.

A key observation of this study is that on-statin Lp(a) was more strongly associated with CVD risk than on-placebo Lp(a). A small angiographic study initially suggested that the risk of Lp(a) is attenuated when LDL-C is well controlled.[39] In contrast, the current study, utilising a far larger body of data, supports the opposite conclusion that risk is independently associated with both LDL-C and Lp(a). When LDL-attributable risk is reduced with statin treatment, Lp(a)-associated risk becomes an even stronger predictor of residual risk. This observation is particularly evident at Lp(a) levels exceeding 50 mg/dL. In support of our observation in this study, the trials FOURIER (European Atherosclerosis Society, May 2018) and ODYSSEY OUTCOMES (International Atherosclerosis Society, June 2018) have recently presented preliminary findings of their data, both showing that elevated baseline Lp(a) remains a risk factor even with on-treatment LDL-C <50 mg/dL in patients treated with statins and PCSK9 inhibitors. The findings raise the importance of determining whether there is a cardiovascular benefit of treatment to reduce Lp(a) when initial levels exceed this threshold, irrespective of concurrent treatment with statin. A second important observation is that all major subgroups of patients seemed to be at risk of elevated Lp(a), including those >70 years old, females, smokers, those with low and high LDL-C_{corr}, low HDL-C and all categories of body-mass index.

It is important to emphasize that the Lp(a) hypothesis remains to be tested. To do so requires a randomized trial that compares cardiovascular outcomes in patients treated with an agent that specifically lowers Lp(a) versus placebo. Such a trial may be possible with antisense oligonucleotide targeting *LPA* messenger RNA, thereby reducing plasma Lp(a) levels. Phase I and II trials with this agent have shown the potential to lower Lp(a) levels by over 90% without major effects on other classes of lipoproteins.[27,40]

One limitation of this study is that individual-patient data could not be obtained from several other statin trials that reported Lp(a) levels and outcomes. It is possible that inclusion of other data would have modified the observed effect sizes. Secondly, the relationship of Lp(a) to residual cardiovascular risk under treatment with non-statin lipid-modifying agents (e.g., ezetimibe, PCSK9 inhibitors) remains undetermined. Third, the Lp(a) assays were heterogeneous and most were in Lp(a) mass rather than in Lp(a) molar concentration and the timepoints at which they were measured in each trial were not uniform. Therefore, the assays not reported in mg/dL had to be mathematically converted to mg/dL, which may have introduced imprecision into the Lp(a) measurement. A recent NHLBI Working Group on Lp(a) recommended global standardization of Lp(a) assays to address this limitation.[2] Fourth, we cannot rule out that index event bias may have attenuated effect sizes in secondary prevention trials, although the scope of this bias was reduced by employment of multivariable adjustment. Fifth, our analysis identified moderate to high between-study heterogeneity, which could not be explained by baseline disease status (i.e. prior CVD or prior diabetes) nor by differing lengths of follow-up periods. Finally, the data for the change in Lp(a) post statin therapy was heterogeneous across studies, with both increases and decreases, but no net change. Due to different assays used in each of the trials, and the need for conversion of all data to mg/dL, and the higher precision required to show intra-individual changes, these data should be considered

hypothesis generating. A more robust test of this particular hypothesis should ideally be performed using the same assay.

In conclusion, this meta-analysis demonstrates an approximately linear relationship of cardiovascular risk to levels of Lp(a), evident at Lp(a) levels 30-50 mg/dL, pronounced at levels ≥50 mg/dL, and persisting despite statin treatment. These data provide a rationale for evaluating drugs that can specifically lower Lp(a) and might have the potential to reduce residual cardiovascular risk independent of statin treatment.

Contributors

PW and ST wrote the analysis plan, collected and harmonized the data, and wrote the first draft of the manuscript. PW and ST had access to all the raw data and PW performed the statistical analysis. PMR, PJN, JS, AMT, TRP, GGS, AGO, HMC, FK, CD, CW, and SM have collected patient data in statin trials and provided cleaned data to the coordinating centre. All authors provided contributed to writing the final report and approved the version to be submitted to the journal.

Declaration of interests

PW reports consultancy fees from Novartis Pharmaceuticals during the conduct of the study, and travel expenses from Bayer, Daiichi Sankyo, and Sanofi-Aventis outside the submitted work. PMR reports grants from AstraZeneca during the conduct of the study, grants from Novartis, Kowa, Pfizer, and NHLBI outside of the submitted work, and personal fees from Novartis, Sanofi outside of the submitted work. AMT reports personal fees from Amgen, personal fees and non-financial support from Bayer, personal fees from Merck, personal fees from Pfizer outside the submitted work. TRP reports personal fees from Amgen and from Sanofi Regeneron outside the submitted work. GGS reports grants from Pfizer during the conduct of the study, and grants from Cerenis, Roche, Sanofi, and The Medicines Company outside the submitted work. HMC reports grants from Astra Zeneca, Boehringer Ingelheim, being a shareholder at Bayer, grants, personal fees, non-financial support and travel expenses from Eli Lilly & company, institutional fees from Novartis Pharmaceuticals, grants, non-financial support and travel expenses from Regeneron, grants and speaker fees from Pfizer Inc, grants from and being a shareholder at Roche Pharmaceuticals, grants and travel expenses from Sanofi Aventis, honorarium and speakers bureau from Sanofi, grants and travel expenses from Novo Nordisk during the conduct of the study. CW reports personal fees from Boehringer Ingelheim and from Sanofi-Genzyme outside the submitted work. SM reports institutional support from NIH grants R01 HL117861, R01 HL134811, K24 HL136852, non-financial support from Quest Diagnostics for measuring Lp(a) in JUPITER, and personal fees from Quest Diagnostics and institutional research grant from Atherotech Diagnostics outside the submitted work. The JUPITER trial was funded by AstraZeneca. AL is an employee of Novartis Pharma AG. ST has research support from the Fondation Leducq and NIH grants R01-HL119828, R01-HL078610, R01 HL106579, R01 HL128550, R01 HL136098, P01 HL136275 and R35 HL135737, currently has a dual appointment at the University of California San Diego and Ionis Pharmaceuticals and is a co-inventor and receive royalties from patents owned by the University of California San Diego on oxidation-specific antibodies and is a co-Founder of Oxitope, Inc. The other authors have nothing to disclose.

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References

1 Tsimikas S. A Test in Context: Lipoprotein(a): Diagnosis, Prognosis, Controversies, and Emerging Therapies. *J Am Coll Cardiol* 2017; **69:** 692–711.

2 Tsimikas S, Fazio S, Ferdinand KC, et al. NHLBI Working Group Recommendations to Reduce Lipoprotein(a)-Mediated Risk of Cardiovascular Disease and Aortic Stenosis. *J Am Coll Cardiol* 2018; **71:** 177–92.

3 van der Valk FM, Bekkering S, Kroon J, et al. Oxidized Phospholipids on Lipoprotein(a) Elicit Arterial Wall Inflammation and an Inflammatory Monocyte Response in Humans. *Circulation* 2016; **134:** 611–24.

4 Wiesner P, Tafelmeier M, Chittka D, et al. MCP-1 binds to oxidized LDL and is carried by lipoprotein(a) in human plasma. *J Lipid Res* 2013; **54:** 1877–83.

5 Leibundgut G, Scipione C, Yin H, et al. Determinants of binding of oxidized phospholipids on apolipoprotein (a) and lipoprotein (a). *J. Lipid Res.* 2013; **54:** 2815–30.

6 Boffa MB, Koschinsky ML. Lipoprotein (a): truly a direct prothrombotic factor in cardiovascular disease? *J Lipid Res* 2016; **57:** 745–57.

7 Emerging Risk Factors Collaboration. Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality. *JAMA* 2009; **302:** 412–23.

8 Clarke R, Peden JF, Hopewell JC, et al. Genetic variants associated with Lp(a) lipoprotein level and coronary disease. *N Engl J Med* 2009; **361:** 2518–28.

9 Kamstrup PR, Tybjaerg-Hansen A, Steffensen R, Nordestgaard BG. Genetically elevated lipoprotein(a) and increased risk of myocardial infarction. *JAMA* 2009; **301:** 2331–39.

10 Schmidt K, Noureen A, Kronenberg F, Utermann G. Structure, function, and genetics of lipoprotein (a). *J Lipid Res* 2016; **57:** 1339–59.

11 Thanassoulis G, Campbell CY, Owens DS, et al. Genetic associations with valvular calcification and aortic stenosis. *N Engl J Med* 2013; **368:** 503–12.

12 Khera AV, Everett BM, Caulfield MP, et al. Lipoprotein(a) concentrations, rosuvastatin therapy, and residual vascular risk: an analysis from the JUPITER Trial (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin). *Circulation* 2014; **129:** 635–42.

13 Albers JJ, Slee A, O'Brien KD, et al. Relationship of apolipoproteins A-1 and B, and lipoprotein(a) to cardiovascular outcomes. The AIM-HIGH trial (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglyceride and Impact on Global Health Outcomes). *J Am Coll Cardiol* 2013; **62:** 1575–79.

14 O'Donoghue ML, Morrow DA, Tsimikas S, et al. Lipoprotein(a) for risk assessment in patients with established coronary artery disease. *J Am Coll Cardiol* 2014; **63:** 520–27.

15 Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA* 1998; **279:** 1615–22.

16 Colhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* 2004; **364:** 685–96.
17 Ridker PM, Danielson E, Fonseca FAH, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med* 2008; **359:** 2195–207.
18 Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med* 1998; **339:** 1349–57.
19 Schwartz GG, Olsson AG, Ezekowitz MD, et al. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. *JAMA* 2001; **285:** 1711–18.
20 Scandinavian Simvastatin Survival Study. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994; **344:** 1383–89.
21 Krane V, Schmidt K-R, Gutjahr-Lengsfeld LJ, et al. Long-term effects following 4 years of randomized treatment with atorvastatin in patients with type 2 diabetes mellitus on hemodialysis. *Kidney Int* 2016; **89:** 1380–87.
22 Deshmukh HA, Colhoun HM, Johnson T, et al. Genome-wide association study of genetic determinants of LDL-c response to atorvastatin therapy: importance of Lp(a). *J Lipid Res* 2012; **53:** 1000–11.
23 Kollerits B, Drechsler C, Krane V, et al. Lipoprotein(a) concentrations, apolipoprotein(a) isoforms and clinical endpoints in haemodialysis patients with type 2 diabetes mellitus: results from the 4D Study. *Nephrol Dial Transplant* 2016; **31:** 1901–08.
24 Nestel PJ, Barnes EH, Tonkin AM, et al. Plasma lipoprotein(a) concentration predicts future coronary and cardiovascular events in patients with stable coronary heart disease. *Arterioscler Thromb Vasc Biol* 2013; **33:** 2902–08.
25 Tsimikas S, Witztum JL, Miller ER, et al. High-dose atorvastatin reduces total plasma levels of oxidized phospholipids and immune complexes present on apolipoprotein B-100 in patients with acute coronary syndromes in the MIRACL trial. *Circulation* 2004; **110:** 1406–12.
26 Berg K, Dahlén G, Christophersen B, Cook T, Kjekshus J, Pedersen T. Lp(a) lipoprotein level predicts survival and major coronary events in the Scandinavian Simvastatin Survival Study. *Clin Genet* 1997; **52:** 254–61.
27 Tsimikas S, Viney NJ, Hughes SG, et al. Antisense therapy targeting apolipoprotein(a): a randomised, double-blind, placebo-controlled phase 1 study. *Lancet* 2015; **386:** 1472–83.
28 Yeang C, Witztum JL, Tsimikas S. 'LDL-C' = LDL-C + Lp(a)-C: implications of achieved ultra-low LDL-C levels in the proprotein convertase subtilisin/kexin type 9 era of potent LDL-C lowering. *Curr Opin Lipidol* 2015; **26:** 169–78.
29 Thompson S, Kaptoge S, White I, et al. Statistical methods for the time-to-event analysis of individual participant data from multiple epidemiological studies. *Int. J. Epidemiol.* 2010; **39:** 1345–59.
30 Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; **21:** 1539–58.
31 Paige E, Masconi KL, Tsimikas S, et al. Lipoprotein(a) and incident type-2 diabetes: results from the prospective Bruneck study and a meta-analysis of published literature. *Cardiovasc Diabetol* 2017; **16:** 38.
32 Tsimikas S. In Search of a Physiological Function of Lp(a): Causality of Elevated Lp(a) levels and Reduced Incidence of Type-2 Diabetes Mellitus. *J Lipid Res* 2018.

33 Rainwater DL, Haffner SM. Insulin and 2-hour glucose levels are inversely related to Lp(a) concentrations controlled for LPA genotype. *Arterioscler Thromb Vasc Biol* 1998; **18:** 1335–41.
34 O'Donoghue ML, Morrow DA, Tsimikas S, et al. Lipoprotein(a) for risk assessment in patients with established coronary artery disease. *Journal of the American College of Cardiology* 2014; **63:** 520–27.
35 Varvel S, McConnell JP, Tsimikas S. Prevalence of Elevated Lp(a) Mass Levels and Patient Thresholds in 532 359 Patients in the United States. *Arterioscler Thromb Vasc Biol* 2016; **36:** 2239–45.
36 Nordestgaard BG, Chapman MJ, Ray K, et al. Lipoprotein(a) as a cardiovascular risk factor: current status. *Eur Heart J* 2010; **31:** 2844–53.
37 Kostner GM, Avogaro P, Cazzolato G, Marth E, Bittolo-Bon G, Qunici GB. Lipoprotein Lp(a) and the risk for myocardial infarction. *Atherosclerosis* 1981; **38:** 51–61.
38 Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. *N Engl J Med* 2017; **376:** 1713–22.
39 Maher VM, Brown BG, Marcovina SM, Hillger LA, Zhao XQ, Albers JJ. Effects of lowering elevated LDL cholesterol on the cardiovascular risk of lipoprotein(a). *JAMA* 1995; **274:** 1771–74.
40 Viney NJ, van Capelleveen JC, Geary RS, et al. Antisense oligonucleotides targeting apolipoprotein(a) in people with raised lipoprotein(a): two randomised, double-blind, placebo-controlled, dose-ranging trials. *Lancet* 2016; **388:** 2239–53.

Research in context

Evidence before this study: Lp(a) has been associated with increased risk of incident cardiovascular disease in primary care populations, but its role in predicting cardiovascular events in high-risk patients treated with statins is unclear. We searched PubMed for relevant clinical trials published up to July 9, 2018, using the search terms "Lipoprotein(a)" or "Lp(a)", plus “statin” and "cardiovascular diseases"[MeSH]. Our review identified seven statin trials (4D, 4S, FLARE, JUPITER, LIPID, MIRACL, and TNT), which reported on the association of Lp(a) with cardiovascular risk. The interpretation of the available evidence is complicated by inconsistent findings across trials (positive vs. null associations), limited statistical power of single trials, limited availability of follow-up Lp(a) measurements, and differing definitions of Lp(a) categories across trials.

Added value of this study: We obtained patient-level data in seven placebo-controlled statin trials encompassing 29069 patients and analysed the relationship of baseline and on-treatment Lp(a) to risk of major adverse cardiovascular events. Elevated Lp(a) of 50 mg/dL or higher, at baseline or on-treatment, was associated with an increased hazard ratio of cardiovascular events independent of other cardiovascular risk factors and evident on treatment with either statin or placebo.

Implications of all the available evidence: These data suggest that residual risk is present in patients with elevated Lp(a) that is not addressed by statins and supports the rationale for outcomes trials to test specific therapies to lower Lp(a).

Tables

Table 1 – Design features of contributing trials.

Cohort	Years of baseline	Target population	Lipid entry criteria, mmol/L	Comparator to placebo	CVD outcome definition				
					MI	Stable angina	Stroke	Revascularisation	Other
AFCAPS[15]	1990-1993	Primary prevention	TC 4·65-6·82, LDL-C 3·36-4·91, TG ≤4·52, HDL-C ≤1·16♂ and ≤1·22♀	Lovastatin 20mg	●	●	●	●	●*
CARDS[22]	1997-2001	Type 2 diabetes	LDL-C ≤4·14, TG ≤6·78	Atorvastatin 10mg	●	○	●	●	○
4D[23]	1998-2002	Type 2 diabetes + hemodialysis	LDL-C 2·07-4·92, TG ≤11·3	Atorvastatin 20mg	●	○	●	●	○
JUPITER[12]	2003-2006	Primary prevention with C-reactive protein >2mg/dL	LDL-C <3·4, TG <5·65	Rosuvastatin 20mg	●	○	●	●	●†
LIPID[24]	1990-1992	Prior myocardial infarction or unstable angina	TC 4·0-7·0, TG <5·0	Pravastatin 40mg	●	○	●	●	○
MIRACL[25]	1997-1999	Acute coronary syndrome	TC <7·0	Atorvastatin 80mg	●	○	●	●	○
4S[26]	1989-1990	Prior myocardial infarction or angina	TC 5·5-8·0, TG ≤2·5	Simvastatin 20mg	●	○	○	●	○

AFCAPS=Air Force/Texas Coronary Atherosclerosis Prevention Study. CARDS=Collaborative Atorvastatin Diabetes Study. CVD=cardiovascular disease. 4D=Die Deutsche Diabetes-Dialyse-Studie. HDL-C=high-density lipoprotein cholesterol. JUPITER=Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin. LDL-C=low-density lipoprotein cholesterol. LIPID=Long-Term Intervention with Pravastatin in Ischaemic Disease. MI=myocardial infarction. MIRACL=Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering. 4S=Scandinavian Simvastatin Survival Study. TC=total cholesterol. TG=triglycerides. *Transient ischemic attack, peripheral vascular disease, sudden death, and deaths from other cardiovascular causes. †Deaths from other cardiovascular causes.

Table 2 – Patient characteristics.

	AFCAPS	CARDS	4D	JUPITER	LIPID	MIRACL	4S	Total
Baseline								
No. of patients	1005	2470	1249	9612	7863	2431	4439	29069
Lp(a), mg/dL, median (IQR)	7 (3-17)	9 (5-22)	12 (5-42)	11 (5-23)	14 (7-44)	10 (5-29)	10 (4-28)	11 (5-29)
<15 mg/dL	733 (73)	1658 (67)	709 (57)	5896 (61)	4118 (52)	1481 (61)	2654 (60)	17249 (59)
15-<30 mg/dL	134 (13)	310 (13)	129 (10)	1867 (19)	1147 (15)	362 (15)	781 (18)	4730 (16)
30-<50 mg/dL	84 (8)	212 (9)	140 (11)	851 (9)	877 (11)	223 (9)	714 (16)	3101 (11)
≥50 mg/dL	54 (5)	290 (12)	271 (22)	998 (10)	1721 (22)	365 (15)	290 (7)	3989 (14)
Age, yrs	59 (7)	62 (8)	66 (8)	66 (8)	61 (8)	65 (11)	59 (7)	62 (8)
Female sex	173 (17)	779 (32)	576 (46)	3556 (37)	1333 (17)	820 (34)	827 (19)	8064 (28)
Prior CVD	0 (0)	6 (0)	513 (41)	0 (0)	7863 (100)	2431 (100)	4439 (100)	15252 (52)
Diabetes	32 (3)	2470 (100)	1249 (100)	0 (0)	676 (9)	548 (23)	202 (5)	5177 (18)
Current smoking	130 (13)	551 (22)	108 (9)	1492 (16)	735 (9)	693 (29)	1138 (26)	4847 (17)
SBP, mmHg	136 (17)	144 (16)	146 (22)	136 (17)	134 (19)	128 (20)	139 (20)	137 (18)
LDL-C_{corr}, mmol/L	–	2·75 (0·78)	3·00 (0·86)	2·57 (0·49)	3·68 (0·74)	3·04 (0·86)	4·74 (0·66)	3·30 (0·67)
HDL-C, mmol/L	–	1·64 (0·50)	0·94 (0·34)	1·35 (0·40)	0·96 (0·24)	1·20 (0·31)	1·19 (0·30)	1·21 (0·35)
BMI, kg/m²	26 (3)	29 (4)	28 (5)	29 (6)	–	28 (5)	26 (3)	28 (5)
eGFR, mL/min	–	–	–	75 (17)	71 (17)	–	–	73 (17)
Apo-B, g/L	–	1·16 (0·24)	1·10 (0·30)	1·08 (0·21)	1·33 (0·25)	–	1·16 (0·18)	1·17 (0·23)
On-statin								
No. of patients	504	1255	616	4802	3941	1200	2218	14536
Time to Lp(a) repeat, yrs, median	1·0	2·5	0·5	1·0	1·0	0·2	2·5	1·0
Lp(a), mg/dL, median (IQR)	7 (3-19)	8 (4-22)	11 (5-40)	11 (4-25)	13 (6-43)	11 (5-33)	11 (4-33)	11 (5-32)
<15 mg/dL	366 (73)	864 (69)	351 (57)	2912 (61)	2106 (53)	707 (59)	1268 (57)	8574 (59)
15-<30 mg/dL	59 (12)	134 (11)	60 (10)	868 (18)	548 (14)	175 (15)	321 (15)	2165 (15)
30-<50 mg/dL	43 (9)	103 (8)	73 (12)	417 (9)	439 (11)	96 (8)	375 (17)	1546 (11)
≥50 mg/dL	36 (7)	154 (12)	132 (21)	605 (13)	848 (22)	222 (19)	254 (12)	2251 (15)
% change vs. baseline (95% CI)	-1% (-6, 4)	-13% (-15, -10)	-6% (-9, -3)	2% (1, 3)	-7% (-8, -5)	9% (6, 12)	15% (13, 17)	-0·4% (-7, 7)
LDL-C_{corr}, mmol/L	–	1·68 (0·58)	1·73 (0·78)	1·43 (0·70)	2·57 (0·71)	1·56 (0·77)	2·97 (0·70)	1·99 (0·70)
% change vs. baseline (95% CI)	–	-37% (-38, -36)	-41% (-43, -39)	-43% (-44, -42)	-29% (-30, -29)	-47% (-49, -46)	-37% (-37, -36)	-39% (-43, -35)
CVD incidence								
Follow-up, yrs, median (IQR)	5·6 (4·8-6·2)	4·1 (3·1-4·8)	2·4 (1·4-3·7)	2·0 (1·5-2·4)	5·4 (3·1-6·0)	0·3 (0·3-0·3)	5·3 (3·9-5·5)	3·0 (1·5-5·3)
No. of events, overall	68	170	338	234	3040	537	1364	5751
No. of events, statin arm	31	71	166	81	1428	258	568	2603

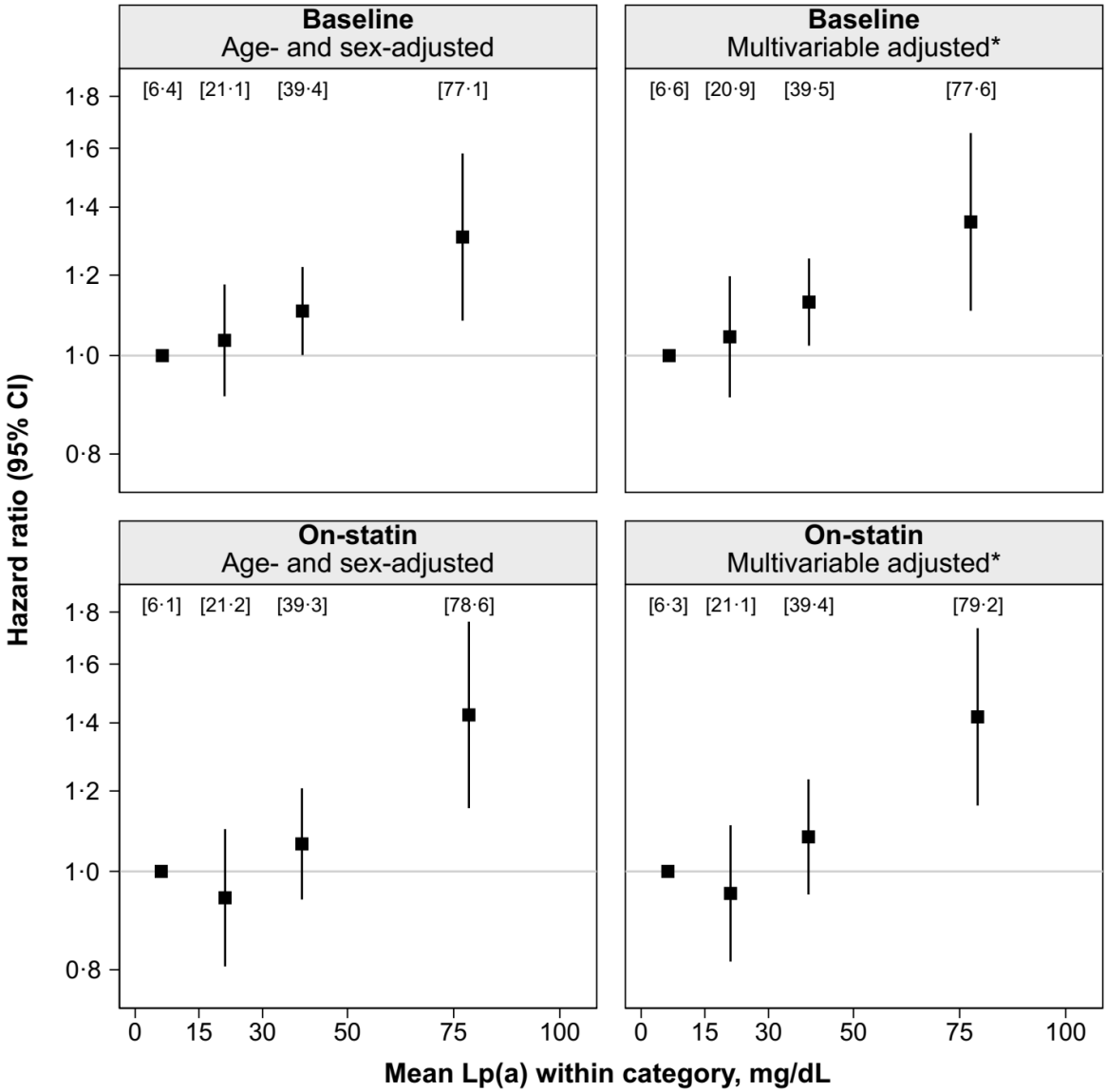
Mean (SD) or n (%), unless stated otherwise. Percentages may not sum up to 100% due to rounding. For full trial names, refer to footnote of Table 1. Total means (standard deviations) and % changes (95% confidence intervals) were calculated by pooling study-specific estimates with random-effects meta-analysis. Apo-B=apolipoprotein B. BMI=body-mass index. CVD=cardiovascular disease. eGFR=estimated glomerular filtration rate. HDL-C=high-density lipoprotein cholesterol. IQR=interquartile-range. LDL-C_{corr}=low-density lipoprotein cholesterol corrected for Lp(a)-cholesterol. SBP=systolic blood pressure.

Table 3 – Associations of baseline and on-statin Lp(a) with incident cardiovascular disease according to different levels of adjustment.

Lp(a) measurement / adjustment	Lp(a) 15-<30 mg/dL			Lp(a) 30-<50 mg/dL			Lp(a) ≥50 mg/dL		
	HR (95% CI)*	P value	I^2 (95% CI)	HR (95% CI)*	P value	I^2 (95% CI)	HR (95% CI)*	P value	I^2 (95% CI)
Baseline Lp(a)									
Basic adjustment: 7 trials – 29069 patients – 5751 events									
Age- and sex-adjusted	1·04 (0·91, 1·18)	0·59	43% (0, 76)	1·11 (1·00, 1·22)	0·047	0% (0, 71)	1·31 (1·08, 1·58)	0·005	73% (43, 88)
Progressive adjustment: 6 trials – 27764 patients – 5649 events									
Age- and sex-adjusted	1·03 (0·90, 1·18)	0·64	54% (0, 81)	1·10 (1·00, 1·22)	0·053	0% (0, 75)	1·30 (1·06, 1·59)	0·010	78% (52, 90)
Plus prior CVD	1·04 (0·90, 1·19)	0·61	53% (0, 81)	1·10 (1·00, 1·22)	0·049	0% (0, 75)	1·31 (1·07, 1·60)	0·009	78% (52, 90)
Plus diabetes	1·04 (0·91, 1·19)	0·60	52% (0, 81)	1·11 (1·01, 1·23)	0·036	0% (0, 75)	1·32 (1·08, 1·61)	0·007	78% (51, 90)
Plus smoking	1·03 (0·91, 1·18)	0·61	50% (0, 80)	1·11 (1·01, 1·22)	0·034	0% (0, 75)	1·31 (1·08, 1·59)	0·007	77% (48, 90)
Plus SBP	1·03 (0·90, 1·18)	0·64	53% (0, 81)	1·11 (1·01, 1·22)	0·031	0% (0, 75)	1·31 (1·07, 1·59)	0·008	77% (49, 90)
Plus LDL-C_{corr}	1·04 (0·90, 1·19)	0·61	55% (0, 82)	1·12 (1·02, 1·24)	0·019	0% (0, 75)	1·34 (1·09, 1·65)	0·005	78% (53, 90)
Plus HDL-C	1·04 (0·91, 1·20)	0·54	54% (0, 82)	1·13 (1·02, 1·25)	0·016	0% (0, 75)	1·35 (1·11, 1·66)	0·003	77% (49, 90)
On-statin Lp(a)									
Basic adjustment: 7 trials – 14536 patients – 2603 events									
Age- and sex-adjusted	0·94 (0·81, 1·10)	0·45	18% (0, 62)	1·06 (0·94, 1·21)	0·33	0% (0, 71)	1·43 (1·15, 1·76)	0·001	62% (13, 83)
Progressive adjustment: 6 trials – 13883 patients – 2561 events									
Age- and sex-adjusted	0·93 (0·79, 1·09)	0·37	18% (0, 63)	1·06 (0·93, 1·21)	0·35	0% (0, 75)	1·39 (1·12, 1·72)	0·002	64% (13, 85)
Plus prior CVD	0·93 (0·79, 1·09)	0·37	18% (0, 63)	1·06 (0·93, 1·21)	0·36	0% (0, 75)	1·39 (1·12, 1·72)	0·002	64% (13, 85)
Plus diabetes	0·94 (0·80, 1·10)	0·43	17% (0, 62)	1·07 (0·94, 1·22)	0·31	0% (0, 75)	1·39 (1·13, 1·71)	0·002	62% (7, 84)
Plus smoking	0·94 (0·81, 1·09)	0·42	8% (0, 77)	1·07 (0·94, 1·22)	0·30	0% (0, 75)	1·39 (1·13, 1·71)	0·002	62% (8, 84)
Plus SBP	0·94 (0·81, 1·09)	0·41	9% (0, 77)	1·07 (0·94, 1·22)	0·30	0% (0, 75)	1·39 (1·13, 1·71)	0·002	61% (6, 84)
Plus LDL-C_{corr}	0·94 (0·81, 1·10)	0·47	13% (0, 78)	1·08 (0·95, 1·23)	0·26	0% (0, 75)	1·41 (1·15, 1·73)	0·001	61% (3, 84)
Plus HDL-C	0·95 (0·82, 1·11)	0·53	13% (0, 78)	1·08 (0·95, 1·23)	0·24	0% (0, 75)	1·42 (1·16, 1·74)	0·001	58% (0, 83)

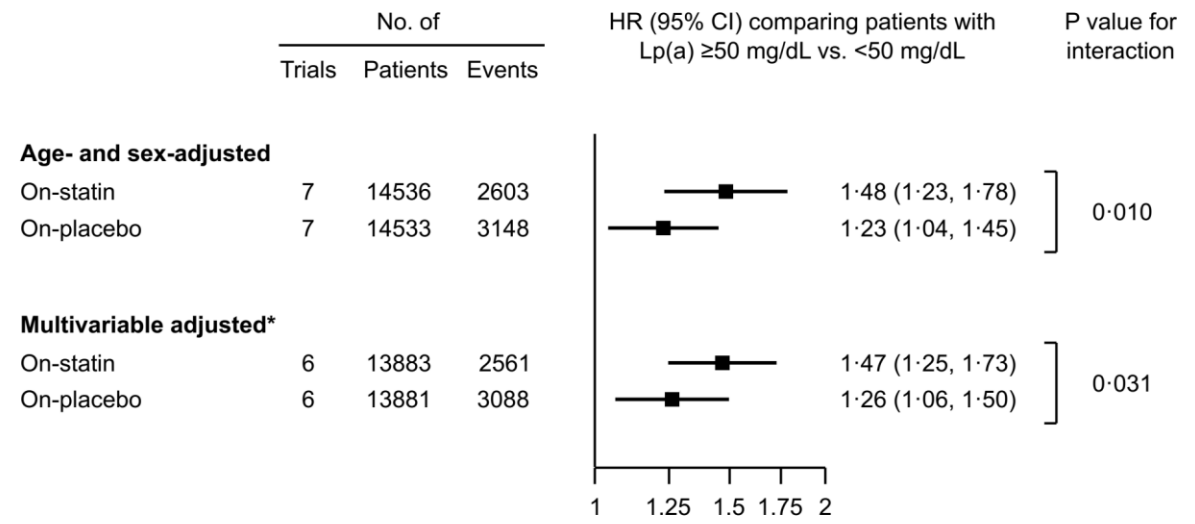
CI=confidence interval. CVD=cardiovascular disease. HDL-C=high-density lipoprotein cholesterol. HR=hazard ratio. LDL-C_{corr}=low-density-lipoprotein cholesterol corrected for Lp(a)-cholesterol. SBP=systolic blood pressure. *The group of patients with Lp(a) values <15 mg/dl served as reference group.

Figure 1 – Shapes of associations of baseline and on-statin Lp(a) with incident cardiovascular disease.



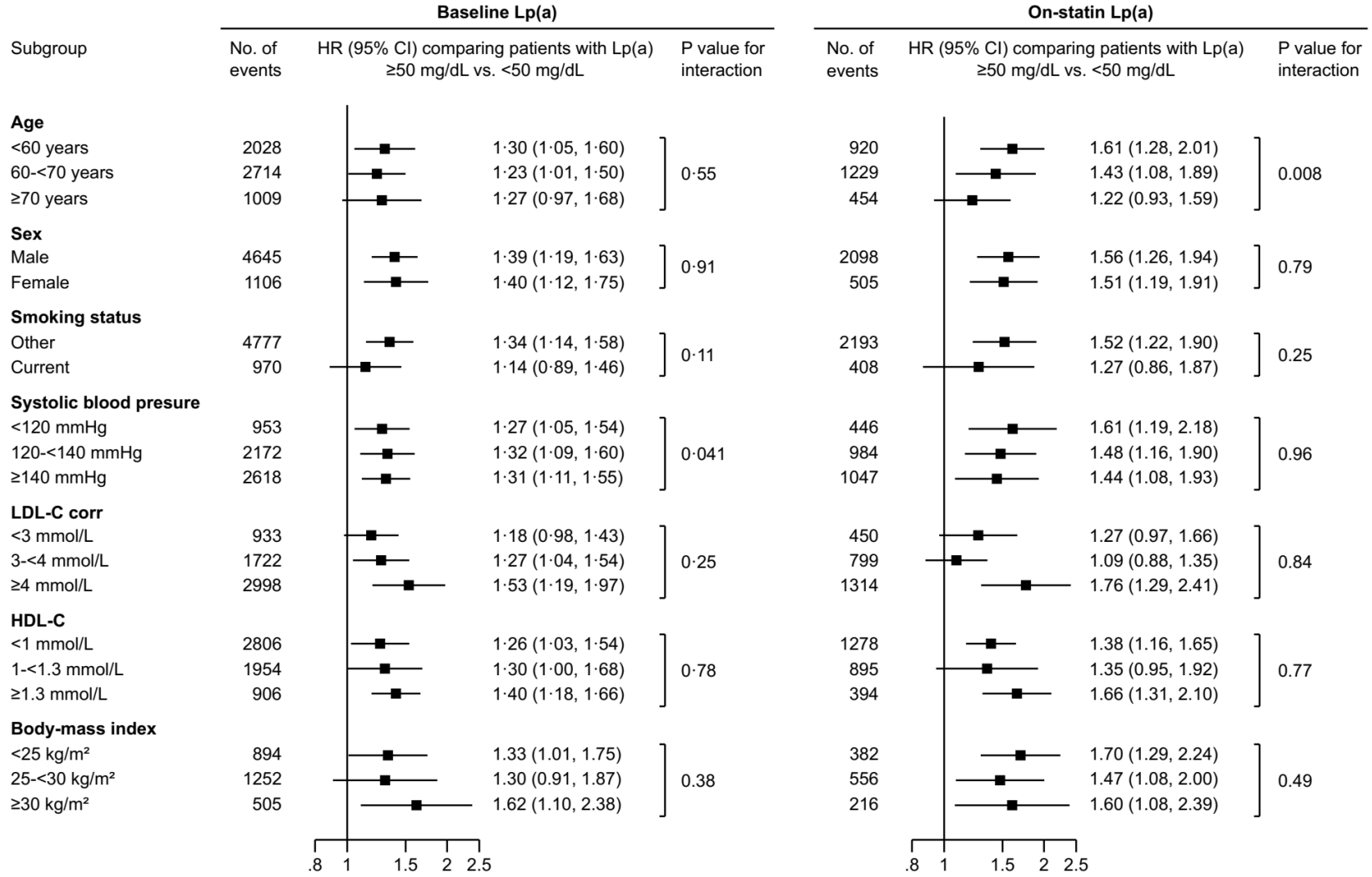
Categories of Lp(a) were defined as <15 mg/dL, 15-<30 mg/dL, 30-<50 mg/dL, and ≥50 mg/dL. Numbers in squared brackets are means of Lp(a) values within each category. The group with the lowest Lp(a) concentration served as reference. The analysis of baseline Lp(a) involved 29069 patients (5751 events) in the age- and sex-adjusted model and 27764 patients (5649 events) in the multivariable adjusted model. Corresponding numbers for the on-statin analysis were 14536 patients (2603 events) and 13883 patients (2561 events), respectively. *The multivariable model was adjusted for age, sex, prior cardiovascular disease, diabetes, smoking, systolic blood pressure, low-density-lipoprotein cholesterol corrected for Lp(a)-cholesterol, and high-density lipoprotein cholesterol.

Figure 2 – Comparative predictive value of on-statin vs. on-placebo Lp(a) for incident cardiovascular disease.



*The multivariable model was adjusted for age, sex, prior cardiovascular disease, diabetes, smoking, systolic blood pressure, low-density-lipoprotein cholesterol corrected for Lp(a)-cholesterol, and high-density lipoprotein cholesterol.

Figure 3 – Associations of baseline and on-statin Lp(a) with incident cardiovascular disease by individual patient characteristics.



CI=confidence interval. HDL-C=high-density lipoprotein cholesterol. HR=hazard ratio. LDL-C_{corr}=low-density-lipoprotein cholesterol corrected for Lp(a)-cholesterol.

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Baseline and on-statin treatment lipoprotein(a) levels predict cardiovascular events: An individual-patient-data meta-analysis of statin outcome trials

Peter Willeit, Paul M. Ridker, Paul J. Nestel, John Simes, Andrew M. Tonkin, Terje R. Pedersen, Gregory G. Schwartz, Anders G. Olsson, Helen M. Colhoun, Florian Kronenberg, Christiane Drechsler, Christoph Wanner, Samia Mora, Anastasia Lesogor, Sotirios Tsimikas

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Supplementary Table 1 – Comparison of baseline characteristics of patients with or without Lp(a) measurements.

Trial	No. of patients	Statin arm, %	Female sex, %	Prior CVD, %	Diabetes, %	Smoking, %	Age, years, mean (SD)	SBP, mmHg, mean (SD)	LDL-C, mmol/L, mean (SD)	HDL-C, mmol/L, mean (SD)	BMI, kg/m^2, mean (SD)
AFCAPS											
Lp(a) available	1005	50%	17%	0%	3%	13%	59 (7)	136 (17)	–	–	26 (3)
Lp(a) unavailable	5600	50%	15%	0%	4%	12%	58 (7)	139 (17)	–	–	27 (3)
Odds ratio or % difference		*1·01*	***1·21****	*NA*	*0·84*	*1·06*	***+1·3%***	***-2·3%****	–	–	***-0·9%****
CARDS											
Lp(a) available	2470	51%	32%	0·2%	100%	22%	62 (8)	144 (16)	2·91 (0·78)	1·64 (0·50)	29 (4)
Lp(a) unavailable	368	47%	35%	0%	99%	22%	62 (9)	144 (17)	2·84 (0·83)	1·64 (0·49)	29 (4)
Odds ratio or % difference		*1·16*	*0·84*	*NA*	*NA*	*1·03*	*-0·4%*	*-0·2%*	*+2·5%*	*0·0%*	*0·0%*
4D											
Lp(a) available	1249	49%	46%	41%	100%	9%	66 (8)	146 (22)	3·25 (0·77)	0·94 (0·34)	28 (5)
Lp(a) unavailable	6	50%	33%	17%	100%	0%	69 (7)	139 (24)	3·18 (0·69)	0·80 (0·27)	28 (3)
Odds ratio or % difference		*0·97*	*1·71*	*3·49*	*NA*	*NA*	*-4·1%*	*+4·7%*	*+2·4%*	*+16·9%*	*-2·5%*
JUPITER											
Lp(a) available	9612	50%	37%	0%	0%	15%	66 (8)	136 (16)	2·72 (0·48)	1·35 (0·40)	29 (6)
Lp(a) unavailable	8190	50%	40%	0%	0%	16%	66 (8)	136 (17)	2·69 (0·49)	1·30 (0·39)	29 (6)
Odds ratio or % difference		*1·00*	***0·89****	*NA*	*NA*	*0·95*	***-0·8%****	*+0·1%*	***+1·1%****	***+3·8%****	*0·0%*
LIPID											
Lp(a) available	7863	50%	17%	100%	9%	9%	61 (8)	134 (19)	3·89 (0·75)	0·96 (0·24)	–
Lp(a) unavailable	1151	50%	16%	100%	9%	12%	60 (8)	133 (18)	3·83 (0·73)	0·95 (0·23)	–
Odds ratio or % difference		*1·00*	*1·08*	*NA*	*0·93*	***0·78****	***+2·0%****	*+0·8%*	***+1·6%****	*+1·1%*	–
MIRACL											
Lp(a) available	2431	49%	34%	100%	23%	29%	65 (11)	128 (20)	3·21 (0·85)	1·20 (0·31)	28 (5)
Lp(a) unavailable	655	52%	39%	100%	26%	25%	67 (13)	128 (20)	3·17 (0·89)	1·20 (0·35)	27 (6)
Odds ratio or % difference		*0·91*	***0·80****	*NA*	*0·85*	***1·24****	***-3·4%****	*-0·1%*	*+1·4%*	*+0·5%*	***+2·0%****
4S											
Lp(a) available	4439	50%	19%	100%	5%	26%	59 (7)	139 (20)	4·88 (0·66)	1·19 (0·30)	26 (3)
Lp(a) unavailable	5	60%	0%	100%	0%	0%	61 (7)	137 (10)	5·10 (0·57)	1·25 (0·07)	28 (4)
Odds ratio or % difference		*0·67*	*NA*	*NA*	*NA*	*NA*	*-4·5%*	*+1·3%*	*-4·3%*	*-5·2%*	*-8·6%*

BMI=body-mass index. CVD=cardiovascular disease. HDL-C=high-density lipoprotein cholesterol. LDL-C=low-density lipoprotein cholesterol. SBP=systolic blood pressure. % differences compare the group with Lp(a) measurements with the group without Lp(a) measurements. *P≤0.05. **P≤0.01. ***P≤0.001.

Supplementary Table 2 – Further adjustment of associations for triglycerides, body-mass index and estimated glomerular filtration rate.

Lp(a) measurement / adjustment	Lp(a) 15-<30 mg/dL			Lp(a) 30-<50 mg/dL			Lp(a) ≥50 mg/dL		
	HR (95% CI)*	P value	I^2 (95% CI)	HR (95% CI)*	P value	I^2 (95% CI)	HR (95% CI)*	P value	I^2 (95% CI)
Baseline Lp(a)									
Further adjustment for log triglycerides: 6 trials – 27764 patients – 5649 events									
Multivariable adjustment†	1·04 (0·91, 1·20)	0·54	54% (0, 82)	1·13 (1·02, 1·25)	0·016	0% (0, 75)	1·35 (1·11, 1·66)	0·003	77% (49, 90)
Plus log triglycerides	1·05 (0·92, 1·20)	0·50	53% (0, 81)	1·13 (1·03, 1·25)	0·013	0% (0, 75)	1·37 (1·12, 1·67)	0·002	77% (49, 90)
Further adjustment for BMI: 5 trials – 19731 patients – 2557 events									
Multivariable adjustment†	1·03 (0·84, 1·25)	0·81	55% (0, 84)	1·17 (1·03, 1·32)	0·012	0% (0, 79)	1·42 (1·11, 1·83)	0·006	71% (26, 89)
Plus BMI	1·02 (0·84, 1·25)	0·83	55% (0, 84)	1·17 (1·03, 1·32)	0·013	0% (0, 79)	1·42 (1·11, 1·83)	0·006	71% (26, 88)
Further adjustment for eGFR: 2 trials – 17460 patients – 3273 events									
Multivariable adjustment†	1·20 (0·79, 1·82)	0·40	NR	1·21 (0·91, 1·60)	0·200	NR	1·44 (0·92, 2·27)	0·111	NR
Plus eGFR	1·20 (0·78, 1·84)	0·42	NR	1·21 (0·89, 1·63)	0·219	NR	1·44 (0·91, 2·27)	0·118	NR
On-statin Lp(a)									
Further adjustment for log triglycerides: 6 trials – 13883 patients – 2561 events									
Multivariable adjustment†	0·95 (0·82, 1·11)	0·53	13% (0, 78)	1·08 (0·95, 1·23)	0·240	0% (0, 75)	1·42 (1·16, 1·74)	0·001	58% (0, 83)
Plus log triglycerides	0·96 (0·82, 1·12)	0·58	10% (0, 77)	1·08 (0·95, 1·24)	0·241	0% (0, 75)	1·44 (1·18, 1·75)	0·0004	57% (0, 83)
Further adjustment for BMI: 5 trials – 9857 patients – 1115 events									
Multivariable adjustment†	0·89 (0·69, 1·15)	0·38	29% (0, 72)	1·09 (0·91, 1·31)	0·355	0% (0, 79)	1·54 (1·24, 1·92)	0·0001	29% (0, 73)
Plus BMI	0·89 (0·69, 1·14)	0·36	25% (0, 70)	1·09 (0·91, 1·31)	0·341	0% (0, 79)	1·54 (1·23, 1·92)	0·0001	28% (0, 72)
Further adjustment for eGFR: 2 trials – 8735 patients – 1508 events									
Multivariable adjustment†	1·06 (0·73, 1·54)	0·76	NR	1·16 (0·84, 1·59)	0·367	NR	1·36 (0·98, 1·89)	0·067	NR
Plus eGFR	1·06 (0·73, 1·55)	0·76	NR	1·16 (0·83, 1·62)	0·377	NR	1·36 (0·98, 1·87)	0·064	NR

BMI=body-mass index. CI=confidence interval. eGFR=estimated glomerular filtration rate. HR=hazard ratio. NR=not reported since only two trial contributed to the specific analysis. *The group of patients with Lp(a) values <15 mg/dl served as reference group. †The multivariable model was adjusted for age, sex, prior cardiovascular disease, diabetes, smoking, systolic blood pressure, low-density-lipoprotein cholesterol corrected for Lp(a)-cholesterol, and high-density lipoprotein cholesterol.

Supplementary Table 3 – Subsidiary analysis further categorising the highest Lp(a) group into patients with levels 50-<75 mg/dL and ≥75 mg/dL.

Lp(a) measurement / adjustment	Lp(a) 15-<30 mg/dL			Lp(a) 30-<50 mg/dL			Lp(a) 50-<75 mg/dL			Lp(a) ≥75 mg/dL		
	HR (95% CI)*	P value	I^2 (95% CI)	HR (95% CI)*	P value	I^2 (95% CI)	HR (95% CI)*	P value	I^2 (95% CI)	HR (95% CI)*	P value	I^2 (95% CI)
Baseline Lp(a)												
Basic adjustment: 7 trials – 29069 patients – 5751 events												
Age- and sex-adjusted	1·04 (0·91, 1·19)	0·56	43% (0, 76)	1·11 (1·00, 1·23)	0·048	0% (0, 71)	1·29 (1·05, 1·59)	0·016	67% (28, 85)	1·35 (1·12, 1·64)	0·002	37% (0, 73)
Progressive adjustment: 6 trials – 27764 patients – 5649 events												
Age- and sex-adjusted	1·03 (0·90, 1·19)	0·65	54% (0, 81)	1·10 (1·00, 1·22)	0·059	0% (0, 75)	1·27 (1·02, 1·58)	0·034	72% (36, 88)	1·34 (1·10, 1·64)	0·004	48% (0, 79)
Plus prior CVD	1·04 (0·90, 1·19)	0·62	53% (0, 81)	1·10 (1·00, 1·22)	0·055	0% (0, 75)	1·27 (1·02, 1·59)	0·030	72% (35, 88)	1·35 (1·11, 1·64)	0·003	47% (0, 79)
Plus diabetes	1·04 (0·90, 1·19)	0·61	52% (0, 81)	1·11 (1·00, 1·23)	0·041	0% (0, 75)	1·28 (1·03, 1·59)	0·027	72% (34, 88)	1·37 (1·12, 1·66)	0·002	47% (0, 79)
Plus smoking	1·03 (0·90, 1·18)	0·62	50% (0, 80)	1·11 (1·01, 1·22)	0·039	0% (0, 75)	1·27 (1·03, 1·58)	0·029	71% (32, 88)	1·36 (1·12, 1·64)	0·002	41% (0, 77)
Plus SBP	1·03 (0·89, 1·19)	0·68	53% (0, 81)	1·11 (1·01, 1·23)	0·035	0% (0, 75)	1·27 (1·03, 1·58)	0·028	71% (32, 88)	1·35 (1·12, 1·64)	0·002	44% (0, 78)
Plus LDL-C_{corr}	1·04 (0·90, 1·20)	0·63	55% (0, 82)	1·12 (1·02, 1·24)	0·022	0% (0, 75)	1·30 (1·04, 1·62)	0·021	72% (36, 88)	1·40 (1·14, 1·73)	0·002	52% (0, 81)
Plus HDL-C	1·04 (0·90, 1·20)	0·57	54% (0, 82)	1·13 (1·02, 1·25)	0·019	0% (0, 75)	1·31 (1·05, 1·62)	0·016	71% (32, 87)	1·43 (1·16, 1·76)	0·001	51% (0, 80)
On-statin Lp(a)												
Basic adjustment: 7 trials – 14536 patients – 2603 events												
Age- and sex-adjusted	0·96 (0·82, 1·11)	0·56	18% (0, 62)	1·08 (0·94, 1·23)	0·27	0% (0, 71)	1·47 (1·19, 1·83)	<0·001	46% (0, 77)	1·47 (1·12, 1·92)	0·005	52% (0, 80)
Progressive adjustment: 6 trials – 13883 patients – 2561 events												
Age- and sex-adjusted	0·94 (0·80, 1·10)	0·45	18% (0, 63)	1·07 (0·94, 1·21)	0·32	0% (0, 75)	1·44 (1·20, 1·73)	0·0001	37% (0, 75)	1·44 (1·09, 1·90)	0·011	60% (1, 84)
Plus prior CVD	0·94 (0·80, 1·10)	0·44	18% (0, 63)	1·07 (0·94, 1·21)	0·33	0% (0, 75)	1·44 (1·19, 1·73)	0·0001	38% (0, 75)	1·44 (1·09, 1·90)	0·010	60% (1, 84)
Plus diabetes	0·95 (0·81, 1·11)	0·51	17% (0, 62)	1·07 (0·94, 1·22)	0·29	0% (0, 75)	1·43 (1·20, 1·71)	<0·0001	34% (0, 74)	1·45 (1·10, 1·91)	0·008	58% (0, 83)
Plus smoking	0·95 (0·82, 1·10)	0·48	8% (0, 77)	1·07 (0·94, 1·22)	0·28	0% (0, 75)	1·43 (1·19, 1·72)	0·0001	37% (0, 75)	1·44 (1·10, 1·89)	0·008	56% (0, 82)
Plus SBP	0·95 (0·82, 1·10)	0·49	9% (0, 77)	1·07 (0·94, 1·22)	0·28	0% (0, 75)	1·43 (1·19, 1·72)	0·0001	36% (0, 74)	1·44 (1·10, 1·87)	0·007	56% (0, 82)
Plus LDL-C_{corr}	0·95 (0·82, 1·11)	0·52	13% (0, 78)	1·08 (0·95, 1·23)	0·24	0% (0, 75)	1·44 (1·20, 1·74)	0·0001	38% (0, 75)	1·46 (1·12, 1·91)	0·006	55% (0, 82)
Plus HDL-C	0·96 (0·82, 1·12)	0·60	13% (0, 78)	1·09 (0·95, 1·24)	0·22	0% (0, 75)	1·45 (1·20, 1·74)	<0·0001	35% (0, 74)	1·48 (1·13, 1·92)	0·004	53% (0, 81)

CVD=cardiovascular disease. HDL-C=high-density lipoprotein cholesterol. HR=hazard ratio. LDL-C_{corr}=low-density-lipoprotein cholesterol corrected for Lp(a)-cholesterol. SBP=systolic blood pressure. *The group of patients with Lp(a) values <15 mg/dl served as reference group.

Supplementary Table 4 – Sensitivity analysis omitting varying time periods of the initial follow-up.

Lp(a) measurement / adjustment	No. of trials / patients / CVD events	Lp(a) 15-<30 mg/dL		Lp(a) 30-<50 mg/dL		Lp(a) ≥50 mg/dL	
		HR (95% CI)*	P value	HR (95% CI)*	P value	HR (95% CI)*	P value
Baseline Lp(a)							
Principal analysis	7 / 29069 / 5751	1·04 (0·91, 1·18)	0·59	1·11 (1·00, 1·22)	0·047	1·31 (1·08, 1·58)	0·005
Omitting initial 3 months	7 / 28161 / 4870	1·07 (0·95, 1·21)	0·25	1·13 (1·01, 1·28)	0·037	1·45 (1·14, 1·85)	0·002
Omitting initial 6 months	6 / 25810 / 4452	1·05 (0·92, 1·20)	0·44	1·12 (0·98, 1·28)	0·10	1·38 (1·07, 1·78)	0·012
Omitting initial 9 months	6 / 25444 / 4127	1·06 (0·94, 1·20)	0·37	1·17 (0·99, 1·37)	0·06	1·42 (1·07, 1·89)	0·014
Omitting initial 12 months	6 / 25098 / 3829	1·07 (0·93, 1·23)	0·33	1·18 (0·99, 1·41)	0·06	1·44 (1·10, 1·90)	0·008
On-statin Lp(a)							
Principal analysis	7 / 14536 / 2603	0·94 (0·81, 1·10)	0·45	1·06 (0·94, 1·21)	0·33	1·43 (1·15, 1·76)	0·001
Omitting initial 3 months	7 / 14093 / 2174	0·98 (0·85, 1·14)	0·82	1·07 (0·93, 1·23)	0·35	1·62 (1·20, 2·18)	0·001
Omitting initial 6 months	6 / 12927 / 1969	0·98 (0·81, 1·19)	0·83	1·05 (0·91, 1·22)	0·48	1·50 (1·13, 1·99)	0·005
Omitting initial 9 months	6 / 12741 / 1799	0·97 (0·81, 1·16)	0·75	1·10 (0·92, 1·31)	0·28	1·57 (1·15, 2·15)	0·005
Omitting initial 12 months	6 / 12592 / 1678	0·97 (0·82, 1·16)	0·75	1·12 (0·93, 1·35)	0·23	1·65 (1·19, 2·28)	0·003

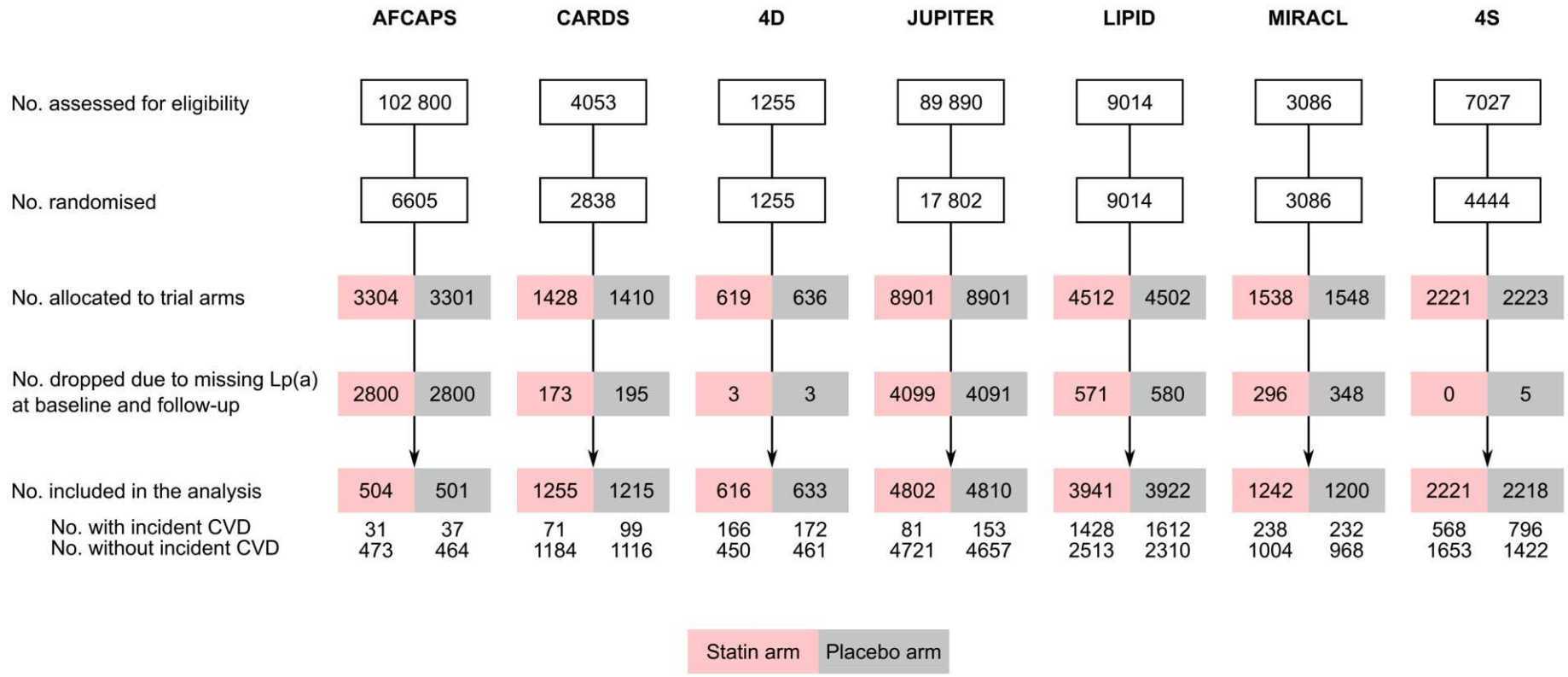
CI=confidence interval. CVD=cardiovascular disease. HR=hazard ratio. *Hazard ratios were adjusted for age and sex. The group of patients with Lp(a) values <15 mg/dl served as reference group.

Supplementary Table 5 – Trial-specific hazard ratios and covariance matrices.

Model / Trial	No. of participants / events	HR (95% CI) vs. Lp(a) <15 mg/dL*			Covariance matrix		
		Lp(a) 15-<30 mg/dL	Lp(a) 30-<50 mg/dL	Lp(a) ≥50 mg/dL	15-<30 vs. 30-<50 mg/dL	15-<30 vs. ≥50 mg/dL	30-<50 vs. ≥50 mg/dL
Baseline Lp(a): Age- and sex-adjusted							
AFCAPS	1005 / 68	1·05 (0·83, 1·34)	1·16 (0·80, 1·68)	1·46 (0·95, 2·26)	0·0211	0·0213	0·0214
CARDS	2470 / 170	1·02 (0·91, 1·15)	0·96 (0·82, 1·13)	1·20 (1·07, 1·35)	0·0086	0·0088	0·0088
4D	1249 / 338	0·92 (0·86, 0·99)	1·01 (0·95, 1·08)	1·06 (1·02, 1·10)	0·0051	0·0052	0·0051
JUPITER	9612 / 234	1·50 (1·42, 1·58)	1·46 (1·33, 1·61)	1·83 (1·70, 1·97)	0·0082	0·0083	0·0082
LIPID	7863 / 3040	0·98 (0·97, 0·98)	1·04 (1·03, 1·05)	1·12 (1·11, 1·12)	0·0006	0·0006	0·0006
MIRACL	2431 / 537	0·82 (0·79, 0·85)	1·17 (1·12, 1·22)	1·16 (1·13, 1·19)	0·0031	0·0031	0·0031
4S	4439 / 1364	1·12 (1·11, 1·13)	1·17 (1·15, 1·18)	1·74 (1·71, 1·77)	0·0013	0·0013	0·0013
Baseline Lp(a): Multivariable adjusted†							
CARDS	2299 / 161	0·97 (0·85, 1·10)	1·01 (0·86, 1·19)	1·39 (1·23, 1·56)	0·0092	0·0096	0·0093
4D	1249 / 338	0·96 (0·90, 1·04)	1·02 (0·96, 1·09)	1·09 (1·04, 1·14)	0·0052	0·0055	0·0059
JUPITER	9601 / 233	1·50 (1·42, 1·58)	1·42 (1·29, 1·57)	1·87 (1·72, 2·02)	0·0084	0·0088	0·0096
LIPID	7863 / 3040	0·99 (0·98, 0·99)	1·07 (1·06, 1·07)	1·17 (1·17, 1·18)	0·0006	0·0006	0·0007
MIRACL	2328 / 517	0·81 (0·78, 0·84)	1·21 (1·15, 1·26)	1·14 (1·10, 1·17)	0·0032	0·0032	0·0034
SSSS	4424 / 1360	1·14 (1·13, 1·16)	1·20 (1·19, 1·22)	1·82 (1·79, 1·85)	0·0013	0·0014	0·0014
On-statin Lp(a): Age- and sex-adjusted							
AFCAPS	504 / 31	1·50 (0·91, 2·46)	0·93 (0·31, 2·74)	2·51 (1·39, 4·54)	0·0510	0·0506	0·0512
CARDS	1255 / 71	1·05 (0·79, 1·40)	1·32 (0·95, 1·81)	0·83 (0·60, 1·15)	0·0205	0·0206	0·0207
4D	616 / 166	0·52 (0·42, 0·65)	0·88 (0·77, 1·00)	1·21 (1·13, 1·30)	0·0099	0·0101	0·0099
JUPITER	4802 / 81	1·40 (1·18, 1·66)	1·63 (1·25, 2·13)	1·79 (1·49, 2·16)	0·0240	0·0243	0·0240
LIPID	3941 / 1428	0·91 (0·90, 0·92)	1·03 (1·01, 1·04)	1·18 (1·17, 1·19)	0·0013	0·0013	0·0013
MIRACL	1200 / 258	0·77 (0·71, 0·84)	1·22 (1·11, 1·35)	1·46 (1·39, 1·53)	0·0070	0·0070	0·0070
4S	2218 / 568	1·01 (0·98, 1·04)	1·07 (1·04, 1·09)	1·86 (1·81, 1·91)	0·0033	0·0033	0·0034
On-statin Lp(a): Multivariable adjusted†							
CARDS	1169 / 70	1·18 (0·88, 1·57)	1·46 (1·05, 2·01)	1·04 (0·75, 1·45)	0·0219	0·0226	0·0219
4D	616 / 166	0·53 (0·42, 0·66)	0·86 (0·75, 0·99)	1·19 (1·10, 1·29)	0·0100	0·0111	0·0112
JUPITER	4796 / 80	1·36 (1·15, 1·61)	1·50 (1·12, 2·02)	1·73 (1·42, 2·11)	0·0240	0·0253	0·0251
LIPID	3941 / 1428	0·94 (0·92, 0·95)	1·05 (1·03, 1·06)	1·22 (1·21, 1·23)	0·0014	0·0014	0·0014
MIRACL	1152 / 251	0·81 (0·75, 0·88)	1·25 (1·13, 1·38)	1·44 (1·37, 1·52)	0·0072	0·0072	0·0072
4S	2209 / 566	1·02 (0·99, 1·06)	1·09 (1·06, 1·12)	1·89 (1·84, 1·94)	0·0033	0·0033	0·0034

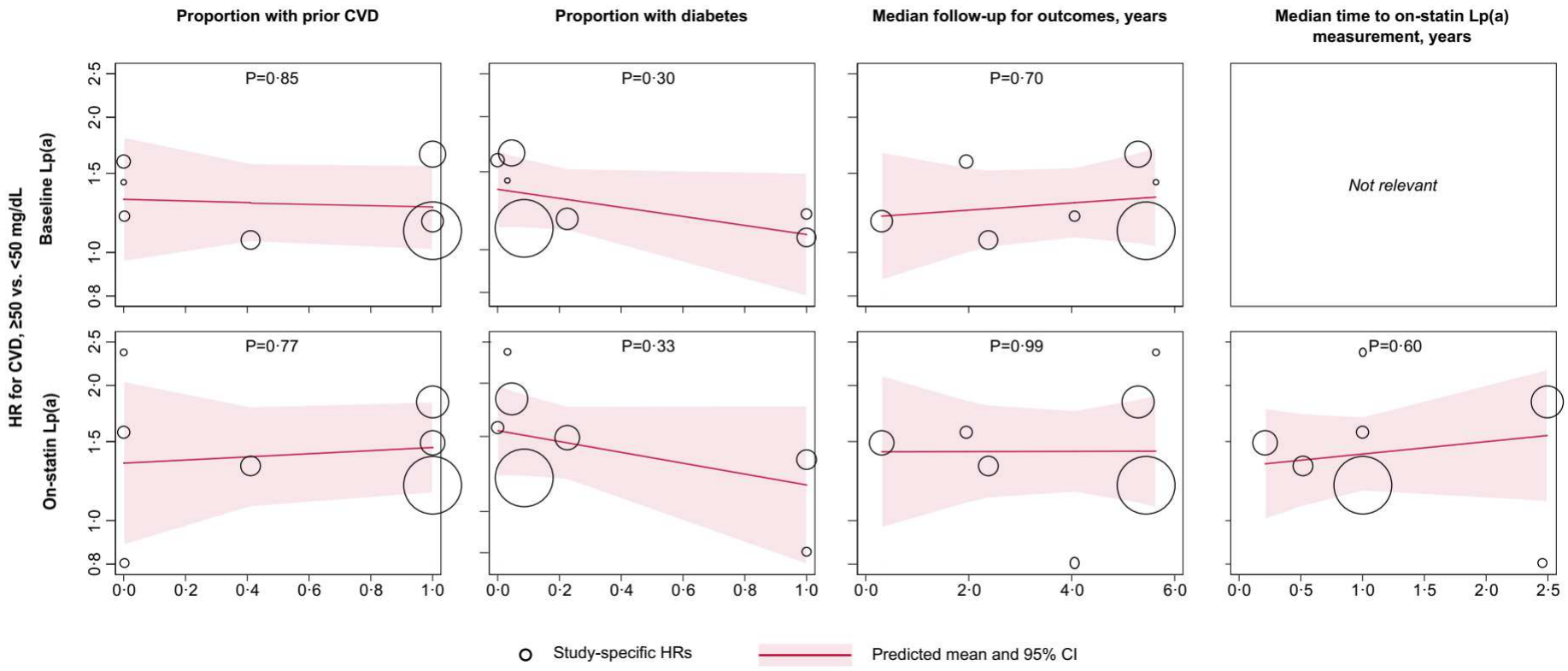
*The group of patients with Lp(a) values <15 mg/dl served as reference group. †The multivariable model was adjusted for age, sex, prior cardiovascular disease, diabetes, smoking, systolic blood pressure, low-density-lipoprotein cholesterol corrected for Lp(a)-cholesterol, and high-density lipoprotein cholesterol.

Supplementary Figure 1 – CONSORT diagram.



For full trial names, refer to footnote of Table 1. CVD=cardiovascular disease.

Supplementary Figure 2 – Associations of baseline and on-statin Lp(a) with incident cardiovascular disease by study-level characteristics.



Each circle represents one study. Sizes of circles are proportional to the inverse variances of study-specific hazard ratios. P values were calculated from meta-regression. HRs=hazard ratios.