# Vorapaxar in Patients With Peripheral Artery Disease: Results From TRA2°P-TIMI 50

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# Vorapaxar in Patients With Peripheral Artery Disease
## Results From TRA2°P-TIMI 50

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***Background***—Vorapaxar is a novel antagonist of protease-activated receptor-1, the primary receptor for thrombin on human platelets that is also present on vascular endothelium and smooth muscle. Patients with peripheral artery disease are at risk of systemic atherothrombotic events, as well as acute and chronic limb ischemia and the need for peripheral revascularization.

***Methods and Results***—The Trial to Assess the Effects of SCH 530348 in Preventing Heart Attack and Stroke in Patients With Atherosclerosis (TRA2°P-TIMI 50) was a randomized, double-blind, placebo-controlled trial of vorapaxar in 26 449 patients with stable atherosclerotic vascular disease (myocardial infarction, stroke, or peripheral artery disease). Patients with qualifying peripheral artery disease (n=3787) had a history of claudication and an ankle-brachial index of <0.85 or prior revascularization for limb ischemia. The primary efficacy end point was cardiovascular death, myocardial infarction, or stroke, and the principal safety end point was Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO) bleeding. In the peripheral artery disease cohort, the primary end point did not differ significantly with vorapaxar (11.3% versus 11.9%; hazard ratio, 0.94; 95% confidence interval, 0.78–1.14; *P*=0.53). However, rates of hospitalization for acute limb ischemia (2.3% versus 3.9%; hazard ratio, 0.58; 95% confidence interval, 0.39–0.86; *P*=0.006) and peripheral artery revascularization (18.4% versus 22.2%; hazard ratio, 0.84; 95% confidence interval, 0.73–0.97; *P*=0.017) were significantly lower in patients randomized to vorapaxar. Bleeding occurred more frequently with vorapaxar compared with placebo (7.4% versus 4.5%; hazard ratio, 1.62; 95% confidence interval, 1.21–2.18; *P*=0.001).

***Conclusions***—Vorapaxar did not reduce the risk of cardiovascular death, myocardial infarction, or stroke in patients with peripheral artery disease; however, vorapaxar significantly reduced acute limb ischemia and peripheral revascularization. The beneficial effects of protease-activated receptor-1 antagonism on limb vascular events were accompanied by an increased risk of bleeding.

***Clinical Trial Registration***—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00526474. (***Circulation.* 2013;127:1522-1529.**)

**Key Words:** ischemia ■ outcome assessment ■ peripheral arterial disease ■ platelet aggregation inhibitors ■ vorapaxar

Patients with peripheral artery disease (PAD) are at a heightened risk of acute atherothrombotic events, including myocardial infarction (MI), stroke, and cardiovascular death.[1–3] Even when patients with PAD do not clinically manifest disease in the coronary or cerebrovascular circulation, subclinical atherosclerosis is often present and puts them at risk for adverse cardiovascular outcomes.[1,2] This risk is exacerbated by underdiagnosis and undertreatment, even in patients with recognized disease.[4] Accordingly, secondary preventive strategies in patients with PAD have been targeted primarily at reducing major cardiovascular outcomes. Nonetheless, the need for peripheral revascularization for claudication and acute and chronic critical limb ischemia are significant sources of morbidity, disability, and cost.[5] Antiplatelet therapy reduces the risk of cardiovascular events in patients with PAD.[6] However, the optimal type and intensity of antiplatelet therapy remain topics of debate because some trials have shown no conclusive benefit of antiplatelet therapy in PAD.[7,8]

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Clinical Perspective on p 1529

Vorapaxar is a novel oral antiplatelet agent that antagonizes activation of the protease-activated receptor-1 (PAR-1) by thrombin. The action of thrombin on PAR-1 on the platelet surface leads to activation, whereas the interaction of thrombin with PAR-1 on endothelial and smooth muscle cells is mitogenic.[9] The Preventing Heart Attack and Stroke in Patients With Atherosclerosis (TRA2°P-TIMI 50) trial evaluated the efficacy and safety of vorapaxar for secondary prevention in patients with established atherosclerosis manifest as a prior MI, ischemic stroke, or PAD and revealed an overall 13% reduction in major cardiovascular events with vorapaxar ($P$<0.001).[10] In the present analysis, we investigated the effect of vorapaxar on cardiovascular and peripheral vascular outcomes in patients who qualified for TRA2°P-TIMI 50 with symptomatic PAD.

## Methods

### Study Population and Procedures

TRA2°P-TIMI 50 was a multinational, randomized, double-blind, placebo-controlled trial of 26 449 subjects with stable atherosclerotic vascular disease. The details of the trial design have previously been reported.[10,11] The plan for the PAD cohort was to enroll ≈15% of the overall trial cohort.[10] To qualify for inclusion on the basis of PAD, patients were required to have a history of intermittent claudication in conjunction with an ankle-brachial index <0.85 or previous revascularization for limb ischemia. Qualifying and follow-up ankle-brachial indexes were performed by trained personnel at the study site using standardized procedures. Randomization was stratified according to the qualifying diagnosis.[10] Patients with MI or stroke in the prior year who also had a history of PAD were assigned to the MI and stroke strata, respectively. Patients were ineligible if they had a planned revascularization that had not yet been performed, had a history of a bleeding diathesis, were receiving vitamin K antagonist therapy, or had active hepatobiliary disease. The trial was approved by the responsible Institutional Review Board or Ethics Committee for each participating institution. All patients gave written informed consent.

Eligible patients were randomized in a 1:1 fashion to receive vorapaxar 2.5 mg daily or matching placebo. All concomitant medical therapy, including use of other antiplatelet agents or anticoagulants during the trial, was managed by the local treating physician. As previously described, after completion of enrollment and a median of ≈2 years of follow-up, the Data and Safety Monitoring Board reported an excess of intracranial hemorrhage with vorapaxar in patients with a history of stroke and recommended discontinuation of study drug in all patients with a prior stroke.[10,11]

### End Points

In the hierarchical analysis of efficacy end points, the first end point evaluated was the composite of MI, stroke, or death from cardiovascular causes (CV death), followed by the composite of CV death, MI, stroke, or hospitalization for urgent coronary revascularization.[11] The principal safety end point was Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO) moderate or severe bleeding. Bleeding events were also classified according to the Thrombolysis in Myocardial Infarction (TIMI) bleeding definition. Definitions of these end points have previously been reported.[10]

Prespecified limb efficacy end points included acute limb ischemia, peripheral revascularization (urgent and elective), and urgent hospitalization for vascular cause of an ischemic nature. Acute limb ischemia was defined as a clinical history suggesting a rapid or sudden decrease in limb perfusion and either a new pulse deficit with associated rest pain, pallor, parasthesias, or paralysis or confirmation of arterial obstruction by imaging, intraoperative findings, or pathological evaluation. Peripheral revascularization was defined as any arterial vascular intervention done to treat ischemia or to prevent major ischemic events, including percutaneous or surgical interventions, and categorized as either urgent or elective. The additional prespecified composite end point of urgent hospitalization for vascular cause of an ischemic nature was defined as unplanned hospitalization for a new coronary, cerebrovascular, or peripheral arterial ischemic event (see the online-only Data Supplement) All elements of this end point were adjudicated by a Clinical Events Committee made up of trained specialists in cardiovascular medicine who were blinded to treatment allocation. Procedures including peripheral revascularization were captured as reported by the investigator on the case record form.

### Statistical Methods

Data were analyzed on an intention-to-treat basis of all randomized patients, including PAD patients with a history of stroke. Baseline characteristics were compared by use of the $\chi^2$ test for categorical variables and the Wilcoxon rank-sum test for continuous variables. The efficacy analyses were performed with a Cox proportional-hazards model, with the investigational treatment allocation and planned use of a thienopyridine as covariates. Cumulative event rates at 3 years were calculated with the Kaplan-Meier method. Safety analyses were performed among patients who received 1 or more doses of study drug and included events through 60 days after premature cessation of study therapy or 30 days after a final visit at the conclusion of the trial. Analyses were performed with Stata version 12.1 (Stata Corp, College Station, TX).

## Results

### Baseline Characteristics

A total of 3787 patients were randomized into the PAD stratum. Median follow-up was 36 months. Baseline characteristics of the patients in the PAD cohort are shown in Tables 1 and 2. Compared with patients who qualified with MI or stroke, those in the PAD group were older and had a greater prevalence of diabetes mellitus, hypertension, hyperlipidemia, current tobacco use, and renal dysfunction (Table 1). Aspirin therapy was less prevalent at baseline in the PAD group compared with the other groups; however, the majority of PAD patients (88%) were on aspirin, approximately one third (37%) were on a thienopyridine at baseline, 28% were on dual antiplatelet therapy, and 11% were on cilostazol (Table 1). Drug discontinuation rates at 3 years in the PAD cohort were higher than those in the overall trial population (33% for the PAD cohort versus 23% overall). The rates by treatment allocation in the PAD group were similar (34% for vorapaxar versus 32% for placebo; $P$=0.083).

Within the PAD group, more than half (57%) had known concomitant coronary artery disease, and 14% had known prior cerebrovascular events (stroke or transient ischemic attack; Table 2), with 8% having a history of stroke. Most patients had a history of peripheral artery revascularization (62%), and ≈10% had a history of carotid artery intervention. Overall, 68% of patients had a baseline ankle-brachial index of <0.85. The majority of patients (75%) were symptomatic from PAD at enrollment, with 72% having symptoms of stable claudication (Fontaine IIa or IIb), 2% having rest pain (Fontaine III), and 1% having ulceration, necrosis, or gangrene (Fontaine IV; Table 2).

### Major Efficacy End Points

Among patients in the PAD cohort, vorapaxar did not significantly reduce the composite of CV death, MI, or stroke

**Table 1. Baseline Characteristics: Comparison of Qualifying Disease Cohorts**

| Variable | PAD Cohort (n=3787) | MI/Stroke Cohorts (n=22 662) | *P* Value |
|---|---|---|---|
| Demographics | | | |
| Age, median (IQR), y | 66 (60–73) | 60 (52–68) | <0.001 |
| Female sex, n (%) | 1115 (29) | 5211 (23) | <0.001 |
| White race, n (%) | 3425 (90) | 19 661 (87) | <0.001 |
| Weight <60 kg, n (%) | 370 (10) | 1482 (7) | <0.001 |
| Clinical characteristics, n (%) | | | |
| Diabetes mellitus | 1358 (36) | 5366 (24) | <0.001 |
| Hypertension | 3157 (83) | 15 017 (66) | <0.001 |
| Hyperlipidemia | 3312 (87) | 18 682 (82) | <0.001 |
| Current smoker | 1167 (31) | 4331 (19) | <0.001 |
| Any coronary artery disease | 2155 (57) | 18 536 (82) | <0.001 |
| Previous cerebrovascular event | 513 (14) | 5755 (25) | <0.001 |
| Prior coronary revascularization | 1592 (42) | 15 669 (69) | <0.001 |
| eGFR <60 mL·min$^{-1}$·1.73 m$^{-2}$ | 1082 (29) | 3002 (13) | <0.001 |
| Medical therapy, n (%) | | | |
| No aspirin or thienopyridine | 128 (3.4) | 218 (1.0) | <0.001 |
| Aspirin | 3332 (88) | 21 402 (94) | <0.001 |
| Thienopyridine | 1394 (37) | 15 048 (66) | <0.001 |
| Cilostazol | 420 (11) | 182 (1) | <0.001 |
| Aspirin and thienopyridine therapy | 1067 (28) | 14 006 (62) | <0.001 |
| Statin therapy | 3098 (82) | 20 639 (91) | <0.001 |

eGFR indicates estimated glomerular filtration rate; IQR, interquartile range; MI, myocardial infarction; and PAD, peripheral artery disease.

**Table 2. Baseline Characteristics: Randomized Treatment Allocation in the PAD Cohort**

| Variable | Vorapaxar (n=1892) | Placebo (n=1895) | *P* Value |
|---|---|---|---|
| Demographics | | | |
| Age, median (IQR), y | 66 (60–73) | 66 (60–73) | 0.90 |
| Female sex, n (%) | 546 (29) | 569 (30) | 0.43 |
| White race, n (%) | 1706 (90) | 1719 (91) | 0.60 |
| Weight <60 kg, n (%) | 185 (10) | 185 (10) | 0.996 |
| Clinical characteristics, n (%) | | | |
| Diabetes mellitus | 691 (37) | 667 (35) | 0.40 |
| Hypertension | 1583 (84) | 1574 (83) | 0.62 |
| Hyperlipidemia | 1642 (87) | 1670 (88) | 0.23 |
| Current smoker | 579 (31) | 588 (31) | 0.78 |
| Any coronary artery disease | 1057 (56) | 1098 (58) | 0.18 |
| eGFR CrCl mL·min$^{-1}$·1.73 m$^{-2}$ | 537 (29) | 545 (29) | 0.88 |
| Pervious cerebrovascular event | 269 (14) | 244 (13) | 0.23 |
| PAD details, n (%) | | | |
| Peripheral arterial revascularization | 1182 (62) | 1155 (61) | 0.33 |
| Prior amputation | 95 (5) | 76 (4) | 0.13 |
| Prior carotid intervention | 206 (11) | 188 (10) | 0.33 |
| ABI <0.85 | 1224 (68) | 1239 (68) | 0.98 |
| ABI >1.3 | 24 (1.3) | 30 (1.6) | 0.98 |
| Claudication (Fontaine class > 1) | 1431 (76) | 1395 (74) | 0.31 |
| Baseline medical therapy, n (%) | | | |
| No antiplatelet therapy | 60 (3.2) | 68 (3.6) | 0.48 |
| Aspirin | 1661 (88) | 1671 (88) | 0.71 |
| Thienopyridine | 696 (37) | 698 (37) | 0.98 |
| Aspirin and thienopyridine therapy | 525 (28) | 542 (29) | 0.56 |
| Cilostazol | 205 (11) | 215 (11) | 0.62 |
| Dipyridamole | 18 (1.0) | 17 (0.9) | 0.86 |

ABI indicates ankle-brachial index; CrCL, creatinine clearance; eGFR, estimated glomerular filtration rate; IQR, interquartile range; and PAD, peripheral artery disease.

compared with placebo (11.3% versus 11.9%; hazard ratio [HR], 0.94; 95% confidence interval [CI], 0.78–1.14; *P*=0.53; Figure 1) or CV death, MI, stroke, or urgent coronary revascularization (*P*=0.57; Table 3). The individual components of the primary end point are shown in Table I in the online-only Data Supplement. However, formal testing for a difference in the effect of vorapaxar in the PAD stratum compared with that observed in the remainder of the trial cohort was not significant (*P* for interaction=0.35), including comparison with the MI group alone, in which there was a clear benefit of vorapaxar[11] (*P* for interaction=0.16).

## Peripheral Vascular End Points

In terms of manifestations of peripheral vascular disease, vorapaxar significantly reduced the risk of limb ischemic events, including hospitalization for acute limb ischemia (2.3% versus 3.9%; HR, 0.58; 95% CI, 0.39–0.86; *P*=0.006; Table 3 and Figure 2A) and peripheral revascularization (18.4% versus 22.2%; HR, 0.84; 95% CI, 0.73–0.97; *P*=0.017; Table 3 and Figure 2B). This reduction was consistent for both urgent (3.1% versus 4.7%; HR, 0.65; 95% CI, 0.46–0.91; *P*=0.012) and elective (16.5% versus 19.5%; HR, 0.86; 95% CI, 0.74–0.9995; *P*=0.049) peripheral revascularization.

The reduction in acute limb ischemia was evident by 30 days (0% versus 0.4%; *P*=0.008) and continued throughout the duration of follow-up (2.3% versus 3.7%; HR, 0.62; 95% CI, 0.42–0.92). In contrast, the reduction in peripheral revascularization became apparent later in follow-up (Figure 2B).

When broadened to include events involving the coronary and cerebral circulations, both urgent vascular hospitalization (5.8% versus 8.0%; HR, 0.72; 95% CI, 0.56–0.93; *P*=0.011; Table 3 and Figure 3) and the need for any arterial revascularization (26.2% versus 30.3%; HR, 0.88; 95% CI, 0.78–0.99; *P*=0.036) were also significantly reduced with vorapaxar compared with placebo. Moreover, the prespecified composite end point combining CV death, MI, or stroke with the broader vascular elements of any arterial revascularization and urgent vascular hospitalization was significantly reduced

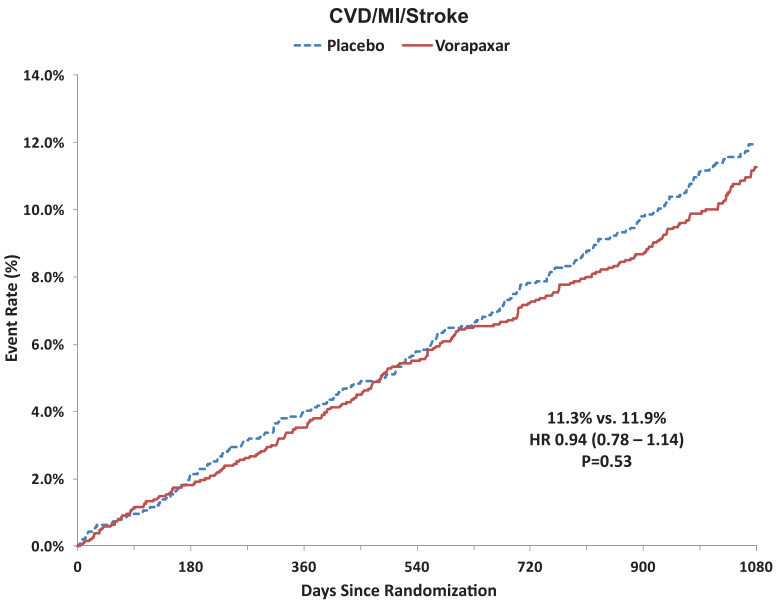


**Figure 1.** Kaplan-Meier rates for the composite of cardiovascular death (CVD), myocardial infarction (MI), or stroke by treatment allocation in the peripheral artery disease cohort. HR indicates hazard ratio.

with vorapaxar compared with placebo (32.7% versus 38.0%; HR, 0.87; 95% CI, 0.78–0.97; *P*=0.009; Table 3 and Figure 4).

Overall, there was no heterogeneity in the effect of vorapaxar when stratified by use of a thienopyridine (primary end point, *P* for interaction=0.42; hospitalization for acute limb ischemia, *P* for interaction=0.22; peripheral revascularization, *P* for interaction=0.23) or by history of peripheral revascularization (primary end point, *P* for interaction=0.55; hospitalization for acute limb ischemia, *P* for interaction=0.82; peripheral revascularization, *P* for interaction=0.78).

A total of 3483 patients in the PAD cohort (92%) had no history of stroke. When analyses were restricted to this cohort, efficacy findings were similar. In this cohort, vorapaxar did not reduce CV death, MI, or stroke (*P*=0.43) but significantly reduced limb ischemic events, including hospitalization for acute limb ischemia (2.2% versus 4.1%; HR, 0.53; 95% CI, 0.35–0.80; *P*=0.002) and peripheral revascularization (18.1% versus 22.0%; HR, 0.83; 95% CI, 0.72–0.97; *P*=0.018), as well as the broader end point of urgent vascular hospitalization (2.3% versus 8.1%; HR, 0.66; 95% CI, 0.51–0.86; *P*=0.002).

### Safety End Points

Compared with placebo, in the PAD cohort, vorapaxar increased the risk of bleeding, including GUSTO moderate or severe bleeding (7.4% versus 4.5%; HR, 1.62; 95% CI, 1.21–2.18; *P*=0.001; Table 3 and Figure I in the online-only Data Supplement). The rates of intracranial hemorrhages with vorapaxar compared with placebo were 0.9% versus 0.4% (HR, 2.03; 95% CI, 0.82–5.02; *P*=0.13; Figure II in the online-only Data Supplement). We found no difference in the risk of intracranial hemorrhage in the PAD cohort compared with those who qualified with MI or stroke (*P* for interaction=0.91) or those who qualified with MI (*P* for interaction=0.60). There was no difference in fatal bleeding (Table 3 and Figure III in the online-only Data Supplement). When patients with a history of cerebrovascular disease were excluded, rates of intracranial hemorrhage were lower (0.7% for vorapaxar versus 0.4% for placebo; *P*=0.37). The risk of GUSTO moderate or severe bleeding with vorapaxar in the PAD cohort was similar for those on thienopyridine (HR, 1.61; 95% CI, 1.04–2.50; *P*=0.032) compared with those not on thienopyridine (HR, 1.63; 95% CI, 1.1–2.42; *P*=0.016) at baseline, with no significant interaction for bleeding (*P* for interaction=0.98 for GUSTO moderate or severe bleeding, *P*=NS for all other safety end points reported). The risk of bleeding also did not differ on the basis of the use of aspirin at baseline (*P* for interaction=0.20 for GUSTO moderate or severe bleeding) or with background dual antiplatelet therapy (*P* for interaction=0.403 for GUSTO moderate or severe bleeding).

## Discussion

When added to standard therapy, vorapaxar did not significantly reduce the risk of CV death, MI, or stroke in the subgroup of patients who qualified for the trial with PAD. However, vorapaxar significantly reduced limb ischemic events, including both hospitalization for acute limb ischemia and peripheral artery revascularization. These events occurred frequently, are associated with significant morbidity and cost, and have few proven preventive medical therapies. Overall, bleeding was increased with vorapaxar, including a trend toward a higher rate of intracranial bleeding.

### Antiplatelet Therapy in PAD

A large meta-analysis by the Antithrombotic Trialists' Collaboration showed a reduction in the odds of major adverse cardiovascular events with antiplatelet therapy in PAD patients; however, there was important heterogeneity in the component trials in terms of population, outcomes, and therapies evaluated.[6] Importantly, recent studies of aspirin for prevention in asymptomatic patients with PAD qualified by ankle-brachial index (<0.99 and ≤0.95) have shown no benefit.[7,8] In addition, a meta-analysis of aspirin for the prevention of major adverse cardiovascular events in patients with PAD did not confirm efficacy.[12]

Reconciling the discordant findings in these trials of antiplatelet therapy in PAD is complex and may be related to differences in the populations studied, whether patients had symptomatic

**Table 3. Efficacy and Bleeding End Points**

| End Point | Vorapaxar (n=1892), n (%) | Placebo (n=1895) , n (%) | Hazard Ratio (95% CI) | *P* Value |
|---|---|---|---|---|
| Overall efficacy | | | | |
| CVD/MI/stroke | 206 (11.3) | 218 (11.9) | 0.94 (0.78–1.14) | 0.53 |
| CVD/MI/stroke/urgent coronary revascularization | 233 (12.7) | 245 (13.4) | 0.95 (0.79–1.14) | 0.57 |
| CVD/MI/stroke/urgent vascular hospitalization | 294 (15.9) | 338 (18.6) | 0.85 (0.73–0.998) | 0.047 |
| CVD/MI/stroke/revascularization/urgent vascular hospitalization | 615 (32.7) | 694 (38.0) | 0.87 (0.78–0.97) | 0.009 |
| Peripheral limb vascular efficacy | | | | |
| Hospitalization for acute limb ischemia | 40 (2.3) | 68 (3.9) | 0.58 (0.39–0.86) | 0.006 |
| Any peripheral revascularization | 341 (18.4) | 401 (22.2) | 0.84 (0.73–0.97) | 0.017 |
| Urgent peripheral revascularization | 56 (3.1) | 85 (4.7) | 0.65 (0.46–0.91) | 0.012 |
| Elective peripheral revascularization | 305 (16.5) | 352 (19.5) | 0.86 (0.74–0.9995) | 0.049 |
| Any vascular* efficacy | | | | |
| Urgent vascular hospitalization | 105 (5.8) | 143 (8.0) | 0.72 (0.56–0.93) | 0.011 |
| Any revascularization | 486 (26.2) | 546 (30.3) | 0.88 (0.78–0.99) | 0.036 |
| Bleeding | | | | |
| GUSTO moderate/severe bleed | 115 (7.4) | 73 (4.5) | 1.62 (1.21–2.18) | 0.001 |
| GUSTO severe bleed | 36 (2.4) | 26 (1.6) | 1.41 (0.85–2.34) | 0.18 |
| Fatal bleed | 7 (0.5) | 7 (0.4) | 1.02 (0.36–2.90) | 0.98 |
| Intracranial hemorrhage | 14 (0.9) | 7 (0.4) | 2.03 (0.82–5.02) | 0.13 |
| Intracranial hemorrhage† | 8 (0.7) | 5 (0.4) | 1.66 (0.54–5.08) | 0.37 |

CI indicates confidence interval; CVD, cardiovascular death; GUSTO, Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries; and MI, myocardial infarction.

*Includes vascular events involving the coronary, cerebral, or peripheral vasculature.

†Excluding patients with cerebrovascular disease.

or asymptomatic PAD, the type and intensity of antiplatelet therapy administered, and concomitant background therapies. In a subgroup analysis of the Clopidogrel Versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial, treatment with clopidogrel without aspirin resulted in a 23.8% relative risk reduction in the composite of vascular death, MI, or stroke among patients with PAD compared with aspirin monotherapy.[13] Notably, the PAD cohort in the CAPRIE trial was defined as symptomatic PAD, requiring an ankle-brachial index ≤0.85 and claudication or a history of claudication and revascularization.[13] However, in the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial, dual antiplatelet therapy with clopidogrel and aspirin compared with aspirin alone did not reduce cardiovascular events in the 2838 patients with symptomatic PAD (*P*=0.28) or in the broader group of 3096 patients with asymptomatic or symptomatic PAD (*P*=0.18).[14–16]

Moreover, it has been uncertain whether antiplatelet therapy reduces the risk of acute limb-threatening events or the need for revascularization. A recent Cochrane meta-analysis suggested a 30% reduction in peripheral revascularization with antiplatelet therapy when 5 trials of patients with intermittent claudication—4 studies of ticlopidine and 1 study of picotamide—were pooled; however, none of the individual trials showed a significant reduction in revascularization.[17]

## Findings With Vorapaxar

Results from the TRA2°P-TIMI 50 trial show a numerically but not statistically significant 6% lower rate of major cardiovascular events with vorapaxar in addition to background antiplatelet therapy in PAD patients. These findings are consistent with the overall reduction of cardiovascular events with vorapaxar observed in the trial and do not differ formally in interaction testing compared with patients who qualified with an MI in the previous year (*P* for interaction=0.16 for PAD versus MI qualifying cohorts). However, taken together with findings in the CHARISMA trial, these data suggest a more modest, if any, reduction in CV death, MI, or stroke with potent multiagent antiplatelet therapy in patients with PAD that must be weighed against the increased risk of bleeding observed in both trials.[14] However, it is unknown whether vorapaxar monotherapy would be beneficial in this population compared with clopidogrel or aspirin monotherapy; clopidogrel and aspirin monotherapy are the treatments currently recommended by professional society guidelines.[18,19]

A novel finding of this study was that vorapaxar reduced acute limb ischemia, a complex atherothrombotic process affecting the primary symptomatic vascular bed. Importantly, this benefit was seen when vorapaxar was added to background antiplatelet therapy, showing a benefit additive to any provided by currently used antiplatelet therapies. In addition, vorapaxar reduced the rate of peripheral revascularization. Intriguingly, although acute events are most likely reduced through direct antiplatelet activity, the significant reduction in all peripheral revascularizations, including nonurgent revascularization, emerged later in the course of therapy and raises the question of non–platelet-mediated effects on the vasculature. PAR-1 is present on a number of cell types, including platelets, endothelial cells, and smooth

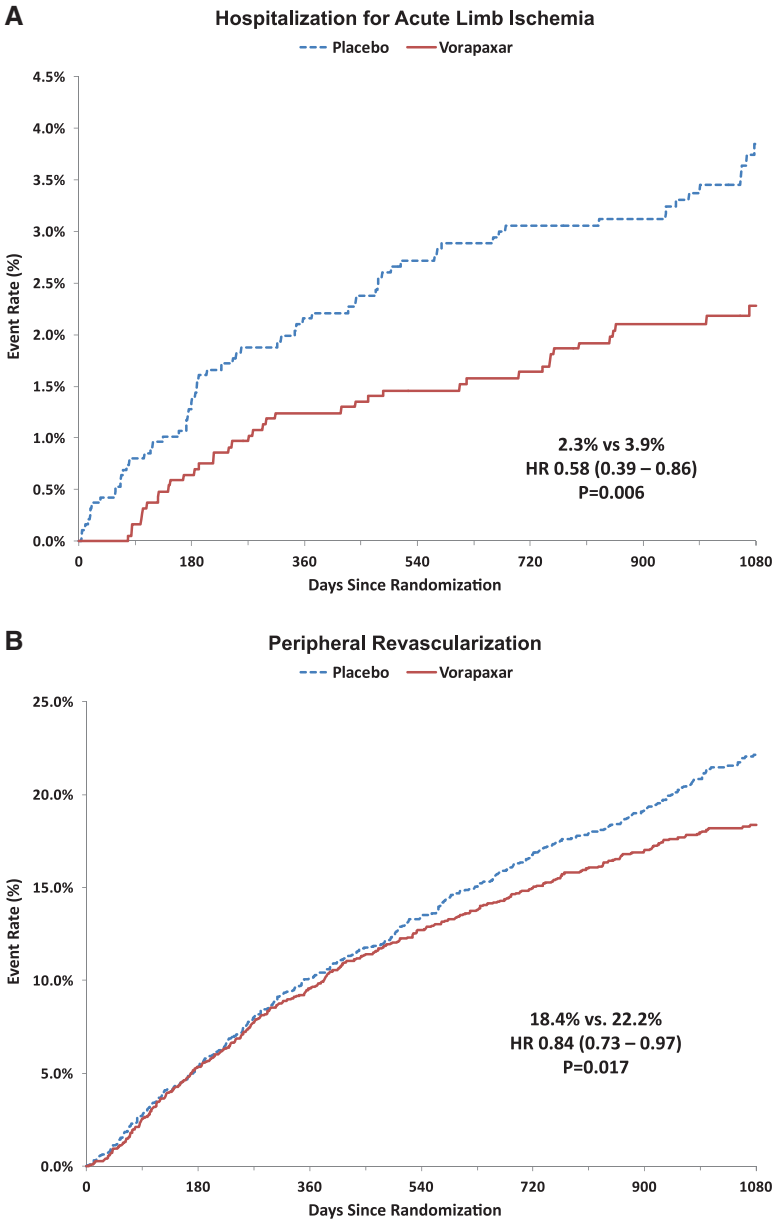


**Figure 2. A,** Kaplan-Meier rates for hospitalization for limb ischemia by treatment allocation in the peripheral artery disease (PAD) cohort. **B**, Kaplan-Meier for peripheral revascularization by treatment allocation in the PAD cohort. HR indicates hazard ratio.

muscle cells. Because activation of PAR-1 by thrombin has been shown to be mitogenic in endothelial and smooth muscle cells, antagonism of PAR-1 with vorapaxar may reduce vascular remodeling, which leads to impaired perfusion.[9,20,21]

When added to background antiplatelet therapy, vorapaxar significantly increased bleeding in patients qualifying for the PAD cohort. Patients with PAD have been shown to be at increased risk of bleeding, and in some studies, the presence of PAD has been identified as an independent predictor of bleeding risk after adjustment for comorbidities.[16,22] Therefore, the reduction in peripheral ischemic events would need to be weighed against the risk of serious bleeding, including intracranial hemorrhage, in individual patients if vorapaxar becomes available for clinical use.

Several limitations of the present study should be noted. Although there was a numeric reduction in the primary end point in the PAD group and no statistical difference from the significant reduction was observed in the overall trial, the present cohort was not sufficiently sized to show a significant reduction in the primary end point with vorapaxar. Also, although the trial was designed to evaluate the efficacy of vorapaxar in addition to standard background antiplatelet therapy, the heterogeneity of background antiplatelet therapy limits the ability to discriminate differential effects when added to specific antiplatelet agents (eg, cilostazol). In addition, the present data set does not permit us to report on the potential efficacy and safety of vorapaxar as monotherapy. Finally, efficacy analyses were performed according to an intention-to-treat principle. Although annualized treatment discontinuation was similar to other trials of antiplatelet therapies in stable populations, premature cessation and treatment nonadherence could have attenuated the magnitude of the efficacy of vorapaxar.[14]

## Conclusions

In patients with symptomatic PAD, vorapaxar did not significantly reduce the risk of cardiovascular death, MI, or stroke

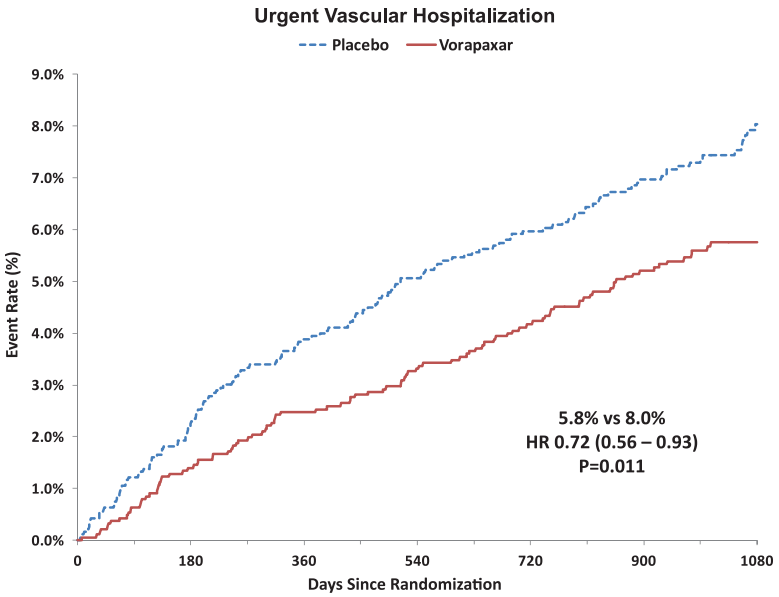


**Figure 3.** Kaplan-Meier rates for urgent hospitalization for vascular cause of an ischemic nature stratified by treatment allocation in the peripheral artery disease cohort. HR indicates hazard ratio.

and increased the risk of bleeding; however, vorapaxar significantly reduced hospitalization for acute limb ischemia and peripheral revascularization. These findings highlight a potential therapeutic approach to reduce acute limb ischemia and the need for peripheral revascularization in patients with symptomatic PAD.

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## Disclosures

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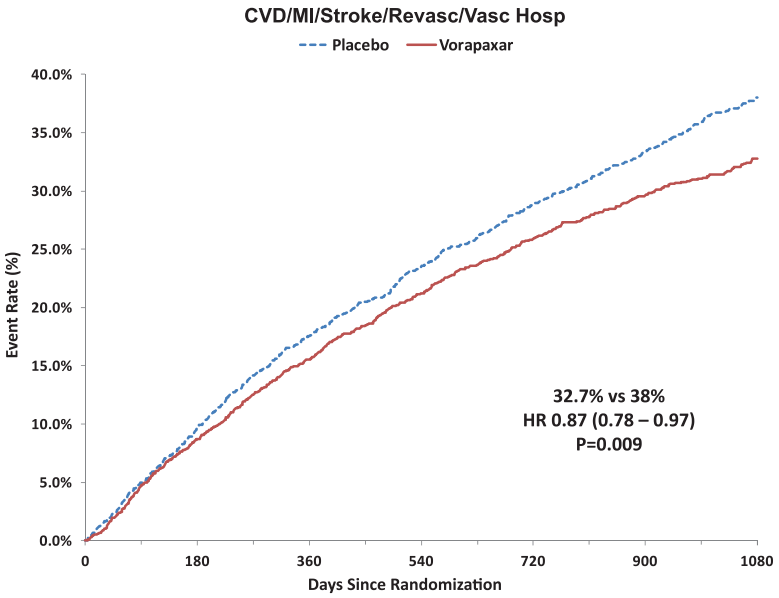


**Figure 4.** Kaplan-Meier rates for the composite of cardiovascular death, myocardial infarction, stroke, revascularization, or urgent hospitalization for vascular cause of an ischemic nature stratified by treatment allocation in the peripheral artery disease cohort. HR indicates hazard ratio.

Laboratory, Merck, Novartis, Roche Diagnostics, and Servier. J.M. Lamp reports no conflicts.

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## CLINICAL PERSPECTIVE

Patients with symptomatic peripheral artery disease are at risk of systemic atherothrombotic events, including cardiovascular death, myocardial infarction, and stroke. In addition, these patients are at a heightened risk of limb vascular events, including acute and chronic limb ischemia and the need for peripheral revascularization. Vorapaxar is a novel antagonist of protease-activated receptor-1, the primary receptor for thrombin on human platelets that is also present on vascular endothelium and smooth muscle. The peripheral artery disease cohort of the Preventing Heart Attack and Stroke in Patients With Atherosclerosis (TRA2°P-TIMI 50) trial evaluated the efficacy and safety of vorapaxar in addition to standard antiplatelet therapy in patients with symptomatic peripheral artery disease. Overall, treatment with vorapaxar resulted in a numeric reduction in cardiovascular death, myocardial infarction, or stroke that did not reach statistical significance. Rates of limb vascular events were frequent in this cohort, including a placebo rate of 3.9% for acute limb ischemia and 22.2% for peripheral revascularization over 3 years. Vorapaxar significantly lowered the rates of hospitalization for acute limb ischemia (2.3% versus 3.9%; hazard ratio, 0.58; 95% confidence interval, 0.39–0.86; $P$=0.006) and peripheral artery revascularization (18.4% versus 22.2%; hazard ratio, 0.84; 95% confidence interval, 0.73–0.97; $P$=0.017). Bleeding occurred more frequently with vorapaxar compared with placebo.

# Vorapaxar in Patients with Peripheral Artery Disease:

# Results from TRA2°P-TIMI 50

## ONLINE SUPPLEMENT

Definition of Urgent Hospitalization for Vascular Cause of an Ischemic Nature

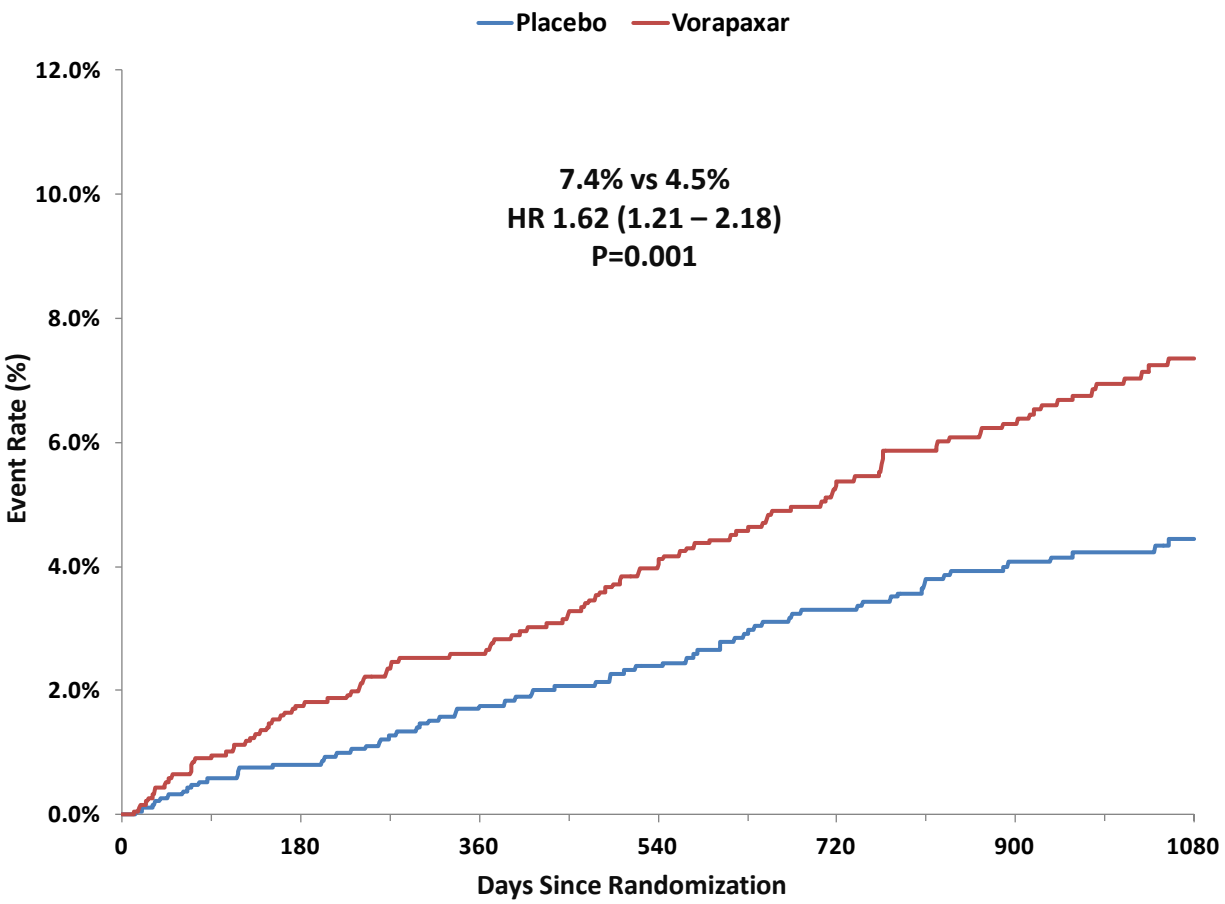
This is defined as any unplanned hospitalization for a new coronary, cerebrovascular or peripheral arterial ischemic event. This definition includes patients with:

1. hospitalization for myocardial ischemia (as defined in CEC charter)
2. hospitalization for transient ischemic attack, defined by:
    a. an acute focal neurological deficit ending lasting <24 hours, and not due to an identifiable non-vascular cause (ie brain tumor, trauma), and
    b. absence of new infarct on brain imaging (if obtained)
3. hospitalization for acute limb ischemia, including acute ischemia caused by arterial emboli, arterial thrombosis, or arterial trauma from a vascular procedure with
    a. Clinical history suggesting a rapid or sudden decrease in limb perfusion, AND
    b. New pulse deficit with associated rest pain, pallor, parasthesias, or paralysis OR
    c. Confirmation of arterial obstruction by imaging (including ultrasound, CT, MRI, or conventional angiography), surgical findings, or pathology

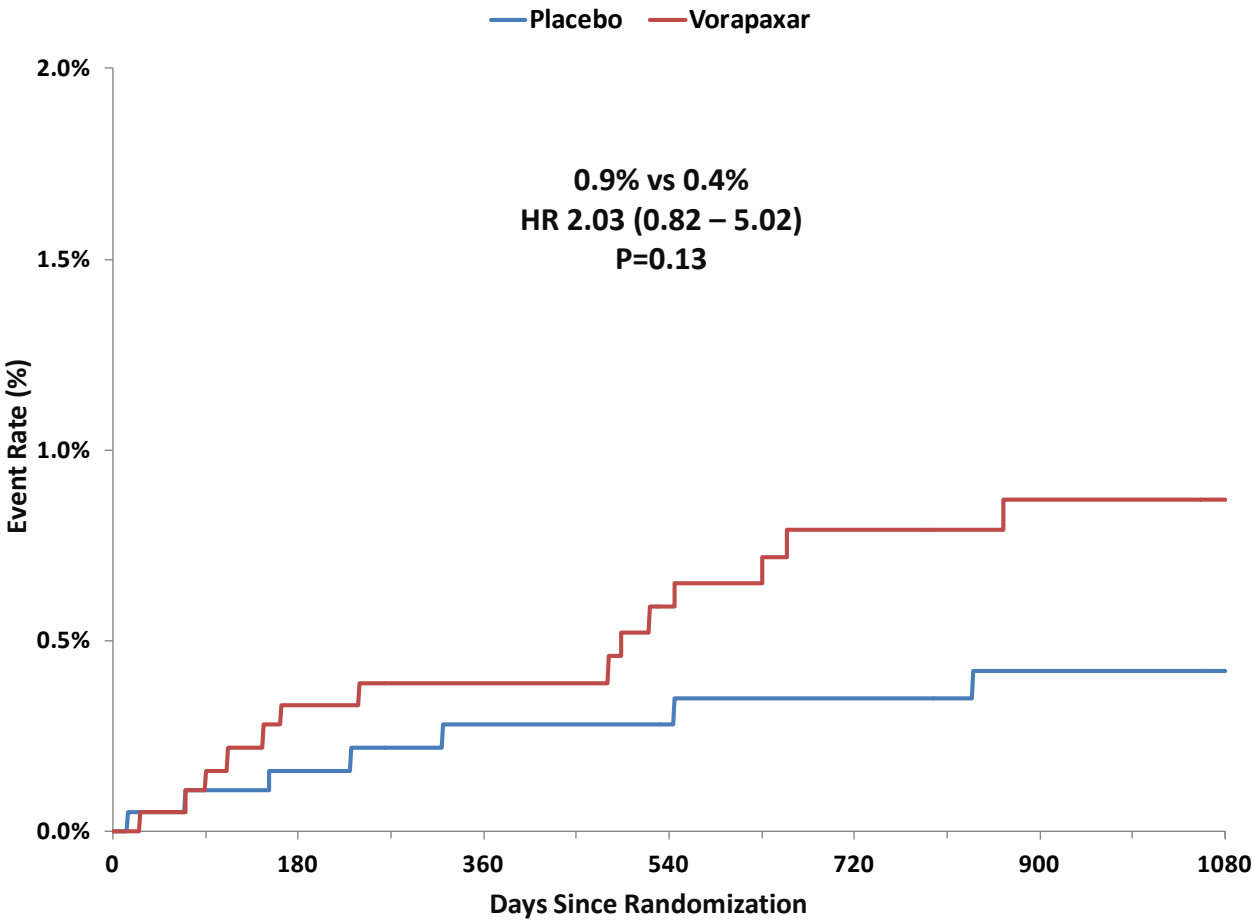
Table 1. Individual Efficacy Components

| End Point | Vorapaxar N=1892 | Placebo N=1895 | Hazard Ratio (95% CI) | P Value |
|---|---|---|---|---|
| *Number (%)* | | | | |
| ***Efficacy Components*** | | | | |
| CV Death | 88 (4.7) | 98 (5.4) | 0.89 (0.67 – 1.19) | 0.45 |
| All-cause Mortality | 172 (8.9) | 191 (9.9) | 0.90 (0.73 – 1.10) | 0.30 |
| MI | 99 (5.5) | 100 (5.6) | 0.99 (0.75 – 1.30) | 0.93 |
| All Stroke | 56 (3.2) | 55 (3.1) | 1.01 (0.70 – 1.47) | 0.95 |
| Ischemic Stroke | 43 (2.4) | 48 (2.7) | 0.89 (0.59 – 1.34) | 0.58 |

Supplemental Figure 1. GUSTO Moderate or Severe Bleeding



Supplemental Figure 2. Intracranial Hemorrhage



Supplemental Figure 3. Fatal Bleeding