Circulation

ORIGINAL RESEARCH ARTICLE

Lipoprotein(a) Levels, Risk of Cardiovascular Events, and Benefit of Evolocumab: Findings From the VESALIUS-CV Trial

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BACKGROUND: Lp(a) (lipoprotein[a]) is a risk factor for coronary heart disease. Whether baseline Lp(a) identifies higher-risk patients who derive more benefit from evolocumab is not established in a population without previous myocardial infarction (MI) or stroke.

METHODS: From June 2019 to November 2021, the VESALIUS-CV trial (Effect of Evolocumab in Patients at High Cardiovascular Risk Without Prior Myocardial Infarctions or Stroke) enrolled patients with qualifying atherosclerosis or high-risk diabetes without previous MI or stroke and randomized them to evolocumab or placebo (median follow-up 4.6 years). In a prespecified analysis, Lp(a) was assessed at baseline in 7557 patients. Cox models were used to assess the adjusted risk of cardiovascular events by baseline Lp(a) in the placebo arm, and the efficacy of evolocumab by baseline Lp(a). The primary outcome of interest was the composite of major coronary events (coronary heart disease death, MI, or urgent coronary revascularization).

RESULTS: Median age was 66 [interquartile range, 60–71] years, and 42.8% were women; median Lp(a) was 28 [interquartile range, 9–132] nmol/L. Higher baseline Lp(a) was associated with an increased risk of major coronary events (adjusted hazard ratio [$HR_{adjusted}$] per 100 nmol/L increase in Lp(a), 1.15 [95% CI, 1.05–1.26]; P=0.004), particularly for MI ($HR_{adjusted}$, 1.23 [95% CI, 1.10–1.38]; P<0.001). There was no association between Lp(a) and ischemic stroke ($HR_{adjusted}$, 1.00 [95% CI, 0.84–1.19]; P=0.99). After 48 weeks, evolocumab reduced LDL-C (low-density lipoprotein cholesterol) by 66.8 mg/dL and Lp(a) by 38.0 nmol/L in patients with baseline Lp(a) >105 nmol/L versus 61.1 mg/dL and 6.0 nmol/L in those with baseline Lp(a) ≤105 nmol/L. The relative reductions in the rate of major coronary events were 41% (HR, 0.59 [95% CI, 0.41–0.83]) in those with Lp(a) >105 nmol/L compared with 35% (HR, 0.65 [95% CI, 0.51–0.82]) in those below (P-interaction=0.45 for Lp[a] modeled as continuous variable). The corresponding absolute reductions were 3.7% versus 2.5% (P-interaction=0.09), corresponding to a number needed to treat of 28 versus 40 to prevent 1 major coronary event at 5 years.

CONCLUSIONS: In patients with atherosclerosis or high-risk diabetes but without previous MI or stroke, Lp(a) was independently associated with an increased risk of major coronary events but not ischemic stroke. Evolocumab reduced the relative risk of major coronary events to a similar degree irrespective of baseline Lp(a), with a numerically greater absolute risk reduction in patients with elevated Lp(a).

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT03872401.

Key Words: atherosclerosis ■ coronary artery disease ■ lipoprotein(a) ■ PCSK9 inhibitors ■ primary prevention

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This work was presented as an abstract at the European Atherosclerosis Society Conference, May 24–27, 2026.
Supplemental Material, the podcast, and transcript are available with this article at https://www.ahajournals.org/doi/suppl/10.1161/CIRCULATIONAHA.126.080999.

Circulation is available at www.ahajournals.org/journal/circ

Clinical Perspective

What Is New?

- We examined the relationship between baseline Lp(a) (lipoprotein[a]), PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibition with evolocumab, and cardiovascular risk in patients without a previous history of myocardial infarction or ischemic stroke.
- Higher baseline Lp(a) was associated with an increased risk of major coronary events, but not ischemic stroke.
- Evolocumab reduced the risk of major coronary events regardless of baseline Lp(a).
- A trend toward a larger absolute risk reduction was observed for those with higher baseline Lp(a) because of higher coronary risk.

What Are the Clinical Implications?

- Lp(a) is associated with the risk of coronary events and may help identify patients without a history of myocardial infarction or stroke who may observe larger absolute benefit from evolocumab.

Nonstandard Abbreviations and Acronyms

$HR_{adjusted}$	adjusted hazard ratio
LDL-C	low-density lipoprotein cholesterol
Lp(a)	lipoprotein(a)
MI	myocardial infarction
PCSK9	proprotein convertase subtilisin/kexin type 9
VESALIUS-CV	Effect of Evolocumab in Patients at High Cardiovascular Risk Without Prior Myocardial Infarctions or Stroke

Despite recent advances in lipid-lowering therapies, substantial residual risk of coronary events persists even among individuals who achieve low LDL-C (low-density lipoprotein cholesterol) levels.[1,2] One factor that is believed to contribute to this residual risk is Lp(a) (lipoprotein[a]),[3–5] an LDL (low-density lipoprotein)–like particle covalently bound to apolipoprotein(a) and a major carrier of oxidized phospholipids.[6] A large body of epidemiologic evidence demonstrates that elevated Lp(a) is independently associated with increased cardiovascular risk,[7–9] and Mendelian randomization studies further support a causal role for Lp(a) in atherogenesis and lifetime cardiovascular risk.[10,11] However, therapeutic options to meaningfully lower Lp(a) remain limited, and no widely available treatments produce substantial reductions sufficient to directly target this pathway. PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors have been shown to reduce Lp(a) concentrations by approximately 25-30%, but are not indicated for Lp(a) lowering.[12–14]

In the VESALIUS-CV trial (Effect of Evolocumab in Patients at High Cardiovascular Risk Without Prior Myocardial Infarctions or Stroke), the PCSK9 inhibitor evolocumab reduced the risk of cardiovascular events in patients without a previous history of myocardial infarction (MI) or stroke.[15] Contemporary guidelines now recommend at least 1 measurement of Lp(a) in all adults to refine cardiovascular risk assessment and to identify individuals who may benefit from more intensive lipid-lowering strategies.[16,17] In a prespecified analysis, we therefore evaluated the association between baseline Lp(a) levels and cardiovascular outcomes and the efficacy of evolocumab according to baseline Lp(a) concentration in patients at risk for a first cardiovascular event.

METHODS

Study Participants

From June 2019 to November 2021, the VESALIUS-CV trial enrolled 12 257 participants with qualifying atherosclerosis or risk factors for atherosclerosis and without a history of MI or ischemic stroke who had an LDL-C ≥90 mg/dL at 774 participating sites in 33 countries. The detailed eligibility criteria and study procedures have been previously published.[18] Participants were randomized to evolocumab 140 mg every 2 weeks or a matching placebo. Randomization was stratified by region (North America, Europe, and other) and baseline LDL-C at screening. Patients and sites were blinded to treatment allocation and results of on-treatment lipid testing, including Lp(a). Written informed consent was collected for all study participants and the study protocol was approved by relevant ethic committees at each participating site. The CONSORT (Consolidated Standard of Reporting Trials) guidelines were followed for study conduct and reporting (Supplemental Material). We encourage parties interested in collaboration and data sharing to contact the corresponding author directly for further discussions.

Lipid Assessments

Baseline Lp(a) was measured centrally in 7557 study participants who participated in the biomarker or lipid substudies and had available samples. Postrandomization assessment of LDL-C and Lp(a) was done at week 48 in 1602 participants who participated in the lipid substudy and had available samples (Figure S1 and Supplemental Methods).

Study End Points

The primary outcome of interest for the current analysis was the composite of major coronary events, defined as coronary heart disease death, MI, or urgent coronary revascularization. This outcome was prespecified based on previous epidemiological data suggesting a stronger relationship between Lp(a) and coronary outcomes,[7] and the use of this composite outcome in select ongoing phase 3 trials of Lp(a)-lowering

therapeutics (NCT05581303, NCT07136012). The composite of cardiovascular death, myocardial infarction, and stroke, along with its individual components and those of the primary outcome were also examined. Outcomes for the current analysis were adjudicated by an independent clinical event committee blinded to treatment arm and on-treatment lipid levels using prespecified definitions.[15]

Statistical Analysis

Baseline Lp(a) was modeled as a continuous variable and dichotomized at a threshold of 105 nmol/L based on previous guidelines that had been specified at the time of analysis.[16] A sensitivity analysis was conducted at a threshold of 125 nmol/L.[17] Participant characteristics were compared using the chi-square test for categorical variables and the Wilcoxon rank-sum test for continuous variables.

The relationship between Lp(a) and incident outcomes was first examined in the placebo arm through use of a Cox proportional hazards model that included Lp(a), trial stratification factors, and relevant covariates (age, sex, body mass index, race, hypertension, diabetes, active smoking, baseline LDL-C, and baseline estimated glomerular filtration rate <60 mL/min per 1.73 m^2). The proportional hazards assumption was assessed and confirmed by visually plotting scaled Schoenfeld residuals against time and formally testing whether the residuals are time-dependent.

The relative and absolute placebo-adjusted changes in LDL-C and Lp(a) were assessed from baseline to week 48, stratified by baseline Lp(a) concentration through use of a mixed model with repeated measures that included terms for trial group, stratification factors, scheduled visit, and the interaction of trial group by study visit. Changes were reported as placebo-adjusted least squares mean changes from baseline in LDL-C and placebo-adjusted median change from baseline in Lp(a), given the skewed distribution of Lp(a) (Figure S2).

The efficacy of evolocumab versus placebo by baseline Lp(a) concentration was then evaluated through Cox proportional hazards models, modeling Lp(a) as either a continuous variable or at the dichotomous threshold. Kaplan-Meier event rates are reported at 5 years. Formal interaction testing was performed by including an interaction term in the model with Lp(a) modeled as continuous variable. Absolute risk reduction interactions were evaluated using pseudo-value regression models for cumulative incidence, incorporating treatment assignment, baseline Lp(a), a treatment-by-Lp(a) interaction term, and trial stratification factors; the interaction *P* value tested whether treatment-associated absolute risk differences varied across baseline Lp(a) levels. A *P* value of <0.05 was considered to be significant. All analyses were considered exploratory and conducted by the TIMI (Thrombolysis in Myocardial Infarction) Study Group using an independent copy of the database.

RESULTS

Baseline Characteristics

Overall, median Lp(a) was 28 [interquartile range, 9–132] nmol/L (Figure S2), and 28.7% of patients had an Lp(a) >105 nmol/L at baseline. Participant characteristics stratified by baseline Lp(a) concentration are presented in the Table. Those participants with higher Lp(a) were more likely to be women (46.6% versus 41.3%) and self-reported Black or African American (3.6% versus 1.1%), but less likely of Hispanic or Latino origin (14.8% versus 18.7%). Median age was similar irrespective of baseline Lp(a) (median [interquartile range], 65 [60–70] years versus 66 [60–71] years). Higher Lp(a) was associated with a lower prevalence of hypertension, diabetes, and current smoking. In contrast, those with high Lp(a) were more likely to have known atherosclerosis, including coronary artery disease, but with a similar prevalence of known cerebrovascular or peripheral arterial disease. Baseline total cholesterol and LDL-C were similar across baseline Lp(a) groups, but with more frequent use of statins in those with higher baseline Lp(a).

Baseline Lp(a) Concentration and Cardiovascular Outcomes in Placebo-Treated Participants

The association between baseline Lp(a) and incident cardiovascular events was assessed in the placebo arm (n=3738; Figure 1). There was a 15% relative increase in the rate of major coronary events (coronary heart disease death, MI, or urgent coronary revascularization) for every increase in 100 nmol/L in Lp(a) (adjusted hazard ratio [$HR_{adjusted}$], 1.15 [95% CI, 1.05–1.26], *P*=0.004). Among individual outcomes, the magnitude of the association between baseline Lp(a) and subsequent risk appeared most robust for incident MI with a 23% relative increase in the rate per each 100 nmol/L increase in Lp(a) ($HR_{adjusted}$, 1.23 [95% CI, 1.10–1.38]), with $HR_{adjusted}$ of 1.15 (95% CI, 1.02–1.29) for urgent coronary revascularization and 1.12 (95% CI, 0.94–1.33) for coronary heart disease death. By contrast, higher Lp(a) was not associated with the rate of ischemic stroke ($HR_{adjusted}$, 1.00 [95% CI, 0.84–1.19]) or cardiovascular death ($HR_{adjusted}$, 1.01 [95% CI, 0.87–1.18]).

Changes in LDL-C and Lp(a) With Evolocumab by Baseline Lp(a)

Overall, compared with placebo, evolocumab reduced Lp(a) by a median of 26.9%. For those with an Lp(a) ≤105 nmol/L, the reduction was 30.0%, translating into an absolute reduction of 6.0 nmol/L. For those with Lp(a) >105 nmol/L, the reduction was 19.4%, leading to an absolute reduction of 38 nmol/L (Figure 2). The relative and absolute mean placebo-adjusted reductions in LDL-C were, respectively, 54.1% and 61.1 mg/dL in patients with Lp(a) ≤105 nmol/L at baseline, and 58.2% and 66.8 mg/dL in those with Lp(a) >105 nmol/L at baseline. Only a modest correlation was seen between the percent change in Lp(a) and LDL-C at 48 weeks (*r*=0.32; *P*<0.001; Figure S3).

Table. Baseline Characteristics by Baseline Lp(a)

Characteristic	Lp(a) ≤105 nmol/L n=5391	Lp(a) >105 nmol/L n=2166	*P* value
Age, y	66.0 (60.0–71.0)	65.0 (60.0–70.0)	0.69
Female sex	2224 (41.3%)	1009 (46.6%)	<0.001
BMI, kg/m²	30.1 (27.0–33.9)	29.5 (26.4–33.5)	<0.001
Race and ethnicity			<0.001
White	5196 (96.4%)	2025 (93.5%)	
Black or African American	60 (1.1%)	79 (3.6%)	
Asian	70 (1.3%)	34 (1.6%)	
Other	62 (1.2%)	27 (1.2%)	
Hispanic	1009 (18.7%)	321 (14.8%)	<0.001
Region			<0.001
North America	717 (13.3%)	350 (16.2%)	
Eastern Europe	2614 (48.5%)	915 (42.2%)	
Western Europe	1073 (19.9%)	569 (26.3%)	
Asia/Pacific	105 (1.9%)	61 (2.8%)	
Latin America	882 (16.4%)	271 (12.5%)	
Medical history			
Hypertension	4700 (87.2%)	1839 (84.9%)	0.009
Diabetes	3341 (62.0%)	1138 (52.5%)	<0.001
Current smoking	1571 (29.1%)	543 (25.1%)	<0.001
Familial hypercholesterolemia	474 (8.8%)	233 (10.8%)	0.008
Family history of premature CAD	1239 (23.0%)	512 (23.6%)	0.54
Any atherosclerosis	3362 (62.4%)	1528 (70.5%)	<0.001
Significant CAD	2136 (39.6%)	1068 (49.3%)	<0.001
Previous PCI or CABG	1753 (32.5%)	890 (41.1%)	<0.001
Multivessel revascularization	1518 (28.2%)	785 (36.2%)	<0.001
Significant CVD	526 (9.8%)	242 (11.2%)	0.066
Significant PAD	971 (18.0%)	374 (17.3%)	0.44
LLTs			
Any LLT	4866 (90.3%)	1986 (91.7%)	0.054
High-intensity LLT	3762 (69.8%)	1563 (72.2%)	0.041
Any statin	4540 (84.2%)	1891 (87.3%)	<0.001
High-intensity statin	3567 (66.2%)	1452 (67.0%)	0.47
Ezetimibe	946 (17.5%)	478 (22.1%)	<0.001
Baseline laboratory results			
Lp(a), nmol/L	15.0 (6.5–33.5)	210.2 (158.5–284.3)	n/a
Total cholesterol, mg/dL	202.6 (179.0–234.5)	201.0 (177.9–232.0)	0.17
Non–HDL-C, mg/dL	154.3 (131.5–184.0)	150.0 (128.2–180.8)	0.001
LDL-C, mg/dL	122.1 (104.4–149.0)	119.9 (103.0–148.1)	0.13
HDL-C, mg/dL	47.0 (39.4–56.5)	49.0 (41.0–58.0)	<0.001
Triglycerides, mg/dL	159.4 (115.1–230.0)	147.0 (107.0–209.5)	<0.001
eGFR <60 mL/min per 1.73 m²	1013 (18.8%)	460 (21.3%)	0.014

Data represent n (%) or median (interquartile range) with *P* values estimated with Wilcoxon rank-sum test for continuous variables and chi-square test for categorical variables. BMI indicates body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; CVD, cerebrovascular disease; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; Lp(a), lipoprotein(a); n/a, not applicable; PAD, peripheral artery disease; and PCI, percutaneous coronary intervention.

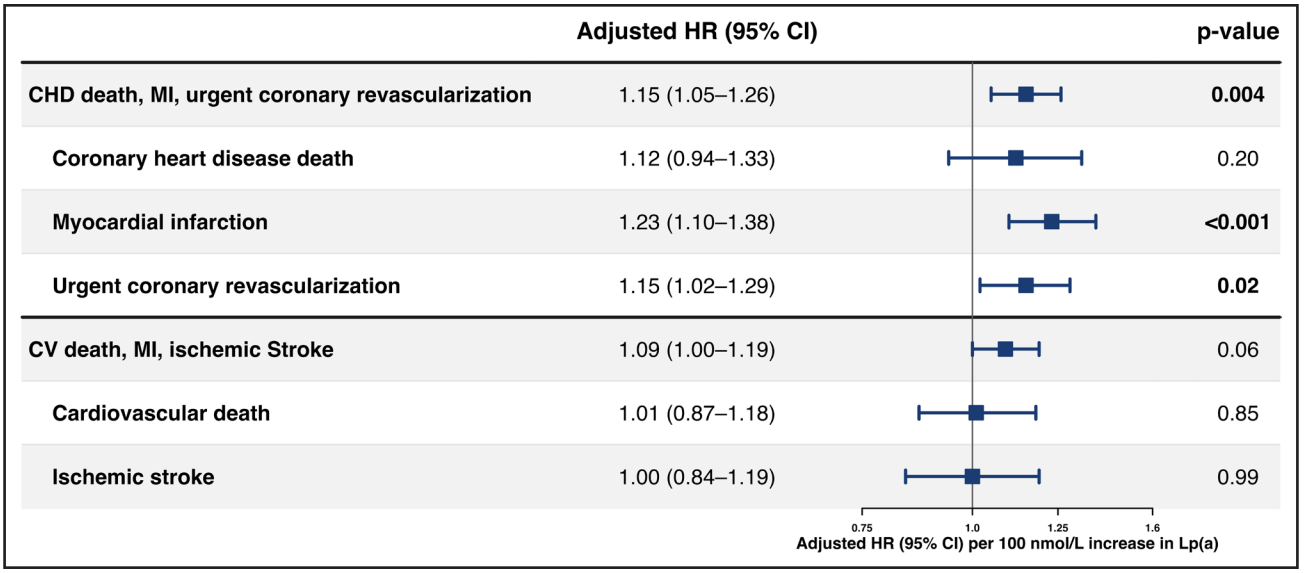

Figure 1. Lp(a) and risk of cardiovascular events in placebo-treated participants.
The adjusted relative risk (HR, 95% CI) of major cardiovascular events modeled per 100 nmol/L increase in Lp(a) in the placebo arm (n=3738). CHD indicates coronary heart disease; CV, cardiovascular; HR, hazard ratio; Lp(a), lipoprotein(a); and MI, myocardial infarction.

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

The relative reductions in the rate of major coronary events were 41% (hazard ratio, 0.59 [95% CI, 0.41–0.83]) in patients with Lp(a) >105 nmol/L compared with 35% (hazard ratio, 0.65 [95% CI, 0.51–0.82]) in those below (Figure 3), with no statistically significant interaction (*P*-interaction=0.45 with Lp[a] modeled as a continuous variable; Figure 4A). In part because of the higher baseline risk for those with higher baseline Lp(a), the absolute risk reductions tended to be greater in those with higher baseline Lp(a) (*P*-interaction=0.09; Figure 4B). The absolute risk reduction was 3.7% (95% CI, 1.5%–5.9%) for those with an Lp(a) >105nmol/L versus 2.5% (95% CI, 1.1%–3.9%) for those with lower Lp(a). This translated into a number needed to treat of 28 to prevent 1 major coronary event at 5 years for those with higher Lp(a) versus 40 for those with lower Lp(a).

Additional outcomes stratified by baseline Lp(a) are included in Table S1 and Figure S4. The differences for MI were more marked, with relative risk reductions of 61% in those with Lp(a) >105 nmol/L (hazard ratio, 0.39 [95% CI, 0.24 to 0.63]) compared with 27% (hazard ratio, 0.73 [95% CI, 0.53 to 1.01]) in those with lower baseline Lp(a) (*P*-interaction=0.17). The corresponding absolute risk reductions were 3.6% (95% CI, 1.9% to 5.4%) and 0.9% (95% CI, −0.1% to 2.0%; *P*-interaction=0.018) (Figure S5).

Qualitatively consistent results were observed when an Lp(a) dichotomous threshold of 125 nmol/L was applied (Table S2). In addition, in analyses stratified by LDL-C and Lp(a) levels, evolocumab appeared efficacious across all subgroups (Table S3).

DISCUSSION

In this large, well-characterized, randomized trial of evolocumab in patients at high risk for a first cardiovascular event, we demonstrate that Lp(a) provides independent and clinically meaningful information for risk stratification. Specifically, higher baseline Lp(a) concentrations were associated with an increased risk of coronary events, particularly MI; in contrast, there was no clear association with ischemic stroke. These findings reinforce previous observations[3,7,19] and may suggest that the clinical impact of Lp(a) is more pronounced toward development of coronary atherosclerosis than cerebrovascular disease, with potential implications for the design and end point selection of ongoing phase 3 trials of new drugs specifically targeting Lp(a).

Moreover, in this randomized trial, evolocumab reduced the risk of cardiovascular events across the full range of baseline Lp(a) concentrations. There was no statistically significant heterogeneity for the relative risk reductions observed with evolocumab, although the values were numerically greater in those with higher baseline Lp(a) levels. Coupled with the higher baseline risk in patients with higher baseline levels, this led to absolute risk reductions that tended to be greater among individuals with higher Lp(a), but this difference was not statistically significant.

PCSK9 inhibitors have been shown to reduce Lp(a) levels an average of 25% to 30%,[12,13] although the underlying mechanisms remain incompletely understood. Proposed pathways include enhanced clearance of Lp(a) particles through upregulation of LDL receptors, as well as potential contributions from LDL receptor-independent pathways, suggesting a more complex

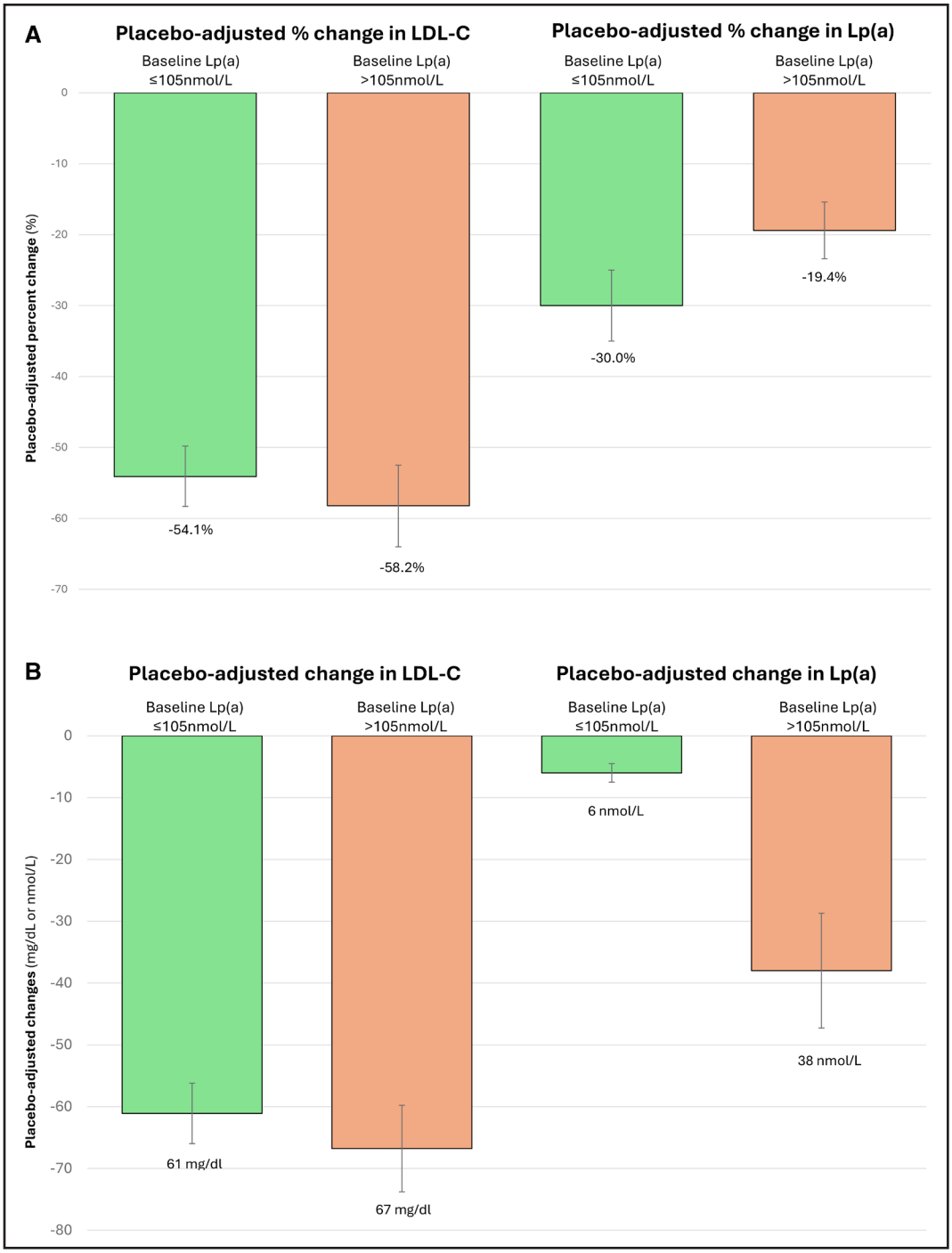

Figure 2. Placebo-adjusted change in LDL-C and Lp(a) with evolocumab by baseline Lp(a) concentration.
Placebo-adjusted change in LDL-C and Lp(a) with evolocumab from baseline to week 48. Serial lipid values were available in participants of a dedicated lipid substudy. (**A**) Relative and (**B**) absolute least square means change is plotted with 95% CIs for LDL-C. Given its nonparametric distribution, Lp(a) is plotted as the median percent change. LDL-C indicates low-density lipoprotein cholesterol; and Lp(a), lipoprotein(a).

biology.[20,21] Consistent with previous reports,[12] the relative reduction in Lp(a) was smaller among individuals with higher baseline levels, whereas absolute reductions were greater, reflecting higher starting concentrations. Yet the overall magnitude of Lp(a) lowering with PCSK9 inhibition remains modest. This is particularly relevant in the context of Mendelian randomization studies indicating that substantially larger absolute reductions in Lp(a) (eg, 150–200 nmol/L) may be required to translate into meaningful reductions in cardiovascular risk.[22] Therefore, among a population not selected to have very high Lp(a) levels, it may be challenging to appreciate differences in relative risk reductions with PCSK9 inhibitors in subgroups stratified by Lp(a) levels.

In this context, our findings extend previous observations from secondary prevention trials, including

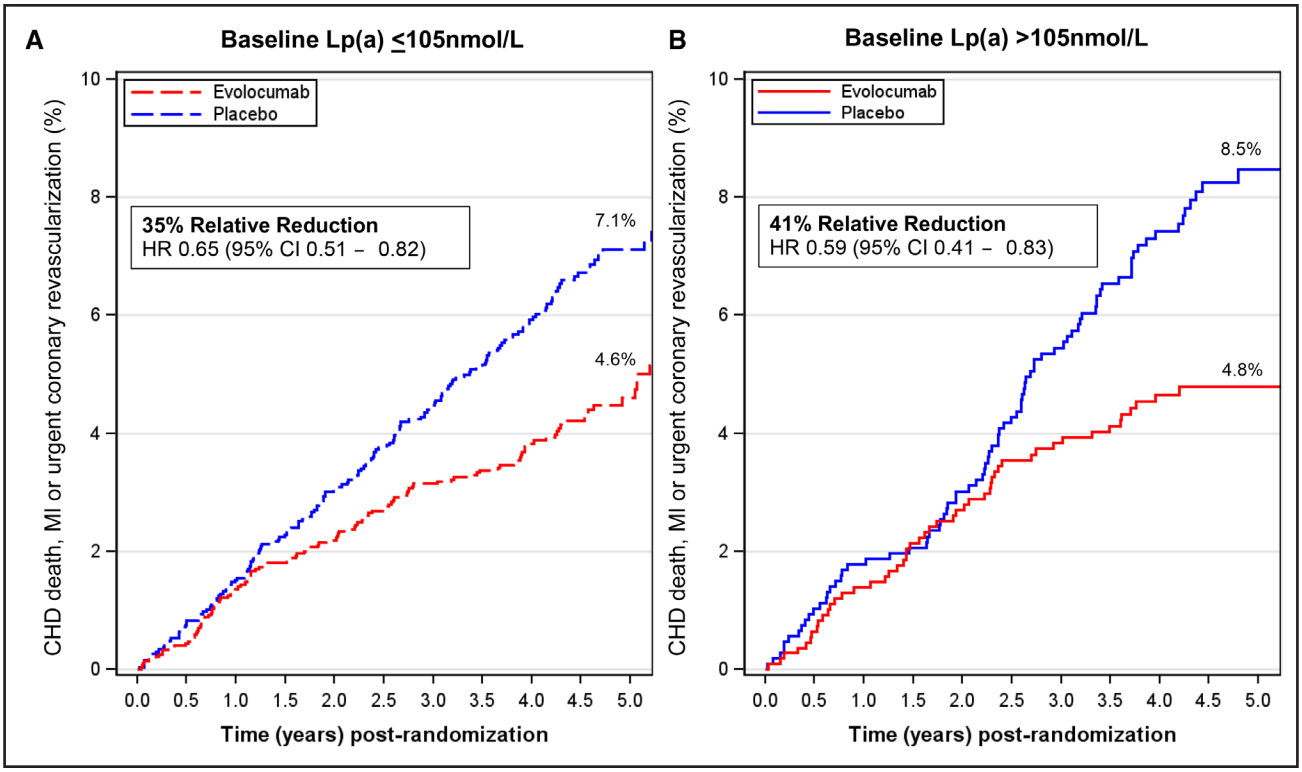

Figure 3. Cumulative incidence of first major coronary by baseline Lp(a).
Cumulative incidence of major coronary event (composite of coronary heart disease death, myocardial infarction, or urgent coronary revascularization) in patients stratified by (**A**) Lp(a) ≤105 nmol/L and (**B**) Lp(a) >105 nmol/L. Hazard ratio and 95% CI were obtained from a Cox model that included trial stratification factors. CHD indicates coronary heart disease; HR, hazard ratio; Lp(a), lipoprotein(a); and MI, myocardial infarction.

FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk) and ODYSSEY OUTCOMES (Alirocumab and Cardiovascular Outcomes After Acute Coronary Syndrome), in which Lp(a) was associated with residual cardiovascular risk and somewhat greater risk reductions were observed with PCSK9 inhibition in patients with higher baseline Lp(a) levels despite similar observed reductions in LDL-C. These observations contributed to the most recent American College of Cardiology/American Heart Association/Multisociety Dyslipidemia Guidelines to recommend adding a PCSK9 inhibitor with proven cardiovascular benefit in patients with clinical atherosclerotic cardiovascular disease who have an elevated Lp(a) and have not achieved LDL-C treatment goals.[17] The present analysis expands these data to those with established atherosclerosis or multiple risk factors for atherosclerosis, but without previous MI or stroke, thereby broadening the relevance of Lp(a) to earlier stages of cardiovascular disease. Although there was a numerically greater relative reduction in major coronary events with evolocumab in those with higher Lp(a) levels, the difference was small and not statistically significant. However, it should be noted that unlike FOURIER and ODYSSEY OUTCOMES, the present study had a longer duration of follow-up and thus a greater overall treatment effect from LDL-C lowering.

Despite recommendations for at least once-in-a-lifetime measurement,[16,17] Lp(a) is not routinely incorporated into clinical risk assessment, in part because of uncertainty about subsequent management.[23,24] Statins reduce LDL-C and cardiovascular risk but do not directly address Lp(a)-mediated residual risk and may modestly increase Lp(a).[25] PCSK9 inhibitors provide modest reductions in Lp(a) in addition to potent LDL-C lowering and have demonstrated cardiovascular benefit in high-risk populations. Our findings suggest that intensification of lipid-lowering therapy with evolocumab may partially mitigate the excess risk associated with elevated Lp(a), even in patients without previous cardiovascular events, whereas dedicated Lp(a)-lowering therapies remain under investigation. To that end, ongoing phase 3 trials of selective Lp(a)-lowering therapies that achieve marked reductions in Lp(a) (NCT04023552, NCT05581303, NCT06292013, NCT07136012, and NCT07157774) will be critical to determine whether more substantial lowering translates into improved clinical outcomes and for which types of cardiovascular outcomes.

Limitations

This prespecified secondary analysis was not adjusted for multiplicity and should be interpreted as exploratory. The study population was predominantly of self-reported

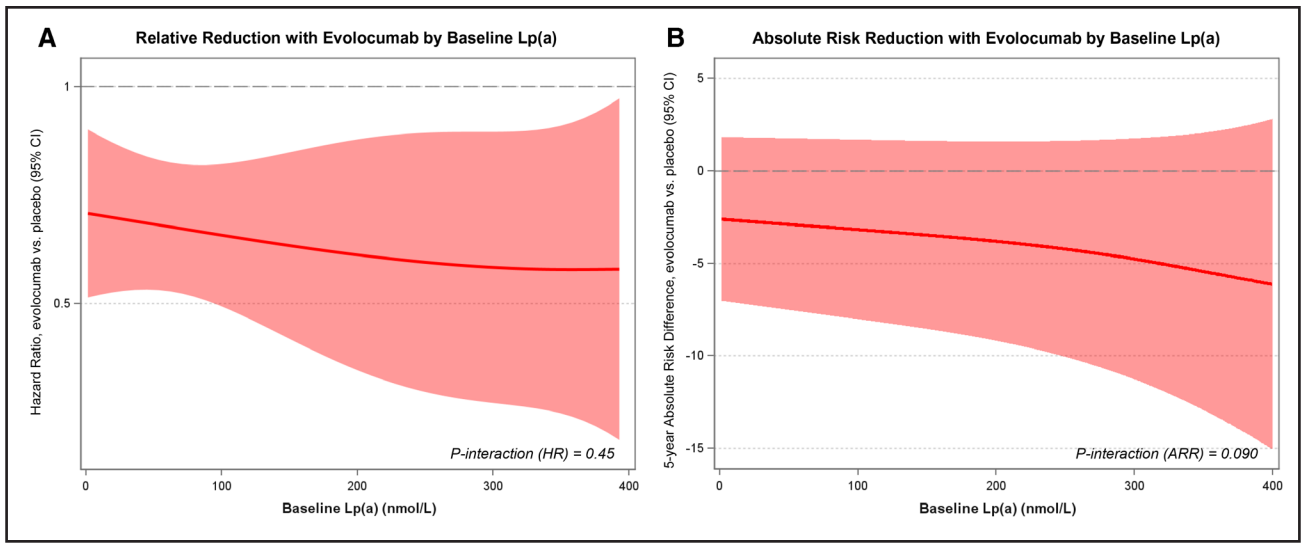

Figure 4. Efficacy of evolocumab by baseline Lp(a) concentration.
A, Relative risk of major coronary events with evolocumab versus placebo (HR, 95% CIs) as a function of baseline Lp(a) on a continuous scale (*P*-interaction=0.45). **B**, Observed absolute risk difference with evolocumab versus placebo for reducing major coronary events at 5 years as a function of baseline Lp(a) (*P*-interaction=0.09). ARR indicates absolute risk reduction; HR, hazard ratio; and Lp(a), lipoprotein(a).

White race, limiting generalizability to more diverse populations in whom Lp(a) distributions and associated risks may differ. Study participants in VESALIUS-CV were required to have an LDL-C of at least 90 mg/dL at screening; therefore, potential interactions between Lp(a) and lower levels of LDL-C could not be explored. We did not observe any clear signal toward earlier time to benefit for evolocumab for those with higher Lp(a) in the current study, but this hypothesis could be explored further across larger or pooled datasets. In addition, the current findings warrant further validation, including relevant thresholds for Lp(a) if they were to be used to help guide clinical management. Because PCSK9 inhibitors lower both Lp(a) and LDL-C, ongoing trials of novel therapeutics that lower Lp(a) will be useful to definitely test the hypothesis that lowering Lp(a) reduces cardiovascular risk.

CONCLUSIONS

Among patients at high risk for a first cardiovascular event, Lp(a) was independently associated with major coronary events, with no association seen for ischemic stroke. Evolocumab reduced cardiovascular risk across the spectrum of Lp(a), with an observed trend toward greater absolute benefit among those with higher baseline levels. These findings support the use of Lp(a) for risk stratification and to help guide decisions about more intensive lipid-lowering therapy and provide important context for ongoing trials targeting Lp(a).

ARTICLE INFORMATION

Received April 15, 2026; accepted May 15, 2026.

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Sources of Funding

The VESALIUS-CV study was funded by Amgen.

Disclosures

Drs Monguillon, Marston, Bohula, Giugliano, Sabatine, and O'Donoghue and Mr Park, Ms Kuder, and Ms Murphy report being members of the TIMI Study Group, which reports grants support through Brigham and Women's Hospital from 4TEEN4 Pharmaceuticals GmbH, Abbott, Abiomed, Inc, Amgen, Anthos Therapeutics, ARCA Biopharma, Inc, AstraZeneca, Beijing Inno Medicine Co, Ltd, Boehringer Ingelheim, Cleerly, Inc, Daiichi-Sankyo, Ionis Pharmaceuticals, Inc, Janssen Research and Development, LLC, Marea Therapeutics, Inc, Merck, Novartis, Pfizer, and Softcell Medical Limited. Dr Monguillon reports research grant support from Federation Francaise de Cardiologie and Action Study Group. Dr Marston reports consultant and speaker fees from Amgen, Ionis Pharmaceuticals, New Amsterdam, and Radence; clinical trial activity from AstraZeneca, Ionis, Novartis, and Pfizer; end point review committee activity from Beckman Coulter, Inc; data and safety monitoring board activities from Janssen Pharmaceuticals; and speaking engagements from Medical Education Speakers Network. Dr Bohula reports consultant fees from Amgen, Daiichi Sankyo Company, Esperion Therapeutics Inc, Novo Nordisk, and Servier Pharmaceuticals LLC; and end point review committee participation for Celecor, Kowa American Corporation, and Novartis. Mr Park reports grant support from Abbott Laboratories, Amgen Inc, Anthos Therapeutics, AstraZeneca, Daiichi Sankyo Company, Merck, Novartis, Pfizer, Regeneron Pharmaceuticals, Roche, Siemens Healthcare Diagnostics Inc, and Zora Biosciences. Dr De Ferrari reports consultant fees from Merck; being

a member of the executive committee or steering committee of clinical trials for Amgen, Merci, and Novartis; and data and safety monitoring activity from UCB. Dr Leiter reports fees for an advisory board from Amgen, Eli Lilly and Company, HLS Therapeutics, Merck, and Novartis Regeneron; executive committee and/or steering committee work for Amgen, AstraZeneca, Eli Lilly and Company, and Novartis; and continuing medical education program and lectures from Amgen, HLS Therapeutics, Merck, and Novartis. Dr Nicolau reports grant contracts from Amgen Inc, Anthos Therapeutics, AstraZeneca, Bayer, CSL Behring, Daiichi Sankyo Company, Dalcor, Esperion Therapeutics Inc, Ionis Pharmaceutics, Janssen Biotech, Novartis, Novo Nordisk, Sanofi US services Inc, and Vifor Pharma. Dr Goudev reports honoraria from Amgen and Ionis Pharmaceuticals as a clinical trial investigator, Kowa Company Ltd and Novartis as national lead investigator, and NovoNordisk as speaker and clinical trial honoraria. Dr Budaj reports research grants from Amgen, Merck Sharp & Dohme, and Novartis. Dr Blankstein reports consulting fees and research support from Amgen Inc and Novartis Inc. Dr Vinereanu has received research grants from Amgen, AstraZeneca, Novartis, and Lilly, and speaker and consultancy fees from Amgen, Sanofi, Novartis, Lilly, and NovoNordisk. Dr Giugliano reports consultant fees from AstraZeneca, Beckman Coulter Inc, Celecor Therapeutics, Daiichi-Sankyo, Dr Reddy's Laboratories, Inari Medical Inc, and Novartis; CME program and lectures from Amgen, BigSky Cardiology, Fondazione Internazionale Menarini, Pfizer, Saja Pharmaceuticals, SHAKE Heart, Entity, and Vox Media; and data and safety monitoring board activity from Artivion. Dr Sabatine reports research grant support through Brigham and Women's Hospital from Amgen, AstraZeneca, Beijing Inno Medicine, Boehringer Ingelheim, Daiichi-Sankyo, Ionis, Marea, Merck, Novartis, Pfizer, Saghmos Therapeutics, and Verve Therapeutics, and consulting for Amgen, AMPEL BioSolutions, Anthos Therapeutics, Inc, AstraZeneca, Beren Therapeutics, Boehringer Ingelheim, Dr Reddy's Laboratories, General Medicines, Merck, and TigerMed. Dr O'Donoghue has received grant funding through Brigham and Women's Hospital from Amgen, Merck, Novartis, AstraZeneca, and Marea. She has received consulting or data and safety monitoring board fees from Amgen, Novartis, AstraZeneca, Janssen, Verve, NovoNordisk, Eli Lilly, and New Amsterdam. The other authors report no conflicts.

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REFERENCES

1. Sabatine MS, Wiviott SD, Im K, Murphy SA, Giugliano RP. Efficacy and safety of further lowering of low-density lipoprotein cholesterol in patients starting with very low levels: a meta-analysis. *JAMA Cardiol*. 2018;3:823–828. doi: 10.1001/jamacardio.2018.2258
2. Sampson UK, Fazio S, Linton MF. Residual cardiovascular risk despite optimal LDL cholesterol reduction with statins: the evidence, etiology, and therapeutic challenges. *Curr Atheroscler Rep*. 2012;14:1–10. doi: 10.1007/s11883-011-0219-7
3. Patel AP, Wang M, Pirruccello JP, Ellinor PT, Ng K, Kathiresan S, Khera AV. Lp(a) (lipoprotein[a]) concentrations and incident atherosclerotic cardiovascular disease: new insights from a large national biobank. *Arterioscler Thromb Vasc Biol*. 2021;41:465–474. doi: 10.1161/atvbaha.120.315291
4. Bhatia HS, Wandel S, Willeit P, Lesogor A, Bailey K, Ridker PM, Nestel P, Simes J, Tonkin A, Schwartz GG, et al. Independence of lipoprotein(a) and low-density lipoprotein cholesterol–mediated cardiovascular risk: a participant-level meta-analysis. *Circulation*. 2025;151:312–321. doi: 10.1161/CIRCULATIONAHA.124.069556
5. Kronenberg F, Mora S, Stroes ESG, Ference BA, Arsenault BJ, Berglund L, Dweck MR, Koschinsky M, Lambert G, Mach F, et al. Lipoprotein(a) in atherosclerotic cardiovascular disease and aortic stenosis: a European Atherosclerosis Society consensus statement. *Eur Heart J*. 2022;43:3925–3946. doi: 10.1093/eurheartj/ehac361
6. Tsimikas S, Brilakis ES, Miller ER, McConnell JP, Lennon RJ, Kornman KS, Witztum JL, Berger PB. Oxidized phospholipids, Lp(a) lipoprotein, and coronary artery disease. *N Engl J Med*. 2005;353:46–57. doi: 10.1056/NEJMoa043175
7. The Emerging Risk Factors Collaboration. Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality. *JAMA*. 2009;302:412. doi: 10.1001/jama.2009.1063
8. Bennet A, Di Angelantonio E, Erqou S, Eiriksdottir G, Sigurdsson G, Woodward M, Rumley A, Lowe GDO, Danesh J, Gudnason V. Lipoprotein(a) levels and risk of future coronary heart disease: large-scale prospective data. *Arch Intern Med*. 2008;168:598–608. doi: 10.1001/archinte.168.6.598
9. Berman AN, Biery DW, Besser SA, Singh A, Shiyovich A, Weber BN, Huck DM, Divakaran S, Hainer J, Kaur G, et al. Lipoprotein(a) and major adverse cardiovascular events in patients with or without baseline atherosclerotic cardiovascular disease. *J Am Coll Cardiol*. 2024;83:873–886. doi: 10.1016/j.jacc.2023.12.031
10. Clarke R, Peden JF, Hopewell JC, Kyriakou T, Goel A, Heath SC, Parish S, Barlera S, Franzosi MG, Rust S, et al; PROCARDIS Consortium. Genetic variants associated with Lp(a) lipoprotein level and coronary disease. *N Engl J Med*. 2009;361:2518–2528. doi: 10.1056/NEJMoa0902604
11. Tsimikas S, Hall JL. Lipoprotein(a) as a potential causal genetic risk factor of cardiovascular disease. *J Am Coll Cardiol*. 2012;60:716–721. doi: 10.1016/j.jacc.2012.04.038
12. O'Donoghue ML, Fazio S, Giugliano RP, Stroes ESG, Kanevsky E, Gouni-Berthold I, Im KA, Lira Pineda A, Wasserman SM, Češka R, et al. Lipoprotein(a), PCSK9 inhibition, and cardiovascular risk: insights from the FOURIER trial. *Circulation*. 2019;139:1483–1492. doi: 10.1161/CIRCULATIONAHA.118.037184
13. Bittner VA, Szarek M, Aylward PE, Bhatt DL, Diaz R, Edelberg JM, Fras Z, Goodman SG, Halvorsen S, Hanotin C, et al; ODYSSEY OUTCOMES Committees and Investigators. Effect of alirocumab on lipoprotein(a) and cardiovascular risk after acute coronary syndrome. *J Am Coll Cardiol*. 2020;75:133–144. doi: 10.1016/j.jacc.2019.10.057
14. Farmakis I, Doundoulakis I, Pagiantza A, Zafeiropoulos S, Antza C, Karvounis H, Giannakoulas G. Lipoprotein(a) reduction with proprotein convertase subtilisin/kexin type 9 inhibitors: a systematic review and meta-analysis. *J Cardiovasc Pharmacol*. 2021;77:397–407. doi: 10.1097/FJC.0000000000000963
15. Bohula EA, Marston NA, Bhatia AK, De Ferrari GM, Leiter LA, Nicolau JC, Park J-G, Kuder JF, Murphy SA, Walsh E, et al; VESALIUS-CV Investigators. Evolocumab in patients without a previous myocardial infarction or stroke. *N Engl J Med*. 2026;394:117–127. doi: 10.1056/NEJMoa2514428
16. Mach F, Koskinas KC, Roeters Van Lennep JE, Tokgözoğlu L, Badimon L, Baigent C, Benn M, Binder CJ, Catapano AL, De Backer GG, et al; ESC/EAS Scientific Document Group. 2025 Focused update of the 2019 ESC/EAS guidelines for the management of dyslipidaemias. *Eur Heart J*. 2025;46:4359–4378. doi: 10.1093/eurheartj/ehaf190
17. Blumenthal RS, Morris PB, Gaudino M, Johnson HM, Anderson TS, Bittner VA, Blankstein R, Brewer LC, Cho L, de Ferranti SD, et al; Writing Committee Members. 2026 ACC/AHA/AACVPR/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of dyslipidemia: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2026;153:e1154–e1276. doi: 10.1161/CIR.0000000000001423
18. Bohula EA, Marston NA, Ruzza A, Murphy SA, De Ferrari GM, Diaz R, Leiter LA, Elliott-Davey M, Wang H, Bhatia AK, et al. Rationale and design of the effect of evolocumab in patients at high cardiovascular risk without prior myocardial infarction or stroke (VESALIUS-CV) trial. *Am Heart J*. 2024;269:179–190. doi: 10.1016/j.ahj.2023.12.004
19. Brandt EJ, Mani A, Spatz ES, Desai NR, Nasir K. Lipoprotein(a) levels and association with myocardial infarction and stroke in a nationally representative cross-sectional US cohort. *J Clin Lipidol*. 2020;14:695–706.e4. doi: 10.1016/j.jacl.2020.06.010
20. Villard EF, Thedrez A, Blankenstein J, Croyal M, Tran T-T-T, Poirier B, Le Bail J-C, Illiano S, Nobécourt E, Krempf M, et al. PCSK9 modulates the secretion but not the cellular uptake of lipoprotein(a) ex vivo. *JACC Basic Transl Sci*. 2016;1:419–427. doi: 10.1016/j.jacbts.2016.06.006
21. Reyes-Soffer G, Pavlyha M, Ngai C, Thomas T, Holleran S, Ramakrishnan R, Karmally W, Nandakumar R, Fontanez N, Obunike J, et al. Effects of PCSK9 inhibition with alirocumab on lipoprotein metabolism in healthy humans. *Circulation*. 2017;135:352–362. doi: 10.1161/CIRCULATIONAHA.116.025253
22. Lamina C, Kronenberg F; Lp(a)-GWAS-Consortium. Estimation of the required lipoprotein(a)-lowering therapeutic effect size for reduction in coronary heart disease outcomes: a Mendelian randomization analysis. *JAMA Cardiol*. 2019;4:575–579. doi: 10.1001/jamacardio.2019.1041
23. Bhatia HS, Hurst S, Desai P, Zhu W, Yeang C. Lipoprotein(a) testing trends in a large academic health system in the United States. *J Am Heart Assoc*. 2023;12:e031255. doi: 10.1161/JAHA.123.031255
24. O'Donoghue ML, Monguillon V. Ignorance is not bliss: the importance of lipoprotein(a) testing. *Eur Heart J*. 2025;46:4776–4778. doi: 10.1093/eurheartj/ehaf422
25. Tsimikas S, Gordts PLSM, Nora C, Yeang C, Witztum JL. Statin therapy increases lipoprotein(a) levels. *Eur Heart J*. 2020;41:2275–2284. doi: 10.1093/eurheartj/ehz310
26. Wyness SP, Genzen JR. Performance evaluation of five lipoprotein(a) immunoassays on the Roche cobas c501 chemistry analyzer. *Pract Lab Med*. 2021;25:e00218. doi: 10.1016/j.plabm.2021.e00218