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An Exploratory Analysis of Proprotein Convertase Subtilisin/Kexin Type 9 Inhibition and Aortic Stenosis in the FOURIER Trial

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IMPORTANCE Despite recent advances in treatment of severe aortic valve stenosis (AS), AS remains a life-threatening condition with no proven disease-modifying therapy. Low-density lipoprotein cholesterol (LDL-C) and lipoprotein(a) (Lp[a]) have been implicated in the pathobiology of AS. The proprotein convertase subtilisin/kexin type 9 inhibitor evolocumab reduces circulating LDL-C concentrations by 50% to 60% and Lp(a) by 20% to 30%.

OBJECTIVE To determine whether evolocumab reduces the risk of AS events in patients with atherosclerotic cardiovascular disease.

INTERVENTIONS Patients were randomized 1:1 to evolocumab or placebo.

DESIGN, SETTING, AND PARTICIPANTS Exploratory analysis of the FOURIER trial, which enrolled 27 564 patients with stable atherosclerotic cardiovascular disease who were taking statin therapy at 1242 sites in 49 countries from February 2013 to November 2016. Patients were randomized to evolocumab or placebo and followed up for a median (interquartile range) of 2.2 (1.8-2.5) years. This post hoc analysis was performed from September 2019 to February 2020.

MAIN OUTCOMES AND MEASURES Site-reported adverse events of new or worsening AS or aortic valve replacement (termed *AS events*). The adjusted risk of AS events was calculated with a multivariable model including concentrations of Lp(a) and LDL-C corrected for Lp(a) content, plus age, sex, diabetes, hypertension, current smoking, and estimated glomerular filtration rate. Evolocumab efficacy was tested using a Cox proportional hazards model.

RESULTS Aortic stenosis events occurred in 63 patients (48 men [76%]; mean [SD] age, 69 [9] years) over a median of 2.2 years. Elevated Lp(a) concentration was associated with higher rates of AS events (adjusted hazard ratio [aHR], 1.55 [95% CI, 1.17-2.05] per SD; $P = .002$), including aortic valve replacement (aHR, 2.22 [95% CI, 1.38-3.58] per SD; $P = .001$), after multivariable adjustment. The corrected LDL-C concentration was not significantly associated with AS events (aHR, 1.23 [95% CI, 0.93-1.61] per SD; $P = .14$). The overall HR for AS events with evolocumab was 0.66 (95% CI, 0.40-1.09), with no apparent association in the first year (HR, 1.09 [95% CI, 0.48-2.47]) but an HR of 0.48 (95% CI, 0.25-0.93) after the first year of treatment.

CONCLUSIONS AND RELEVANCE In this exploratory analysis of the FOURIER trial, higher Lp(a) levels, but not Lp(a)-corrected LDL-C levels, were associated with a higher risk of subsequent AS events, including aortic valve replacement. Long-term therapy with evolocumab may reduce AS events, and this raises the possibility that specific pharmacologic lipid-lowering therapy could offer a means to prevent or slow the progression of AS. These exploratory findings merit further investigation with a dedicated randomized clinical trial.

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Supplemental content

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Despite recent advances in aortic valve replacement (AVR), aortic stenosis (AS) remains a life-threatening condition with no disease-modifying pharmacotherapy. Calcific AS is characterized by valvular lipid infiltration and inflammation, followed by calcification.[1] Epidemiological and genetic studies have found associations between elevated lipid levels and risk of AS,[1-3] yet statins have failed to slow hemodynamic progression or reduce the risk of clinical AS events in patients with established AS.[4-6] One possible explanation is that low-density lipoprotein cholesterol (LDL-C) is not the principal lipid mediator of calcific AS. Indeed, there is evidence that lipoprotein(a) (Lp[a]) may be more centrally implicated in the pathobiology of AS than LDL-C.[7,8]

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibition with monoclonal antibiodies reduces LDL-C and Lp(a) concentrations by 50% to 60% and 20% to 30%, respectively,[9-11] and sequence variants in the *PCSK9* gene are associated with lower rates of AS.[12] We therefore performed a post hoc analysis of the Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) trial,[10] which randomized patients to the PCSK9 inhibitor evolocumab or placebo, to investigate the association of evolocumab with AS events.

Key Points

Question What is the association between lipoprotein(a) and low-density lipoprotein–cholesterol concentrations and aortic stenosis events, and does proprotein convertase subtilisin/kexin type 9 inhibition reduce the risk of aortic stenosis events?

Findings In this secondary analysis of 63 patients in a randomized clinical trial, elevated lipoprotein(a) concentrations were associated with higher rates of aortic stenosis events, including aortic valve replacement. The overall hazard ratio for aortic stenosis events with evolocumab was 0.66 (95% CI, 0.40-1.09), with no apparent association in the first year (hazard ratio, 1.09 [95% CI, 0.48-2.47]) but a hazard ratio of 0.48 (95% CI, 0.25-0.93) after the first year of treatment.

Meaning Long-term therapy with evolocumab may reduce the risk of aortic stenosis events, although these findings require validation in a dedicated randomized clinical trial.

Methods

Study Design, Patients, and End Point Definitions

The design and primary findings of the FOURIER trial have been published previously.[10,13] A total of 27 564 patients with atherosclerotic cardiovascular disease at increased cardiovascular (CV) risk were randomized to evolocumab or placebo and followed for a median of 2.2 (interquartile range [IQR], 1.8-2.5) years. Eligible patients had an LDL-C concentration of 70 mg/dL or more (to convert to mmol/L, multiply by 0.0259) while taking statin therapy. There was no exclusion criterion for AS or prior AVR. The FOURIER trial was approved by all relevant institutional review boards, and written informed consent was obtained from all participants.

For this post hoc analysis, the safety database was searched for events of new or worsening AS or aortic valve replacement (termed *AS events*). Events were included if the verbatim or preferred term was *aortic stenosis* or *aortic valve stenosis* or if the accompanying narrative described a new diagnosis or worsening of AS or a surgical or percutaneous AVR. For example, a patient hospitalized with atrial fibrillation who underwent AVR during the hospitalization would be included (eTable in the Supplement). The search was performed while blinded to lipid levels, randomized treatment arm, and all other clinical variables. A detailed description of the Lp(a) assay used has been published.[9]

Statistical Analyses

Kaplan-Meier rates were calculated by quartile of week-12 achieved Lp(a) and corrected LDL-C concentrations. Adjusted risk of AS events was calculated with a multivariable model, including Lp(a) and corrected LDL-C levels, plus age, sex, diabetes, hypertension, current smoking, and estimated glomerular filtration rate. Models were performed using quartiles and 1-SD increase in log-transformed week-12 achieved Lp(a) and corrected LDL-C concentrations. Corrected LDL-C concentration was used to account for the portion of measured LDL-C that is Lp(a), and this was calculated using the formula corrected LDL-C = measured LDL-C − 0.3 × Lp(a). Concentrations of Lp(a) were converted from nmol/L to mg/dL by dividing by 2.4.

The time to a first AS event was compared between treatment arms using a Cox proportional hazards model with a landmark analysis performed at 1 year, because this is the time frame over which a clinical benefit for other adverse CV events becomes evident with evolocumab.[10] The proportional hazards assumption was tested using Schoenfeld residuals, with a P value of .22. A sensitivity analysis was performed removing patients who experienced a major adverse CV event (CV death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization) prior to or concurrent with the AS event (including if the AS event was concurrent with CV death).

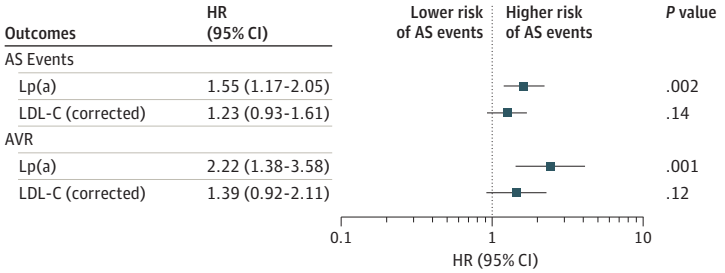
All analyses were performed by the TIMI Study Group using commercially available statistical software (SAS version 9.4 [SAS Institute] and Stata version 16.1 [StataCorp]). A 2-sided P value of .05 was considered significant for all tests. Data were collected from February 2013 to November 2016. The present analyses were conducted from September 2019 to February 2020.

Results

Aortic stenosis events occurred in 63 patients (48 men [76%]; mean [SD] age, 69 [9] years) in the full trial cohort. Among these, 26 events were AVRs, and the remainder were site-reported AS events without AVR. Twenty-three events occurred in the first year of treatment and 40 after 12 months or more.

The median week-12 Lp(a) concentration was 12.1 (IQR, 3.8-61.3) mg/dL in the full trial cohort, and the median corrected LDL-C concentration was 52 (IQR, 20-81) mg/dL. Unadjusted

Figure 1. Adjusted Risk for Aortic Stenosis (AS) Events by 1-SD Increase in Lipoprotein(a) (Lp[a]) and Corrected Low-Density Lipoprotein Cholesterol Concentrations



There was a significant association between week-12 Lp(a) concentration and AS events as well as aortic valve replacement (AVR) specifically. In addition to lipoprotein (Lp[a]) and corrected low-density lipoprotein cholesterol (LDL-C) level, the multivariable model included terms for age, sex, diabetes, hypertension, current smoking, and estimated glomerular filtration rate. HR indicates hazard ratio.

rates of AS events in the full cohort were significantly higher in patients with week-12 Lp(a) concentrations in the fourth quartile compared with quartile 1 (0.37% vs 0.21%; hazard ratio [HR], 2.42 [95% CI, 1.05-5.58]; *P* = .04). Patients with week-12 corrected LDL-C concentrations in the fourth quartile had AS event rates similar to those with concentrations in quartile 1 (0.35% vs 0.39%; HR, 0.99 [95% CI, 0.51-1.94]; *P* = .87). There was a robust association between Lp(a) concentration and AS events after full multivariable adjustment, including for corrected LDL-C concentration (adjusted HR per 1-SD increase in Lp[a], 1.55 [95% CI, 1.17-2.05]; *P* = .002; **Figure 1**), whereas the association with AS events was not significant for corrected LDL-C concentration (adjusted HR per 1-SD increase in corrected LDL-C level, 1.23 [95% CI, 0.93-1.61]; *P* = .14).

Aortic valve replacements were performed in 26 patients (18 surgical, 7 transcatheter, and 1 unspecified type). Concentration of Lp(a) was significantly associated with AVR (quartile 4 vs quartile 1, 0.19% vs 0.02%; adjusted HR per 1-SD increase in Lp[a], 2.22 [95% CI, 1.38-3.58]; *P* = .001; Figure 1). Rates of AVR did not vary significantly with week-12 corrected LDL-C concentration (quartile 4 vs quartile 1: 0.16% vs 0.18%; adjusted HR per 1-SD increase in corrected LDL-C level, 1.39 [95% CI, 0.92-2.11]; *P* = .12).

As expected, the clinical characteristics and baseline laboratory values were similar between patients randomly assigned to evolocumab and placebo (**Table**). Patients assigned to receive evolocumab had numerically lower incidence of AS events (0.27% [95% CI, 0.17%-0.44%]) than patients assigned to receive placebo (0.41% [95% CI, 0.28%-0.59%]). The overall HR for AS events with evolocumab was 0.66 (95% CI, 0.40-1.09), with no apparent association in the first year (HR, 1.09 [95% CI, 0.48-2.47]) but an HR of 0.48 (95% CI, 0.25-0.93) after the first year of treatment (**Figure 2**).

Results were similar in a sensitivity analysis that removed patients experiencing a major adverse CV event prior to or concurrent with the AS event (n = 9). Overall, the HR was 0.63 (95% CI, 0.37-1.10; *P* = .10); beyond the first year, it was 0.35 (95% CI, 0.17-0.77; *P* = .008).

Patients assigned to evolocumab also had numerically lower rates of AVR overall (0.10% vs 0.14%; HR, 0.73 [95% CI, 0.33-1.59]). The HR for AVR after the first year of treatment was 0.49 (95% CI 0.17-1.45), similar to the HR for all AS events after the first year of treatment.

Table. Baseline Patient Characteristics by Randomized Treatment Arm[a]

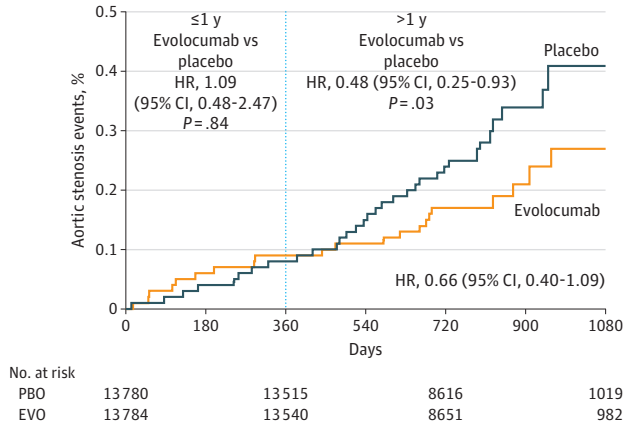
Characteristic	Patients, No. (%)	
	Evolocumab (n = 13 784)	Placebo (n = 13 780)
Age, mean (SD), y	63 (9)	62 (9)
Male	10 397 (75.4)	10 398 (75.5)
White race	11 748 (85.2)	11 710 (85.0)
Weight, mean (SD), kg	85.0 (17.3)	85.5 (17.4)
Prior		
Myocardial infarction	11 145 (80.9)	11 206 (81.3)
Nonhemorrhagic stroke	2686 (19.5)	2651 (19.2)
Peripheral artery disease	1858 (13.5)	1784 (12.9)
Hypertension	11 045 (80.1)	11 039 (80.1)
Diabetes mellitus	5054 (36.7)	5027 (36.5)
Current smoking	3854 (28.0)	3923 (28.5)
Statin use, intensity		
High	9585 (69.5)	9518 (69.1)
Moderate	4161 (30.2)	4231 (30.7)
Low or unknown	38 (0.3)	31 (0.2)
Ezetimibe	726 (5.3)	714 (5.2)
Other medications		
Aspirin, P2Y12 inhibitor, or both	12 766 (92.7)	12 666 (92.0)
β-Blocker	10 441 (75.8)	10 374 (75.4)
Angiotensin-converting enzyme inhibitor, angiotensin-receptor blocker, or aldosterone blocker	10 803 (78.4)	10 730 (77.9)
Lipid concentrations, median (IQR), mg/dL		
Cholesterol		
Low-density lipoprotein	92 (80-109)	92 (80-109)
Corrected low-density lipoprotein	81 (68-98)	81 (68-98)
Total	168 (151-188)	168 (151-189)
High-density lipoprotein	44 (37-53)	44 (37-53)
Triglycerides	134 (101-183)	133 (99-181)
Lipoprotein(a)	15.4 (5.4-69.2)	15.4 (5.4-68.3)

Abbreviation: IQR, interquartile range.

SI conversion factors: To convert lipoprotein(a) to nmol/L, multiply by 2.4; to convert cholesterol to mmol/L, multiply by 0.0259; to convert triglycerides to mmol/L, multiply by 0.0113.

[a] *P* values were nonsignificant for all between-group comparisons except for body weight (*P* = .01) and the use of antiplatelet agents (*P* = .03). Continuous variables are shown as means (SDs) unless otherwise noted.

Figure 2. Association of Evolocumab With Aortic Stenosis (AS) Events



The overall hazard ratio for AS events with evolocumab was 0.66 (95% CI, 0.40-1.09), with no apparent association in the first year (hazard ratio, 1.09 [95% CI, 0.48-2.47]) but a hazard ratio of 0.48 (95% CI, 0.25-0.93) after the first year of treatment. EVO indicates evolocumab; HR, hazard ratio; PBO, placebo.

Discussion

Despite rapid evolution in AVR technique, no disease-modifying pharmacotherapy has yet been identified. Here, in a post hoc analysis of the FOURIER trial, we observed what may be an apparent sizeable reduction in AS events emerging after 1 year of treatment with the PCKS9 inhibitor evolocumab.

Early epidemiological observations identified an association between hypercholesterolemia and incident AS.[3] These findings, in conjunction with genetic associations and translational studies demonstrating a pathobiology of nonrheumatic calcific AS similar to those of vascular atherosclerosis, led to trials of statin therapy in patients with AS.[4-6] These trials, performed largely in patients with mild to moderate AS, found no effects on echocardiographic markers of AS progression or clinical AS events. Numerous possible explanations exist, including the lipid subfractions affected by statins, achieved LDL-C concentrations higher than those achieved in PCSK9 inhibitor trials, and inadequate power for small differences.

The first of these possibilities deserves particular attention. We observed robust associations between Lp(a) levels and AS events, but no significant associations with LDL-C levels after correction for Lp(a) content. Recently, Lp(a) has been closely linked to the development of AS in genetic and epidemiological studies.[7,8,14,15] The concentration of Lp(a) is not lowered by statin therapy and in fact increased with statin treatment in one of the AS statin trials.[7] The use of PCSK9 inhibition was recently shown to significantly reduce Lp(a) concentration in 2 large randomized trials.[9,11] Paired with observations of lower rates of AS among patients with sequence variants in the PCSK9 allele,[12] there is a biologically plausible role for pharmacologic PCSK9 inhibition to slow AS progression. Here, we observed a reduction in AS events after the first year of treatment with evolocumab, which is consistent with the time frame over which a treatment benefit might be expected to emerge.

Limitations

Important limitations should be noted. This was a post hoc analysis of a randomized clinical trial in which there were relatively few events of interest and the presence or severity of baseline AS was not known. Additionally, the AS events included were not adjudicated, and for many events, there was little or no information available beyond the event term. Detection bias is a consideration, because evolocumab reduces other CV events, although this concern is mitigated by a sensitivity analysis showing no attenuation when patients experiencing adverse CV events prior to the AS event were removed. Landmark analyses are subject to nonrandom dropout and censoring subsequent to initial randomization. Finally, the FOURIER trial enrolled only patients with preexisting atherosclerotic cardiovascular disease.

Conclusions

In conclusion, we have identified a possible beneficial outcome of PCSK9 inhibition on the risk of AS events, raising the possibility that specific pharmacologic lipid-lowering therapy could offer a means to prevent or slow the progression of AS. These exploratory findings merit further investigation with a dedicated randomized clinical trial.

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Concept and design: Bergmark, Pedersen, Sabatine.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Bergmark.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Murphy, Kuder.
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