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Lipoprotein(a), PCSK9 Inhibition, and Cardiovascular Risk

Insights From the FOURIER Trial

Editorial, see p 1493

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BACKGROUND: Lipoprotein(a) [Lp(a)] may play a causal role in atherosclerosis. PCSK9 (proprotein convertase subtilisin/kexin 9) inhibitors have been shown to significantly reduce plasma Lp(a) concentration. However, the relationship between Lp(a) levels, PCSK9 inhibition, and cardiovascular risk reduction remains undefined.

METHODS: Lp(a) was measured in 25 096 patients in the FOURIER trial (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk), a randomized trial of evolocumab versus placebo in patients with established atherosclerotic cardiovascular disease (median follow-up, 2.2 years). Cox models were used to assess the independent prognostic value of Lp(a) and the efficacy of evolocumab for coronary risk reduction by baseline Lp(a) concentration.

RESULTS: The median (interquartile range) baseline Lp(a) concentration was 37 (13–165) nmol/L. In the placebo arm, patients with baseline Lp(a) in the highest quartile had a higher risk of coronary heart disease death, myocardial infarction, or urgent revascularization (adjusted hazard ratio quartile 4: quartile 1, 1.22; 95% CI, 1.01–1.48) independent of low-density lipoprotein cholesterol. At 48 weeks, evolocumab significantly reduced Lp(a) by a median (interquartile range) of 26.9% (6.2%–46.7%). The percent change in Lp(a) and low-density lipoprotein cholesterol at 48 weeks in patients taking evolocumab was moderately positively correlated (r=0.37; 95% CI, 0.36–0.39; P<0.001). Evolocumab reduced the risk of coronary heart disease death, myocardial infarction, or urgent revascularization by 23% (hazard ratio, 0.77; 95% CI, 0.67–0.88) in patients with a baseline Lp(a) >median, and by 7% (hazard ratio, 0.93; 95% CI, 0.80–1.08; P interaction=0.07) in those ≤median. Coupled with the higher baseline risk, the absolute risk reductions, and number needed to treat over 3 years were 2.49% and 40 versus 0.95% and 105, respectively.

CONCLUSIONS: Higher levels of Lp(a) are associated with an increased risk of cardiovascular events in patients with established cardiovascular disease irrespective of low-density lipoprotein cholesterol. Evolocumab significantly reduced Lp(a) levels, and patients with higher baseline Lp(a) levels experienced greater absolute reductions in Lp(a) and tended to derive greater coronary benefit from PCSK9 inhibition.

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Clinical Perspective

What Is New?

- We examined the relationship between lipoprotein(a) [Lp(a)] levels, PCSK9 (proprotein convertase subtilisin/kexin 9) inhibition with evolocumab, and cardiovascular risk reduction in patients with established atherosclerotic cardiovascular disease
- Patients with a higher concentration of Lp(a) were at increased risk of coronary events independent of low-density lipoprotein cholesterol concentration
- Individuals with higher baseline Lp(a) concentration tended to have a greater relative and absolute coronary risk reduction with evolocumab and, therefore, a lower number needed to treat.

What Are the Clinical Implications?

- Evolocumab reduces Lp(a) concentration, and patients with higher baseline Lp(a) concentration may derive enhanced benefit from treatment with evolocumab.

Lipoprotein [Lp(a)] consists of an low-density lipoprotein (LDL)–like particle that also contains apolipoprotein(a) [apo(a)] linked to apolipoprotein B. Lp(a) plasma concentrations are highly heritable and predominantly controlled by the apo(a) gene (LPA).[1] Several epidemiological studies have demonstrated an association between higher plasma Lp(a) concentrations and coronary risk[2]; however, the strength of the association in patients with well-controlled plasma LDL cholesterol (LDL-C) concentration has been inconsistent.[3–5]

It is important to note that genetic studies support that Lp(a) plays a causal role in the development of coronary atherosclerosis; in particular, data from 2 large Mendelian randomization studies demonstrated that genetic polymorphisms in the LPA gene are associated with Lp(a) concentration and future coronary risk.[6,7]

To date, few therapies are available to reduce the concentration of Lp(a), and it remains unclear whether lowering Lp(a) will translate into improved cardiovascular (CV) outcomes.[8–10] PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors may offer clinical utility because they have been shown in phase 2 trials to reduce Lp(a) concentration by ≈25% to 30%.[11–13] However, it remains unknown whether the effect of evolocumab on risk of coronary events may be modified by baseline Lp(a) concentrations. Therefore, as a prespecified analysis of the FOURIER trial (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk), we assessed the relationship between Lp(a) levels, PCSK9 inhibition with evolocumab, and CV risk reduction.[14]

METHODS

Study Population and Design

The FOURIER trial was a randomized, double-blind, placebo-controlled clinical trial that enrolled 27 564 patients between 40 and 85 years of age who had established atherosclerotic CV disease, determined by a prior myocardial infarction (MI), prior nonhemorrhagic stroke, or symptomatic peripheral artery disease, in addition to predictors of high CV risk. Patients were required to have a fasting LDL-C concentration ≥70 mg/dL (1.8 mmol/L) or a non–high-density lipoprotein cholesterol concentration ≥100 mg/dL (2.6 mmol/L) while on a background of optimized lipid-lowering therapy, defined as preferably a high-intensity statin and a minimum dose of 20 mg atorvastatin daily or its equivalent, with or without ezetimibe. There were no entry criteria based on Lp(a) concentration. The study protocol was approved by all relevant ethics committees and all participating subjects provided informed consent. The data, analytical methods, and study materials will not be made universally available to other researchers for purposes of reproducing the results or replicating the procedure. However, we encourage parties interested in collaboration and data sharing to contact the corresponding author directly for further discussions.

Blood Sampling and Analysis

As part of the protocol, samples of venous blood were collected at time points throughout the trial. Lp(a) was assessed at randomization, week 12, week 24, and week 48. The plasma component was frozen and shipped to a central laboratory where samples were stored at –70°C or colder. Lp(a) was measured at Medpace Reference Laboratories (Medpace Inc) based on the Denka Seiken reagents (Denka Seiken, Ltd; Polymedco) using an isoform-independent immunoturbidometric assay (Polymedco) with a Beckman AU series analyzer (Olympus, Beckman Coulter Instruments). A 6-point calibration curve was constructed using Polymedco calibrators formulated in units of nmol/L and traceable to the reference assay at the Northwest Lipid Metabolism and Diabetes Research Laboratories, University of Washington. Results ≥150 nmol/L were manually diluted (up to ×10) and reassayed using deionized water. All Lp(a) measurements in the FOURIER study are reported in nmol/L. An isoform independent assay is agnostic to the size of the apo(a) protein that can vary markedly because of a kringle IV type 2 size polymorphism in the LPA gene resulting in variable numbers of kringle IV repeats and various apolipoprotein(a) isoforms.[15] LDL-C levels were estimated using the Friedewald equation except when estimated LDL-C was <40 mg/dL or triglycerides were ≥400 mg/dL, in which case preparative ultracentrifugation was performed.[16]

Statistical Analysis

Baseline characteristics by quartile of baseline Lp(a) were compared using the Cochran-Armitage test for binary variables and Jonckheere-Terpstra test for continuous variables. To evaluate its association with clinical outcomes, baseline Lp(a) was first analyzed in the placebo arm as a log-transformed continuous variable (log base 2) and subsequently categorized into quartiles according to baseline Lp(a) concentration. Given

the prior evidence suggesting a curvilinear relationship with events,[2] sensitivity analyses were conducted categorizing clinical risk by decile of baseline Lp(a). Cox proportional hazard models were used to estimate the association between Lp(a) and CV outcomes, primarily focusing on major coronary events consisting of coronary heart death, MI, and urgent coronary revascularization, given prior data.[2,17] Multivariable models were created adjusting for age, sex, race, region, prior MI, history of stroke, peripheral artery disease, hypertension, diabetes mellitus, current smoking, high-intensity statin use, ezetimibe use, and baseline LDL-C. A supplementary analysis was conducted with apolipoprotein B in the model rather than LDL-C. For exploratory analyses of the association of achieved Lp(a) levels at 12 weeks and outcomes, landmark analyses were performed including all patients alive at 12 weeks and the same covariates were used, with the exception that the LDL-C level achieved at week 12 was used instead of baseline. Baseline high-sensitivity C-reactive protein was also included. Proportional hazards assumption was assessed using scaled Schoenfeld residuals and all models met the assumption. Event rates were estimated at 3 years using the Kaplan–Meier method.

Changes in Lp(a) concentration that are reported are placebo controlled. The effects of evolocumab and placebo on Lp(a) and LDL-C concentrations were assessed from randomization to week 48 and then stratified by baseline Lp(a) concentration. The correlation between the change in Lp(a) and change in LDL-C in the evolocumab arm was assessed by the Spearman test. The effect of evolocumab versus placebo on risk for major coronary events was assessed for patients with a baseline Lp(a) concentration either above or below the median. Patients were stratified into deciles on the basis of baseline Lp(a), and the difference in Lp(a) and LDL-C at 48 weeks between the evolocumab and placebo arms was calculated within each decile. The hazard ratio (HR) for major coronary events with evolocumab versus placebo was also calculated within each decile. Weighted least-square linear regression was then performed on the log-transformed HR to examine the association between the treatment effect on major coronary events and per unit decrease in Lp(a), adjusting for differences in LDL-C. All tests were 2-sided with a *P* value <0.05 considered to be significant (SAS, version 9.4 and R version 3.5.1 with metafor package).

The FOURIER trial was sponsored by Amgen. All analyses were conducted at the TIMI Study Group using an independent copy of the study database. Dr O'Donoghue wrote the first draft, had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Lp(a) was measured at baseline in 25 096 patients enrolled in FOURIER; the median baseline value was 37 (interquartile range, 13–165) nmol/L (Figure I in the online-only Data Supplement). Baseline levels of Lp(a) and LDL-C were weakly positively correlated (r=0.14; 95% CI, 0.13–0.15; P<0.001; Figure II in the online-only Data Supplement). Patients with higher baseline concentrations of Lp(a) were more likely to be female and have a history of MI or peripheral artery disease. Conversely, patients with higher baseline Lp(a) concentrations were less likely to be smokers and have a history of ischemic stroke or diabetes mellitus (Table 1).

Association of Lp(a) Plasma Levels and Clinical Outcomes

In the placebo arm, each doubling of baseline Lp(a) concentration was associated with an 8% higher risk of coronary heart disease (CHD) death, MI, or urgent coronary revascularization (major coronary events: unadjusted HR per doubling of Lp(a), 1.08; 95% CI, 1.04–1.11; P<0.001). Patients with baseline Lp(a) concentration in the highest quartile (>165 nmol/L) had a 33% higher risk of CHD death, MI, or urgent coronary revascularization (HR, 1.33; 95% CI, 1.10–1.60; P=0.003) than those in the first quartile (Table 2).

After multivariable adjustment, elevated baseline Lp(a) concentration remained significantly associated with an increased risk of major coronary events (adjusted HR per doubling of Lp(a), 1.06; 95% CI, 1.02–1.09; P=0.002). Patients with Lp(a) in the highest quartile continued to have a higher risk of CHD death, MI, or urgent coronary revascularization (adjusted HR, 1.22; 95% CI, 1.01–1.48; P=0.04; Table 2). When categorized by decile of Lp(a), the greatest coronary risk appeared to be in patients in the top decile (≥230 nmol/L) of Lp(a) concentration (decile 10 versus decile 1: adjusted HR, 1.33; 95% CI 1.02–1.74; P=0.04; Figure III in the online-only Data Supplement). Qualitatively consistent results were observed when apolipoprotein B replaced LDL-C in the model (Table I in the online-only Data Supplement).

Effect of Evolocumab on Lp(a) Concentration

From baseline to 48 weeks, evolocumab decreased the concentration of Lp(a) by a median of 26.9% (interquartile range, 6.2%–46.7%) or 11 (interquartile range, 1–32) nmol/L (P<0.001). The absolute reduction in Lp(a) was greatest for individuals with higher baseline Lp(a) concentrations (P trend <0.001; Figure IVA in the online-only Data Supplement). However, the percent reduction decreased with increasing baseline Lp(a) levels (P trend=0.03; Figure IVB in the online-only Data Supplement).

In patients treated with evolocumab, the percent change in Lp(a) and LDL-C from baseline to 48 weeks was moderately positively correlated (r=0.37; 95% CI, 0.36–0.39; P<0.001; Figure VA in the online-only Data Supplement). A weaker correlation was observed when the 2 parameters were assessed on an absolute basis (r=0.21; 95% CI, 0.19–0.22; P<0.001; Figure VB in the online-only Data Supplement).

Table 1. Baseline Characteristics by Quartile of Baseline Lp(a) in FOURIER

Characteristics	Lp(a) Quartile 1 (n=6565) ≤13 nmol/L	Lp(a) Quartile 2 (n=6081) >13–37 nmol/L	Lp(a) Quartile 3 (n=6217) >37–165 nmol/L	Lp(a) Quartile 4 (n=6233) >165 nmol/L	*P* Value for Trend
Age, y	62.3±9.0	62.8±9.1	62.5±9.1	62.6±8.8	0.36
Male sex, n (%)	5239 (79.8)	4638 (76.3)	4704 (75.7)	4262 (68.4)	<0.001
White race, n (%)	5904 (89.9)	5245 (86.3)	4986 (80.2)	5365 (86.1)	<0.001
Weight, kg	87.3±17.1	84.8±17.1	84.6±17.6	84.6±17.7	<0.001
Region, n (%)					
North America	917 (14.0)	898 (14.8)	1068 (17.2)	1455 (23.3)	<0.001
Europe	4567 (69.6)	4006 (65.9)	3682 (59.2)	3726 (59.8)	<0.001
Latin America	425 (6.5)	372 (6.1)	462 (7.4)	455 (7.3)	0.008
Asia Pacific	656 (10.0)	805 (13.2)	1005 (16.2)	597 (9.6)	0.27
Type of atherosclerosis, n (%)					
History of MI	5188 (79.0)	4803 (79.0)	5061 (81.4)	5203 (83.5)	<0.001
History of stroke	1369 (20.9)	1288 (21.2)	1221 (19.6)	1033 (16.6)	<0.001
Peripheral artery disease	859 (13.1)	767 (12.6)	814 (13.1)	937 (15.0)	0.001
Cardiovascular risk factors, n (%)					
Hypertension	5337 (81.3)	4912 (80.8)	4939 (79.4)	5003 (80.3)	0.044
Diabetes mellitus	2671 (40.7)	2190 (36.0)	2246 (36.1)	2125 (34.1)	<0.001
Current cigarette use	1966 (29.9)	1812 (29.8)	1772 (28.5)	1579 (25.3)	<0.001
Statin use					
High intensity	4434 (67.5)	4015 (66.0)	4222 (67.9)	4716 (75.7)	<0.001
Moderate intensity	2107 (32.1)	2058 (33.8)	1980 (31.8)	1504 (24.1)	<0.001
Low intensity, unknown intensity, or no data	24 (0.4)	8 (0.1)	15 (0.2)	13 (0.2)	0.17
Ezetimibe	213 (3.2)	247 (4.1)	306 (4.9)	527 (8.5)	<0.001
Biochemical measures*					
Lp(a), nmol/L	6.5 (5–9)	23.0 (18–29)	88.0 (53–134)	216.0 (191–280)	
LDL cholesterol, mg/dL	93.2±25.1	96.3±27.1	98.0±30.7	101.5±27.2	<0.001
Total cholesterol, mg/dL	170.6±30.2	171.7±32.1	172.0±35.0	176.7±32.8	<0.001
HDL cholesterol, mg/dL	45.2±12.6	45.7±12.3	45.6±12.5	46.9±13.1	<0.001
Triglycerides, mg/dL	144 (106–199.5)	133.5 (100.5–183)	127.5 (97–172.5)	128 (97.5–172)	<0.001
Apolipoprotein B, mg/dL	84.6±20.0	85.3±20.8	85.4±22.2	88.5±20.5	<0.001
Non-HDL cholesterol, mg/dL	125.3±28.9	126.1±31.2	126.5±33.9	129.8±31.1	<0.001
hs-C-reactive protein, mg/L	3.1±5.1	3.5±5.8	3.4±5.6	3.6±6.8	<0.001

FOURIER indicates Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk; HDL, high-density lipoprotein; hs, high sensitivity; IQR, interquartile range; LDL, low-density lipoprotein; Lp(a), lipoprotein(a); and MI, myocardial infarction.

*All lipid measures are expressed as mean±SD, with the exception of triglycerides and Lp(a) that are expressed as median (IQR)

Effect of Evolocumab on Major Coronary Events by Baseline Lp(a) Concentration

Overall, evolocumab reduced the risk of CHD death, MI, or urgent coronary revascularization by 16% (HR, 0.84; 95% CI, 0.76–0.93). Evolocumab tended to reduce the risk of major coronary events to a greater degree in patients with higher baseline Lp(a) levels, with a reduction of 23% in those with a baseline Lp(a) above the median (HR, 0.77; 0.67–0.88) versus 7% for those at or below the median (HR, 0.93; 0.80–1.08; *P* interaction=0.07; Figure 1A). Coupled with higher CV risk, the absolute risk reductions were greater (2.49% versus 0.95%) and number needed to treat were lower (40 versus 105) over 3 years for patients with an Lp(a) concentration above versus below the median. When a clinical threshold of 120 nmol/L (50 mg/dL) was applied, the absolute risk reductions and numbers needed to treat over 3 years were 2.41% and 41 for those above the threshold versus 1.41% and 71 below the threshold (*P* interaction=0.096; Figure 1B). The efficacy of evolocumab versus placebo for reducing individual

Table 2. Unadjusted and Adjusted Risk of CV Events in the Placebo Arm by Baseline Quartile of Lp(a) Adjusting for LDL-C in the Model

Outcome	Lp(a) Quartile 1 (n=6565) ≤13 nmol/L	Lp(a) Quartile 2 (n=6081) >13–37 nmol/L	Lp(a) Quartile 3 (n=6217) >37–165 nmol/L	Lp(a) Quartile 4 (n=6233) >165 nmol/L	*P* Value for Trend
Coronary heart death, MI, or urgent coronary revascularization					
3-year KM rate	8.1%	6.9%	9.7%	10.1%	
Unadjusted HR (95% CI)	1	0.87 (0.71–1.07)	1.24 (1.02–1.50)	1.33 (1.10–1.60)	<0.001
Adjusted HR (95% CI)	1	0.86 (0.70–1.06)	1.17 (0.96–1.41)	1.22 (1.01–1.48)	0.004
CV death, MI, stroke, hospitalization for unstable angina, or urgent coronary revascularization					
3-year KM rate	13.9%	11.9%	16.6%	15.9%	
Unadjusted HR (95% CI)	1	0.90 (0.77–1.05)	1.21 (1.05–1.40)	1.20 (1.04–1.38)	<0.001
Adjusted HR (95% CI)	1	0.89 (0.76–1.04)	1.17 (1.01–1.35)	1.14 (0.98–1.32)	0.006
CV death, MI, or stroke					
3-year KM rate	9.5%	7.8%	11.7%	10.3%	
Unadjusted HR (95% CI)	1	0.88 (0.72–1.07)	1.21 (1.01–1.44)	1.17 (0.98–1.40)	0.006
Adjusted HR (95% CI)	1	0.87 (0.71–1.05)	1.13 (0.95–1.36)	1.11 (0.92–1.33)	0.06
Coronary heart death					
3-year KM rate	1.6%	1.3%	1.5%	2.0%	
Unadjusted HR (95% CI)	1	0.69 (0.42–1.12)	1.04 (0.68–1.62)	1.23 (0.81–1.87)	0.13
Adjusted HR (95% CI)	1	0.65 (0.40–1.07)	0.93 (0.59–1.44)	1.24 (0.81–1.89)	0.16
Myocardial infarction					
3-year KM rate	5.5%	5.5%	7.0%	6.8%	
Unadjusted HR (95% CI)	1	1.10 (0.86–1.40)	1.33 (1.05–1.68)	1.42 (1.12–1.78)	<0.001
Adjusted HR (95% CI)	1	1.09 (0.85–1.40)	1.24 (0.98–1.58)	1.28 (1.01–1.62)	0.02
Urgent coronary revascularization					
3-year KM rate	5.0%	4.2%	6.2%	6.0%	
Unadjusted HR (95% CI)	1	0.84 (0.64–1.10)	1.29 (1.01–1.65)	1.30 (1.02–1.66)	0.002
Adjusted HR (95% CI)	1	0.84 (0.64–1.10)	1.24 (0.97–1.59)	1.18 (0.92–1.51)	0.03
Stroke					
3-year KM rate	2.4%	2.1%	3.3%	2.4%	
Unadjusted HR (95% CI)	1	0.85 (0.59–1.24)	1.22 (0.87–1.72)	0.92 (0.64–1.32)	0.86
Adjusted HR (95% CI)	1	0.83 (0.57–1.20)	1.16 (0.83–1.64)	0.93 (0.64–1.34)	0.85

CV indicates cardiovascular; KM, Kaplan–Meier; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); HR, hazard ratio; and MI, myocardial infarction.

components of the composite outcomes is shown in Tables II and III in the online-only Data Supplement.

When stratifying patients into deciles by baseline Lp(a) concentration, whereas the LDL-C reduction was virtually the same (59–62 mg/dL) across each decile of baseline Lp(a), the median Lp(a) reductions ranged from 0 to 60.5 mg/dL at 48 weeks. In a weighted least-square linear regression analysis that examined the association between treatment effect on CHD death, MI, or urgent coronary revascularization and per unit decrease in Lp(a) adjusting for differences in LDL-C, there was a significant relationship with a 15% relative risk reduction (95% CI, 2%–26%; *P*=0.0199) per 25 nmol/L reduction in Lp(a) (Figure 2). In contrast, the relationship between the percent change in Lp(a) and the HR for major coronary events was not significant (*P*=0.79).

Risk of CHD Events by Achieved Lp(a) and Achieved LDL-C at Week 12

An exploratory analysis examined achieved levels at 12 weeks and subsequent risk of CHD death, MI, or urgent coronary revascularization in a landmark analysis through long-term follow-up. After 12 weeks, there was a significant relationship between achieved Lp(a) level and the adjusted risk of CHD death, MI, or urgent coronary revascularization (Figure 3; HR, 1.04; 95% CI, 1.01–1.06; *P*=0.01 per doubling of achieved Lp(a) concentration). There was no evidence of effect modification by randomized treatment arm (*P* interaction=0.57), nor was there effect modification by achieved LDL-C level (*P* interaction=0.83).

There was a stepwise decrease in the risk of CHD death, MI, or urgent coronary revascularization for pa-

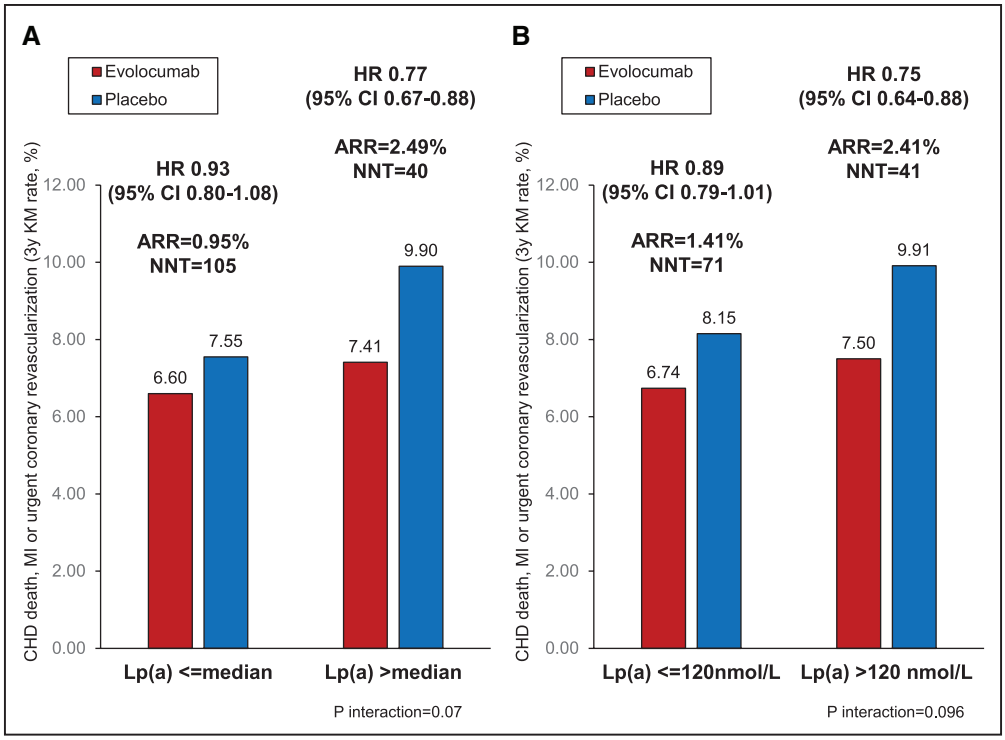

Figure 1. The efficacy of evolocumab by Lp(a) concentration.
The efficacy of evolocumab vs placebo stratified by baseline Lp(a) concentration split at the median (**A**) and split at 120 nmol/L (50 mg/dL) for reducing CHD death, MI, or urgent coronary revascularization (**B**). ARR indicates absolute risk reduction; CHD, coronary heart disease; KM, Kaplan–Meier; Lp(a), lipoprotein(a); MI, myocardial infarction; and NNT, number needed to treat.

tients who achieved either an Lp(a) or LDL-C value below the achieved median with the lowest event rate observed for those who achieved lower levels of both values (Figure VI in the online-only Data Supplement). In comparison with patients above the median achieved level for both lipid parameters, patients with at least

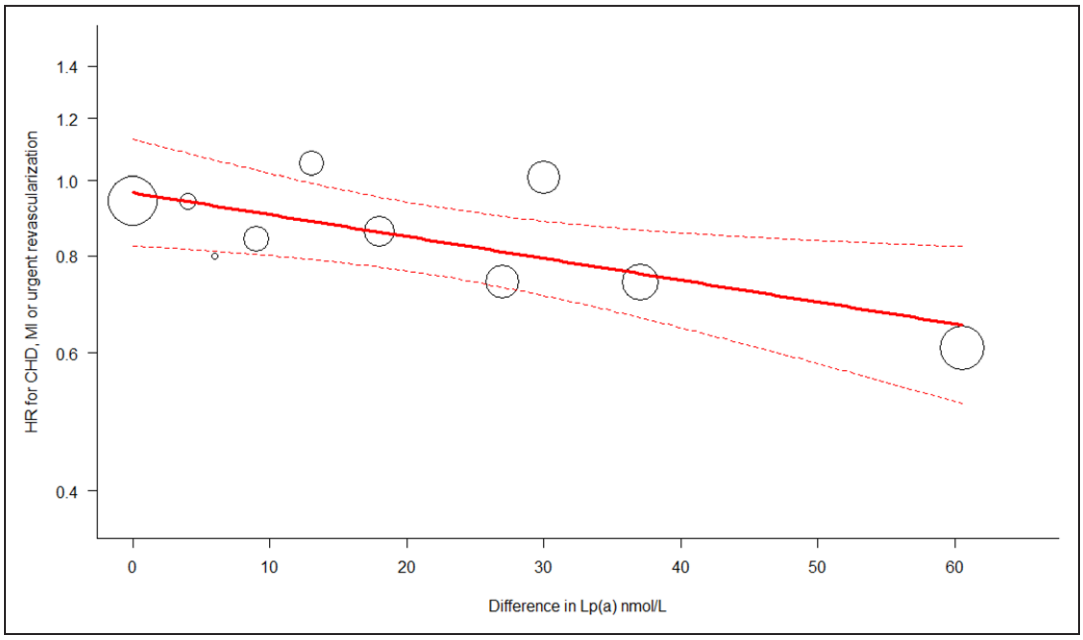

Figure 2. Treatment effect on major coronary events per unit decrease in Lp(a).
Patients were stratified into deciles on the basis of baseline Lp(a), and the difference in Lp(a) and LDL-C at 48 weeks between the evolocumab and placebo arms was calculated within each decile. The hazard ratio (HR) for major coronary events with evolocumab vs placebo was also calculated within each decile. Weighted least-square linear regression was then performed on the log-transformed HR to examine the association between the treatment effect on major coronary events and per unit decrease in Lp(a), adjusting for differences in LDL-C. There was a significant relationship with a 15% lower risk (95% CI, 2%–26%; *P*=0.0199) per 25 nmol/L reduction in Lp(a) after adjusting for the change in LDL-C (model accounts for 57% of total variability of clinical benefit). Red dotted lines represent 95% CIs. CHD indicates coronary heart disease; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); and MI, myocardial infarction.

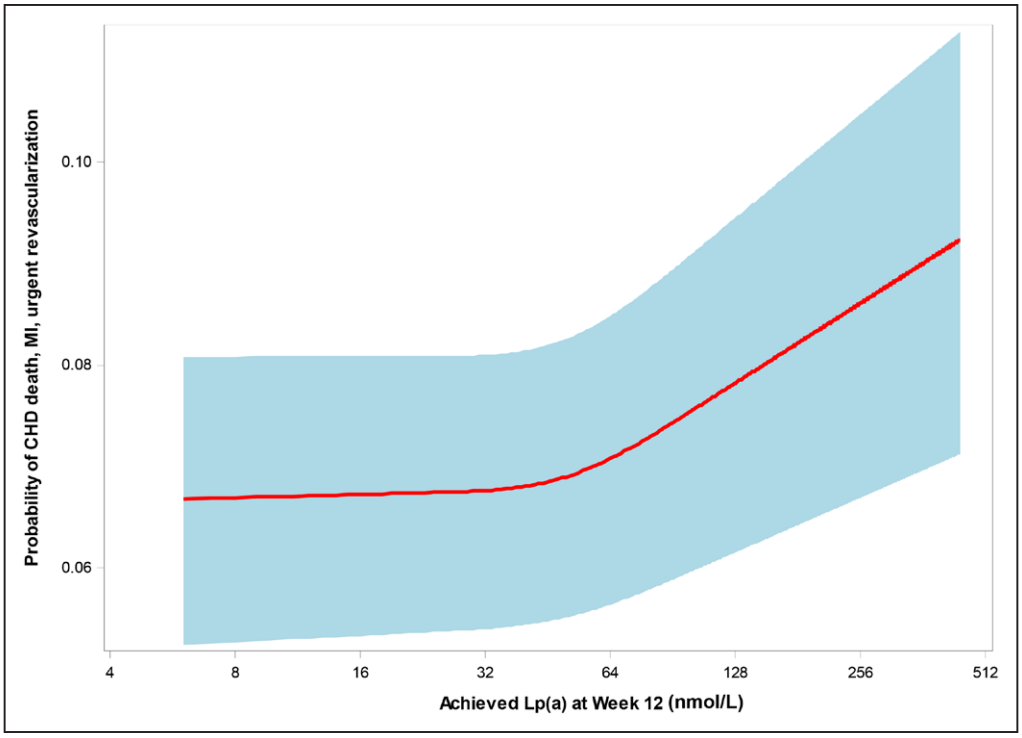

Figure 3. The probability of coronary events by achieved Lp(a) concentration.
The probability of CHD death, MI, or urgent coronary revascularization conducted as a landmark analysis by achieved Lp(a) concentration at week 12 (adjusted HR, 1.04; 95% CI, 1.01–1.06; *P*=0.01 per doubling of achieved Lp(a) concentration). Blue shaded area represents 95% confidence region. CHD indicates coronary heart disease; HR, hazard ratio; Lp(a), lipoprotein(a); and MI, myocardial infarction.

one level below the median had a 15% lower risk of major coronary events (adjusted HR, 0.85; 95% CI, 0.75–0.97; *P*=0.01) and those with both levels below their respective medians had a 28% lower risk of major coronary events (adjusted HR, 0.72; 95% CI, 0.62–0.83; *P*<0.0001). Consistent results were observed when patients were stratified by achieved values of LDL-C 70 mg/dL and Lp(a) 120 nmol/L (Figure VII in the online-only Data Supplement).

DISCUSSION

In patients enrolled in the FOURIER trial, higher baseline Lp(a) concentration was independently associated with an increased risk of major coronary events and evolocumab significantly reduced Lp(a) concentration by ≈27%. Moreover, patients with higher Lp(a) concentration at baseline experienced greater absolute Lp(a) reductions and tended to derive greater clinical benefit in terms of evolocumab's ability to reduce the risk of major coronary events. Patients who achieved lower levels of LDL-C and Lp(a) were found to be at lowest risk of subsequent major coronary events.

In FOURIER, we observed a modest but significant association between Lp(a) concentration and the risk of major coronary events. The magnitude of the observed association tended to be greatest for those patients with baseline concentrations above the 90th percentile (≥230 nmol/L, or ≈96 mg/dL). Although epidemiological studies have been conflicting,[17] the association appeared to be strongest with major coronary events rather than stroke. This is perhaps related to the heterogeneous etiology and different pathobiology of ischemic stroke subtypes. Of interest, it was reported previously that Lp(a) confers CV risk predominantly when LDL-C levels are elevated.[3,18,19] However, we found that the relationship between Lp(a) and coronary risk remained similar throughout the entire LDL-C range, thereby suggesting a consistent association of Lp(a) with CV risk in patients with established CV disease independent of concomitant baseline or achieved LDL-C levels. In support, patients who achieved lower levels of both LDL-C and Lp(a) were those who were at lowest risk of subsequent events.

Although Lp(a) is believed to be a risk factor for coronary disease,[6,7] the therapeutic targeting of Lp(a) has proven difficult to date. Niacin has been shown to modestly reduce Lp(a) concentration in a dose-dependent manner[20]; however, its use may be associated with an increased risk of non-CV serious adverse events and there is no evidence that treatment with niacin reduces CV risk on a background of statin.[10,21] The effects of statins on plasma Lp(a) concentration have been inconsistent.[1,22] Cholesteryl ester transfer protein inhibitors reduce Lp(a), but are not approved for clinical use.[8] Mipomersen, an antisense oligonucle-

otide directed at human apo B100, has been shown to reduce both LDL-C and Lp(a) and is approved in the United States for patients with homozygous familial hypercholesterolemia, but its clinical utility beyond LDL-C lowering remains unknown.[23] The microsomal triglyceride transfer protein inhibitor, lomitapide, has also been shown to reduce both Lp(a) and LDL-C, but adverse effects include liver function abnormalities, gastrointestinal side effects, and hepatic fat accumulation.[8] Tocilizumab, a humanized monoclonal antibody directed against the interleukin-6 receptor, has been shown to decrease Lp(a) concentrations without concomitant lowering of LDL-C. This effect is believed to be mediated by an interleukin-6–responsive element in the promoter region of the LPA gene leading to a reduction in apo(a) synthesis;[8] however, its clinical efficacy for attenuating CV risk remains unknown. Lipoprotein apheresis is used in some countries to reduce Lp(a) concentration, although its CV benefit has only been evaluated in small-scale studies.[8]

Although their exact mechanism of action remains under study, recent evidence suggests that PCSK9 inhibitors may reduce Lp(a) concentration by both enhancing clearance[24] and reducing its production.[25,26] In a study of healthy volunteers, evolocumab monotherapy has been demonstrated to lower plasma Lp(a) concentration by decreasing production of Lp(a) particles.[26] However, in the presence of a statin, evolocumab may also act to increase Lp(a) catabolism through marked upregulation of the LDL receptor, leading to enhanced Lp(a) holoparticle clearance.[26] In Lp(a) uptake studies in human hepatocytes and dermal fibroblasts, secretion of apo(a) appears to increase briskly in the presence of the PCSK9 protein, and this effect is reversed in the presence of the PCSK9 inhibitor alirocumab.[25] Discordance between LDL-C and Lp(a) reductions has been reported, which may argue against upregulation of LDL receptor as the sole mechanism for Lp(a) lowering by PCSK9 inhibitors.[27] In the current study of >25 000 patients in the FOURIER trial, patients with higher baseline Lp(a) levels also tended to experience greater reductions in major coronary events with evolocumab. This observation is supported by a recent Mendelian randomization study that suggested that genetically mediated lower Lp(a) is associated with a lower risk of major coronary events, although the relationship is not as strong as LDL-C on a mg/dL basis.[28] Qualitatively consistent with these findings, we observed that a 34 nmol/L (95% CI, 18.5–97 nmol/L) absolute reduction in Lp(a) may be required to translate into a 20% relative risk reduction in CV events, which approximates the median reduction in Lp(a) that was seen in patients in the top quartile of Lp(a) concentration. These findings suggest that the benefit of Lp(a)-lowering therapies might be largely restricted to patients with elevated levels at baseline, therapies that produce large reductions in Lp(a), or both. These observations may also help to explain why higher baseline Lp(a) concentration was useful for helping to identify individuals with greater clinical efficacy with evolocumab.

It is interesting to note that the percent reduction in Lp(a) with evolocumab tended to diminish with higher baseline levels of Lp(a), possibly because of the reduced clearance of smaller isoforms or other as yet to be defined mechanisms. However, dedicated therapies that markedly reduce Lp(a) concentration by directly targeting the apo(a) protein remain in development and may be able to directly and more robustly test the Lp(a) hypothesis because they can reduce levels by up to ≈ 90%.[29,30]

Practically, the current study suggests that Lp(a) may be useful to help identify patients who derive greater absolute risk reduction from evolocumab and thereby a lower number needed to treat to prevent a major adverse CV event. In patients with an Lp(a) concentration greater than the median (>37 nmol/L), the number needed to treat to prevent one major coronary event over 3 years was 40 in comparison with 105 for patients with a baseline Lp(a) concentration less than the median. Prior analyses from the same patient population have demonstrated that high-sensitivity C-reactive protein may also predict CV risk and identify patients with a larger absolute benefit from evolocumab.[31] Although high-sensitivity C-reactive protein is a well-established risk marker, it does not appear to be an independent risk factor,[32] and evolocumab does not lower high-sensitivity C-reactive protein concentration. In contrast, Lp(a) appears to be a causal factor in coronary heart disease,[6,7] and its concentration is lowered by evolocumab.

Although the current analysis was prespecified, all cut points should be viewed as exploratory. Because the current analysis was observational in nature, observed associations should not imply causality. Patients in FOURIER were not selected based on an elevated Lp(a) concentration; therefore, there was no enrichment on this basis. Nonetheless, ≈33.1% of patients had a baseline concentration >120 nmol/L (or ≈50 mg/dL) which is believed to be the 80th percentile in a general patient population.[1] Although there remains disagreement about the optimal method to assess Lp(a) concentration, the current study used an assay system that was isoform independent, as supported by previous consensus panels.[33] In addition, the current study population predominantly enrolled male and white participants; therefore, it will be of interest to further examine these findings in additional cohorts given the sex and racial differences that exist in Lp(a) concentrations. The study was not designed to achieve statistical significance within subgroups, and tests for interaction were relatively underpowered to achieve statistical significance; therefore, numbers needed to treat within subgroups

should be considered exploratory. In addition, analyses that examined achieved values of Lp(a) and LDL-C are at risk of residual confounding and therefore do not directly imply causality.

In summary, the current findings suggest that plasma Lp(a) concentration is associated with the risk of CV events in patients with stable atherosclerotic disease regardless of LDL-C concentration. Furthermore, Lp(a) may be useful for identifying individuals with a greater absolute benefit from evolocumab and lend support to the study of additional therapies that can lead to marked reductions in Lp(a) concentration.

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