

ORIGINAL RESEARCH

Efficacy and Safety of Vorapaxar by Intensity of Background Lipid-Lowering Therapy in Patients With Peripheral Artery Disease: Insights From the TRA2P-TIMI 50 Trial

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BACKGROUND: Patients with peripheral artery disease are at increased risk of both major adverse cardiovascular events (MACEs) and limb events. The pathobiology of limb events is likely multifactorial. Observational studies suggest a benefit of statin therapy for reducing the risk of limb ischemic events while randomized trials demonstrate a benefit with more potent antithrombotic therapies, particularly those targeting thrombin. Whether the effects of these therapeutic pathways are independent and complementary is not known.

METHODS AND RESULTS: The TRA 2°P-TIMI 50 (Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events–Thrombolysis in Myocardial Infarction 50) trial demonstrated that vorapaxar significantly reduced MACEs and limb events. The purpose of the current analysis was to evaluate the association of statin use and intensity and the occurrence of MACEs and limb events in 5845 patients with symptomatic peripheral artery disease randomized in TRA 2°P-TIMI 50 and then to understand whether statin use modified the benefits of vorapaxar for MACEs or limb ischemic events. We found that statin therapy was associated with significantly lower risk of MACEs (hazard ratio [HR], 0.77; 95% CI, 0.66–0.89; $P < 0.001$) and limb ischemic events (HR, 0.73; 95% CI, 0.60–0.89; $P = 0.002$). The benefit of vorapaxar for reducing MACEs and limb events was consistent regardless of background statin (P -interaction = 0.715 and 0.073, respectively). Event rates were lowest in patients receiving the combination of statin therapy and vorapaxar.

CONCLUSIONS: In conclusion, statin use and intensity is associated with significantly lower rates of MACEs and limb ischemic events. Thrombin inhibition with vorapaxar is effective regardless of background statin therapy. These results suggest that targeting both lipid and thrombotic risk in peripheral artery disease is necessary in order to optimize outcomes.

Key Words: acute limb ischemia ■ peripheral artery disease ■ peripheral revascularization ■ statin ■ vorapaxar

Peripheral artery disease (PAD) affects ≈200 million people worldwide including ≈8 to 10 million in the United States.^{1–5} Patients with PAD often have other regional manifestations of atherosclerosis including coronary artery disease (CAD) and cerebrovascular disease, putting them at heightened risk of both

systemic cardiovascular events such as cardiovascular death, myocardial infarction (MI), and stroke, and major adverse limb events (MALEs).^{6–10} An important cause of morbidity in patients with PAD is symptomatic limb ischemia. Lower-extremity atherosclerosis may result in a spectrum of limb ischemic complications ranging

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CLINICAL PERSPECTIVE

What Is New?

- Statin therapy is associated with significantly lower rates of major adverse cardiac events and limb ischemic events in patients with peripheral artery disease.
- Vorapaxar provides additional benefit regardless of background statin with lowest events rates with combination of statin and vorapaxar.

What Are the Clinical Implications?

- Targeting both lipid and thrombotic risk in patient with peripheral artery disease is necessary to optimize outcomes.

Nonstandard Abbreviations and Acronyms

MACE	major adverse cardiac event
MALE	major adverse limb event

from intermittent claudication to chronic critical limb-threatening ischemia, as well as the abrupt loss of tissue perfusion from thrombotic occlusion manifesting as acute limb ischemia, with the latter outcome associated with high rates of amputation.¹¹ The pathobiology underlying these limb outcomes is multifactorial, including progressive atherosclerosis leading to worsening claudication and the need for revascularization as well as thrombosis leading to acute limb ischemia. Therefore, therapies targeting several pathways of risk may be necessary in reducing limb morbidity.

Current PAD guidelines recommend medical therapies that have been shown to reduce cardiovascular risk, including antiplatelet drugs, statins, and renin-angiotensin system inhibitors as well as smoking cessation.^{12–18} Data demonstrating the efficacy of statins come from several trials, including the Heart Protection Study, which randomized 20 536 high-risk patients to either simvastatin (40 mg) or placebo and found a 24% reduction in the risk of cardiovascular events. In a subanalysis of 6748 patients with PAD, a similar risk reduction of 22% for cardiovascular events was seen. In addition, several studies have shown that statin therapy is associated with lower rates of adverse limb events and improvements in exercise duration.^{12,16,19,20} These data are reflected in current guidelines, which recommend statin therapy for all patients with PAD.¹⁷ Based on trials that show greater benefit with high versus low intensity statins, current American College of Cardiology/American Heart Association lipid guidelines further recommend high-intensity statin therapy for high-risk patients including those with PAD.²¹

Recently, intensive low-density lipoprotein cholesterol (LDL-C)-lowering therapy with the proprotein convertase subtilisin/kexin type 9 inhibitor evolocumab or alirocumab was shown to robustly reduce the risk of major adverse cardiac events (MACEs) and MALEs in patients with PAD on moderate- or high-intensity statin therapy.^{22,23} The addition of ezetimibe to simvastatin was also shown to reduce MACEs in patients with PAD who presented with acute coronary syndrome, particularly if they had concomitant diabetes mellitus.²⁴

In the TRA 2°P-TIMI 50 (Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events–Thrombolysis in Myocardial Infarction 50) trial, the protease activated receptor antagonist, vorapaxar, significantly reduced MACEs, acute limb ischemia, and peripheral revascularization procedures when compared with placebo while also increasing bleeding.^{25,26} Because both antithrombotic and lipid-lowering therapies reduce the risk for MACEs and MALEs in patients with PAD, it is of clinical importance to understand whether the benefits of antithrombotic therapy are maintained in patients receiving more intensive lipid-lowering therapy. In this post hoc analysis, we evaluated the associated reduction in MACEs and limb ischemic adverse events with high-versus low- or moderate-intensity statins in patients with symptomatic PAD. We then evaluated if background statin intensity modifies the benefit of vorapaxar for MACEs and limb vascular events.

METHODS

The data for the analyses are held at the TIMI Study Group, and the corresponding author may be contacted for requests with regard to the sharing of data, methods, and materials specific to this analysis.

Study Population

The TRA 2°P-TIMI 50 trial was a multinational, randomized, double-blind, placebo-controlled trial of 26 449 subjects with stable atherosclerotic vascular disease.²⁷ Subjects were randomized to either vorapaxar 2.5 mg daily or matching placebo in addition to antiplatelet therapy with aspirin and/or an ADP antagonist with a median duration of 3 years. Background therapy including type and dose of statin were determined by the treating physician and recorded in the electronic case report form at baseline and during the trial. Patients could qualify for the trial on the basis of a recent myocardial infarction or stroke (>2 weeks, ≤12 months) or the presence of symptomatic PAD defined as symptoms of intermittent claudication and an ankle-brachial index <0.85 or a history of claudication and revascularization for limb ischemia. Randomization was hierarchical so that patients with recent MI or stroke were randomly assigned to the MI or stroke group even if they fulfilled the PAD criteria.

For the purposes of the current analysis, all patients with symptomatic PAD were included regardless of qualifying diagnosis. When analyzing vorapaxar's effect on background statin therapy, the cohort was further restricted to patients without a history of stroke/transient ischemic attack (population approved for use by the Food and Drug Administration). A Consolidated Standards of Reporting Trials diagram is available in Figure S1. Full details of the trial design have been published previously.^{27,28} Appropriate institutional review board and ethics approval was obtained for the study and all participating sites. All subjects gave informed consent.

Exposure Variables

Statin use and dose was based on the case report form completed at baseline visit with sensitivity analyses for patients on statin at baseline. Statins were defined as high intensity if they typically reduce LDL-C levels by $\geq 50\%$ and were otherwise considered low intensity if they reduce LDL-C levels by $< 50\%$.²¹ Therefore, atorvastatin ≥ 40 mg, rosuvastatin ≥ 20 mg, and simvastatin 80 mg were defined as high intensity. All other doses of these statins, other statins regardless of dose, and statins at unknown doses were considered low intensity.

End Points

The dual primary end points for this analysis were (1) limb ischemic adverse events, which included the composite of acute limb ischemia, any peripheral revascularization, and major vascular amputation; and (2) the composite end point of MI, stroke, or death from cardiovascular cause (MACE). Secondary end points included composite end point (MALE) of acute limb ischemia, urgent peripheral revascularization, and major vascular amputation, as well as the components of limb ischemic adverse events and MACEs. Hospitalization for acute limb ischemia was prospectively adjudicated as a clinical history suggesting a rapid or sudden decrease in limb perfusion and either a new pulse deficit with rest pain, pallor, paresthesia, or paralysis or confirmation of arterial obstruction by imaging, surgical findings, or pathology.²⁹ These end points were adjudicated by a clinical events committee during the trial by trained specialists in cardiovascular medicine, who were blinded to treatment allocation. Procedures including elective peripheral revascularization and amputation were captured as reported by the investigator on the case report form.

Statistical Analysis

Baseline characteristics were stratified by statin intensity at baseline and were compared by using the chi-square test for categorical variables and the Wilcoxon

rank-sum test for continuous variables. Event rates are presented as 3-year Kaplan-Meier estimates. Multivariable Cox models evaluating the relationship between statin intensity and clinical outcomes were adjusted for all baseline variables shown in Table 1 including background antiplatelet therapy. A 2-sided *P* value of 0.05 was considered significant for all tests. A subgroup analysis for patients with a history of PAD and complete covariate information by statin use was performed. Unadjusted hazard ratios (HRs), 95% CIs, 3-year Kaplan-Meier rates, and absolute risk reduction of vorapaxar and placebo within statin use group are reported. All analyses were performed with statistical software packages R (version 3.6.0, R Foundation for Statistical Computing, Vienna, Austria) and Stata (version 14, StataCorp, College Station, TX).

RESULTS

Overall, 26 449 patients were randomized, of which 5845 patients had a documented history of symptomatic PAD and formed the primary cohort for this analysis. The subset of 4677 of these patients without a history of stroke/transient ischemic attack (population approved for use by the Food and Drug Administration) formed the cohort for the analysis of vorapaxar's effects on background statin therapy. From the overall PAD cohort, 3223 (59.4%) had an ankle-brachial index < 0.85 , 2821 (48.3%) had previously undergone a peripheral arterial revascularization, and 231 (4.0%) had an amputation because of limb ischemia.

Overall statin therapy was used at baseline in 85.0%. Statin use was less frequent in subjects with a history of PAD and no history of CAD (1934; 73.3%) compared with subjects with a history of PAD and CAD (3352; 90.9%; $P < 0.001$). Of those on statin therapy, 3811 (76.7%) were on low-intensity statin therapy and 1159 (23.3%) were on high-intensity statin therapy. Patients with PAD and no CAD were significantly less likely to be treated with high-intensity statin (9.7%) compared with patients with PAD and concomitant CAD (24.8%) or concomitant cerebrovascular disease (19.4%; $P < 0.001$).

Baseline characteristics of the study population stratified by statin intensity are presented in Table 1. Baseline characteristics of patients without a history of stroke/transient ischemic attack were similar to the primary cohort and are presented in Table S1. High-intensity statin use was associated with younger age, concomitant CAD, coronary revascularization, atherosclerotic risk factors, and use of cardiac medications (thienopyridine, beta blockers, and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers). Low-intensity or no statin use was associated with PAD without CAD, lower

Table 1. Baseline Characteristics: Comparison of Statin Intensity

Patients with PAD (N=5845)	High intensity (n=1159)	Low intensity (n=3811)	No statin (n=875)
Demographics			
Age, y, mean	63	65	67
Female sex, %	28.4	28.7	27.1
Region, %			
North America	58.0	37.3	32.7
Europe I*	29.9	42.5	33.7
Europe II*	6.3	6.2	5.0
Latin America	2.7	12.4	24.6
Australia/New Zealand	3.1	1.0	0.6
Asia	0.0	0.6	3.4
Comorbidities, %			
Diabetes mellitus	41.1	37.8	33.4
Hyperlipidemia	96.8	92.1	57.5
Hypertension	83.3	81.5	80.5
BMI ≥30 kg/m ²	38.4	28.7	22.8
Current smoker	29.3	29.1	32.0
Heart failure	17.1	11.9	10.2
CrCl <60 mL/min	19.9	24.3	31.4
Extend of vascular disease, %			
Coronary artery disease	83.8	67.7	40.8
Cerebrovascular vascular disease	19.4	19.6	22.1
Prior coronary revascularization	70.4	52.2	28.0
Prior carotid revascularization	11.6	8.8	8.5
Prior limb revascularization	50.6	47.1	50.4
Prior limb ischemia/amputation	3.4	3.5	6.7
Baseline ABI value, mean	0.84	0.81	0.76
ABI <0.85	51.8	57.8	64.9
Medications, %			
Aspirin	91.6	90.3	82.3
Thienopyridine	62.8	46.6	31.9
ACE or ARB	76.6	73.1	57.0
Beta blocker	71.6	60.2	40.5
Cilostazol	4.9	7.5	15.4
Vorapaxar	50.0	48.7	53.1

ABI indicates ankle-brachial index; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; CrCl, creatinine clearance; and PAD, peripheral artery disease.

*Europe I: Austria, Belgium, Denmark, Finland, France, Germany, Israel, Italy, Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, United Kingdom, South Africa; Europe II: Czech Republic, Hungary, Poland.

ankle-brachial index, peripheral revascularization, and renal dysfunction.

Statin Therapy and MACEs/Limb Ischemic Adverse Events

After multivariable analysis, including all variables in Table 1, statin therapy overall compared with no statin

was associated with significantly lower risk of either a MACE or limb ischemic adverse event (HR, 0.77; 95% CI, 0.66–0.89; *P*<0.001; Figure 1). When stratified by statin intensity, both low- and high-intensity statins were associated with a statistically significant lower hazard relative to no statin therapy (Table 2). Statin therapy overall compared with no statin was associated with a statistically significant lower rate of major cardiovascular events including the composite end point of MI, stroke, or cardiovascular death (HR, 0.77; 95% CI, 0.61–0.96; *P*=0.021). When stratified by statin intensity, both low- and high-intensity statins showed a consistent pattern with a lower hazard of MACEs relative to no statin therapy (Table 2). Statin therapy was associated with significantly lower risk of limb ischemic adverse events when compared with no statin therapy (HR, 0.73; 95% CI, 0.60–0.89; *P*=0.002). A statistically significant association with lower risk was consistent between high- and low-intensity statins compared with no statin therapy, with a numerically greater reduction seen with high-intensity statins (HR, 0.69; 95% CI, 0.55–0.88; *P*=0.003). A consistent pattern of association with lower risk with high-intensity statin therapy was seen across reasons for revascularization as well as MALEs and their components (Table 2).

Benefit of Vorapaxar by Background Statin Therapy

Of the 4677 patients with no history of stroke or transient ischemic attack, vorapaxar reduced MACEs and limb ischemic adverse events consistently regardless of whether the patient was on a statin (*P*-interaction=0.770 and 0.089, respectively, Figure 2). MALEs were also reduced consistently, but the event rate was low and may not be high enough to observe an interaction (*P*-interaction=0.242). In addition, the benefit of vorapaxar for any peripheral revascularization, including elective revascularization, appeared to be greater in patients who were not on a statin (*P*-interaction=0.066; Figure 2, Table S2). Events rates for the reported outcomes were lower in those receiving statin therapy, vorapaxar, and particularly the combination of both. This pattern was also present for the composite end point of MACEs, limb ischemic adverse events, and MALEs (Figure 2). These data suggest that the benefits of these 2 therapeutic approaches are independent and additive.

DISCUSSION

The current analysis provides several key findings. First, we found that even in a modern clinical trial cohort, while statin use was frequent (>85%), it was still

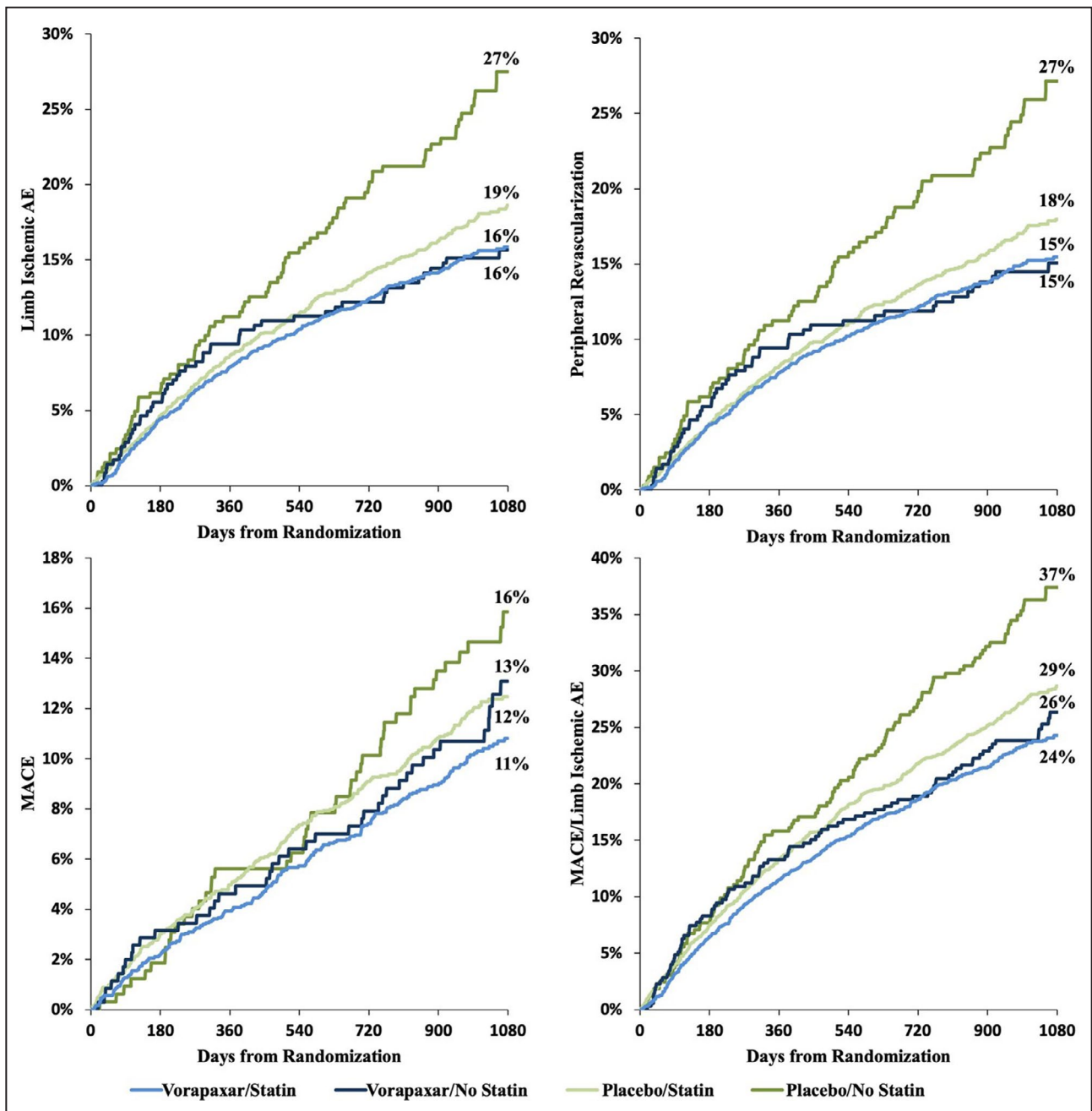


Figure 1. Three-year Kaplan-Meier curves for vorapaxar or placebo with statin therapy at baseline for subjects with peripheral artery disease without a history of stroke of transient ischemic attack (n=4677).

AE indicates adverse event (limb ischemic AE, composite of acute limb ischemia, any peripheral revascularization, and major vascular amputation); and MACE, major adverse cardiac event (composite of cardiovascular death, myocardial infarction, or stroke).

lower in patients with PAD and no CAD than in patients with concomitant CAD, confirming undertreatment in patients with symptomatic PAD alone. Second, we found an association between intensity of statin use and MALEs consistent with the findings of other LDL-C-lowering therapies in PAD. Third, we found no interaction between the benefits of vorapaxar, an antithrombotic, for reducing MACEs and MALEs in PAD

and background LDL-C-lowering therapy, suggesting that treating both axes of risk are important in PAD.

After >20 years since initial development, statin use is widespread because of their clear efficacy, safety, and cost effectiveness. Our primary cohort of 5845 subjects with established symptomatic PAD enrolled in the TRA 2°P-TIMI 50 trial showed frequent use of statin therapy in patients with PAD, although

Table 2. Multivariable Adjusted HRs for Limb Vascular Events and Systemic Outcome

End point	Statin vs no statin Use at baseline (n=5521), HR (95% CI); P value	High-intensity vs no statin use at baseline (n=1909), HR (95% CI); P value	Low-intensity vs no statin use at baseline (n=4424), HR (95% CI); P value
Systemic outcome			
MACE	0.77 (0.61–0.96); 0.021	0.80 (0.61–1.05); 0.11	0.76 (0.60–0.95); 0.018
MACE+limb ischemic AE	0.77 (0.66–0.89); <0.001	0.75 (0.62–0.91); 0.003	0.77 (0.66–0.90); 0.001
Limb vascular event			
Limb ischemic AE	0.73 (0.60–0.89); 0.002	0.69 (0.55–0.88); 0.003	0.74 (0.61–0.90); 0.003
Any peripheral revascularization	0.73 (0.60–0.89); 0.002	0.71 (0.56–0.90); 0.004	0.74 (0.60–0.90); 0.003
MALE	0.91 (0.62–1.35); 0.652	0.76 (0.46–1.24); 0.27	0.95 (0.64–1.40); 0.797
Hospitalization for acute limb ischemia	1.10 (0.64–1.90); 0.732	0.85 (0.42–1.75); =0.665	1.15 (0.66–1.98); 0.627
Amputation	0.81 (0.49–1.32); 0.388	0.63 (0.33–1.20); 0.156	0.85 (0.52–1.39); 0.506

AE indicates adverse event (limb ischemic AE, composite of acute limb ischemia, any peripheral revascularization, and major vascular amputation); HR, hazard ratio; MACE, major adverse cardiac event (composite of cardiovascular death, myocardial infarction, or stroke); and MALE, major adverse limb event (composite of acute limb ischemia, urgent peripheral revascularization, and major vascular amputation).

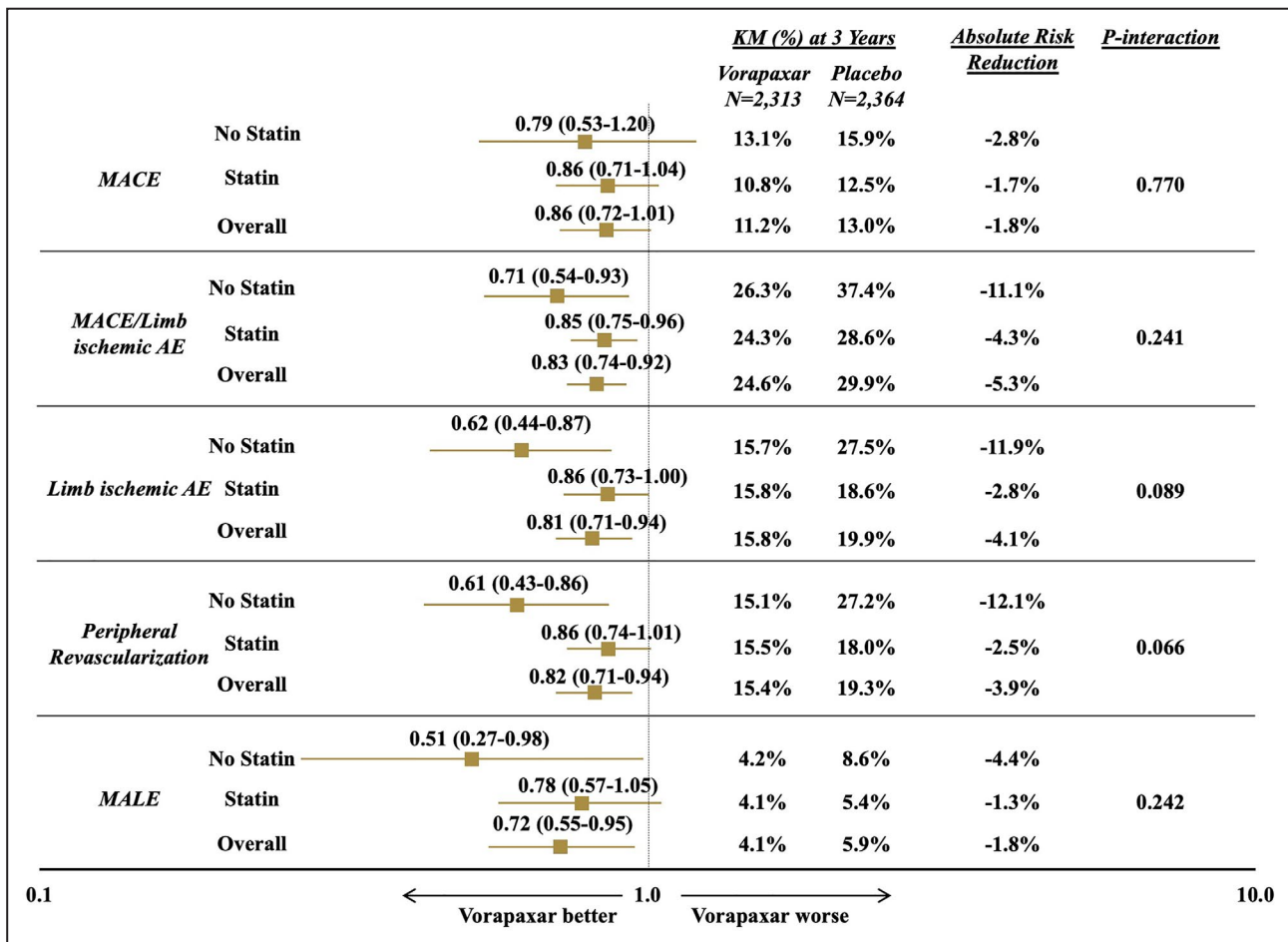


Figure 2. Forest plot comparing vorapaxar to placebo stratified by statin therapy in subjects with peripheral artery disease without a history of stroke or transient ischemic attack (n=4677).

Dotted line represents the 1.0 value. Squares are the point estimates for the hazard ratios and the diamonds are the overall estimate (combining the subgroups). AE indicates adverse event (limb ischemic AE, composite of acute limb ischemia, any peripheral revascularization, and major vascular amputation); KM, Kaplan-Meier; MACE, major adverse cardiac event (composite of cardiovascular death, myocardial infarction, or stroke); and MALE, major adverse limb event (composite of acute limb ischemia, urgent peripheral revascularization, and major vascular amputation).

less so than in those with PAD and no history of CAD as compared with patients who had both PAD and CAD. Our findings support previous studies showing that patients with PAD only are more likely to be undertreated with preventative therapies, including statins, and underuse of these therapies contribute to the high mortality rate.¹⁵ These observations coupled with others confirming this relationship underscore the need for greater awareness of the risk profile of PAD, the benefits of statins in PAD, and enhanced efforts to improve the provision of care in this population.

LDL-C-lowering therapies for the reduction of MACEs has been well studied, and our data are consistent with data from the HPS (Heart Protection Study) and the REACH (Reduction of Atherothrombosis for Continued Health) registry showing an $\approx 17\%$ risk reduction with statin therapy.^{12,16} The role of LDL-C-lowering therapies, including statin therapy, for preventing adverse limb events is less robust but becoming clearer. In a subanalysis of patients with PAD in HPS, simvastatin use was shown to have a 20% decreased rate of noncoronary revascularization procedures but no decrease in the rate of amputation.¹² A randomized trial of atorvastatin versus placebo showed functional improvements (increase in pain-free walking distance) over 12 months of therapy; however, the trial was small and not powered for limb ischemic events.²⁰ Observational data from the REACH registry show an association between statin use and lower rates of amputation. This observation has also been seen in Veterans Affairs observational data with higher-intensity statin use associated with lower rates of amputation and death.³⁰ Recently, data from the FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk) study show that LDL-C lowering reduces MALEs, with a continuous relationship between achieved LDL-C and MALEs down to concentrations <10 mg/dL.²² This analysis supports these findings and the importance of LDL-C lowering in reducing the risk of MALEs in patients with PAD.

Among antithrombotic therapies, rivaroxaban has been shown to reduce MACEs and MALEs in PAD.^{31,32} The benefit of rivaroxaban for MACEs and MALEs in PAD are driven through antithrombotic mechanisms, including direct anti-Xa inhibition with downstream reduction in thrombin generation. Vorapaxar also demonstrated benefits for MACEs and MALEs. The findings from the trials with rivaroxaban and vorapaxar confirm the importance of antithrombotic therapies and targeting thrombin for improving outcomes in PAD. These benefits, however, are accompanied by an increase in bleeding. Therefore, a question of clinical importance is whether the benefits of lipid-modifying therapies and therapies to target thrombin are additive or whether treating 1 axis of

risk modifies the benefit of the other. The current analysis shows that the benefits of thrombin inhibition with vorapaxar for MACEs, MALEs, and the composite of both is maintained regardless of the intensity of background lipid-lowering therapy. In addition, statin use was associated with lower rates of MACEs and MALEs regardless of vorapaxar use. These data suggest that the benefits of treating both axes of risk (lipid and thrombin mediated) are important and complementary, and that optimal therapy likely requires both.

A limitation of this study is that statin therapy was not randomized. Unadjusted analyses, however, show higher risk in statin-treated patients, suggesting confounding by indication (eg, more use in those with CAD), which would only attenuate the observed benefits of statins. In addition, multivariable adjustment was used to address measured potential confounders. In addition, it is possible that statin intensity changed during the study; however, such changes also would only be expected to attenuate observed differences. An additional limitation is that LDL-C levels were not measured during the study, which would have given more details about further improvement in LDL-C improving outcomes. Despite these limitations regarding the analyses of statin efficacy, the key observation of this study, that the benefits of vorapaxar were maintained regardless of statin intensity at baseline, was based on randomized, blinded treatment allocation, and used prespecified, adjudicated outcomes.

CONCLUSIONS

Statin use and intensity is associated with a significantly lower rate of adverse limb events in patients with symptomatic PAD. Vorapaxar reduces adverse limb and cardiovascular events in patient with PAD with consistent benefits regardless of background lipid-lowering intensity. These data support intensive medical therapy for patients with symptomatic PAD and suggest that the combination of intensive lipid-lowering and intensive antithrombotic therapy is useful to optimize outcomes.

ARTICLE INFORMATION

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Supplementary Material

Tables S1–S2

Figure S1

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Supplemental Material

Table S1. Baseline Characteristics: Comparison of Statin Intensity, patients without history stroke/TIA.

N=5,845	High Intensity (n=993)	Low Intensity (n=3063)	No Statin (n=681)
Demographics			
Age, mean, years	63	65	67
Female sex- %	27.9	29.4	27.8
Region			
North America- %	59.2	37.6	31.9
Europe I*- %	28.9	42.8	36.1
Europe II*- %	5.9	5.9	4.4
Latin America-%	2.7	12.3	25.3
Australia/New Zealand-%	3.3	1.1	0.7
Asia-%	0.0	0.3	1.6
Comorbidities-%			
Diabetes Mellitus	38.2	36.1	31.0
Hyperlipidemia	97.5	92.3	57.1
Hypertension	81.5	80.0	78.0
BMI ≥ 30 kg/m ²	39.1	28.9	23.7
Current Smoker	29.8	30.5	33.6
Heart Failure	16.8	11.9	8.7
CrCl <60 ml/min	18.0	22.9	30.1
Extend of Vascular Disease-%			
Coronary Artery Disease	86.5	69.9	40.9
Cerebrovascular Vascular Disease	0	0	0
Prior coronary revascularization	73.6	54.7	27.5
Prior carotid revascularization	8.5	6.1	6.0
Prior limb revascularization	52.1	49.7	53.2
Prior limb ischemia/amputation	2.4	3.6	6.5
Baseline ABI value, mean	0.85	0.81	0.76
ABI <0.85	51.1	58.2	66.6
Medications- %			
Aspirin	93.5	92.1	83.0
Thienopyridine	58.6	42.4	27.0
ACE or ARB	77.3	72.0	56.2
Beta-Blocker	74.5	61.8	39.8
Cilostazol	4.8	7.9	15.6
Vorapaxar	50.3	48.7	51.7

* Europe I = Austria, Belgium, Denmark, Finland, France, Germany, Israel, Italy, Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, United Kingdom, South Africa; Europe II = Czech Republic, Hungary, Poland.

Table S2. Multivariable adjusted hazard ratios for high, low and no statin therapy comparing Vorapaxar vs Placebo in patients without history of stroke/TIA.

Endpoint	High intensity statin, Vorapaxar vs Placebo, HR (95% CI)	Low intensity statin, Vorapaxar vs Placebo, HR (95% CI)	No statin, Vorapaxar vs Placebo, HR (95% CI)
MACE	0.79 (0.54-1.14)	0.89 (0.72-1.11)	0.79 (0.53-1.20)
MACE/Limb ischemic AE	0.78 (0.61-1.00)	0.87 (0.75-1.00)	0.71 (0.54-0.93)
Limb ischemic AE	0.88 (0.65-1.20)	0.85 (0.71-1.01)	0.62 (0.44-0.87)
Peripheral Revascularization	0.85 (0.62-1.16)	0.87 (0.72-1.04)	0.61 (0.43-0.86)
MALE	1.02 (0.52-1.99)	0.72 (0.51-1.01)	0.51 (0.27-0.98)

p-interaction non-significant for all endpoints

Figure S1. Consort diagram of patients randomized into TRA2P-TIMI 50 Trial.

