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## Lipoprotein (a) For Risk Assessment in Patients with Established Coronary Artery Disease

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### Abstract

**Objectives**—To assess the prognostic utility of lipoprotein (a) [Lp(a)] in individuals with coronary artery disease (CAD).

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**Conflicts of Interest** Dr. O'Donoghue has received grant funding from GlaxoSmithKline, AstraZeneca and Genzyme and has received consulting fees from Aegerion. Dr Morrow reports that the Thrombolysis in Myocardial Infarction (TIMI) Study Group has received research grants from Abbott, AstraZeneca, Amgen, Bristol-Myers Squibb, Daiichi Sankyo, Eisai, Eli Lilly, GlaxoSmithKline, Merck, Novartis, and Johnson & Johnson; he reports having served as a consultant for BG Medicine, Critical Diagnostics, Eli Lilly, Genentech, Gilead, Instrumentation Laboratory, Johnson & Johnson, Konica/Minolta, Merck, Roche Diagnostics, Servier. Dr. Tsimikas is a co-inventor and receives royalties from patents owned by the University of California for the commercial use of oxidation-specific antibodies, is a consultant to Quest, Sanofi, Genzyme, Regeneron and ISIS and has received investigator-initiated grants from Pfizer and Merck. Dr. Cannon has received grant funding from Accumetrics, AstraZeneca, CSL Behring, Essentialis, GlaxoSmithKline, Merck, Regeneron, Sanofi, Takeda; he has served on the advisory board for Alnylam, Bristol-Myers Squibb, Lipimedix, Pfizer; he is a clinical advisor and has equity in Automedics Medical Systems. Dr. Sacks has served as a consultant to Amgen, Eli Lilly, Merck, Roche and Sanofi and has received lecture fees from AstraZeneca. Dr. Sabatine has received grants from Amgen, AstraZeneca, AstraZeneca / Bristol-Myers Squibb Alliance, Bristol-Myers Squibb / Sanofi-aventis Joint Venture, Daiichi-Sankyo, Eisai, Genzyme, GlaxoSmithKline, Intarcia, Merck, Sanofi-aventis, Takeda, Abbott Laboratories, Accumetrics, Critical Diagnostics, Nanosphere, Roche Diagnostics; he has received consulting fees from Aegerion, Amgen, AstraZeneca / Bristol-Myers Squibb Alliance, Diasorin, GlaxoSmithKline, Merck, Pfizer, Sanofi-aventis, Vertex. Dr. Solomon, Dr. Domanski, Dr. Desai, Dr. Hoffman, Dr. Arai, Ms. Chiuve, Ms. Ren and Ms. Sloan report no relevant conflicts.

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**Background**—Data regarding an association between Lp(a) and cardiovascular (CV) risk in secondary prevention populations are sparse.

**Methods**—Plasma Lp(a) was measured in 6762 subjects with CAD from three studies; data were then combined with eight previously published studies for a total of 18,979 subjects.

**Results**—Across the three studies, increasing levels of Lp(a) were not associated with the risk of CV events when modeled as a continuous variable (OR 1.03 per log-transformed SD, 95% CI 0.96-1.11) or by quintile (OR Q5:Q1 1.05, 95% CI, 0.83-1.34). When data were combined with previously published studies of Lp(a) in secondary prevention, subjects with Lp(a) levels in the highest quantile were at increased risk of CV events (OR 1.40, 95% CI 1.15-1.71), but with significant between-study heterogeneity ( $P=0.001$ ). When stratified on the basis of LDL cholesterol, the association between Lp(a) and CV events was significant in studies in which average LDL cholesterol was  $\geq 130$  mg/dl (OR 1.46, 95% CI 1.23-1.73,  $P<0.001$ ), whereas this relationship was not significant for studies with an average LDL cholesterol  $<130$  mg/dl (OR 1.20, 95% CI 0.90-1.60,  $P=0.21$ ).

**Conclusions**—Lp(a) is significantly associated with the risk of CV events in patients with established CAD; however, there exists marked heterogeneity across trials. In particular, the prognostic value of Lp(a) in patients with low cholesterol levels remains unclear.

### Keywords

lipoprotein (a); biomarkers; secondary prevention; risk stratification

### Introduction

Lp(a) is a class of lipoprotein particles consisting of a cholesterol-rich LDL moiety that is covalently linked to apolipoprotein(a). Evidence from genetic studies indicates that Lp(a) may play a causal role in the development of atherosclerosis(1). In the first of two large Mendelian randomization studies conducted in Denmark, genetic polymorphisms in the LPA gene were shown to influence Lp(a) levels and increase the risk of myocardial infarction (MI). In particular, a doubling of Lp(a) levels throughout life was associated with a 22% increase in the risk of MI(2,3). In a case-control study in four European countries, two common variants in the LPA gene were found to be strongly associated with Lp(a) levels and those individuals had more than a 50% increased risk of heart disease(2,3). Further, genetically determined Lp(a) levels as determined by the LPA genotype are associated with aortic valve calcification and incident clinical aortic stenosis(4).

Although Lp(a) may prove to be a causal risk factor for the development of ischemic heart disease, its clinical utility as a prognostic biomarker in secondary prevention remains a separate issue that is incompletely defined. Recently, a large pooled analysis in primary prevention populations confirmed that Lp(a) was an independent risk factor for CHD death, non-fatal MI and stroke; albeit the strength of the relationship appeared to be modest when Lp(a) was modeled as a continuous variable(5). In quantile analysis, the relationship appeared curvilinear(5), with significantly greater risk observed for those patients with Lp(a) levels in the highest quartile, consistent with prior reports from individual studies(6-8). As well, there was a trend toward a stronger association between Lp(a) and CV events for patients with higher non-HDL cholesterol levels(5), a finding that has been observed with LDL cholesterol in other analyses(7,9).

Although data in secondary prevention populations are limited, some professional societies have now endorsed routine one-time screening for Lp(a) in individuals at intermediate or high risk of CV events, including selected patients with established CAD(10,11). Moreover,

it has been proposed that an Lp(a) level <50 mg/dl (~80<sup>th</sup> percentile in the general population) be targeted with therapies that lower Lp(a) such as niacin(10).

Given that data regarding the prognostic value of Lp(a) in secondary prevention are sparse and new lipid-modifying therapies are in development that reduce Lp(a)(12-15), we assessed the independent prognostic utility of Lp(a) and evaluated proposed screening cutpoints in three large clinical trial populations of patients with either stable CAD or after an ACS. We further assessed the prognostic utility of Lp(a) by combining the new data with previously published secondary prevention studies, and assessed for effect modification by LDL or total cholesterol concentration.

## Methods

### Study populations and design

The PEACE trial enrolled patients with stable CAD and preserved left ventricular function(16). The CARE trial randomized patients who had experienced a MI within the past 3 to 20 months to pravastatin 40 mg daily versus placebo(17). The PROVE IT-TIMI 22 trial randomized patients following an ACS to atorvastatin 80 mg daily versus pravastatin 40 mg daily(18). Further details regarding the study designs are provided in the Supplementary Appendix.

Based on prior data for Lp(a)(5), the clinical endpoint of interest for this analysis was MACE defined as the composite of CV death, MI or stroke, where available. Of note, in the CARE trial, Lp(a) was measured in an age-matched case-control population of subjects who had or had not experienced fatal CHD or recurrent MI. Endpoints were adjudicated by clinical events committees who were blinded to treatment assignment and to Lp(a) levels.

### Blood Sampling and Analysis

As part of the study protocols, samples of venous blood were to be collected in EDTA-treated tubes from participating subjects in the PEACE, PROVE IT-TIMI 22, and CARE trials. The plasma component was frozen and shipped to a central laboratory where samples were stored at -70°C or colder. Details regarding the assays used to measure Lp(a) concentration in each trial are provided in the Supplementary Appendix.

### Statistical Analysis

In order to evaluate its association with clinical outcomes, Lp(a) was first analyzed as a log-transformed continuous variable and subsequently categorized into quintiles according to Lp(a) concentration. Given the previously demonstrated curvilinear relationship with events(5), further analyses were performed to evaluate previously proposed cutpoints (e.g., 50 mg/dl and 95<sup>th</sup> percentile). Event rates were estimated using the Kaplan-Meier method. Cox proportional hazard or logistic regression models were used to estimate the association between Lp(a) and CV events where appropriate. Multivariable models were created adjusting for baseline characteristics, lipid levels, and treatments that were significantly associated with Lp(a) concentration (see detailed list of covariates in Supplementary Tables 4-6). *In toto*, PEACE, CARE and PROVE IT-TIMI 22 had 80% power to detect: a 10% increase in the odds of MACE per standard deviation of log-transformed Lp(a), a 27% increase in MACE in the top quintile, and a 51% increase in MACE for those patients with Lp(a) levels in the top 5<sup>th</sup> percentile.

In order to place the current findings in the context of previously published studies, data were extracted from previously published reports of Lp(a) in secondary prevention. Since variable thresholds of Lp(a) were used in each study, the relative risk or odds of MACE in

the highest versus lowest quantile of Lp(a) was employed where available (Supplementary figure 1)(19-26). For the purpose of the meta-analysis, odds ratios (95% CI) were calculated for each study wherever possible using logistic regression models. A meta-analysis was then conducted based on random-effects models using the method by Der Simonian and Laird(27). Between-study heterogeneity of risk was assessed using Cochran's Q statistic and the degree assessed using the  $I^2$  measure (the percentage of total variability due to true between-study heterogeneity)(28). The meta-analysis was then stratified by the average study-specific baseline LDL cholesterol (or baseline total cholesterol when LDL cholesterol was not available). For randomized trials of lipid-lowering therapy, achieved rather than baseline LDL cholesterol was used, since the baseline value did not reflect the patients' LDL cholesterol during the period at risk. An LDL cholesterol threshold of  $< \text{or } 130 \text{ mg/dl}$  ( $3.37\text{mM}$ ) [or total cholesterol  $< \text{or } 200 \text{ mg/dl}$  ( $5.18 \text{ mM}$ )] was used, consistent with National Cholesterol Education Program Adult Treatment Panel III Guidelines(29). Since all analyses were considered to be exploratory, all tests were two-sided with a P value  $<0.05$  considered to be significant. Further statistical considerations are provided in the Supplementary Appendix.

## Results

In the current analysis, Lp(a) was measured in 6762 patients, including 3395 patients with stable CAD from the PEACE trial, 785 patients with a prior MI from the CARE trial, and 2529 patients stabilized after a recent ACS from the PROVE IT-TIMI 22 trial. The baseline characteristics of patients in the three trials by Lp(a) concentration are shown in Supplementary Tables 1-3. In general, Lp(a) was not consistently associated with traditional CV risk factors, except that patients with higher Lp(a) levels had mildly higher levels of LDL cholesterol or apolipoprotein B, which is consistent with the contribution of Lp(a) to these measures.

### Association of Lp(a) levels and clinical outcomes

When modeled as a continuous variable per one SD increase in log-transformed Lp(a) concentration, there was no association between baseline Lp(a) levels and the subsequent risk of MACE in the PEACE trial (HR 1.03, 95% CI 0.93-1.14), the CARE trial (OR 1.04, 95% CI 0.92-1.18), or the PROVE-IT TIMI 22 trial (HR 1.04, 95% CI 0.90-1.20). When data were meta-analyzed across the 3 trials, there remained no association between higher levels of log-transformed Lp(a) and the risk of MACE (OR per 1 SD=1.03, 95% CI 0.96-1.11,  $P=0.46$ ; Figure 1) or the odds of CV death or MI (OR per 1 SD=1.05, 95% CI 0.97-1.13,  $P=0.25$ ).

### Exploration of threshold effect

There was no evidence of a threshold effect for CV events when patients were categorized into quintiles of Lp(a) levels across the three trials (Figure 2). Compared with quintile 1, patients in the top quintile of Lp(a) concentration did not have a significant increase in the risk of MACE in the PEACE trial (HR 1.06, 95% CI 0.76-1.49), the CARE trial (OR 1.08, 95% CI 0.69-1.68), or the PROVE-IT TIMI 22 trial (HR 1.02, 95% CI 0.65-1.58). When baseline data were meta-analyzed across the three trials, patients with levels in the top quintile were not at higher risk for MACE (OR 1.05, 95% CI 0.8-1.34,  $P=0.67$ ) or CV death or MI (OR 1.13, 95% CI 0.88-1.44,  $P=0.34$ ) versus those in the lowest quintile. Data for individual components of MACE in each of the trials by quintile of Lp(a) are shown in Supplementary Tables 4-6.

Dichotomizing patients at an Lp(a) concentration of 50 mg/dl did not reveal a threshold of risk at this cutpoint. Specifically, the HR (95% CI) for MACE was 1.02 (95% CI 0.78-1.33)

in PEACE, the OR for fatal CHD or MI was 1.01 (95% CI 0.66-1.57) in CARE, and the HR was 1.13 (95% CI 0.73-1.76) in PROVE-IT TIMI 22. Meta-analyzing data from all 3 trials yielded an OR of 1.08 (0.87-1.34,  $P=0.47$ ) for MACE for patients with an Lp(a) concentration above compared to below 50mg/dl.

Comparing patients with Lp(a) levels above the 95<sup>th</sup> percentile to those with levels below the median, the HR (95% CI) for MACE was 1.13 (0.67-1.89) in PEACE, the OR was 0.99 (0.51-1.89) for fatal CHD or MI in CARE, and the HR for MACE was 1.37 (0.77-2.44) in PROVE-IT TIMI 22. When data were meta-analyzed across the three trials, there remained no significant association between Lp(a) and CV risk for those patients with Lp(a) levels in the top 5<sup>th</sup> percentile (OR 1.20, 95% CI 0.86-1.68,  $P=0.29$  for MACE), although the point estimate was nominally higher than for models that employed lower thresholds as cutpoints for Lp(a).

The results did not materially change after multivariable adjustment (Supplementary Tables 4-6). There was no evidence of effect modification by sex, race and the presence of diabetes mellitus (data not shown).

### Effect of statin therapy on Lp(a) concentration

In the PROVE-IT TIMI 22 trial, in addition to values at randomization, Lp(a) was also measured in 2573 subjects who were statin-naïve prior to randomization and provided a venous blood sample 30 days following randomization. From baseline to 30 days, median levels of Lp(a) rose by 13% (IQR -19 to 60%,  $P<0.001$ ) in patients randomized to pravastatin 40 mg daily and rose by 25% (IQR -15 to 86%,  $P<0.001$ ) in patients randomized to atorvastatin 80 mg daily ( $P<0.001$  for difference between treatment arms). There was no correlation between the change in Lp(a) and the change in LDL from baseline to day 30 for patients treated with pravastatin ( $\rho = -0.05$ ,  $P=0.12$ ) or atorvastatin ( $\rho = -0.01$ ,  $P=0.69$ ). As well, higher levels of Lp(a) measured at 30 days were not associated with an increased risk of CV death, MI or stroke (Supplementary Table 7).

### Meta-analysis of Lp(a) in secondary prevention studies

The current results from PEACE, CARE and PROVE IT-TIMI 22 were then combined using meta-analysis with those of eight previously published studies of Lp(a) in secondary prevention (Supplemental Table 8), for a total of 18,979 subjects and more than 3000 MACE(19-26). When the 11 studies were combined, patients with Lp(a) levels in the highest quantile had a significant 40% increase in the odds of MACE (OR 1.40, 95% CI 1.15-1.71,  $P=0.001$ , Figure 3). However, when assessing for heterogeneity, the Q statistic was 34.0 (df 12),  $P=0.001$ ;  $I^2$  was 65%, indicating a high degree of between-study heterogeneity.

We then examined whether there was effect modification on the basis of the average LDL cholesterol concentration (or total cholesterol concentration if LDL cholesterol was unavailable) for each study. When results were stratified on this basis, the association between Lp(a) levels in the highest quantile and MACE was highly significant in studies with an average LDL cholesterol  $\geq 130$  mg/dl (OR 1.46, 95% CI 1.23-1.73,  $P<0.001$ ). In contrast, the relationship between Lp(a) and MACE was not significant in those studies where LDL cholesterol was lower (OR 1.20, 95% CI 0.90-1.60,  $P=0.21$ ;  $P$  for interaction=0.26, Figure 4).

Stratification on the basis of LDL cholesterol concentration resolved between-study heterogeneity for those studies with a higher average LDL cholesterol ( $Q_{df5}=5.5$ ,  $P=0.36$ ;  $I^2=9\%$ ; Figure 4). In contrast, between-study heterogeneity remained high among those studies with lower LDL cholesterol concentration ( $Q_{df8}=22.7$ ,  $P=0.004$ ;  $I^2=65\%$ ). Removing

one study at a time revealed that heterogeneity was eliminated when the results of AIM-HIGH were excluded ( $Q_{df6}=6.2$ ,  $P=0.40$ ;  $I^2=3\%$ ). After doing so, the odds of MACE for patients with elevated Lp(a) levels in those studies with an average LDL cholesterol concentration  $<130$  mg/dl was 0.99 (95% CI 0.82-1.20,  $P=0.95$ ;  $P$  for interaction between Lp(a), MACE, and LDL cholesterol=0.003).

## Discussion

Although Lp(a) may be a risk factor for the development of coronary disease, its prognostic utility as a marker of risk in the setting of secondary prevention is not well established. The current findings suggest that high levels of Lp(a) may help to identify individuals at increased risk of CV events in patients with established CAD; however, there exists marked heterogeneity in findings across studies. In particular, the prognostic value of Lp(a) in patients whose cholesterol is well controlled remains unclear. These findings are relevant given the recent recommendations by the European Atherosclerosis Society Consensus Panel and National Lipid Association Biomarkers Expert Panel to consider assessment of Lp(a) concentration in selected patients with an intermediate-to-high risk of CV events, including those with established CAD(10,11).

Although several prior epidemiologic studies have demonstrated an association between Lp(a) levels and CV risk, these studies have been largely restricted to primary prevention studies(30-34). In a large pooled analysis that combined data from 126,634 subjects across 32 prospective studies of patients without known CAD, Lp(a) was shown to be significantly associated with the risk of a first CV event, including CV death, MI and stroke(5). While the relationship was significant, the excess risk conferred by elevated levels of Lp(a) was relatively modest. Assuming a log-linear association, for every one standard deviation increase in Lp(a) concentration, there was a 13% increase in the risk of CHD. In keeping with other studies(7,35), the pooled analysis appeared to demonstrate a threshold effect, with much of the risk concentrated for those patients in the top quartile of Lp(a) values(5). Similarly, a recent analysis in the Danish general population in 8720 subjects concluded that Lp(a) levels 80<sup>th</sup> percentile (47 mg/dl) may be most useful for patient risk reclassification(36). To date, relatively few studies have examined the prognostic utility of Lp(a) in patients with established CAD and with mixed results(19-26,31,37). An older meta-analysis that examined data in primary and secondary prevention populations concluded that the prognostic utility of Lp(a) was not as strong in secondary prevention as in population-based studies(31).

In the three studies in which we measured Lp(a), only when we examined Lp(a) levels above the 95<sup>th</sup> percentile did we observe a signal toward increased risk [OR 1.20 (95% CI 0.86-1.68) for MACE]. The observed association was not statistically significant, but the findings are similar to the risk ratios seen in the primary prevention setting with very high levels of Lp(a) (adjusted RR 1.2-1.3)(5). Of note, though, all three studies enrolled patients on the basis of relatively low cholesterol levels and/or there was widespread use of lipid-lowering therapies, leading to LDL levels  $<130$  and/or total cholesterol levels  $<200$  mg/dl.

Since we observed no significant association between Lp(a) and the risk of CV events across three large secondary prevention studies, we conducted a meta-analysis in order to place the current findings in the context of previously published studies. The meta-analysis enabled us to examine studies which spanned a broader range of statin use and LDL cholesterol levels (with study mean LDL cholesterol levels ranging from 71-188 mg/dL). The meta-analysis highlighted that there exists marked heterogeneity across studies that have examined the prognostic utility of Lp(a). Moreover, our findings strengthen prior observations suggesting that the relationship between Lp(a) and CV events may be attenuated in patients with lower

levels of LDL cholesterol. Specifically, in both the Physicians' Health Study and the Women's Health Study, the association between Lp(a) and MACE was apparent only in the subset of the study population with higher cholesterol levels (LDL >121-160 mg/dL)(7,9). Similarly, in a meta-analysis of primary prevention populations, there was a trend toward a stronger association between Lp(a) and CV events for patients with higher non-HDL cholesterol levels(31). Similar observations were also reported in an early study that examined the association between Lp(a) and the odds of CAD at angiography in a population of men(38). In a subsequent study of men with known CAD and elevated apolipoprotein B concentration, Lp(a) levels appeared to be no longer atherogenic in individuals whose LDL cholesterol decreased by more than 10% from baseline after starting lipid-lowering therapy(19). As previously reported for one of the trials within our meta-analysis, the 4S trial, higher levels of Lp(a) were associated with an increased risk of death or MI, but the relationship appeared to be largely attenuated for those patients randomized to simvastatin when compared to those patients randomized to placebo(21). In an angiographic trial, Lp(a) was no longer a determinant of CAD progression in patients whose LDL cholesterol concentration had been effectively lowered by diet and exercise(39). As well, in patients with familial hypercholesterolemia, there may be a lack of benefit from reducing Lp(a) in patients whose LDL cholesterol had been effectively lowered by apheresis or drug therapy(40). Interestingly, two recent trials of niacin, which lowers Lp(a) by ~30% in addition to its other lipoprotein effects, failed to show any clinical benefit in two populations whose baseline total cholesterol levels was well controlled at 128-145 mg/dL(41,42).

It should be noted that the observed trend toward effect modification by LDL cholesterol concentration may also be related to the direct effects of statins on Lp(a) levels and/or the effect of statins on any mechanisms by which Lp(a) increases risk of MACE, since the vast majority of the subjects in studies with a LDL cholesterol <130 mg/dL were on statins. For example, with regard to the former, consistent with prior observations(43), we observed that the use of more potent statin therapy may increase Lp(a) concentration; therefore, the relationship between Lp(a) and MACE may be partly attenuated in this setting.

Limitations for the current study include the fact that it was designed *post hoc* and sensitivity analyses to explore cutpoints can only be considered exploratory in nature. Since apo(a) is extremely heterogeneous in size and in content of epitopes that are recognized by antibodies, harmonization of Lp(a) levels as assessed by different assays cannot be readily achieved(44). Although each of the trials in our analysis used different assays to quantify Lp(a) concentration, consistent results were observed across each of the three studies included in the primary analysis. Lp(a) isoform number or single nucleotide polymorphisms that predict high Lp(a) levels were not measured(3). Since small apo(a) isoforms with high Lp(a) levels have been shown to be more atherogenic, it is possible that these measures of Lp(a) may provide more incremental information for risk stratification. Although there was no statistically significant association between CV events and Lp(a) levels in the 3 study populations that we analyzed, if the risk was limited to those in the top 5<sup>th</sup> percentile of Lp(a) levels, we had limited power to detect such an association. For the meta-analysis, we did not have access to subject-level data, precluding the ability to examine heterogeneity by stratifying subjects on the basis of several factors simultaneously. As is inherent to the process, there are challenges when data are combined from different studies which enrolled different patients and used different laboratory assays and clinical definitions. Further variability can stem from different approaches to combining data and examining non-predefined subgroups. Additional data from very large studies, ideally with broad ranges of cholesterol levels in patients taking and not taking a statin, would add clarity.

In summary, although the current study demonstrates that patients with established CAD who have a high level of Lp(a) are at an increased risk of subsequent MACE, the marked



heterogeneity between studies raises questions regarding the value of Lp(a) as a clinically useful biomarker for risk assessment, particularly among patients with well controlled LDL cholesterol. Moreover, although Lp(a) may directly contribute to CHD, there is currently insufficient evidence to suggest that Lp(a) levels above a discrete cutpoint should be used to guide therapy or that treatment will translate into improved clinical outcomes(41,42). Trials are now ongoing with novel therapies that reduce Lp(a), such as the novel CETP inhibitors anacetrapib(12), mipomersen(45) and PCSK9 inhibitors(13,15); although, such therapies influence other lipid components in tandem. Recently, a specific antisense oligonucleotide directed toward apo(a) was shown to lower apo(a) and Lp(a) levels in transgenic mice, and a phase I trial is underway(46). If a strategy of Lp(a) reduction should ultimately prove to be successful, it will be of interest to determine whether benefit is observed regardless of baseline Lp(a) concentration or specific reduction in Lp(a).

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Abbreviations

<b>CARE</b>	Cholesterol and Recurrent Event
<b>CETP</b>	cholesteryl ester transfer protein
<b>HDL</b>	high-density lipoprotein
<b>LDL</b>	low-density lipoprotein
<b>Lp(a)</b>	lipoprotein (a)
<b>MACE</b>	major adverse cardiovascular event
<b>PEACE</b>	Prevention of Events with Angiotensin Converting Enzyme Inhibition
<b>PCSK9</b>	proprotein convertase subtilisin/kexin type 9
<b>PROVE IT-TIMI 22</b>	Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22
<b>SD</b>	standard deviation
<b>TC</b>	total cholesterol

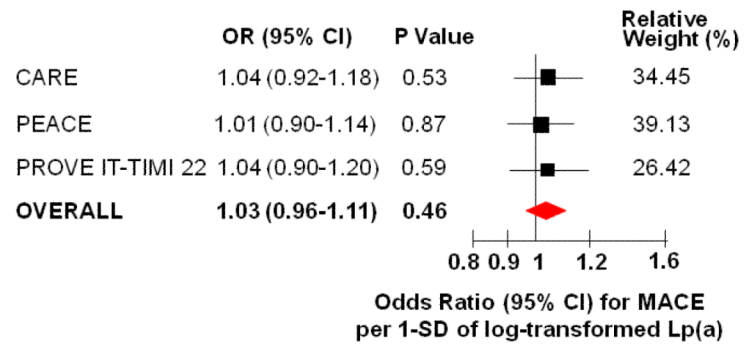
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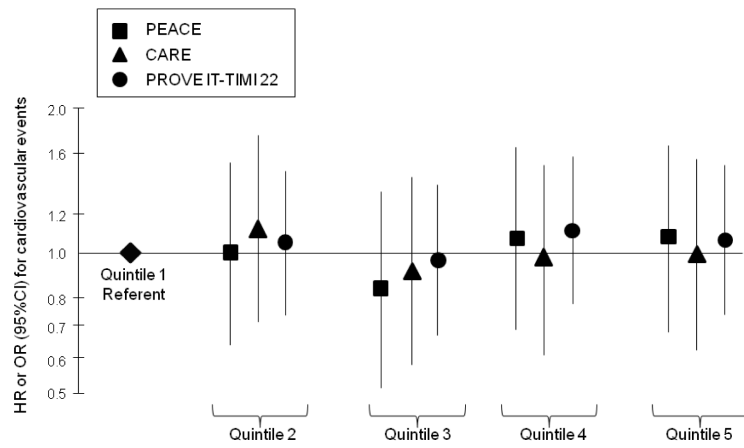
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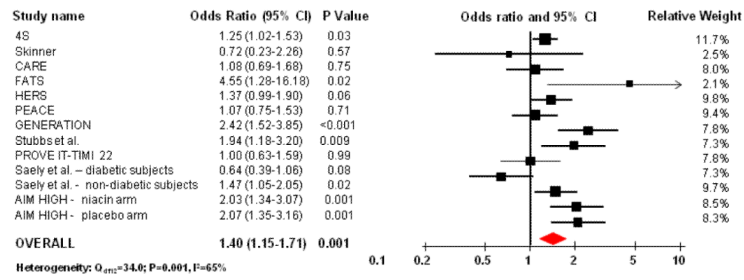
**Figure 1. Lp(a) and Odds of MACE**

Effect estimates are per 1 SD of log-transformed Lp(a). For PEACE and PROVE-IT TIMI 22 MACE consisted of CV death, MI or stroke; for CARE MACE consisted of fatal CHD or MI due to its case-control design. Results from individual studies combined using meta-analysis.



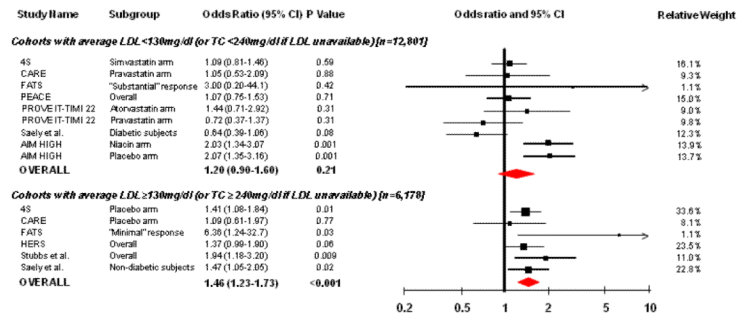
**Figure 2. Risk of MACE by Quintile of Lp(a)**

The adjusted relative hazard (adjusted HR, 95% CI) of CV death, MI or stroke by quintile of Lp(a). For the CARE trial, the adjusted relative odds (adjusted OR, 95% CI) of fatal CHD or MI are shown.



**Figure 3. Meta-analysis of Published Studies of Lp(a) in Secondary Prevention**

The odds of MACE for those subjects with the highest levels of Lp(a) when the current findings from PEACE, CARE and PROVE IT-TIMI 22 were combined with 8 previously published studies of Lp(a) in secondary prevention. Marked heterogeneity existed across studies when the eight other studies were included (P=0.001).



**Figure 4. Lp(a) and Odds of MACE by Cholesterol Concentration**

The odds of MACE for those subjects with the highest levels of Lp(a) were combined across 9 studies and stratified by a study-wide average LDL cholesterol concentration of less than vs. greater than or equal to 130 mg/dl (or total cholesterol < or = 200 mg/dl). Heterogeneity for studies with LDL <130mg/dl:  $Q_{df8}=22.7$ ;  $P=0.004$ ,  $I^2=65\%$ . Heterogeneity for studies with LDL  $\geq$  130mg/dl:  $Q_{df5}=5.5$ ;  $P=0.36$ ,  $I^2=9\%$