The Effect of PCSK9 (Proprotein Convertase Subtilisin/Kexin Type 9) Inhibition on the Risk of Venous Thromboembolism

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ORIGINAL RESEARCH ARTICLE

The Effect of PCSK9 (Proprotein Convertase Subtilisin/Kexin Type 9) Inhibition on the Risk of Venous Thromboembolism

BACKGROUND: The relationship between cholesterol levels and risk of venous thromboembolism (VTE) is uncertain. We set out to determine the effect of PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibition on the risk of VTE, explore potential mechanisms, and examine the efficacy in subgroups with clinically and genetically defined risk.

METHODS: We performed a post hoc analysis of the FOURIER trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk) testing whether evolocumab reduces the risk of VTE events (deep venous thrombosis or pulmonary embolism). Data from FOURIER and ODYSSEY OUTCOMES (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment with Alirocumab) were then combined in a meta-analysis to assess the class effect of PCSK9 inhibition on the risk of VTE. We also analyzed baseline lipids in FOURIER to investigate potential mechanisms explaining the reduction in VTE with evolocumab. Last, an exploratory genetic analysis was performed in FOURIER to determine whether a VTE polygenic risk score could identify high-risk patients who would derive the greatest VTE reduction from evolocumab.

RESULTS: In FOURIER, the hazard ratio (HR) for VTE with evolocumab was 0.71 (95% CI, 0.50–1.00; *P*=0.05), with no effect in the 1st year (HR, 0.96 [95% CI, 0.57–1.62]) but a 46% reduction (HR, 0.54 [95% CI, 0.33–0.88]; *P*=0.014) beyond 1 year. A meta-analysis of FOURIER and ODYSSEY OUTCOMES demonstrated a 31% relative risk reduction in VTE with PCSK9 inhibition (HR, 0.69 [95% CI, 0.53–0.90]; *P*=0.007). There was no relation between baseline low-density lipoprotein cholesterol levels and magnitude of VTE risk reduction. In contrast, in patients with higher baseline lipoprotein(a) (Lp[a]) levels, evolocumab reduced Lp(a) by 33 nmol/L and risk of VTE by 48% (HR, 0.52 [95% CI, 0.30–0.89]; *P*=0.017), whereas, in patients with lower baseline Lp(a) levels, evolocumab reduced Lp(a) by only 7 nmol/L and had no effect on VTE risk ($P_{interaction}$ 0.087 for HR; $P_{heterogeneity}$ 0.037 for absolute risk reduction). Modeled as a continuous variable, there was a significant interaction between baseline Lp(a) concentration and magnitude of VTE risk reduction ($P_{interaction}$=0.04). A polygenic risk score identified patients who were at >2-fold increased risk for VTE and who derived greater relative ($P_{interaction}$=0.04) and absolute VTE reduction ($P_{heterogeneity}$=0.009) in comparison with those without high genetic risk.

CONCLUSIONS: PCSK9 inhibition significantly reduces the risk of VTE. Lp(a) reduction may be an important mediator of this effect, a finding of particular interest given the ongoing development of potent Lp(a) inhibitors.

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Clinical Perspective

What Is New?

- This is the first study to demonstrate a significant reduction in venous thromboembolism (VTE) with PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibition.
- The reduction in VTE was associated with the degree of lipoprotein(a) lowering, not low-density lipoprotein cholesterol lowering, suggesting that lipoprotein(a) may be a mediator of VTE risk.

What Are the Clinical Implications?

- In patients with atherosclerotic cardiovascular disease being prescribed a PCSK9 inhibitor to reduce the risk of major adverse cardiovascular events, an additional benefit will be a reduction in the risk of VTE.
- With both RNA interference and antisense oligonucleotide therapies against lipoprotein(a) being studied in phase 2 and phase 3 trials, assessment of VTE may be warranted.

The relationship between cholesterol levels and the risk of venous thromboembolism (VTE) is uncertain. Observational studies have yielded mixed results, with some having found an association between low-density lipoprotein cholesterol (LDL-C) levels and increased risk of VTE,[1–6] whereas others failed to show a relationship.[7–10] Recent genetic studies, however, have suggested a potential link. A mendelian randomization study, taking advantage of nature's random allocation of genetic variants that predispose individuals to higher and lower cholesterol levels, found that individuals with a genetic predisposition to elevated LDL-C had a significantly increased risk of developing VTE.[11] Moreover, the JUPITER randomized clinical trial (Justification for the Use of Statin in Prevention: An Intervention Trial Evaluating Rosuvastatin) found that high-intensity statin therapy in patients without hypercholesterolemia but with elevated high-sensitivity C-reactive protein levels reduced the incidence of VTE by 43%.[12] However, the authors attributed these findings to statins' pleiotropic effects, including potential antithrombotic or anti-inflammatory mechanisms, rather than LDL-C lowering. Other investigations have focused on the atherogenic and prothrombotic particle, lipoprotein(a) (Lp(a)), with some, but not all, studies suggesting it may be a potential mediator for VTE risk.[13–19]

The emergence of PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors allow an opportunity to directly test the benefit of a class of drugs that reduces both LDL-C and Lp(a) on the risk of VTE without other known nonlipid anti-inflammatory or antithrombotic effects.[20,21] In this study, we set out to determine if PCSK9 inhibitors reduce the risk of VTE, to explore the potential mechanism, and to examine the efficacy in clinically and genetically defined risk subgroups.

METHODS

Study Design

We performed a post hoc analysis of the FOURIER trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk)[20] testing whether evolocumab reduces VTE events in comparison with placebo. Summary-level data from FOURIER and ODYSSEY OUTCOMES (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment with Alirocumab)[22] were then combined in a meta-analysis to assess the aggregate data for the effect of PCSK9 inhibition on the risk of VTE. This was followed by stratified baseline lipid analyses in the FOURIER trial to gain insights into whether the reduction in LDL-C or Lp(a) are associated with the reduction in VTE observed with evolocumab. Last, we performed an exploratory genetic analysis in FOURIER to determine whether a polygenic risk score for VTE could identify high-risk patients who would derive the greatest VTE risk reduction from evolocumab therapy.[11]

Study Populations

All patients randomly assigned in the FOURIER trial, a trial of 27 564 patients with stable atherosclerosis and hyperlipidemia on statin therapy, were included in the primary and subgroup analyses of the effect of evolocumab on VTE risk. In the meta-analysis of FOURIER and ODYSSEY OUTCOMES (a trial of 18 924 patients 1–12 months after acute coronary syndrome), the study population included all patients randomly assigned in these 2 trials. In analyses examining the association between baseline lipid levels and the risk of VTE, analyses were restricted to the placebo arm of the FOURIER trial. In the genetic analysis, a subset of patients in the FOURIER trial who consented to genetic testing, passed genetic quality control, and were of European ancestry were included. Approval for this study was obtained by the local institutional review committee. Although data and study material will not be made universally available, we encourage parties interested in collaboration to contact the corresponding author directly.

Clinical End Points

The primary end point of interest was VTE, defined as either deep venous thrombosis or pulmonary embolism. VTE events during the trial were reported by the site study physician as per standard adverse event reporting for clinical trials. Physicians blinded to treatment assignment systematically reviewed the investigator-reported adverse event database using preferred terms, lower level terms, and verbatim terms to identify and confirm VTE events.

Genotyping and Imputation

Our methods for genotyping and imputation in the FOURIER trial have previously been published.[23] In brief, genotyping was

performed on the Infinium Global Array chip. Preimputation quality control was performed using PLINK v2.0.[24] Imputation was accomplished using the Michigan Imputation server[25] and TOPMed Freeze5 reference panel.[26] Postimputation quality control was performed, including assessment of cryptic relatedness. The 1000 Genomes phase 3 v5 reference panel[27] and ADMIXTURE tool[28] were used to identify individuals of European ancestry.

Genetic Risk Score

The polygenic risk score applied to this analysis comprised an initial list of 297 single-nucleotide polymorphisms as reported by Klarin et al,[11] which represent the most up-to-date results of single variants associated with VTE. Of these, 273 single-nucleotide polymorphisms were available for inclusion in the polygenic risk score after genotyping and imputation. The score was calculated using the genotype dosage for each allele, multiplied by its weight, and then summed across all variants. Those in the top one-third of the genetic risk score were categorized as high genetic risk for VTE.

Statistical Analysis

To assess whether evolocumab significantly reduced VTE, cumulative event curves and hazard ratios between treatment and placebo arms were compared using the Kaplan-Meier method and Cox proportional hazards model, respectively. As was done in the parent trial, a landmark analysis at 1 year was performed because the full clinical benefit of lipid-lowering therapy does not generally manifest until at least 1 year.[20,29] The meta-analysis was run using fixed effects given that both trials tested PCSK9 inhibition in similar populations, with similar reported effects of treatment on LDL-C.

A series of subgroup analyses based on baseline lipid analyses were performed. First, we tested whether tertiles of baseline LDL-C and Lp(a) were associated with VTE risk in the placebo arm. Then, we assessed treatment benefit of evolocumab stratified by baseline LDL-C and Lp(a) levels (dichotomized at the median) to create subgroups that differed in the absolute magnitude of LDL-C or Lp(a) lowering on the basis of baseline (prerandomization) lipid values. Interaction testing for the magnitude of relative risk reductions and heterogeneity testing for the magnitude of absolute risk reductions in these subgroups was performed. To further explore the interaction between Lp(a) levels and the efficacy of evolocumab, 2 additional analyses were performed. First, patients were divided into quartiles of baseline Lp(a) levels, and a meta-regression was performed to assess the reduction in VTE with evolocumab per unit absolute decrease in Lp(a). Second, a Cox proportional hazards model for VTE was created that contained terms for evolocumab, baseline Lp(a), and the interaction between the two. All *P* values were 2-sided with values <0.05 considered significant.

For the genetic analysis, patients with high genetic risk for VTE (highest tertile) were compared with the remainder of the genetic cohort for both VTE risk prediction and treatment benefit. For risk prediction, Cox proportional hazards regression (assumptions tested and criteria were met) was used to calculate hazard ratios comparing high genetic risk versus those without high genetic risk in the placebo arm. Analyses were adjusted for age, sex, ancestry (principal components 1–4) and established clinical risk factors including obesity (body mass index ≥30), smoking, heart failure, and diabetes mellitus. To assess treatment benefit, relative and absolute risk reductions were calculated across genetic risk groups, followed by gene×treatment interaction testing.

RESULTS

Baseline Characteristics

Demographics of the FOURIER trial population are shown in the Table. The average age was 63 years, 75% were male, 39% were obese, 28% were smokers, 23% had heart failure, and 37% had diabetes mellitus. The median LDL-C was 92 mg/dL and the median Lp(a) was 37 nmol/L. The median follow-up time was 2.2 years.

Effect of PCSK9 Inhibition on Risk of VTE

In the FOURIER trial, a total of 128 patients had a VTE event (72 deep vein thrombosis and 56 pulmonary embolism). The event rate in the placebo arm was 0.63% in comparison with 0.45% in the treatment arm. The hazard ratio (HR) for VTE with evolocumab was 0.71 (95% CI, 0.50–1.00; *P*=0.05; Figure 1A). Sensitivity analyses removing patients on baseline anticoagulation if anything strengthened this finding (HR, 0.67 [95% CI, 0.46–0.97]; *P*=0.035) and total event analyses including the 12 recurrent VTE events were consistent (Table I in the Data Supplement). There was a late divergence of the curves after 1 year that was similar to the pattern observed with key primary and key secondary outcomes in the FOURIER trial. Specifically, there was no effect of evolocumab on VTE in the 1st year (HR, 0.96 [95% CI, 0.57–1.62]; *P*=0.89; Figure 1B), whereas there was a 46% reduction (HR, 0.54 [95% CI, 0.33–0.88]; *P*=0.014) in a landmark analysis starting at 12 months (Figure 1C). Only 7 VTE events were preceded by an atherosclerotic cardiovascular disease event during the trial, and all were separated by at least 50 days. A sensitivity analysis removing these 7 cases remained consistent with the primary analysis (Table I in the Data Supplement).

Next, we combined data from FOURIER and ODYSSEY OUTCOMES. In ODYSSEY OUTCOMES, the average age was 59 years, 75% were male, 24% were smokers, 15% had heart failure, and 29% had diabetes mellitus.[21] There were 92 VTE events in ODYSSEY OUTCOMES, and there was a trend toward alirocumab reducing the risk of VTE (HR, 0.67 [95% CI, 0.44–1.01]; *P*=0.06).[22] A meta-analysis of the 2 trials demonstrated a statistically significant 31% relative risk reduction in VTE with PCSK9 inhibition in comparison with placebo (HR, 0.69 [95% CI, 0.53–0.90]; *P*=0.007; Figure 2).

Table. Baseline Characteristics in the FOURIER Trial

Baseline Characteristics	Evolocumab n=13 784	Placebo n=13 780
Demographics		
Age, y (±SD)	62.5 (9.1)	62.5 (8.9)
Male	10 397 (75)	10 398 (76)
White	11 748 (85)	11 710 (85)
Obese (body mass index ≥30)	5419 (39)	5523 (40)
Medical history		
Myocardial infarction	11 145 (81)	11 206 (81)
Ischemic stroke	2686 (20)	2651 (19)
Peripheral artery disease	1858 (14)	1784 (13)
Heart failure	3224 (23)	3170 (23)
Hypertension	11 045 (80)	11 039 (80)
Diabetes mellitus	5054 (37)	5027 (37)
Current cigarette use	3854 (28)	3923 (29)
Hormone replacement therapy	518 (3.8)	520 (3.8)
Median laboratory measures (interquartile range)		
Low-density lipoprotein cholesterol, mg/dL	92 (80–109)	92 (80–109)
Total cholesterol, mg/dL	168 (151–188)	168 (151–189)
High-density lipoprotein cholesterol, mg/dL	44 (37–53)	44 (37–53)
Triglycerides, mg/dL	134 (101–183)	133 (99–181)
Lipoprotein(a), nmol/L	37 (13–166)	37 (13–164)

Values shown are n (%) unless otherwise indicated. FOURIER indicates Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk.

Exploring Potential Lipid-Related Mechanisms for VTE Reduction

In the placebo arm of FOURIER, there was no trend for increased risk of VTE by baseline LDL-C; however, there appeared to be a pattern of increasing risk of VTE with higher levels of baseline Lp(a) (Figure I in the Data Supplement). When comparing the efficacy of evolocumab in patients with baseline LDL-C above and below the median, there was a consistent reduction in VTE with evolocumab despite differences in the magnitude of LDL-C reduction (67 versus 55 mg/dL; Figure 3). However, when comparing efficacy in patients stratified by baseline Lp(a) above and below the median, in patients with higher Lp(a) levels, evolocumab reduced Lp(a) by 33 nmol/L and VTE risk by 48% (HR, 0.52 [95% CI, 0.30–0.89]; *P*=0.017), whereas in those below the median there was only a 7 nmol/L reduction in Lp(a) and no reduction in VTE risk (despite a similarly large reduction in LDL-C, 59 mg/dL versus 61 mg/dL, respectively, in the 2 groups; $P_{interaction}$ 0.087 for HR; $P_{heterogeneity}$ 0.037 for absolute risk reduction). When further dividing baseline Lp(a) into quartiles, LDL-C reduction remained stable across these groups (58–61 mg/dL), but, as expected, Lp(a) reduction ranged from 2 to 34 nmol/L. A greater reduction in Lp(a) tended to be correlated with greater reduction in risk of VTE events (*P*=0.098; Figure II in the Data Supplement). Moreover, when modeling a formal interaction term between the benefit of evolocumab and baseline Lp(a) level as a continuous variable, the term was significant (*P*=0.04).

Polygenic Risk and the Benefit of Treatment With Evolocumab

The genetic substudy included 14 298 patients from FOURIER (who were similar to the overall trial cohort; Table II in the Data Supplement) with 76 VTE events. Each increase by 1 SD in genetic risk score carried a 57% greater risk of VTE (adjusted HR, 1.57 [95% CI, 1.23–2.01]; *P*=0.0003). More specifically, patients in the top one-third of genetic risk carried a >2-fold increased risk of VTE in comparison with those in the lower two-thirds (adjusted HR, 2.32 [95% CI, 1.27–4.26]; *P*=0.007). The predictive value of the genetic risk score remained when Lp(a) was included in the model (Table III in the Data Supplement). Patients in

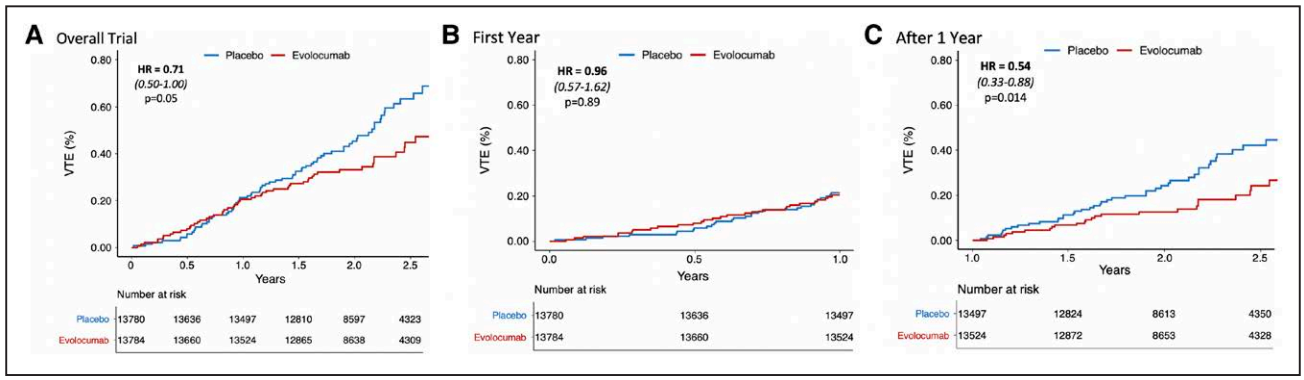

Figure 1. Effect of evolocumab on the reduction in VTE.
A, A 29% reduction in the overall FOURIER trial (HR, 0.71 [95% CI, 0.50–1.00]; *P*=0.05) is demonstrated. **B**, No difference in VTE during the first year (HR, 0.96 [95% CI, 0.57–1.62]; *P*=0.89) is shown. **C**, A landmark analysis highlighting the 46% reduction in VTE beyond 1 year (HR, 0.54 [95% CI, 0.33–0.88]; *P*=0.014). FOURIER indicates Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk; HR, hazard ratio; and VTE, venous thromboembolism.

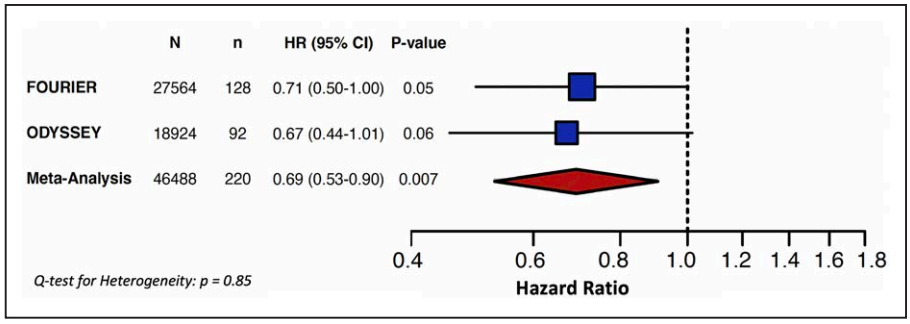

Figure 2. Meta-analysis for the effect of PSCK9 inhibitors on VTE.
A total of 46488 patients with 220 VTE events were included from the FOURIER and ODYSSEY OUTCOMES trials. Both trials demonstrated a trend toward reduction in VTE and, when combined in a meta-analysis, there was a significant 31% relative risk reduction in VTE with PCSK9 inhibition (HR, 0.69 [95% CI, 0.53–0.90]; *P*=0.007). FOURIER indicates Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk; HR, hazard ratio; ODYSSEY OUTCOMES, Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment with Alirocumab; and VTE, venous thromboembolism.

this high genetic risk group (top one-third) also appeared to derive greater VTE reduction from evolocumab (Figure 4). They had a relative risk reduction of 55% (HR, 0.45 [95% CI, 0.21–0.95]; *P*=0.035) in comparison with no apparent benefit in those without high genetic risk (HR, 1.20 [95% CI, 0.66–2.17], $P_{interaction}$=0.04) and an absolute risk reduction of 0.7% (95% CI, 0.2–1.3) in comparison with –0.1% (95% CI, –0.4 to 0.2; $P_{heterogeneity}$=0.009).

DISCUSSION

This is the first study to demonstrate a significant reduction in VTE with PCSK9 inhibitors, evidenced by a consistent benefit across 2 PCSK9 inhibitor trials. These data also suggest that the reduction in VTE with PCSK9 inhibition may be mediated by a reduction in Lp(a) rather than LDL-C. In addition, the use of a polygenic risk score identified one-third of the population who was not only at >2-fold risk for VTE, but also appeared to derive the greatest relative and absolute reduction in VTE from evolocumab.

Our findings are novel in regard to PCSK9 inhibition in humans, and also supported by a reduction in VTE in PSCK9 knockout animal models.[30] As noted earlier, data from the JUPITER trial demonstrated that high-intensity statin therapy in patients without hypercholesterolemia but with inflammation reduced the risk of VTE.[12] However, a meta-analysis of multiple statin trials (which did not require inflammation at baseline) suggested a more modest effect of statins on VTE risk.[31] These clinical trial data offer complementary insights into potential pathobiology and mechanism of benefit. High-intensity statin therapy reduces LDL-C and high-sensitivity C-reactive protein, but not Lp(a).[32] PCSK9 inhibitors reduce LDL-C and Lp(a), but not high-sensitivity C-reactive protein.[20,21] Although both reduce LDL-C and there are some data for an association between LDL-C and VTE,[1–4,11] the data are inconsistent,[7–10] and we did not see any relation in FOURIER between the magnitude of LDL-C lowering and the magnitude of VTE risk reduction. It may be that statins reduce the risk of VTE by reducing inflammation and PCSK9 inhibitors reduce the risk by reducing levels of Lp(a).

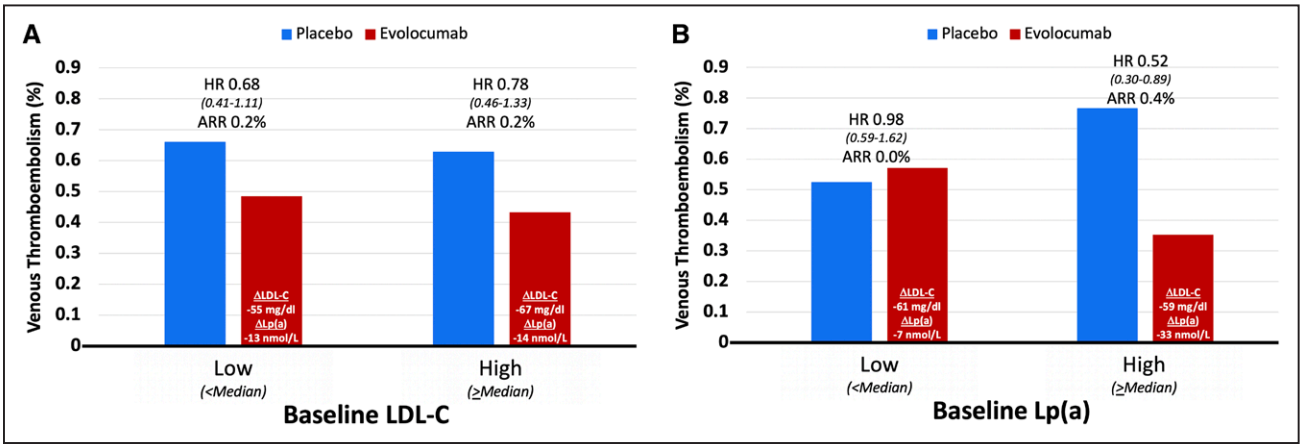

Figure 3. Benefit of evolocumab for reducing VTE by baseline LDL-C and Lp(a) category.
A, In high (≥median) vs low (<median) baseline LDL-C groups, the reduction in LDL-C was 67 and 55 mg/dL, respectively, and the reduction in Lp(a) was 14 and 13 nmol/L. VTE reduction was similar in both groups. **B**, In high (≥median) vs low (<median) baseline Lp(a) groups, the reduction in Lp(a) was 33 and 7 nmol/L, respectively, and the reduction in LDL-C was 59 and 61 mg/dL. Patients with high baseline Lp(a) had greater VTE reduction (HR, 0.52 [95% CI, 0.30–0.89]; *P*=0.017) in comparison with those with low baseline Lp(a) ($P_{interaction}$ for HR, 0.087; $P_{heterogeneity}$ for absolute risk reduction, 0.037). ARR indicates absolute risk reduction; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; Lp(a), apolipoprotein(a); and VTE, venous thromboembolism.

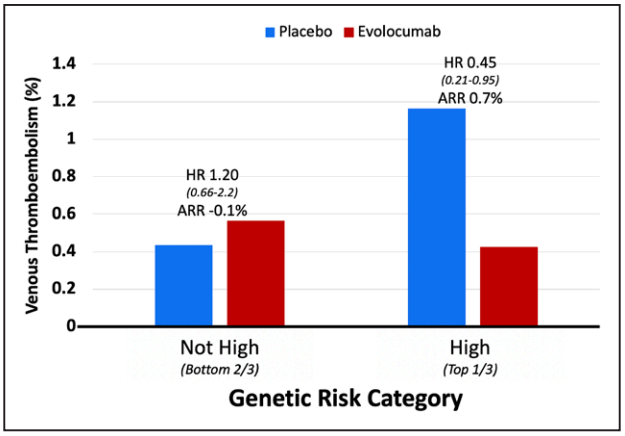

Figure 4. Benefit of evolocumab for reducing VTE by genetic risk category.
Patients in the top one-third of genetic risk had a 55% relative risk reduction (HR, 0.45 [95% CI, 0.21–0.95]; *P*=0.035) and 0.7% absolute risk reduction (95% CI, 0.2–1.3). The VTE reduction was significantly greater in patients with high genetic risk than in those without high genetic risk ($P_{interaction}$=0.04; $P_{heterogeneity}$=0.009). ARR indicates absolute risk reduction; HR, hazard ratio; and VTE, venous thromboembolism.

Along with its known atherogenicity, Lp(a) is thought to have prothrombotic properties, with multiple epidemiological studies supporting its association with VTE.[13–17] These data have been somewhat tempered by genetic studies that have not supported a causal association.[18,19] However, our data suggest a trend of increased risk of VTE with higher levels of Lp(a), and we found that greater reductions in Lp(a) correlated with greater decreases in risk of VTE events. These observations are especially intriguing because both RNA interference and antisense oligonucleotide therapies against Lp(a) are being studied in phase 2 and phase 3 clinical trials, and suggest that the assessment of VTE in these trials may be warranted.

Further work is needed to confirm the mechanism for VTE reduction with PCSK9 inhibition. Although these data suggest that the benefit may be associated with Lp(a), the potential pathway mediating this effect is uncertain. One possibility is the prothrombotic effect of Lp(a), although late divergence of the cumulative incidence curves resembles the pattern observed in atherosclerosis-mediated mechanisms. If an antithrombotic effect is operational, the emergence of this benefit may not follow the time course we expect from antiplatelet or anticoagulant medications with a direct effect on hemostatic/thrombotic factors and for which the effect is more immediate.

Although there was a substantial relative risk reduction in VTE with evolocumab, the absolute risk reduction was modest because of the low event rate. Therefore, given the current cost of the drug, prescribing PCSK9 inhibitors to this population for the prevention of VTE alone is probably not warranted. However, in patients with atherosclerotic cardiovascular disease being prescribed a PCSK9 inhibitor to reduce the risk of major adverse cardiovascular events, an additional benefit will be a reduction in the risk of VTE.

Limitations

VTE was not a prespecified end point in the FOURIER trial and the incidence was low; however, the total number of events was greater than any previous lipid-modifying trial reporting on VTE. The addition of ODYSSEY OUTCOMES data increased our power to allow us to definitively demonstrate a significant reduction in VTE with PCSK9 inhibition. In addition, this study was performed in patients with established atherosclerotic disease participating in clinical trials, so may not be generalizable to all populations. Although the primary analysis included patients from all ethnicities, the genetic analysis was limited to individuals of European ancestry to be consistent with the studies from which the genetic risk score was derived. The stratification of genetic risk by tertiles was exploratory, and optimal thresholds for the VTE polygenic risk score need to be prospectively validated before clinical implementation. The observed association between genetic risk of VTE and treatment with PCSK9 will require future independent replication as additional clinical trial data become available.

Conclusions

PCSK9 inhibition significantly reduces VTE events. The association between the degree of Lp(a) lowering and the magnitude of VTE reduction suggests that Lp(a) may be a mediator of this effect, a finding of particular interest given the ongoing development of potent Lp(a) inhibitors.

ARTICLE INFORMATION

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Dr Marston contributed to study design, literature search, statistical analysis, data interpretation, figures, and drafting of the manuscript. Drs Gurmu, Melloni, Bonaca, and Gencer, and C. Roselli contributed to data preparation, study design, and statistical analysis. Drs Sever, Pedersen, Keech, Lubitz, Ellinor, O'Donoghue, and Giugliano contributed to data interpretation and critical review of the manuscript. Drs Ruff and Sabatine contributed to study design, statistical analysis, data interpretation, figures, and critical review of the manuscript. Drs Ruff and Sabatine are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Disclosures

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Supplemental Materials

Data Supplement Tables I–III
Data Supplement Figures I–II

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