Baseline and on-statin treatment lipoprotein(a) levels for prediction of cardiovascular events

individual patient-data meta-analysis of statin outcome trials

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

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Abstract: 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.

Responses to comments of editors and reviewers

Note: Lines numbers listed in this document are for the version of the manuscript with track changes.

Editors' comments

Comment #1:
In responses to reviewers' points, provide text changes together with line numbers.

Response: As requested, we provide the text changes together with line numbers

Comment #2:
When interpreting editorial points made by reviewers, please remember we will further edit the final manuscript if accepted.

Response: Thank you for pointing this out to us.

Comment #3:
Please indicate any authors who are full professors.

Response: In the revised list of affiliations of the manuscript (**lines 8-28**), it is now specified who of the co-authors are full professors.

Comment #4:
For randomised trials please follow the CONSORT reporting guidelines http://www.consort-statement.org and include a CONSORT checklist.

Response: Our study was a meta-analysis evaluating the association of Lp(a) with disease risk of clinical trial data and not a primary report of a clinical trial reporting on the effect of an intervention on disease risk. We therefore believe this point does not apply to our study; nevertheless, in **Supplementary Table 2**, we provide a flow chart designed per CONSORT recommendations showing – for each trial – the numbers of people who were assessed for eligibility, were randomised, had missing Lp(a), were included in the analysis, and developed the CVD outcome during follow-up.

Comment #5:
Please follow CONSORT for abstracts (eg method of randomisation).

Response: Please see reply to editorial comment #4.

Comment #6:
At the end of the methods section please state the role of the funder in: data collection, analysis, interpretation, writing of the manuscript and the decision to submit. Please also state which author(s) had access to all the data, and which author(s) were responsible for the decision to submit the manuscript etc.

Response: We report this information on **lines 166-169** of the revised manuscript.

Comment #7:
Please give 95% confidence intervals for hazard ratios/odds ratios.

Response: Done.

Comment #8:
Limit summary to pre-defined primary endpoints and safety endpoints.

Response: Done.

Comment #9:
Report all outcomes specified in the protocol.

Response: We confirm that we report on all outcomes pre-specified in the statistical analysis plan for this project (developed prior to any combined analyses being undertaken, but after results of some trials were known).

Comment #10:
Please explain any deviations from the protocol.

Response: There were no deviation from the pre-specified statistical analysis plan of this project.

Comment #11:
Clearly denote analyses of exploratory outcomes as post-hoc.

Response: Done.

Comment #12:
P values should be exact to 4 decimal places (eg $p<0.0001$). Two decimals are acceptable in tables for non-significant p-values.

Response: Done.

Comment #13:
Please provide absolute numbers to accompany all percentages.

Response: We have revised the text in **lines 172-175** accordingly.

Comment #14:
Please provide numbers at risk for Kaplan-Meier plots.

Response: As requested, the Kaplan-Meier plot in this document (**Response Figure 1**) is provided together with numbers at risk. The main manuscript does not contain Kaplan-Meier plots.

Comment #15:
Please provide the text, tables and figures in an editable format.

Response: Done.

Comment #16:
Ensure that figures conform with the Lancet artwork guidelines.

Response: Done.

Comment #17:
Include a maximum of six main figures or tables, moving others to the web appendix.

Response: Done.

Comment #18:
Provide a research in context panel.

Response: The research context panel has been updated to include a systematic review of prior evidence done.

Comment #19:
Provide signed authorship statements and conflict of interest forms and summarise authors' disclosures in the manuscript.

Response: Done.

Comment #20:
Provide statements for any personal communication and for any named person in the acknowledgements saying that they agree to be acknowledged.

Response: Done.

Comment #21:
Add a statement of author contributions at the end of the text.

Response: Already done.

Comment #22:
Please ensure that there is a section in the Methods section confirming ethics approval and consent from all patients has been obtained.

Response: We now state in the methods section on **line 110** that: "All contributing trials have obtained ethics approval and patients' informed consent."

Comment #23:
Confirm that all authors have seen and approved of the final text.

Response: The corresponding authors Peter Willeit and Sam Tsimikas confirm that all authors have seen and approved the final text.

Comment #24:
Avoid endnotes.

Response: Done.

Comment #25:
Please note our guideline length for research articles is 3000 words. Allowing for additional material requested by reviewers and editors we can allow a little leeway but we hope for final manuscript below 3500 words (4500 words for RCTs).

Response: Done.

Comment #26:
Provide a revised manuscript, a tracked changes version showing the changes made, and a point-by-point response to ALL EDITORS' and reviewers' comments - typed immediately following each specific point.

Response: Done.

Comment #27:
Avoid boxes for replies.

Response: Done.

Reviewer #1

This analysis addresses an important question regarding Lp(a) risk in patients treated with statins. Thus, these data differ from the Lp(a) Collaboration Study. The use of patient specific data, statistical methods and analysis are a strength. The authors use these data to present a case for the Novartis antisense therapy for Lp(a). Overall, the data is important, but the commercial link is overdone in the view of this Reviewer.

Comment #1:
In the introduction, revise the statement on the limitation of single statin RCT analyses.

Response: We have now clarified on **lines 86-93** of the revised manuscript that "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."

Comment #2:
Discussion. Page 8. Paragraph 2. Lines 2-3. A small angiographic study. Provide reference. If the authors are using FATS or HATS as a reference, how do they account for the reduction in Lp(a) in the niacin arm as a confounder?

Response: We used the post-hoc analysis of FATS as a reference (Maher et al JAMA 1995, now cited). The study combined three treatment arms (i.e. lovastatin 40 mg daily plus colestipol 30 g daily, niacin 4 g daily plus colestipol, and placebo) and compared LDL-C non-responders (+6%, n=36) with responders (-40%, n=84). The baseline and on-treatment Lp(a) levels were not significantly different between LDL-C responders and non-responders (37 vs. 35 mg/dL at baseline; 34 vs. 29 mg/dL on-treatment). Therefore, this appears to address potential confounding. However, our point is that the paper's conclusion may be faulty due to low power, low baseline Lp(a), and type-2 error. It is contradicted by our much larger study. This paper has been cited very frequently and has made it into treatment paradigms of the practicing physician that, if LDL-C is controlled, Lp(a) is not a risk factor. This had likely led to many physicians not measuring or even thinking about Lp(a) as a risk factor. The potential adverse impact to patients of this underpowered post-hoc analysis cannot be quantitated but is likely significant.

In further proof, both FOURIER and ODYSSEY OUTCOMES have now presented (but not published yet) their data and both show elevated baseline Lp(a) remains a risk factor even with exceedingly low LDL-C <50 mg/dL.

We have added the following statement to the revised discussion (**lines 309-314**): "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." Moreover, data presented from ODYSSEY OUTCOMES indicate that lowering of Lp(a) with alirocumab is associated with reduced major adverse cardiac outcomes, independent of the effects of alirocumab on LDL-C.

Comment #3:
Omit the speculative comment on association shapes and clinical benefit at different levels of Lp(a) concentration.

Response: We have now omitted this comment on **lines 319-321** of the revised manuscript.

Reviewer #2

Lipoprotein(a) (Lp(a)) is one of the last bastions in lipid management and new potent therapies for lowering Lp(a) will be a major focus of future clinical trials. Nine of ten WHO criteria to justify screening for Lp(a) are met and reduction of ASCVD risk with intervention is the missing link that could revolutionize lipid management in high risk patients and their families in the next decade. Most of the observational evidence supporting Lp(a) as a risk factor for ASCVD (and aortic stenosis to lesser extent) comes from primary prevention cohorts. The present analysis from the Lp(a) Studies Collaboration shows that in patients derived from several large statin trials Lp(a) remains an independent risk factor for incident events. This finding is crucially important, because of antecedent uncertainties in part related to faulty or biased analyses. The results of this powerful analysis will pave the way for future intervention trials with ASO and siRNa directed at apo(a).

Comment #1:
The selection process for the 29,069 patients from the seven statin trials might have biased the results. What re-assurance can you provide for lack of bias from the study design adopted?

Response: As noted by the reviewer, the seven statin trials we analysed involved 29,069 patients with Lp(a) measurements and 15,975 patients without Lp(a) measurements. In none of these trials were patients selected on the basis of Lp(a) levels. The choice for selecting patients for Lp(a) assessment in the current analysis was entirely based on the availability of sufficient blood sample at baseline and/or follow-up. The analysis shown in revised **Supplementary Table 1** confirms that there were minimal differences in baseline characteristics of patients with or without Lp(a) measurements. This is now also stated in the methods section, **lines 116-118**.

Comment #2:
Clarify why results differ from those of the previous study by O'Donoghue *et al* in JACC.

Response: Associations in the three trials reported by O'Donoghue *et al* (PROVE-IT, CARE, and PEACE) were somewhat weaker than our analysis (see summary in **Response Table 1** below). Three features crucially distinguish our analysis from the O'Donoghue paper. First, the three trials in the paper by O'Donoghue *et al* recorded a low number of incident events (i.e. 191 in PROVE-IT, 15 in CARE, and 343 in PEACE vs. 5751 in our analysis), leading to limited statistical power and wide 95% confidence intervals of estimated hazard ratios. Second, in contrast to our analysis which defined Lp(a) categories informed by ESC/EAS guideline recommendations (Eur Heart J 2016;37:2999–3058) (i.e. <15, 15-<30, 30-<50, and ≥50 mg/dL), O'Donoghue *et al* defined Lp(a) categories in each trial differently (i.e. trial-specific quintiles). Third, the boundaries of these Lp(a) categories were lower than the ones used in our analysis (see **Response Table 1**) and hence a threshold effect at high Lp(a) concentrations might have been missed. It has to be noted that the O'Donoghue paper also includes a meta-analysis of eight additional trials, but neither of these additional trials evaluated a statin intervention.
We have now added the following statement to the discussion (**lines 272-276**) to address this important point: "In contrast to a previous analysis of individual-patient data by O'Donoghue et al, 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."

Response Table 1. Comparison of results from the paper by O'Donoghue *et al* to our analysis.

Trial	No. of patients / events	Comparison groups	Hazard ratio (95% CI)
PROVE-IT	2529 / 191	<1.8 vs. >31.3 mg/dL	1.00 (0.63-1.59)
CARE	785 / 15	<3 vs. ≥41 mg/dL	1.08 (0.69-1.68)
PEACE	3394 / 343	<4.6 vs. >49 mg/dL	1.07 (0.75-1.53)
Our analysis	29069 / 5751	<15 vs. ≥50 mg/dL	1.35 (1.11-1.66)

Comment #3:
Index event bias can plague the assessment of a risk factor for recurrent events. This can be an issue in secondary prevention trials. Was this a problem and how was it addressed?

Response: We expect that effects of index event bias are limited in our present analysis because: (i) we observed similarly strong associations between Lp(a) and CVD risk in people with and without baseline CVD; (ii) we observed concordant correlations between Lp(a) and other CVD risk factors in people with and without baseline CVD, whereas index event bias typically characterised by such correlations being directionally discordant (**Response Table 2**); and (iii) we employed multivariable adjustment, which can partial control index event bias (discussed in JAMA 2011; 305(8): 822–823) Still, because we cannot entirely rule out presence of index event bias, we now state in the limitation section of the discussion on **lines 338-340** that: "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."

Response Table 2. Correlates of Lp(a) at baseline in patients with and without pre-existing CVD.

Clinical variables	% difference in Lp(a) (95% CI) per SD higher value of clinical variables or compared to reference group of clinical variables	
	Patients without CVD at baseline (n=13817)	Patients with CVD at baseline (n=15252)
Age	1% (-2 to 4)	-1% (-3 to 1)
Sex, females vs. males	14% (-4 to 36)	8% (2 to 15)
Diabetes, yes vs. no	-41% (-60 to -11)	-15% (-22 to -8)
Smoking, yes vs. no	5% (-0 to 11)	-2% (-7 to 4)
SBP	-1% (-6 to 4)	-3% (-6 to -1)
LDL-C_{corr}	-17% (-27 to -6)	-16% (-27 to -3)
HDL-C	9% (4 to 14)	6% (0 to 11)
BMI	-4% (-6 to -2)	-8% (-11 to -4)

For categorical clinical variables, % differences shown are for females compared to males, patients with diabetes compared to those without, and patients who were smokers compared to those who were not.

Comment #4:
Lp(a) is notoriously difficult to assay accurately. Isoform independent assays are essentially non-existent, despite apparent claims to the contrary. What assays were employed in the various studies and how were the mass values standardised? How long were samples stored for and under what conditions; was this uniform across studies?

Response: The assays used are noted below in **Response Table 3**. All studies with two exceptions used commercially available assays used in routine clinical care, which disposed of acceptable metrics of accuracy and precision. MIRACL used a UCSD validated in-house ELISA, and 4D applied an in-house ELISA with a combination of poly- and monoclonal antibodies used in many dozens of studies before. As shown in **Response Table 3** below, duration of storage of blood samples before Lp(a) measurement was variable within and between trials, ranging from immediate processing to storage for up to 18 years. We did note this previously as a limitation and have now further expanded this point to take your comments into consideration (discussion section, **lines 332-334**).

Response Table 3. Assays used to measure Lp(a).

Trial	Assay manufacturer (assay type)	Sample	Storage	Storage

		type	time	temperature
AFCAPS	NR	NR	NR	NR
CARDS	Technoclone (Immunoturbidimetric assay)	Serum	5-9 yrs	-70°C
4D	In-house (ELISA)	Serum	10 yrs	-70°C
JUPITER	Randox (Immunoturbidimetric assay)	Plasma	6-10 yrs	-70°C
LIPID	Abbott Diagnostics (Latex particle immunoassay)	Plasma	17-18 yrs	-70°C
MIRACL	In-house (ELISA)	Plasma	5 yrs	-70°C
4S	Pharmacia (Radioimmunoassay)	Serum	0-1.8 yrs	-70°C

NR=not reported.

Comment #5:

The studies included in this analysis were heterogeneous: primary and secondary stable coronary prevention; diabetics; CKD on hemodialysis; an ACS group. The MIRACL study was a short trial and measurement of Lp(a) in an ACS setting may be unreliable. Was this accounted for in the statistical analyses?

Response: It is correct that we investigated the association of baseline and on-statin Lp(a) with CVD risk in a broad range of types of patient populations, enhancing the generalisability of our findings and their clinical translation. To account for the differences in population types in our analysis, we estimated (and provide in **Supplementary Table 5**) hazard ratios within each study separately, before calculating a pooled estimate using random-effects meta-analysis (which in contrast to fixed-effects models relaxes the strong assumption that the studies estimate the same true effect and rather estimates a distribution of effects). Besides a more pronounced association at younger ages, subsidiary meta-regression analyses showed similar magnitudes of associations according to prior CVD, diabetes, or length of follow-up (for detailed results, please see **Supplementary Figure 2**), thereby leaving some of the between-study heterogeneity unexplained. In the revised discussion on **lines 340-342**, we therefore acknowledge that "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, in MIRACL, acute phase response effects on Lp(a) are unlikely to be significant because Lp(a) levels in the placebo group remained unchanged between the baseline to the 16-week assessment. In specific, the mean % change of Lp(a) in this timeframe was -0.7% (95% confidence interval: -3.2 to +1.9%; P=0.600).

Comment #6:

Assay heterogeneity can be addressed by genotyping apo(a) for CNV in K-IV2 or for the 2 Clarke SNPs. Do the authors have data on apo(a) gene variants in this cohort to corroborate their assertions or at least to check for the validity of their Lp(a) mass assay(s) and the back calculation of mass from apparent molar values, as was suggested in the methods.

Response: LPA SNPs were not measured in these studies nor is DNA available to do so now. KIV2 repeats were measured in 4D, but this study only contributed 1249/29,069 patients. KIV-2 repeats also can only explain 25-50% of Lp(a) levels, so this is not likely to be an appropriate method to test assay heterogeneity.

Comment #7:

Did the authors examine heterogeneity of effect sizes by country of origin of participants in the trials? For example, in Europe a negative gradient in plasma Lp(a) levels has been described from north to south; were the results different in 4S from other trials?

Response: This is an important point, but these data are not available for all the studies in the meta-analysis to perform this analysis.

Comment #8:

The relationship between Lp(a) and ASCVD may vary by gender; how was this adjusted for given wide differences in proportion of women in the trials; should the inferences from the analyses be guarded in women?

Response: Our data indicates that the associations between high Lp(a) and CVD risk are not modified by sex. As shown in **Figure 3**, the hazard ratio for CVD with Lp(a) ≥50 mg/dL was 1.39 (1.19, 1.63) in men vs. 1.40 (1.12, 1.75) in females for baseline Lp(a) and 1.56 (1.26, 1.94) in men vs. 1.51 (1.19, 1.91) in females for on-statin Lp(a). P values for interaction were 0.91 for baseline Lp(a) and 0.79 for on-statin Lp(a).

Comment #9:
Lp(a) levels are often inversely related to plasma triglycerides (TGs), because theoretically apo(a) can transfer after secretion into plasma to TRL, especially in the postprandial status; while HDL-C is described and adjusted for, TG levels are not accounted for; can these data be provided?

Response: We obtained triglyceride data from the trials CARDS, 4D, JUPITER, LIPID, MIRACL, and 4S. In analyses further adjusted for triglyceride levels, hazard ratios were virtually identical. These results have been added to **Supplementary Table 2** and are commented on in the results section (**line 210-213**).

Reviewer #3

Comment #1:
The authors excluded 35.5% of the data because these patients had missing Lp(a) measurements. Did these patients with missing data systematically differ from patients with Lp(a) data?

Response: Revised **Supplementary Table 1** demonstrated that there were little differences in baseline characteristics of patients with or without Lp(a) measurements (also now commented on in the methods section, **lines 116-118**). The same point has been raised reviewer #2 (comment #1), where a more detailed response can be found.

Comment #2:
The authors reported imputing using a study-specific mixed model, can the authors detail this model? Was missing data mean-imputed based on this model?

Response: For each trial separately, we fitted a linear mixed-effects model, as

$$Y_{ij} = \beta_0 + \beta_1 \times S_i + \beta_2 \times t_{ij} + \beta_3 \times S_i \times t_{ij} + b_{0i} + \in_{ij}$$

where Y_{ij} is the *j*-th log-transformed Lp(a) measurements for patient *i*, S_i is the assigned treatment group (1 if statin and 0 if placebo), and t_{ij} is the time from baseline of the *j*-th Lp(a) measurement. β_0, β_1, and β_3 are fixed effects, whereas b_{0i} is the random intercept allowed to vary at the patient level and $\in_{ij}$ is the random error term. For patients who had Lp(a) available only at one of the two time points (i.e. either at baseline or at follow-up), Lp(a) at the other time point was mean-imputed based on the expected Lp(a) change estimated from assigned treatment and duration of the trial. To help clarify the model specification, we have rephrased the methods section (**lines 122-128**) accordingly.

Comment #3:
How did the authors test the proportional hazards assumption? Did they test this assumption per-trial or over all trials?

Response: We tested the proportional assumption using on Schoenfeld residuals in models fitted separately to each study, before combining estimates in a meta-analysis. Detailed results of this analysis are provided in **Response Table 4**. We have expanded our statement on this in the revised manuscript on **line 145-146**: "The assumption for the proportionality of hazards was tested using Schoenfeld residuals and was met".

Response Table 4. Results from testing the PH assumption using Schoenfeld residuals.

Trial	Baseline Lp(a) χ^2 (d.f.)	Baseline Lp(a) P value	On-statin Lp(a) χ^2 (d.f.)	On-statin Lp(a) P value
AFCAPS	2.15 (3)	0.543	0.23 (3)	0.973
CARDS	3.48 (3)	0.324	0.55 (3)	0.907
4D	1.06 (3)	0.786	2.36 (3)	0.501
JUPITER	2.74 (3)	0.433	3.02 (3)	0.388
LIPID	1.54 (3)	0.674	4.83 (3)	0.185
MIRACL	5.51 (3)	0.138	3.13 (3)	0.372
4S	4.97 (3)	0.174	3.45 (3)	0.328
Overall	**21.44 (21)**	**0.432**	**17.57 (21)**	**0.676**

d.f.=degrees of freedom.

Comment #4:

In the results the authors report incidences per 1,000 person years. I'm not certain readers could easily digest how 55.3/1000 person years relates to risk.

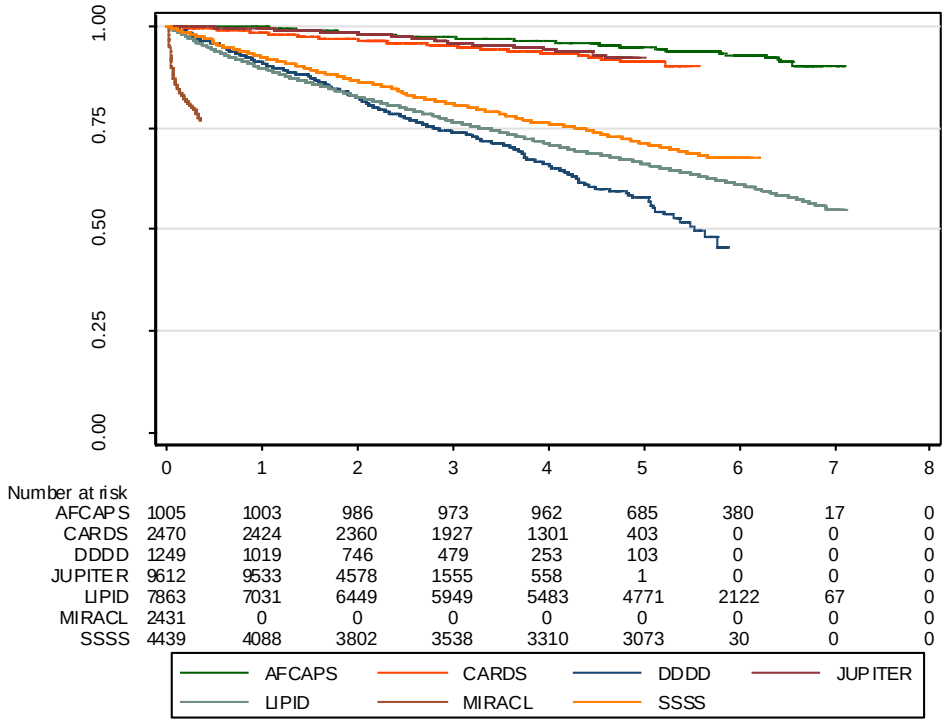
Response: We agree with the reviewer that the interpretation of cumulative incidences over a specified time period (for example, cumulative 1-year CVD risk) would be more intuitive for readers than the interpretation of incidence rates. Nevertheless, because this project involved time-to-event data with different durations of follow-up contributed by each patient, we identified CVD incidence rate as the appropriate measure of disease incidence. In analogy to this, we chose to report hazard ratios rather than risk ratios as a measure of relative risk. If the reviewer or editorial team has a strong view on this, the results section containing the incidence rates (**lines 194-198**) could be omitted.

Comment #5:

How did CVD hazard rates differ by trial? May I ask to see Kaplan-Meier curves of CVD per trial? Even random-effects CpH models cannot overcome disparate baseline hazard rates between trials.

Response: Incidence rates varied substantially across trials, as expected given their different inclusion criteria (listed in **Table 1** of the manuscript). The incidence rates for CVD per 1,000 person-years (in descending order) are: 832.42 in MIRACL, 105.5 in 4D, 84.48 in LIPID, 68.65 in 4S, 17.97 in CARDS, 12.29 in AFCAPS, and 11.21 in JUPITER. A Kaplan-Meier plot with numbers-at-risk is provided in **Response Figure 1**. Because of these expected differences, we pre-specified in our analysis plan the use of a two-stage approach (rather than a single random-effects Cox model), whereby separate Cox models are fitted for each trial first, before study-specific effect estimates are pooled using random-effects meta-analysis.

Response Figure 1. Kaplan-Meier plots for incident CVD for each trial.



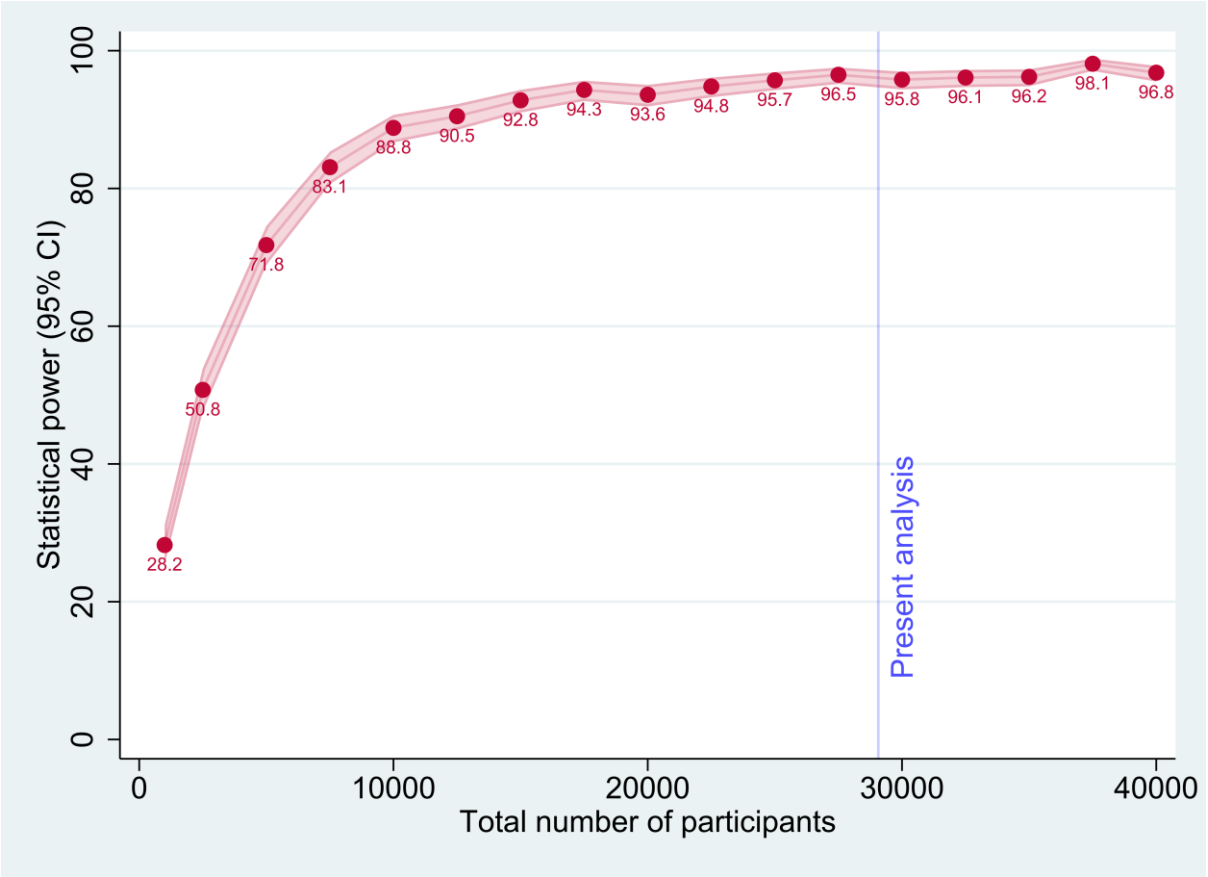
Comment #6:
Why did the authors choose to discretize Lp(a) rather than analyze as a continuous variable?

Response: We decided *a priori* to use Lp(a) categories in our analysis because we regard this as clinically more relevant. In particular, we aimed to provide clarity concerning any threshold effects for CVD risk. While the 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias considers CVD risk to be significant in people with Lp(a) values above 50 mg/dL (European Heart Journal 2016;37,2999–3058), many clinical laboratories and practitioners designate Lp(a) levels already above 30 mg/dL as being elevated (Arterioscler Thromb Vasc Biol 2015;35:996–1001). Furthermore, our focus on these guideline-informed categorisations of Lp(a) is also relevant to upcoming clinical trials because people with Lp(a) ≥50 mg/dL are considered a potential target subpopulation for therapeutic intervention specifically aimed at lowering Lp(a).

Comment #7:
The authors note this analysis is well-powered but do not present any formal power analysis.

Response: We have conducted a series of simulation studies to evaluate the statistical power in this random-effects meta-analysis. **Response Figure 2** plots statistical power as a function of the total number of participants to detect a hazard ratio of 1.4 or greater, assuming a similar distribution of patients across Lp(a) categories as in our dataset, a cumulative CVD incidence in the reference group similar as in our dataset (17.2%), and moderate-to-high between-study heterogeneity (τ^2 = 0.4). By conducting a total of 1000 repetitions, the simulation evaluated statistical power in an modelled meta-analysis involving between 1000 and 40000 participants. Point estimates for statistical power are presented together with binomial confidence intervals. Details of the methods involved in this simulation are available in a separate methods paper (Journal of Statistical Software 2016;74(12)1-25; DOI: 10.18637/jss.v074.i12).

Response Figure 2. Statistical power according to total number of participants in a modelled meta-analysis (for modelling parameters, please see text above).



Reviewer #4

The investigators have conducted a meta-analysis using patient-level data from seven randomized placebo-controlled statin outcomes trials to evaluate CVD risk in patients on statin therapy. The investigators concluded 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 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, the methodology of the study conducted is robust.

My main concern is that I do not find the results to be surprising. There is prior evidence that the effect of statin therapy on Lp(a) levels is minimal. The LDL receptor does not seem to have a major role in lipoprotein(a) clearance; hence statins are generally ineffective in the reduction of lipoprotein(a) concentration. In the absence of such evidence, it is hard for me to even justify the premise of the study and it is hard to think of a valid reason why the investigators have gone through this effort of conducting an IPD meta-analysis. There is no other finding in this study which is novel. All of the findings described in the paper have been published previously by larger IPD meta-analyses.

Response: Although we agree with you on the issue of the statin therapy affecting Lp(a) levels and the role of the LDLR, the general thinking among clinicians has been that once one is on statin therapy, the need to measure Lp(a) or to consider it a risk factor is no longer relevant. Furthermore, several underpowered trials and observational studies have suggested as such (for instance, O'Donoghue *et al*, discussed in detail in our response to comment #2 of reviewer #2), while others suggested residual risk when Lp(a) is elevated. Thus, pending a randomized trial, this meta-analysis which specifically addressed the statin question and which has not been studied previously in secondary prevention cohorts is ideal to address this question. This is the first, adequately powered analysis to formally assess the effect of baseline and on-statin treatment effect that resolves this controversy with the best possible data pending an outcomes trial.

Technical points

Comment #1:
When you submit the revised paper, please provide: (i) one "clean" copy of your manuscript; (ii) one copy where your changes are highlighted (tracked changes); (iii) A separate, point by point response to the editorial and referee comments typed immediately following each specific point above. (iv) Any images and/or tables (even if no revisions have been made).

Response: Done.

Comment #2:
Please do NOT include a copy of your original manuscript. All text files should be supplied as MS Word files.

Response: Done.

Comment #3:
Please also supply the word count for the body of your paper and your abstract (word count for the body of your paper should not include abstract, references, figures or tables).

Response: Done.

Comment #4:
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Response: The Lipoprotein(a) Studies Collaboration is described at the webpage https://clinicalepi.i-med.ac.at/research/lpasc/.

Comment #5:
We ask all authors of, and all contributors (including medical writers and editors) to specify their conflicts of interest (if any) and individual contributions to a manuscript under consideration at The Lancet. The Lancet will not publish any articles unless we have a completed author statement form, conflict of interest form, and the signatures of all authors. Please sign and complete the author statement form (http://www.thelancet.com/for-authors/forms#author-sigs) and the ICMJE conflicts of interest statement form (http://www.thelancet.com/for-authors/forms#icmje-coi), and either upload the signed copies in to EES with your manuscript, scan and email to editorial@lancet.com. In addition, please also include written consent of any cited individual(s) noted in acknowledgments or personal communications.

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Response: Done.

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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Key words: Lipoprotein(a), cardiovascular disease, statin, outcomes, meta-analysis

3458 words, **3** tables, **3** figures, **5** supplementary tables, **2** supplementary figures

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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.

Funding: Novartis Pharma AG provided support for the performance of the meta-analysis.

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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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

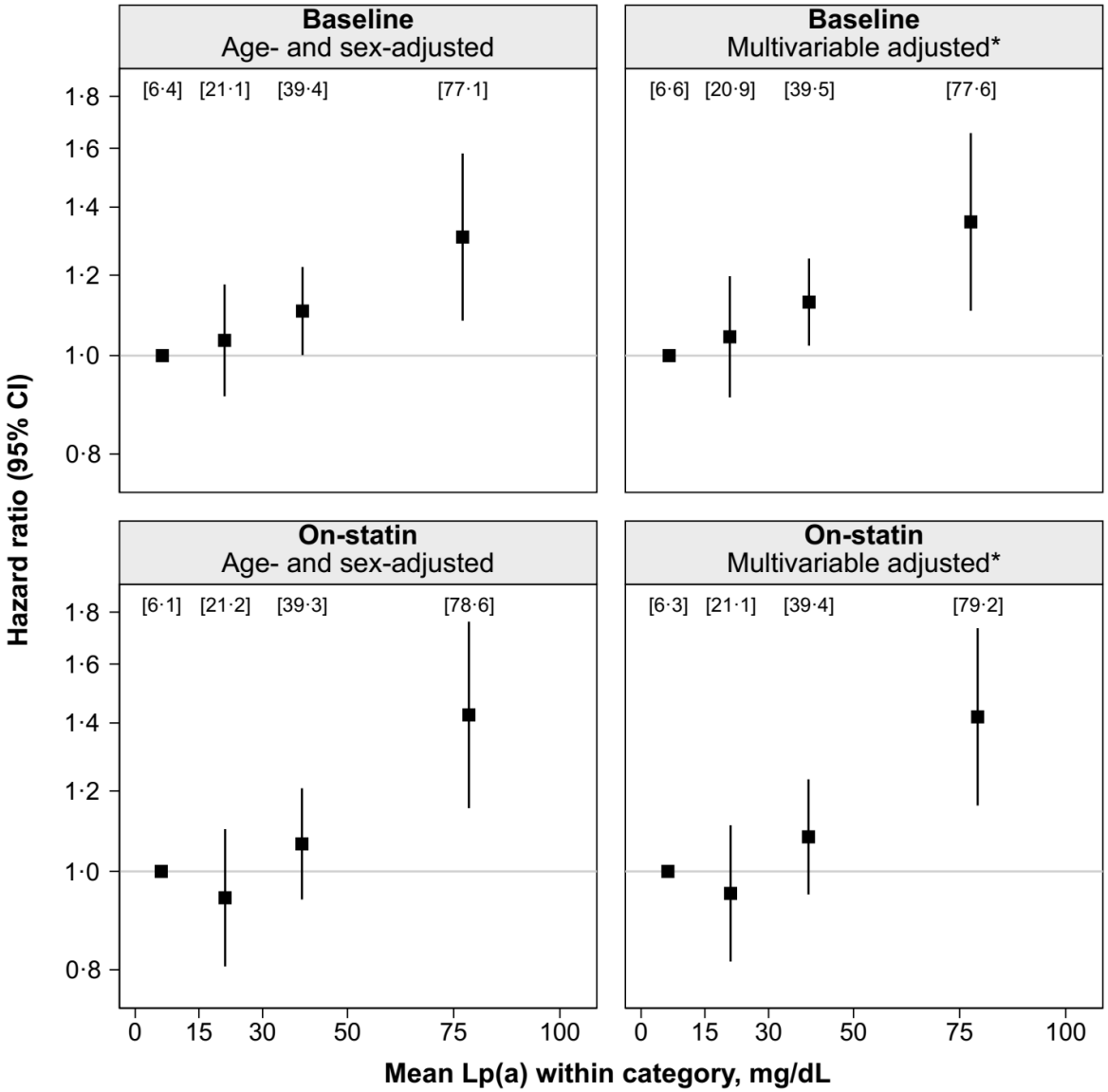
Mean (SD) or n (%), unless stated otherwise. Percentages may not sum up to 100% due to rounding. For full trial names, refer to footnote of Table 1. Total means (standard deviations) and % changes (95% confidence intervals) were calculated by pooling study-specific estimates with random-effects meta-analysis. 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)

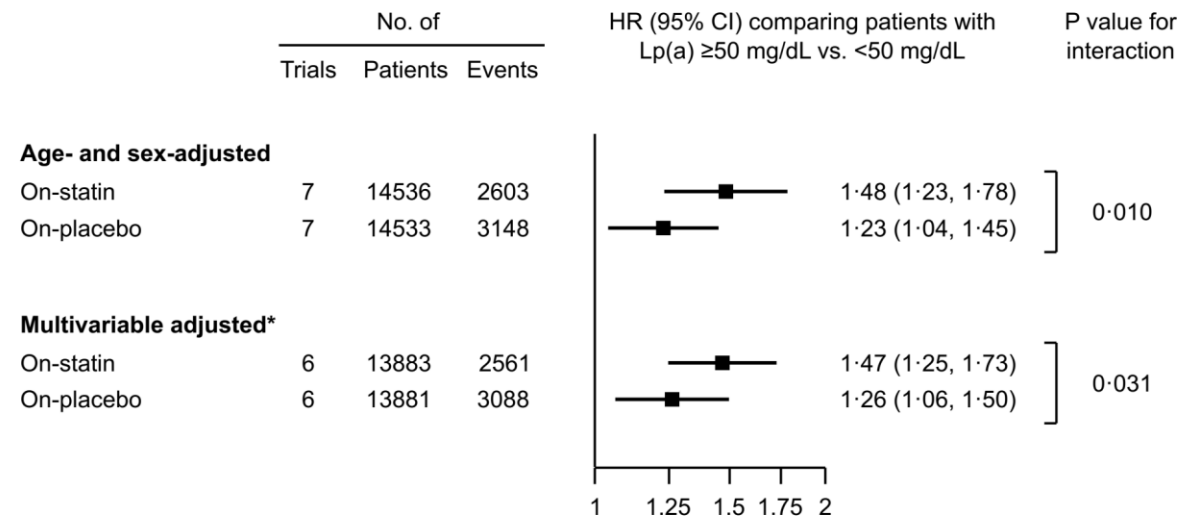
CI=confidence interval. CVD=cardiovascular disease. HDL-C=high-density lipoprotein cholesterol. HR=hazard ratio. LDL-C_{corr}=low-density-lipoprotein cholesterol corrected for Lp(a)-cholesterol. SBP=systolic blood pressure. *The group of patients with Lp(a) values <15 mg/dl served as reference group.

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



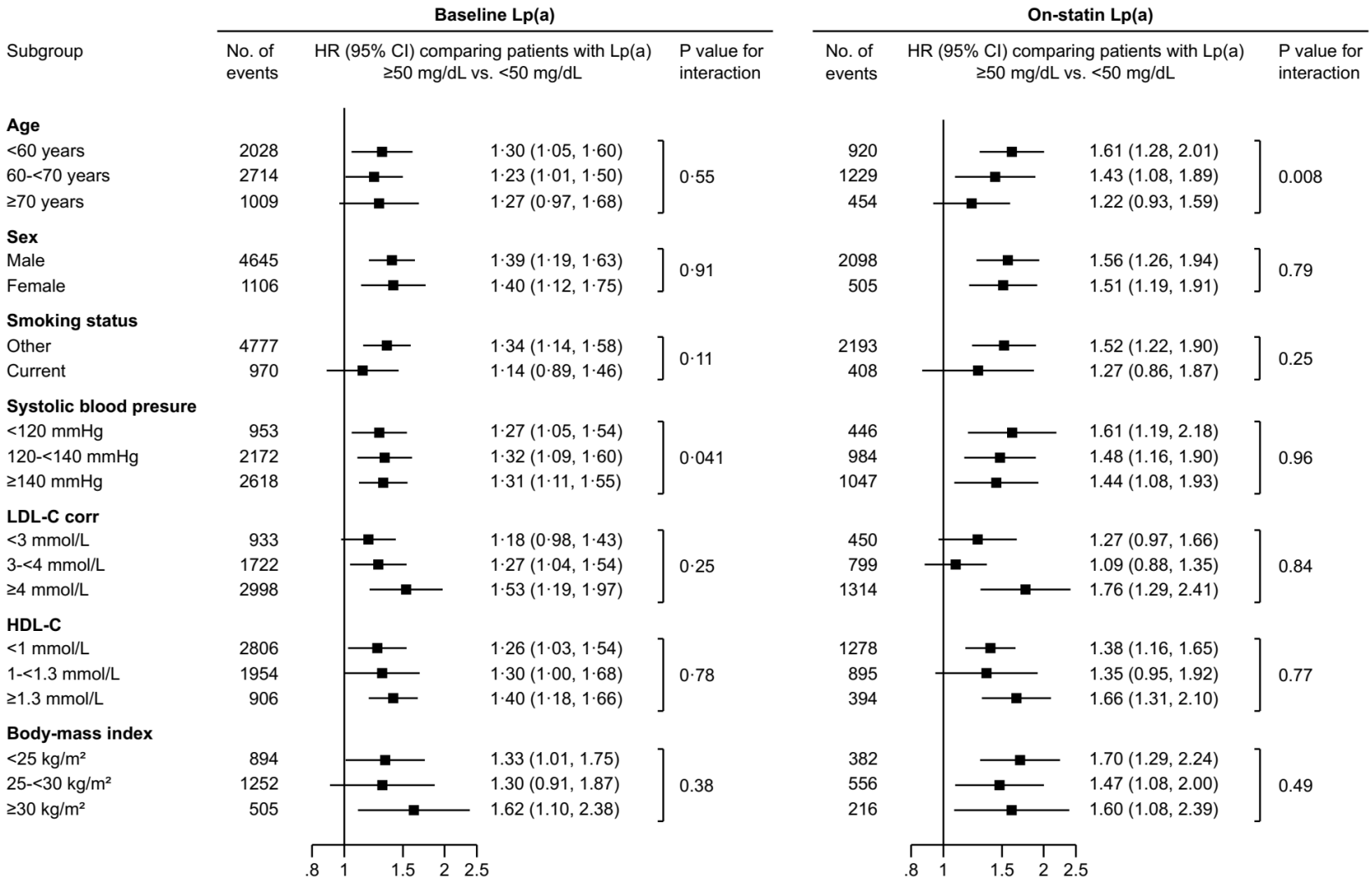
Categories of Lp(a) were defined as <15 mg/dL, 15-<30 mg/dL, 30-<50 mg/dL, and ≥50 mg/dL. Numbers in squared brackets are means of Lp(a) values within each category. The group with the lowest Lp(a) concentration served as reference. The analysis of baseline Lp(a) involved 29069 patients (5751 events) 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.

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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Key words: Lipoprotein(a), cardiovascular disease, statin, outcomes, meta-analysis

~~3231~~ 3458 words, **3** tables, ~~2~~ 3 figures, **5** supplementary tables, **2** supplementary figures

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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]: -3839% [-4443, -3335]) 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.

Funding: Novartis Pharma AG provided support for the performance of the meta-analysis.

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 ~~none recruited patients with elevated Lp(a) *a priori*, and therefore the entry Lp(a) levels are usually in the normal range in 70%-80% of study participants. Therefore, all studies thus far have relied on subgroup analyses and are~~ uniformly underpowered to test the hypothesis that elevated Lp(a) levels ~~in the setting of statin therapy and prior history of CVD~~ 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**). ~~Clinical~~There were minimal differences in baseline characteristics of patients with or without available Lp(a) measurements ~~excluded were similar to those of patients included in the analysis~~ (**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~~included fixed effects of Lp(a) values available for that patient at other time points, the time between repeat measurements, and trial arm, plus random effects 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] ~~The analysis of baseline Lp(a) involved all patients, whereas the analysis of on-treatment Lp(a) was restricted to patients assigned to the intervention arm.~~ 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~~s~~ for the proportionality of hazards was tested using Schoenfeld residuals and ~~were~~ 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~~28%~~ were female (28%), 15252~~52%~~ had prior CVD (52%), 5177~~18%~~ had diabetes (18%), 4847~~17%~~ 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 14~~,~~536 patients were randomized to receive statin therapy (**Table 2**). Initiation of statin therapy reduced LDL-C_{corr} by -~~38~~39% (95% confidence interval: -~~44~~43, -~~33~~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 ~~were~~ remained robust to additional ~~multivariable~~ adjustment for ~~age, sex,~~ 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 ~~that~~ 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, ~~diabetes,~~ acute coronary syndromes, patients on dialysis and highly elevated LDL-C in the familial hypercholesterolemia range. Therefore, they broadly reflect ~~the~~ patients with high residual

risk despite statin treatment, potentially due to other, unmodified risk factors such as elevated Lp(a)~~at risk for Lp(a) mediated CVD~~.

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. ~~The current study suggests that the relationship of Lp(a) to risk is curvilinear if plotted on a geometric mean scale, but linear if plotted on continuous scale, suggesting that potent reduction in Lp(a) may be clinically beneficial across all elevated Lp(a) levels.~~

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 ~~introduce bias into~~ the Lp(a) measurement ~~precision~~. 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 ~~hihger~~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 ~~CW~~ 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.

~~PJN, TRP, GGS, AGO, CW, PMR, and HC have contributed to data acquisition as principal investigators of statin trials. 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. All authors 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

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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 ~~the risk of~~ high-risk patients ~~in the setting of statin therapy is not known~~ 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) ~~in the setting of statin therapy~~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 ~~disease~~ 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 ~~in~~ 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, -	-29% (-30, -29)	-47% (-49, -46)	-37% (-37, -36)	-389% (-443, -
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.

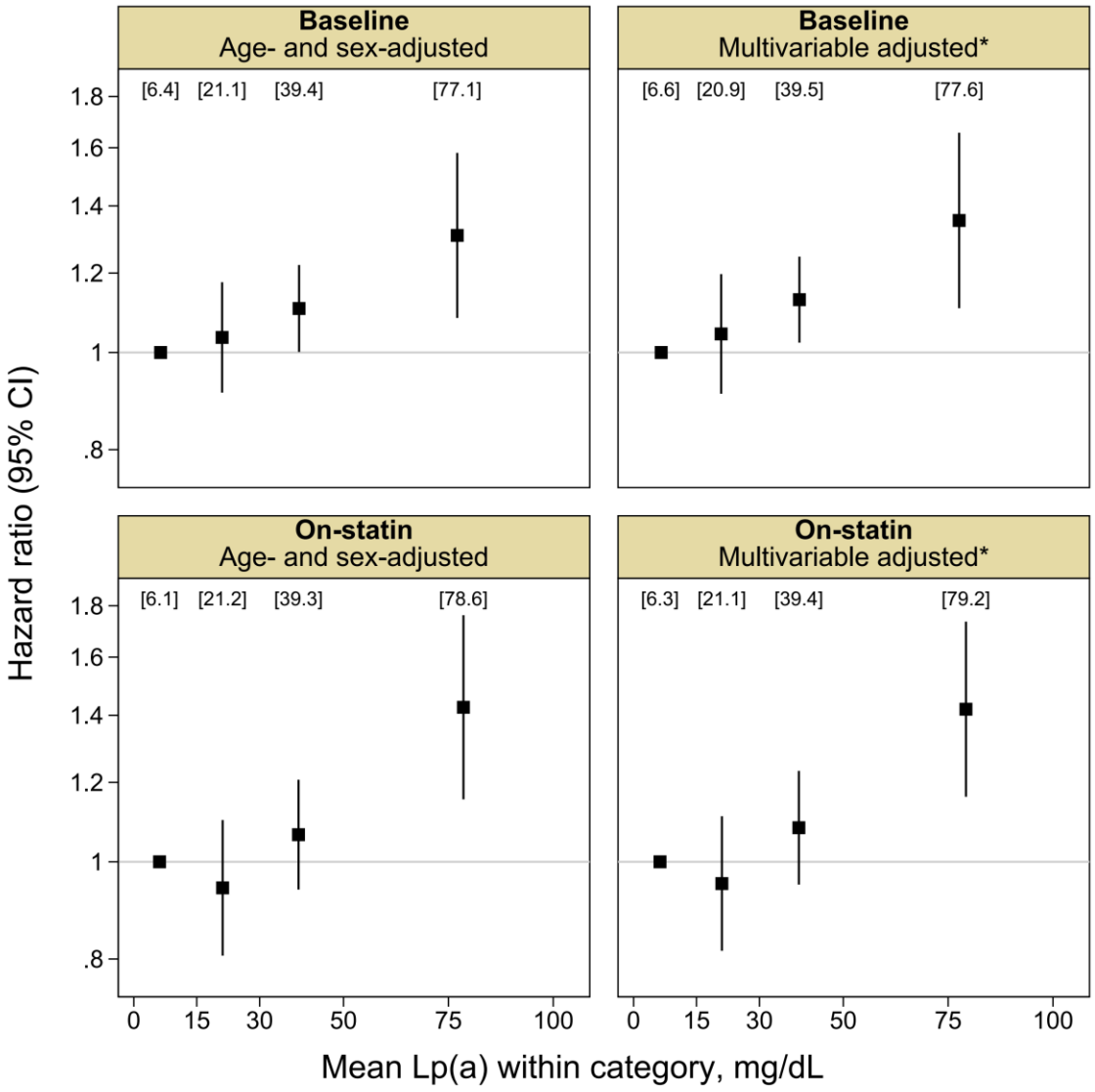
Table 3 – Associations of baseline and on-statin Lp(a) with incident cardiovascular disease according to different levels of adjustment.

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)	0·594	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)	0·642	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)	0·6071	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)	0·604	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)	0·613	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)	0·6364	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)	0·6071	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)	0·543	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)	0·451	18% (0, 62)	1·06 (0·94, 1·21)	0·332	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)	0·3667	18% (0, 63)	1·06 (0·93, 1·21)	0·351	0% (0, 75)	1·39 (1·12, 1·72)	0·002	64% (13, 85)
Plus prior CVD	0·93 (0·79, 1·09)	0·3667	18% (0, 63)	1·06 (0·93, 1·21)	0·3596	0% (0, 75)	1·39 (1·12, 1·72)	0·002	64% (13, 85)
Plus diabetes	0·94 (0·80, 1·10)	0·431	17% (0, 62)	1·07 (0·94, 1·22)	0·3071	0% (0, 75)	1·39 (1·13, 1·71)	0·002	62% (7, 84)
Plus smoking	0·94 (0·81, 1·09)	0·4152	8% (0, 77)	1·07 (0·94, 1·22)	0·30297	0% (0, 75)	1·39 (1·13, 1·71)	0·002	62% (8, 84)
Plus SBP	0·94 (0·81, 1·09)	0·412	9% (0, 77)	1·07 (0·94, 1·22)	0·30299	0% (0, 75)	1·39 (1·13, 1·71)	0·002	61% (6, 84)

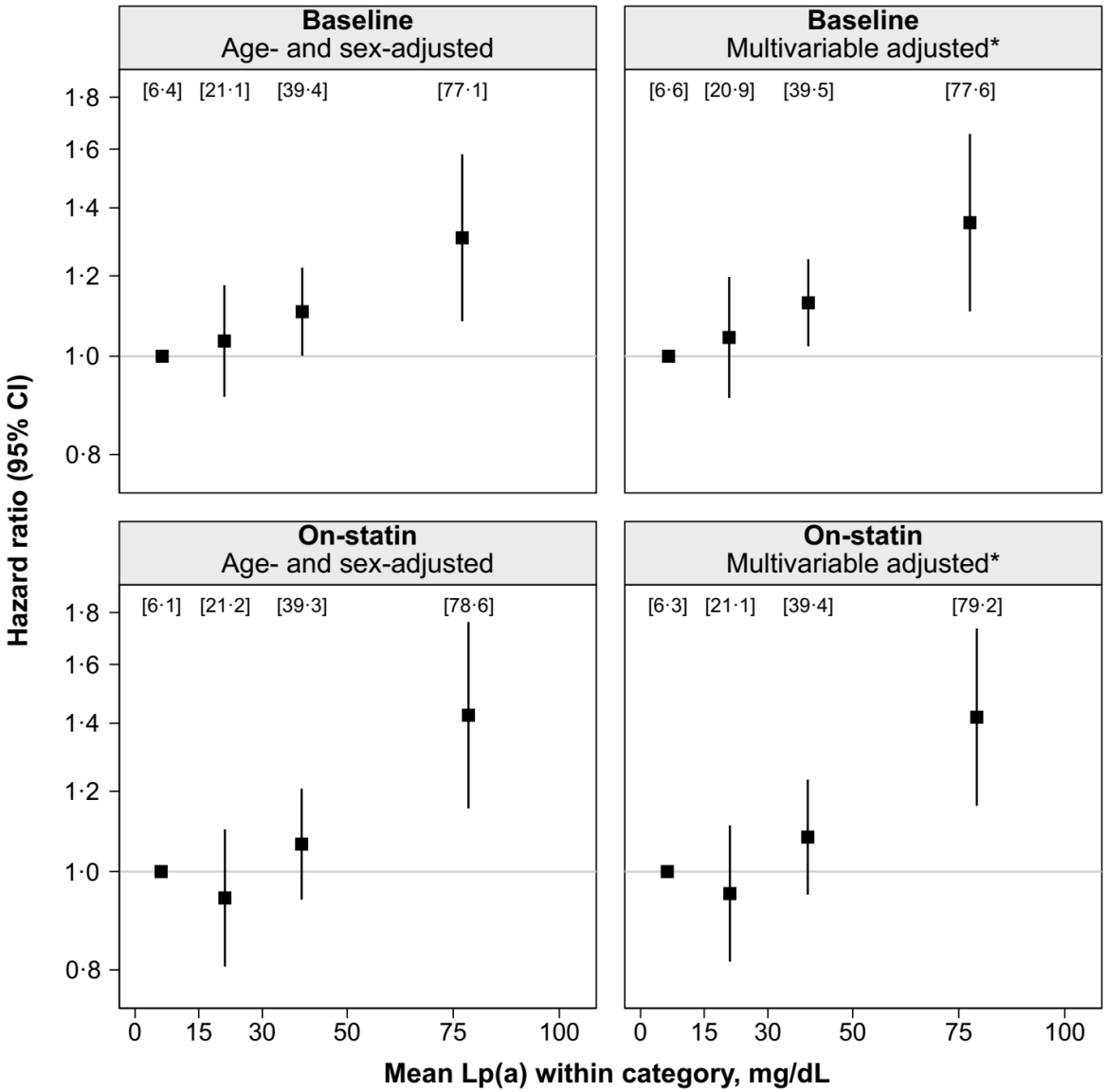
Plus LDL-C_{corr}	0·94 (0·81, 1·10)	0·4657	13% (0, 78)	1·08 (0·95, 1·23)	0·2556	0% (0, 75)	1·41 (1·15, 1·73)	0·001	61% (3, 84)
Plus HDL-C	0·95 (0·82, 1·11)	0·5273	13% (0, 78)	1·08 (0·95, 1·23)	0·240	0% (0, 75)	1·42 (1·16, 1·74)	0·001	58% (0, 83)

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.

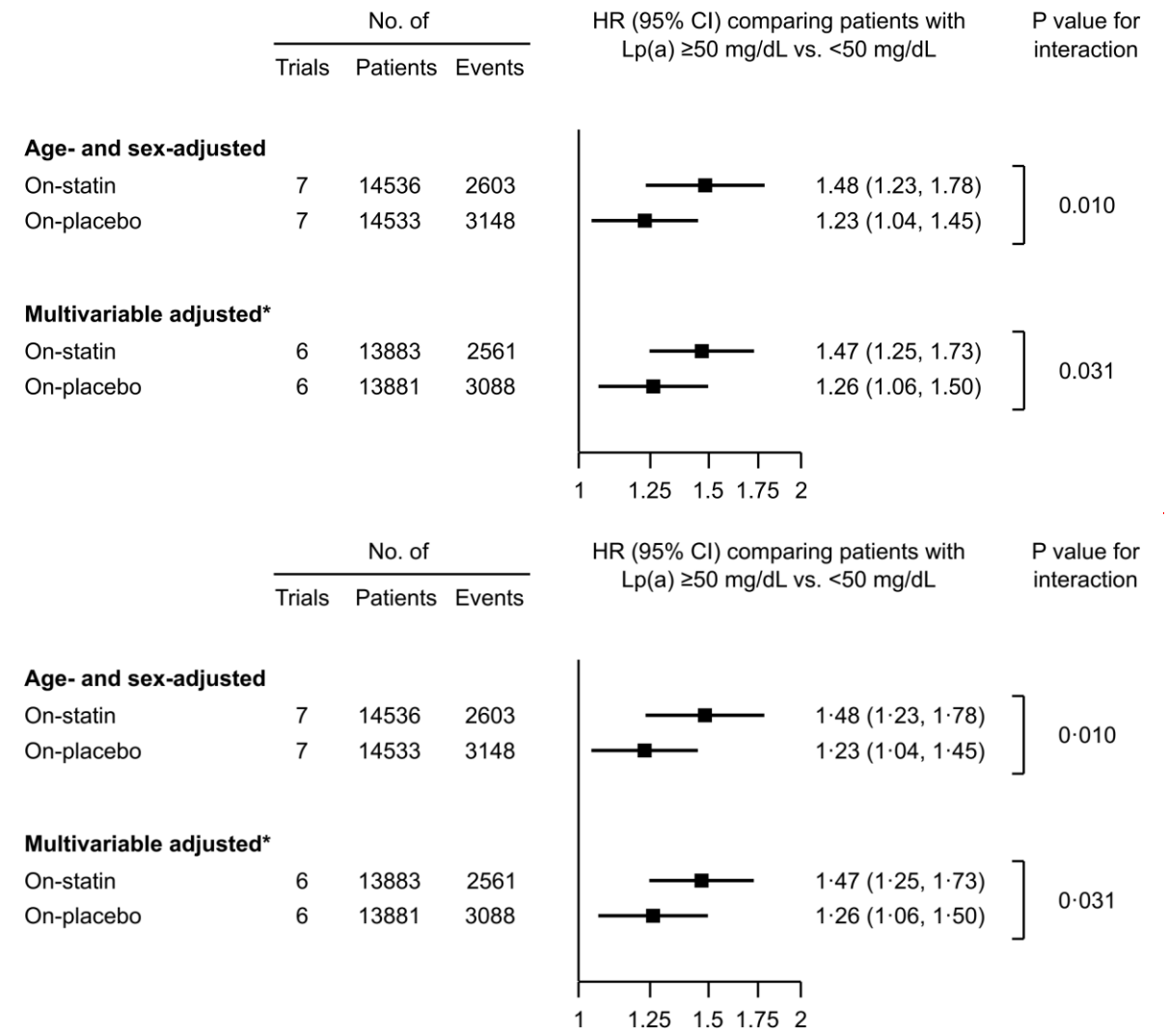

Baseline
Age- and sex-adjusted
[6.4] [21.1] [39.4] [77.1]
Baseline
Multivariable adjusted*
[6.6] [20.9] [39.5] [77.6]
On-statin
Age- and sex-adjusted
[6.1] [21.2] [39.3] [78.6]
On-statin
Multivariable adjusted*
[6.3] [21.1] [39.4] [79.2]
Hazard ratio (95% CI)
1.8
1.6
1.4
1.2
1
.8
0 15 30 50 75 100
Mean Lp(a) within category, mg/dL

561



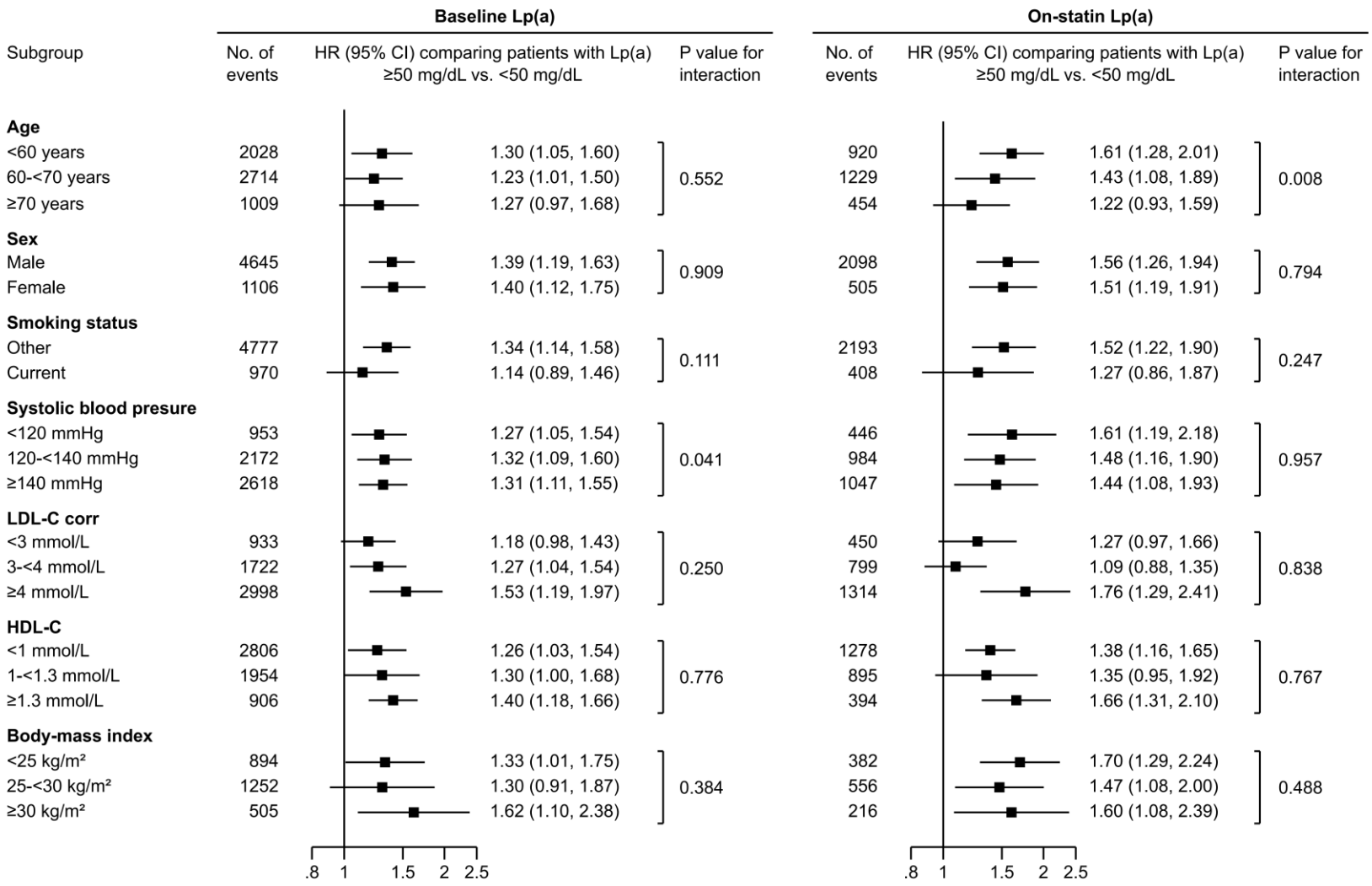
Categories of Lp(a) were defined as <15 mg/dL, 15-<30 mg/dL, 30-<50 mg/dL, and ≥50 mg/dL. Numbers in squared brackets are means of Lp(a) values within each category. The group with the lowest Lp(a) concentration served as reference. The analysis of baseline Lp(a) involved 29069 patients (5751 events) 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.

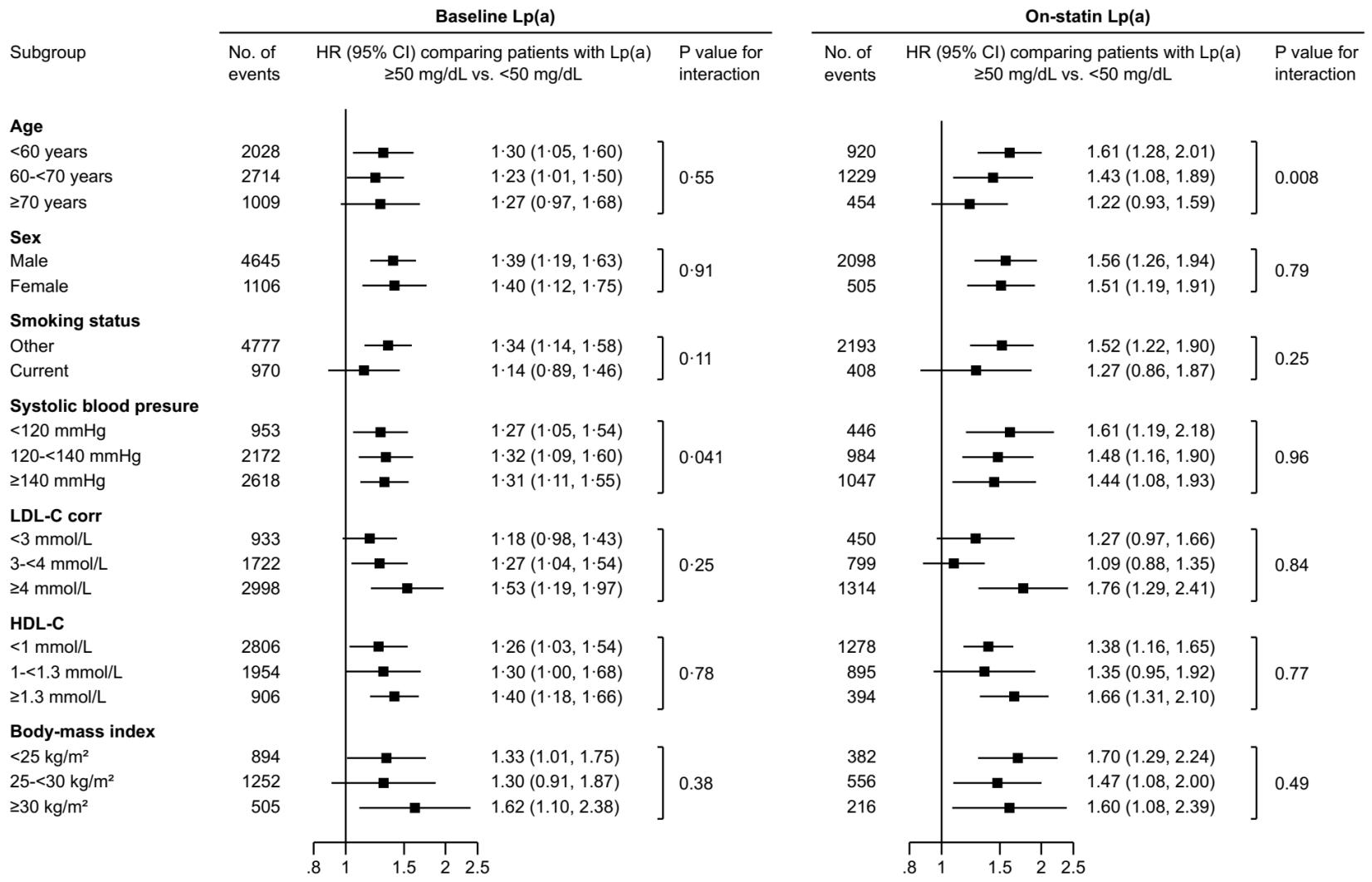
Figure 2 – Comparative predictive value of on-statin vs. on-placebo Lp(a) for incident cardiovascular disease.



*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.


Baseline Lp(a)
On-statin Lp(a)
Subgroup
No. of events
HR (95% CI) comparing patients with Lp(a) ≥50 mg/dL vs. <50 mg/dL
P value for interaction
Age
<60 years 2028 1.30 (1.05, 1.60) 920 1.61 (1.28, 2.01)
60-<70 years 2714 1.23 (1.01, 1.50) 0.552 1229 1.43 (1.08, 1.89) 0.008
≥70 years 1009 1.27 (0.97, 1.68) 454 1.22 (0.93, 1.59)
Sex
Male 4645 1.39 (1.19, 1.63) 2098 1.56 (1.26, 1.94)
Female 1106 1.40 (1.12, 1.75) 0.909 505 1.51 (1.19, 1.91) 0.794
Smoking status
Other 4777 1.34 (1.14, 1.58) 2193 1.52 (1.22, 1.90)
Current 970 1.14 (0.89, 1.46) 0.111 408 1.27 (0.86, 1.87) 0.247
Systolic blood presure
<120 mmHg 953 1.27 (1.05, 1.54) 446 1.61 (1.19, 2.18)
120-<140 mmHg 2172 1.32 (1.09, 1.60) 0.041 984 1.48 (1.16, 1.90) 0.957
≥140 mmHg 2618 1.31 (1.11, 1.55) 1047 1.44 (1.08, 1.93)
LDL-C corr
<3 mmol/L 933 1.18 (0.98, 1.43) 450 1.27 (0.97, 1.66)
3-<4 mmol/L 1722 1.27 (1.04, 1.54) 0.250 799 1.09 (0.88, 1.35) 0.838
≥4 mmol/L 2998 1.53 (1.19, 1.97) 1314 1.76 (1.29, 2.41)
HDL-C
<1 mmol/L 2806 1.26 (1.03, 1.54) 1278 1.38 (1.16, 1.65)
1-<1.3 mmol/L 1954 1.30 (1.00, 1.68) 0.776 895 1.35 (0.95, 1.92) 0.767
≥1.3 mmol/L 906 1.40 (1.18, 1.66) 394 1.66 (1.31, 2.10)
Body-mass index
<25 kg/m² 894 1.33 (1.01, 1.75) 382 1.70 (1.29, 2.24)
25-<30 kg/m² 1252 1.30 (0.91, 1.87) 0.384 556 1.47 (1.08, 2.00) 0.488
≥30 kg/m² 505 1.62 (1.10, 2.38) 216 1.60 (1.08, 2.39)
.8 1 1.5 2 2.5
.8 1 1.5 2 2.5



579

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

Supplementary Material

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