Lipoprotein(a) Concentrations, Rosuvastatin Therapy, and Residual Vascular Risk

An Analysis From the JUPITER Trial (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin)

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Background—Lipoprotein(a) [Lp(a)] is a low-density lipoprotein–like particle largely independent of known risk factors and predictive of cardiovascular disease. Statins may offset the risk associated with elevated Lp(a), but it is unknown whether Lp(a) is a determinant of residual risk in the setting of low low-density lipoprotein cholesterol after potent statin therapy.

Methods and Results—Baseline and on-treatment Lp(a) concentrations were assessed in 9612 multiethnic participants in the JUPITER trial (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin) before and after random allocation to rosuvastatin 20 mg/d or placebo, with outcomes reported for whites (n=7746). Lp(a) concentrations (median [25th–75th percentile], in nmol/L) were highest in blacks (60 [34–100]), then Asians (38 [18–60]), Hispanics (24 [11–46]), and whites (23 [10–50]; $P<0.001$). Although the median change in Lp(a) with rosuvastatin and placebo was zero, rosuvastatin nonetheless resulted in a small but statistically significant positive shift in the overall Lp(a) distribution ($P<0.0001$). Baseline Lp(a) concentrations were associated with incident cardiovascular disease (adjusted hazard ratio per 1-SD increment in Ln[Lp(a)], 1.18; 95% confidence interval, 1.03–1.34; $P=0.02$). Similarly, on-statin Lp(a) concentrations were associated with residual risk of cardiovascular disease (adjusted hazard ratio, 1.27; 95% confidence interval, 1.01–1.59; $P=0.04$), which was independent of low-density lipoprotein cholesterol and other factors. Rosuvastatin significantly reduced incident cardiovascular disease among participants with baseline Lp(a) greater than or equal to the median (hazard ratio, 0.62; 95% confidence interval, 0.43–0.90) and Lp(a) less than the median (hazard ratio, 0.46; 95% confidence interval, 0.30–0.72), with no evidence of interaction. Similar results were obtained when analyses included nonwhites.

Conclusion—Among white JUPITER participants treated with potent statin therapy, Lp(a) was a significant determinant of residual risk. The magnitude of relative risk reduction with rosuvastatin was similar among participants with high or low Lp(a).

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Medical therapies, including statins, have demonstrated efficacy in the prevention of cardiovascular events across a wide spectrum of baseline risk[1]; however, substantial residual risk has fostered interest in identifying the underlying risk factors in hopes of identifying novel targets of therapy. Lipoprotein(a) [Lp(a)] is a low-density lipoprotein (LDL)–like particle with apolipoprotein B covalently linked to apolipoprotein(a) by a single disulfide bond.[2]

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Since its initial description by Berg in 1963 as a variant of LDL, the Lp(a) molecule has generated interest regarding its potential proatherogenic or prothrombotic role in human disease.[3] Circulating concentrations of Lp(a) differ widely across individuals and ethnic subgroups, mediated in large

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part by genetic variation at the *LPA* gene locus.[2] Individuals contain highly polymorphic copy numbers of the kringle IV type 2 domain, with lower numbers relating to smaller apolipoprotein(a) size and increased plasma Lp(a) concentrations.[4] Robust associations between Lp(a) and cardiovascular disease (CVD) outcomes have been noted in previous studies conducted in general populations, with Lp(a) concentrations providing small, statistically significant improvement in risk prediction when added to conventional risk factors.[5,6] Recent mendelian randomization studies have linked genetic variations at the *LPA* locus to both circulating plasma concentrations and the risk of CVD, which supports a possible causal role of Lp(a) in CVD pathogenesis.[7,8]

Previous studies have suggested that statin therapy may attenuate the risk associated with Lp(a), although current data addressing this common clinical question remain very limited.[9] After the completion of the Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial but before obtaining the Lp(a) measurements, we prespecified the hypothesis that the residual risk of CVD may be related in part to increased Lp(a) concentrations. Therefore, we determined the association of baseline and on-treatment Lp(a) concentrations with incident CVD events in the context of potent rosuvastatin therapy and very low achieved LDL cholesterol concentrations in JUPITER.

Methods

Study Population

JUPITER was a primary prevention, randomized, double-blind, placebo-controlled trial investigating whether rosuvastatin 20 mg/d would decrease incident CVD in 17 802 asymptomatic individuals with LDL cholesterol <130 mg/dL and a high-sensitivity C-reactive protein (hsCRP) level ≥2.0 mg/L.[10] Exclusion criteria for the JUPITER trial were diabetes mellitus, previous or current use of lipid-lowering therapy, or triglycerides >500 mg/dL. The trial protocol stipulated both a baseline and 12-month visit for blood draws and immediate trial assays. Study participants were requested but not required to provide samples for additional phenotyping: 11 953 participants provided these additional samples at both baseline and 1 year, and of these, 9612 had sufficient sample remaining for Lp(a) assessment. Because of ethnic variation in Lp(a) concentrations and the smaller proportion of nonwhite participants in JUPITER, the primary outcomes analysis is reported among white participants (n=7746), with subsequent sensitivity analyses that included all 9612 white and nonwhite participants. A small number of samples failed assay quality control criteria (<0.2%), which led to an effective size of 7730 and 7739 individuals for the baseline and on-statin white cohort, respectively.

Laboratory Measurements

Lipid, apolipoprotein, and hsCRP values were assayed in a core laboratory as described previously.[10–12] Consistent with previous JUPITER biomarker analyses, on-treatment Lp(a) concentrations were defined as values obtained after 1 year of randomized treatment.[11–14] Lp(a) concentrations were measured in a blinded manner at Quest Diagnostics Nichols Institute (San Juan Capistrano, CA) with a commercially available assay (Randox Laboratories; Crumlin, Co. Antrim, United Kingdom) that is not affected by kringle IV type 2 repeats. Given substantial interindividual variability in the number of kringle IV type 2 repeats and thus Lp(a) molecular weight, values were measured and reported in nanomoles per liter to reflect the concentration of Lp(a) particles. This methodology of Lp(a) assessment is in accordance with a recent National Heart, Lung, and Blood Institute workshop recommendation.[15] An assessment of 5 standard samples across a broad range of Lp(a) concentrations indicated that conversion to milligrams per deciliter can be approximated by dividing values in nanomoles per liter by 2.15 (r^2=0.998 for linearity). Mean coefficients of variation for the assay were 3.5%, 4.0% and 2.6% at Lp(a) concentrations of 38, 60, and 138 nmol/L, respectively.

Outcomes

Our primary outcome was the prespecified JUPITER trial primary end point, a composite CVD end point that included incident myocardial infarction, stroke, hospitalization for unstable angina, arterial revascularization, or cardiovascular death. In the present analysis, we also examined a combined end point of CVD and all-cause mortality consistent with prior analyses of lipids and residual risk in JUPITER.[12] End-point criteria have been described previously; all were adjudicated by an independent committee blinded to treatment assignment.[10]

Statistical Analysis

Statistical analyses were performed with SAS version 9.1 (SAS Institute Inc, Cary, NC). Medians and 25th and 75th percentiles were calculated for continuous variables. The significance of variation in Lp(a) values across categorical clinical characteristics was assessed with the nonparametric Wilcoxon rank sum or Kruskal-Wallis 1-way ANOVA tests. Spearman coefficients were used to express the magnitude of correlation between baseline and on-treatment biomarkers with corresponding Lp(a) concentrations.

Tests of outcomes were performed by calculating incidence rates per 100 person-years, with exposure time calculated as the time from randomization to occurrence of the primary end point or the date of death, last study visit, withdrawal, or loss to follow-up. As in prior reports,[11-14] we decided a priori to include all postrandomization events in the on-treatment analysis of associations with incident events given the minimal impact of statin therapy on Lp(a) and given that that any such change would have occurred within the first few weeks of randomization. Cox proportional hazard regression models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for first CVD. HRs are reported both per SD increment in the natural logarithm (ln) of Lp(a), expressed as a continuous variable, and according to Lp(a) quartiles. *P* values for trend were obtained by including quartile number as a variable in the regression model. Regression models were adjusted for age, sex, and treatment group, with subsequent additional adjustment for smoking status, family history of premature coronary disease, body mass index, systolic blood pressure, fasting glucose, high-density lipoprotein cholesterol, LDL cholesterol, and log-transformed values for triglycerides and hsCRP. Results were also unaffected in a sensitivity analysis that removed family history of premature coronary disease from the adjusted model. Similar analyses were subsequently conducted with an expanded end point of the primary end point plus all-cause mortality. Additional sensitivity analyses were performed that included nonwhite participants. We assessed for nonlinearity in the association of Lp(a) and outcomes by repeating the analyses after adding a quadratic term to the models. The quadratic terms were not statistically significant.

The risk reduction for the primary end point with rosuvastatin therapy was calculated in participant subgroups dichotomized by the median baseline Lp(a) concentration to assess for heterogeneity of effect. Statistical tests for interaction between Lp(a) concentration and treatment allocation in relation to outcomes were obtained by use of likelihood ratio tests. Cut-point analysis implemented a threshold of 50 mg/dL (≈108 nmol/L with a correction factor of 2.15) and the 90th percentile of Lp(a) in accordance with the recommendations of a recent expert panel and a previous cohort analysis, respectively.[16,17] All *P* values were 2-tailed, with a value <0.05 considered to indicate statistical significance.

Results

Lp(a) concentrations were greatest in black participants (n=853; median 60 nmol/L), then Asians (n=138; median 38 nmol/L), then Hispanics (n=784; median 24 nmol/L) and whites (n=7730; median 23 nmol/L), as displayed in Table I in

the online-only Data Supplement. Subsequent analyses were thus restricted to white participants unless otherwise noted.

Baseline characteristics of the white JUPITER Lp(a) cohort were similar to those in which Lp(a) was not available and the overall study population, except for a slightly decreased prevalence of metabolic syndrome in patients included in the present analysis (Table 1). As shown in Table 2, women had higher Lp(a) concentrations than men (26 versus 22 nmol/L, $P<0.0001$). Participants with metabolic syndrome had lower Lp(a) than those without metabolic syndrome (20 versus 25 nmol/L, $P<0.0001$). As anticipated, Lp(a) was weakly correlated with other risk factors at baseline and on-statin treatment (Table II in the online-only Data Supplement). Spearman correlation coefficients between baseline Lp(a) and LDL cholesterol, apolipoprotein B, and hsCRP were 0.13, 0.08, and 0.04, respectively.

Among the placebo group, Lp(a) concentrations at baseline and 12 months were stable and highly self-correlated (Spearman $r=0.95$; intraclass correlation coefficient, 0.93 [95% CI, 0.89–0.97]). Similar results were noted in the rosuvastatin arm, with Spearman $r=0.95$ and an intraclass correlation coefficient of 0.92 (95% CI, 0.87–0.97). Although the median change in Lp(a) with rosuvastatin and placebo was zero, rosuvastatin nonetheless resulted in a small but statistically significant positive shift in the overall Lp(a) distribution; the 25th and 75th percentile change, respectively, in Lp(a) was −1 and 5 for rosuvastatin and −3 and 2 for placebo ($P<0.0001$). No relationship was noted between change in LDL cholesterol and change in Lp(a) with statin therapy (Spearman $r=0.02$; $P=0.14$).

Incident Cardiovascular Events According to Baseline Lp(a) Concentrations

During a median follow-up of 2.0 years, the primary and expanded CVD end points occurred in 210 and 283 white JUPITER participants, respectively. Baseline Lp(a) was associated with increased risk of CVD (Table 3), with a fully adjusted HR per 1-SD increment in ln Lp(a) [representing an ≈2.5-fold increment in Lp(a)] of 1.18 (95% CI, 1.03–1.35) and 1.21 (95% CI, 1.08–1.36) for the primary and expanded end point, respectively. Incidence rates and HRs also indicated a statistically significant increased risk in the quartile of patients with the highest Lp(a) concentrations (>50 nmol/L) compared with those in the referent quartile with the lowest Lp(a) values, with an adjusted HR of 1.64 (95% CI, 1.12–2.41) for the primary end point and 1.61 (95% CI, 1.16–2.25) for the expanded end point. The association of baseline Lp(a) with CVD did not differ according to randomized treatment group, with no significant interaction in an unadjusted model that included treatment group and Lp(a) as a continuous variable

Table 1. Clinical Characteristics of White Participants in the JUPITER Lp(a) Cohort and Overall Study Population

	Lp(a) Cohort (n=7746)*	Lp(a) Unavailable (n=4937)	Overall Cohort (n=17 802)
Age, y	66 (60–71)	66 (60–71)	66 (60–71)
Females	2574 (33)	1623 (33)	6801 (38)
Rosuvastatin group	3882 (50)	2476 (50)	8901 (50)
BMI, kg/m^2	28 (25–32)	29 (26–32)	28 (25–32)
SBP, mm Hg	135 (125–146)	134 (125–145)	134 (124–145)
DBP, mm Hg	80 (74–86)	80 (75–87)	80 (75–87)
Current smoker	1111 (14)	733 (15)	2820 (16)
FH of premature CHD†	1054 (14)	656 (13)	2045 (11.5)
Metabolic syndrome	2892 (38)	2151 (44)	7375 (42)
Aspirin use	1463 (19)	929 (19)	2958 (16.6)
hsCRP, mg/L	4.0 (2.7–6.4)	4.1 (2.8–6.6)	4.3 (2.9–7.1)
Lp(a), nmol/L	23 (10–50)	…	…
LDL cholesterol, mg/dL	110 (96–120)	110 (97–120)	108 (94–119)
HDL cholesterol, mg/dL	50 (41–61)	48 (40–59)	49 (40–60)
Triglycerides, mg/dL	114 (82–160)	120 (87–174)	118 (85–169)
Total cholesterol, mg/dL	187 (172–201)	187 (171–201)	185 (169–200)
Glucose, mg/dL	95 (89–101)	96 (89–104)	94 (88–102)
Glycohemoglobin, %	5.6 (5.4–5.8)	5.7 (5.4–5.9)	5.7 (5.5–5.9)
GFR, mL·min^{-1}·1.73 m^{-2} of body surface area	73 (65–82)	72 (64–81)	74 (65–84)

Values are n (%) or median (25th–75th percentile). BMI indicates body mass index; CHD, coronary heart disease; DBP, diastolic blood pressure; FH, family history; GFR, glomerular filtration rate; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; JUPITER, Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin; LDL, low-density lipoprotein; Lp(a), lipoprotein(a); and SBP, systolic blood pressure.

*Baseline Lp(a) measurements available on 7730 white participants.

†Family history of premature coronary disease was defined as diagnosis of the disease in a male first-degree relative before the age of 55 y or in a female first-degree relative before the age of 65 y.

Table 2. Baseline Lipoprotein(a) Concentration According to Clinical Subgroups Among White Participants in JUPITER

	n	Median (25th–75th %)	*P* Value
Sex			
Men	5172	22 (10–47)	<0.0001
Women	2574	26 (12–53)	
Treatment group			
Placebo	3864	23 (10–48)	0.96
Rosuvastatin	3882	24 (10–51)	
Current smoker			
No	6635	23 (10–49)	0.61
Yes	1111	25 (10–52)	
Family history of premature CHD*			
No	6666	23 (10–49)	0.09
Yes	1054	25 (11–53)	
Metabolic syndrome			
No	4788	25 (11–53)	<0.0001
Yes	2892	20 (10–44)	
Aspirin use			
No	6283	23 (10–49)	0.16
Yes	1463	23 (11–54)	

CHD indicates coronary heart disease; and JUPITER, Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin.

*Family history of premature coronary disease was defined as diagnosis of the disease in a male first-degree relative before the age of 55 y or in a female first-degree relative before the age of 65 y.

(*P* for interaction=0.80; Tables III and IV in the online-only Data Supplement) or quartile number (*P* for interaction=0.80). Furthermore, the association of Lp(a) with CVD was similar across clinically relevant clinical subgroups, as displayed in Table V in the online-only Data Supplement (*P* for interaction >0.05 for all). The observed relationship was somewhat stronger in participants with baseline hsCRP below the cohort median of 4.0 mg/L, with an HR of 1.32 (95% CI, 1.10–1.59), compared with those equal to or above the median, with an HR of 1.05 (95% CI, 0.88–1.26), although this interaction did not achieve statistical significance in formal interaction testing (*P* for interaction=0.09).

Residual Risk According to On-Statin Lp(a) Concentrations

Among patients allocated to rosuvastatin, greater on-treatment Lp(a) concentrations were similarly associated with residual risk of CVD, with adjusted HRs of 1.27 for each SD change in Lp(a) (95% CI, 1.01–1.59) for the primary end point and 1.29 (95% CI, 1.07–1.56) for the expanded end point (Table 4). Quartile analysis showed directionally consistent results. Additional models that examined on-treatment Lp(a) adjusted for on-statin (instead of baseline) concentrations of high-density lipoprotein cholesterol, LDL cholesterol, ln triglycerides, and ln hsCRP yielded similar results (Table VI in the online-only Data Supplement).

Threshold Analysis

The previously recommended threshold of 50 mg/dL (≈108 nmol/L) was exceeded by 11% of white participants at baseline. Compared with participants whose baseline Lp(a) was <50 mg/dL, those with Lp(a) ≥50 mg/dL had increased risk of CVD, with fully adjusted HRs of 1.57 (95% CI, 1.08–2.27; *P*=0.02) and 1.69 (95% CI, 1.24–2.31; *P*=0.001) for the primary and expanded end points, respectively. Similarly, participants whose on-statin Lp(a) exceeded this threshold (13% of the cohort) exhibited a trend toward increased risk for the primary (HR, 1.67; 95% CI, 0.93–3.02; *P*=0.09) and expanded (HR, 1.54; 95% CI, 0.93–2.55; *P*=0.09) end point.

A similar analysis dichotomized white participants based on the 90th percentile value (116 nmol/L at baseline; 134 nmol/L in the on-statin group). Compared with white participants whose Lp(a) was <90th percentile, individuals with baseline Lp(a) ≥90th percentile had a trend toward increased risk of the primary end point (adjusted HR, 1.48; 95% CI, 1.00–2.20; *P*=0.05) which was statistically significant for the expanded end point (adjusted HR, 1.64; 95% CI, 1.18–2.27; *P*=0.003). On-statin analyses indicated similar results (primary end point adjusted HR, 1.96 [95% CI, 1.04–3.67], *P*=0.04; expanded end point adjusted HR, 1.75 [95% CI, 1.02–3.00], *P*=0.04).

Lp(a) Associations in Multiethnic Cohort and by Ethnic Subgroups

A sensitivity analysis was conducted in the multiethnic cohort that included all participants with Lp(a) concentrations available. The baseline cohort included 9591 multiethnic participants, in whom the primary and expanded end points occurred in 234 and 327 participants, respectively. The adjusted HRs per 1-SD (roughly 2.5-fold) increase were 1.19 (95% CI, 1.04–1.35; *P*=0.01) for the primary end point and 1.19 (95% CI, 1.06–1.32; *P*=0.002) for the expanded end point. A similar analysis was conducted with the on-statin subgroup that involved 4797 participants with 81 primary and 118 expanded end points observed. The adjusted HRs per 1-SD increase were 1.29 (95% CI, 1.03–1.61; *P*=0.02) and 1.25 (95% CI, 1.04–1.50; *P*=0.02) for the primary and expanded end points.

Few primary events occurred in blacks (n=13) or Hispanics (n=6), which limited the power to explore relationships with incident events. The adjusted HRs per 1-SD increment were 1.43 (95% CI, 0.69–2.98; *P*=0.34) in black participants and 1.23 (95% CI, 0.55–2.75) in Hispanic participants in this cohort. There was no evidence of interaction by ethnicity when the model involved all ethnic groups (*P* for interaction=0.52) or in an additional analysis that dichotomized participants as white versus nonwhite (*P* for interaction=0.37).

Efficacy of Rosuvastatin According to Baseline Lp(a)

Rosuvastatin had similar efficacy in reducing the incidence of the primary and expanded end points in participant subgroups with above- or below-median baseline Lp(a) concentrations (Figure; *P* for interaction=0.33 and 0.10 for the primary and expanded end points, respectively).

Table 3. Association Between Baseline Lipoprotein(a) and Incident CVD Among White Participants in JUPITER

	Quartile One (≤10 nmol/L)	Quartile Two (11–23 nmol/L)	Quartile Three (24–49 nmol/L)	Quartile Four (≥50 nmol/L)	*P* for Trend	HR per SD Increment	*P* Value
Primary end point							
No. of events/N	44/1991	50/1884	45/1957	71/1898		210/7730	
Incidence rate, per 100 person-years	0.99	1.17	1.02	1.62	0.02	1.20	
Model One	1.00	1.18 (0.79–1.78) *P*=0.44	1.04 (0.68–1.58) *P*=0.87	1.70 (1.16–2.47) *P*=0.006	0.01	1.19 (1.05–1.36)	0.008
Model Two	1.00	1.19 (0.79–1.79) *P*=0.40	1.02 (0.67–1.56) *P*=0.93	1.64 (1.12–2.41) *P*=0.01	0.02	1.18 (1.03–1.35)	0.02
Primary end point plus total mortality							
No. of events/N	59/1991	63/1884	67/1957	94/1898		283/7730	
Incidence rate, per 100 person-years	1.32	1.47	1.53	2.14	0.004	1.62	
Model One	1.00	1.11 (0.78–1.59) *P*=0.56	1.15 (0.81–1.63) *P*=0.44	1.66 (1.20–2.29) *P*=0.002	0.002	1.22 (1.09–1.37)	0.0005
Model Two	1.00	1.12 (0.78–1.60) *P*=0.54	1.14 (0.80–1.63) *P*=0.47	1.61 (1.16–2.25) *P*=0.005	0.005	1.21 (1.08–1.36)	0.001

Hazard ratios are expressed per 1-SD increment in the natural logarithm of lipoprotein(a), with 1-SD representing an ≈2.5-fold increment in Lp(a). n=7730, reflective of number of white participants with baseline lipoprotein(a) value available.

Model One: Adjusted for age, sex, and treatment group.

Model Two: Adjusted for age, sex, treatment group, smoking, family history of premature coronary disease, body mass index, systolic blood pressure, fasting glucose, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, natural logarithm of triglycerides, and natural logarithm of high-sensitivity C-reactive protein.

CVD indicates cardiovascular disease; HR, hazard ratio; and JUPITER, Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin.

Discussion

This evaluation from the JUPITER trial among participants with initially low LDL cholesterol and elevated hsCRP demonstrated that baseline Lp(a) concentrations were associated with increased CVD risk. In addition, among white participants randomly allocated to potent statin therapy who achieved very low LDL cholesterol (median on-treatment LDL cholesterol 54 mg/dL), baseline and on-statin Lp(a) concentrations were associated with residual risk of CVD. This was independent of other risk factors, including LDL cholesterol. Rosuvastatin had similar efficacy in reducing CVD regardless of baseline Lp(a). Threshold analyses that used previously proposed clinical cut points demonstrated potential utility in identifying asymptomatic individuals at increased CVD risk. This increased risk in the context of robust lowering of LDL cholesterol and C-reactive protein with statin therapy reinforces growing interest in targeting Lp(a) for residual risk assessment and potential modulation for therapeutic gain.

The present data complement recent studies that demonstrated that genetic polymorphisms conferring higher Lp(a) concentrations were associated with increased risk for atherosclerotic events, thus supporting the notion that lifelong elevation in Lp(a) may be causally associated with CVD.[7,8] However, the relative contribution of multiple potential mechanisms remains unclear.[2] Apolipoprotein(a) may lead to a prothrombotic state based on interference with plasminogen activation. Additional data have demonstrated an effect of Lp(a) on endothelial cell permeability, adhesion molecule expression, and regulation of vascular proliferation.[2] Lp(a) also serves as a carrier of oxidized phospholipids, which may propagate atherosclerosis via inflammatory pathways. Indeed, Lp(a) concentrations are increased in humans with a broad range of inflammatory conditions.[18–20]

The results from the present study are broadly consistent with a recent individual-participant meta-analysis that noted adjusted risk ratios per 1-SD increment of ln Lp(a) for coronary disease of 1.13 (95% CI, 1.09–1.18).[5] We confirmed the substantially increased Lp(a) concentrations in blacks and modest elevations in women noted in previous reports.[5] Lp(a) concentrations were highest in blacks, followed by Asians, then Hispanics and whites. Although the present study included fewer nonwhite than white participants, a recent analysis from the Atherosclerosis Risk in Communities study found similar associations with CVD among whites and blacks.[21] We also noted a lower concentration of Lp(a) in participants with the metabolic syndrome, a finding that is consistent with previous data indicating an inverse relationship between baseline Lp(a) and incident diabetes mellitus in 2 large population-based cohorts.[22]

Prior data regarding the relationship between Lp(a) and CVD outcomes in the setting of statin therapy are limited and inconsistent. An analysis of the Familial Atherosclerosis Treatment Study involving 146 males with both hypercholesterolemia and a family history of premature coronary disease suggested that baseline Lp(a) concentrations were associated with coronary disease severity but that the impact of high Lp(a) on clinical events was attenuated if LDL cholesterol reduction >10% was achieved pharmacologically, a concept that was not supported by the current JUPITER results.[9] In the Scandinavian Simvastatin

Table 4. Association Between On-Statin Lipoprotein(a) and Residual Risk Among White JUPITER Participants Randomly Allocated to Rosuvastatin

	Quartile One (≤10 nmol/L)	Quartile Two (11–23 nmol/L)	Quartile Three (24–53 nmol/L)	Quartile Four (≥54 nmol/L)	*P* for Trend	HR per SD Increment	*P* Value
Primary end point							
No. of events/N	19/1068	10/872	22/984	24/953		75/3877	
Incidence rate, per 100 person-years	0.79	0.52	0.98	1.10	0.13	0.86	
Model One	1.00	0.65 (0.30–1.39) *P*=0.26	1.16 (0.63–2.15) *P*=0.63	1.47 (0.81–2.69) *P*=0.21	0.10	1.29 (1.03–1.60)	0.02
Model Two	1.00	0.64 (0.30–1.39) *P*=0.26	1.17 (0.63–2.18) *P*=0.62	1.37 (0.73–2.57) *P*=0.32	0.17	1.27 (1.01–1.59)	0.04
Primary end point plus total mortality							
No. of events/N	23/1068	17/872	31/984	35/953		106/3877	
Incidence rate, per 100 person-years	0.96	0.88	1.38	1.61	0.02	1.21	
Model One	1.00	0.90 (0.48–1.69) *P*=0.75	1.33 (0.77–2.28) *P*=0.31	1.75 (1.03–2.97) *P*=0.04	0.02	1.30 (1.08–1.56)	0.006
Model Two	1.00	0.91 (0.48–1.70) *P*=0.65	1.35 (0.78–2.32) *P*=0.37	1.71 (0.99–2.95) *P*=0.06	0.03	1.29 (1.07–1.56)	0.01

Hazard ratios are expressed per 1-SD increment in the natural logarithm of lipoprotein(a), with 1-SD representing an ≈2.5-fold increment in lipoprotein(a).

Model One: Adjusted for age and sex.

Model Two: Adjusted for age, sex, smoking, family history of premature coronary disease, body mass index, systolic blood pressure, glucose, and on-treatment levels of high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, natural logarithm of triglycerides, and natural logarithm of high-sensitivity C-reactive protein.

HR indicates hazard ratio; and JUPITER, Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin.

Survival Study of secondary prevention among individuals with hypercholesterolemia, baseline Lp(a) concentrations were moderately higher in patients who ultimately experienced a major coronary event or all-cause death, but on-treatment Lp(a) concentrations were not measured.[23] The Air Force/Texas Coronary Atherosclerosis Prevention Study (21 coronary events) reported an HR of 1.15 (95% CI, 0.72–1.84) per 3.5-fold increase (roughly 1 SD) in baseline Lp(a) concentrations, a point estimate similar in magnitude to the present analysis.[5] By contrast, null associations were noted in a small case-control study (108 cases) from the West of Scotland Coronary Prevention Study.[24] These disparate findings may reflect varying methodologies in Lp(a) measurement and mixed adherence to current recommendations to use size-independent metrics of Lp(a).

Therapeutic targeting of Lp(a) concentrations to achieve cardiovascular risk reduction is not currently practiced clinically. Niacin is known to decrease Lp(a) by up to 40%, in addition to having other effects on lipids.[25] The recently completed AIM-HIGH (Atherosclerosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides: Impact on Global Health Outcomes) and HPS2-THRIVE (Heart Protection Study 2: Treatment of HDL to Reduce the Incidence of Vascular Events) studies, which failed to demonstrate clinical benefit with the addition of niacin or niacin/laropiprant to LDL-reduction therapy, may afford an opportunity for additional analyses of these interventions in subgroups of participants with elevated Lp(a).[26,27]

Beyond niacin, multiple novel agents currently in various stages of development have been noted to decrease Lp(a) concentrations. For example, the cholesteryl ester transfer protein inhibitor anacetrapib decreased Lp(a) by 36%[28] and is currently being evaluated in the phase III REVEAL (Randomized Evaluation of the Effects of Anacetrapib Through Lipid Modification) trial (ClinicalTrials.gov unique identifier: NCT01252953). Inhibition of proprotein convertase subtilisin/kexin 9 (PCSK9) has also demonstrated moderate ability to decrease Lp(a) in addition to LDL cholesterol reduction.[29] Mipomersen, an antisense oligonucleotide that targets apolipoprotein B, also decreased Lp(a) by 17% and was approved recently by the US Food and Drug Administration for the treatment of familial hypercholesterolemia.[30] Interventions that specifically target Lp(a) are not available at present, although an antisense oligonucleotide directed against kringle IV repeats demonstrated the ability to reduce Lp(a) in transgenic murine models.[31] Enthusiasm has increased for an intervention trial that selectively enrolls patients with elevated Lp(a) concentrations, although no specific trial plans have been announced.[2]

Limitations of the present study include the 2-year median length of follow-up in the JUPITER trial related to the study's early termination because of clinical benefit. Generalizability may be limited beyond the population studied, specifically asymptomatic and nondiabetic participants meeting LDL cholesterol and hsCRP eligibility criteria. Strengths of the study include the large number of participants with randomized baseline and on-treatment Lp(a) concentrations assayed with a validated immunoassay independent of kringle IV type 2 repeats, detailed baseline cardiovascular risk assessment, prospective

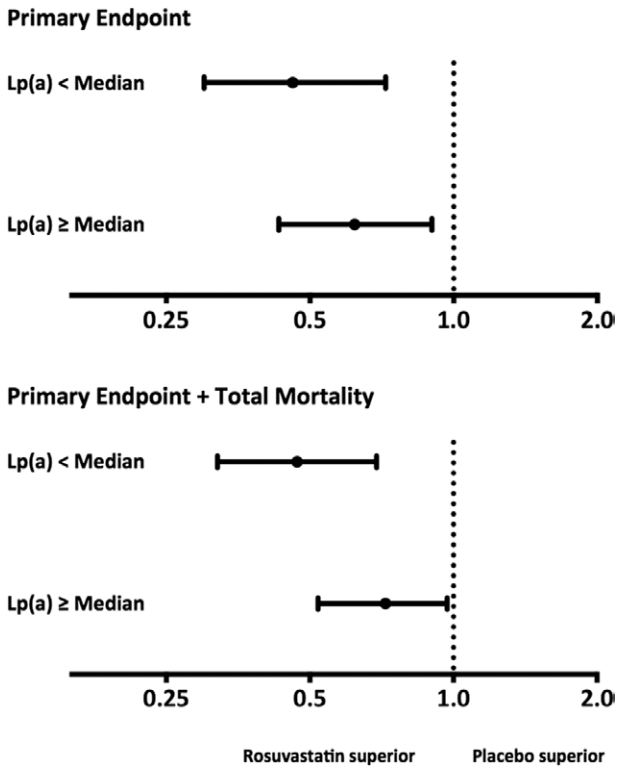

Figure. Efficacy of rosuvastatin according to baseline lipoprotein(a) [Lp(a)] concentration. Hazard ratios and 95% confidence intervals according to intention-to-treat analysis for the primary end point (top) and the expanded end point (bottom) by baseline Lp(a) concentrations. For the primary end point, hazard ratio with rosuvastatin therapy was 0.47 (95% confidence interval, 0.30–0.72) for participants with baseline Lp(a) concentration below the median and 0.62 (95% confidence interval, 0.43–0.90) in those above the median (*P* for interaction=0.33). Similarly, for the expanded end point, hazard ratios were 0.46 (95% confidence interval, 0.32–0.69) and 0.72 (95% confidence interval, 0.52–0.97) for those below and above the median, respectively (*P* for interaction=0.10).

end-point adjudication, and the use of potent statin therapy with very low achieved LDL cholesterol concentrations.

Conclusions

In the present cohort of asymptomatic white JUPITER participants with low LDL cholesterol and elevated hsCRP, Lp(a) was a significant determinant of residual risk. Furthermore, the efficacy of rosuvastatin in reducing CVD was similar among participants with high or low Lp(a) concentrations. Future studies are needed to directly assess the impact of specifically lowering Lp(a) concentrations for potentially reducing residual risk.

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CLINICAL PERSPECTIVE

Lipoprotein(a) is a low-density lipoprotein (LDL)–like particle with apolipoprotein B covalently linked to apolipoprotein(a). Lipoprotein(a) has been associated with cardiovascular disease via both mechanistic evidence of a proatherogenic or prothrombotic role and epidemiological and genetic studies in general populations. Several novel lipid therapeutic agents that lower lipoprotein(a) have recently entered phase III clinical trials, yet little is known about lipoprotein(a) and residual risk in the setting of potent statin therapy and low achieved LDL cholesterol. In this analysis from the JUPITER trial (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin), lipoprotein(a) was measured both at baseline and on-treatment in 9612 participants with elevated high-sensitivity C-reactive protein but normal LDL cholesterol who were randomly allocated to rosuvastatin or placebo. Lipoprotein(a) concentrations were stable over time, largely independent of other cardiovascular risk factors, and minimally effected by rosuvastatin. Lipoprotein(a) concentrations were greatest in blacks (median 60 nmol/L), then Asians (38 nmol/L), and then Hispanics (24 nmol/L) and whites (23 nmol/L). Among white participants, baseline lipoprotein(a) concentrations were associated with ≈20% higher relative risk of cardiovascular events per 1-SD (≈2.5-fold) increase, independent of LDL cholesterol or other risk factors. Similarly, on-statin lipoprotein (a) concentrations were associated with residual risk. The magnitude of relative risk reduction with rosuvastatin was similar among participants with high or low lipoprotein(a). Similar results were obtained when analyses included non-whites. This study provides the first evidence to date that lipoprotein(a) concentrations are a determinant of residual risk after potent statin therapy. Future studies are needed to directly assess the impact of specifically lowering lipoprotein(a) on cardiovascular risk.