New Ischemic Stroke and Outcomes With Vorapaxar Versus Placebo

Results From the TRA 2°P-TIMI 50 Trial

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ABSTRACT

BACKGROUND Vorapaxar, a novel antiplatelet therapy, reduces thrombotic events in patients with a history of myocardial infarction (MI) or peripheral artery disease (PAD); however, because of an increased risk of intracranial hemorrhage, it is contraindicated in patients with a history of stroke.

OBJECTIVES The aim of this study was to investigate the incidence of new ischemic stroke and subsequent death or intracerebral hemorrhage in patients with MI or PAD and no cerebrovascular disease (CVD) treated with vorapaxar.

METHODS The TRA 2°P-TIMI 50 (Trial to Assess the Effects of Vorapaxar in Preventing Heart Attack and Stroke in Patients With Atherosclerosis-Thrombolysis In Myocardial Infarction 50) was a randomized, double-blind, placebo-controlled trial of vorapaxar 2.5 mg daily in 26,449 patients with atherosclerosis, stratified by qualifying disease (MI, PAD, or CVD). A total of 20,170 patients with MI/PAD, but no CVD, were enrolled.

RESULTS In patients with MI/PAD and no prior stroke or transient ischemic attack, vorapaxar reduced first ischemic stroke (hazard ratio [HR]: 0.57, 95% confidence interval [CI]: 0.49 to 0.67; p = 0.001). The risk of hemorrhagic conversion after stroke (HR: 1.19, 95% CI: 0.95 to 1.49; p = 0.14) or death (HR: 1.09, 95% CI: 0.61 to 1.97; p = 0.79) during follow-up was not significantly increased with vorapaxar in patients who had a new ischemic stroke (n = 204). Although hemorrhagic stroke was increased (HR: 2.79, 95% CI: 1.00 to 7.73; p = 0.049), overall stroke was significantly reduced (HR: 0.67, 95% CI: 0.52 to 0.87; p = 0.002).

CONCLUSIONS Vorapaxar reduces ischemic stroke in patients with MI or PAD and no known CVD. There does not appear to be a significant increase in the risk of hemorrhagic conversion or death in patients who experienced a first ischemic stroke on vorapaxar. Although primary hemorrhagic stroke is increased, vorapaxar reduces the total incidence of stroke. (Trial to Assess the Effects of Vorapaxar (SCH 530348; MK-5348) in Preventing Heart Attack and Stroke in Patients With Atherosclerosis [TRA 2°P-TIMI 50]; NCT00526474) (J Am Coll Cardiol 2014;64:2318-26) © 2014 by the American College of Cardiology Foundation.
Vorapaxar is a novel thrombin receptor antagonist that has potent antiplatelet effects and reduces atherothrombotic events in patients with stable atherosclerotic vascular disease (1). This benefit is balanced against an increased risk of bleeding, including a risk of intracranial hemorrhage that is highest in patients with a prior stroke or transient ischemic attack (TIA) (1,2). A similar heterogeneous response by symptomatic vascular territory was observed with other potent antiplatelet agents and is reflected in current guidelines for patients with cerebrovascular disease (CVD) (3-8). Vorapaxar was recommended for approval for clinical use in the United States in patients with prior myocardial infarction (MI) or peripheral artery disease (PAD), but no prior stroke or TIA (9). Because this population is at a heightened risk of a first ischemic stroke, and any such event occurring on vorapaxar could expose a patient to an increased risk of harm, understanding the incidence of stroke and subsequent outcomes with vorapaxar in this population will be important to clinicians (5,10,11).

The TRA 2-P-TIMI 50 (Trial to Assess the Effects of Vorapaxar in Preventing Heart Attack and Stroke in Patients With Atherosclerosis-Thrombolysis In Myocardial Infarction 50) studied vorapaxar for secondary prevention of atherothrombosis in patients with stable atherosclerosis, including prior MI, symptomatic PAD, or ischemic stroke (1,12). We previously characterized the risks of intracranial hemorrhage and total stroke in the overall population and in the key subgroup of patients who qualified for the trial with prior MI, including those with a comitant history of CVD (13).

The present report is, therefore, focused on the key clinical issue of the incidence of first stroke and associated outcomes in patients with history of MI or PAD, and no history of CVD, who are treated with vorapaxar in addition to standard antiplatelet therapy. Because antiplatelet therapy has directionally opposite effects on ischemic stroke versus primary hemorrhagic stroke, we now discriminate between the occurrences of these forms of stroke and provide an analysis of their functional severity.

**METHODS**

**STUDY POPULATION AND PROCEDURES.** TRA 2-P-TIMI 50 (Trial to Assess the Effects of Vorapaxar in Preventing Heart Attack and Stroke in Patients With Atherosclerosis) was a multinational, randomized, double-blind, placebo-controlled trial among 26,449 subjects with stable atherosclerotic vascular disease manifest by prior MI, PAD, or ischemic stroke (12). Details of the trial design were previously reported (1,12). Participants entering the trial with a prior MI or PAD and without a history of prior CVD, defined as prior stroke or TIA, are the basis for the present study. Patients with MI qualified on the basis of a history of spontaneous MI occurring 2 weeks to 12 months before randomization (1). Patients with PAD qualified by a history of intermittent claudication in conjunction with an ankle-brachial index <0.85 or previous revascularization for limb ischemia. Randomization was stratified according to the qualifying diagnosis (12). Patients were ineligible if they had a planned revascularization, a history of a bleeding diathesis, were receiving vitamin K antagonist therapy, or had a history of intracranial bleeding (12).

Eligible patients were randomized in a 1:1 fashion to receive vorapaxar 2.5 mg daily or matching placebo. After the data safety monitoring board’s recommendation, the protocol was amended to discontinue the study drug in patients with a history of stroke or at the time of an occurrence of a new stroke during the trial (1,12). Randomization was stratified both by qualifying disease state and by the pre-randomization variable of planned thienopyridine use (12).

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**ABBREVIATIONS AND ACRONYMS**

- **CI** = confidence interval
- **CVD** = cerebrovascular disease
- **DAPT** = dual antiplatelet therapy
- **HR** = hazard ratio
- **MI** = myocardial infarction
- **MRS** = modified Rankin Scale
- **PAD** = peripheral artery disease
- **TIA** = transient ischemic attack

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ENDPOINTS. The primary efficacy and safety definitions, as well as the main trial results, were previously described (1). Stroke was a pre-specified component of the overall trial primary endpoint. A stroke endpoint was defined as the new onset of focal neurological symptoms lasting more than 24 h or evidence of new infarct on brain imaging, even if symptoms were <24 h in duration (12). Stroke events were further classified as ischemic or primary hemorrhagic. Ischemic strokes associated with hemorrhagic conversion were also identified. Non-hemorrhagic infarction with hemorrhagic conversion was defined as evidence of cerebral infarction, with blood felt to represent hemorrhagic conversion, and not a primary hemorrhage, on the basis of location and imaging characteristics. Microhemorrhage evident on magnetic resonance imaging, whether in the cortex or deep brain structures, was not considered to meet the definition of hemorrhagic conversion. All potential stroke events were adjudicated by a clinical events committee comprised of neurology specialists blinded to treatment allocation (12).

CLINICAL ASSESSMENT. Site investigators were trained in the assessment of disability after stroke using the modified Rankin Scale (MRS). Investigators were instructed to complete an assessment at baseline,

### TABLE 1 Baseline Characteristics (Randomized Treatment Allocation)

<table>
<thead>
<tr>
<th></th>
<th>Vorapaxar (n = 10,080)</th>
<th>Placebo (n = 10,090)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>60 (52–67)</td>
<td>60 (52–67)</td>
<td>0.90</td>
</tr>
<tr>
<td>Female</td>
<td>2,204 (22)</td>
<td>2,165 (21)</td>
<td>0.48</td>
</tr>
<tr>
<td>White race</td>
<td>8,939 (89)</td>
<td>8,924 (88)</td>
<td>0.54</td>
</tr>
<tr>
<td>Weight &lt; 60 kg</td>
<td>597 (6)</td>
<td>580 (6)</td>
<td>0.61</td>
</tr>
<tr>
<td><strong>Clinical characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2,385 (24)</td>
<td>2,377 (24)</td>
<td>0.86</td>
</tr>
<tr>
<td>Hypertension</td>
<td>6,520 (65)</td>
<td>6,564 (65)</td>
<td>0.57</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>8,554 (85)</td>
<td>8,573 (85)</td>
<td>0.85</td>
</tr>
<tr>
<td>Current smoker</td>
<td>2,143 (21)</td>
<td>2,214 (22)</td>
<td>0.24</td>
</tr>
<tr>
<td>Any coronary artery disease</td>
<td>9,341 (93)</td>
<td>9,377 (93)</td>
<td>0.44</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>2,313 (23)</td>
<td>2,364 (23)</td>
<td>0.42</td>
</tr>
<tr>
<td>CrCl at baseline &lt; 60 ml/min</td>
<td>1,186 (12)</td>
<td>1,131 (11)</td>
<td>0.21</td>
</tr>
<tr>
<td>Carotid revascularization</td>
<td>191 (2)</td>
<td>169 (2)</td>
<td>0.24</td>
</tr>
<tr>
<td>Coronary revascularization</td>
<td>7,953 (79)</td>
<td>7,954 (79)</td>
<td>0.91</td>
</tr>
<tr>
<td>Peripheral arterial revascularization</td>
<td>1,171 (12)</td>
<td>1,199 (12)</td>
<td>0.56</td>
</tr>
<tr>
<td><strong>Baseline medical therapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No antiplatelet therapy</td>
<td>77 (1)</td>
<td>102 (1)</td>
<td>0.061</td>
</tr>
<tr>
<td>Aspirin</td>
<td>9,746 (97)</td>
<td>9,756 (97)</td>
<td>0.99</td>
</tr>
<tr>
<td>Thienopyridine</td>
<td>7,177 (71)</td>
<td>7,215 (72)</td>
<td>0.63</td>
</tr>
<tr>
<td>Aspirin and thienopyridine therapy</td>
<td>6,920 (69)</td>
<td>6,983 (69)</td>
<td>0.39</td>
</tr>
<tr>
<td>ACE inhibitor or ARB</td>
<td>7,584 (75)</td>
<td>7,713 (76)</td>
<td>0.046</td>
</tr>
</tbody>
</table>

Values are median (interquartile range) or n (%).

ACE = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CrCl = creatinine clearance.

Protase-activated receptor 1 (PAR-1) is expressed on platelets, endothelial and vascular smooth muscle cells and is activated by thrombin. Vorapaxar is a PAR-1 antagonist, which blocks thrombin mediated platelet activation and reduces ischemic stroke.

at stroke presentation, at discharge from stroke hospitalization, and for the remainder of follow-up. Scores on the MRS increase with greater disability and range from 0 (no symptoms) to a maximum of 6 (death), with a score of 3 indicating moderate disability (14).

**STATISTICAL METHODS.** Baseline characteristics were compared using the chi-square test for categorical variables and the Wilcoxon rank sum test for continuous variables. The efficacy analyses were performed using a Cox proportional hazards model, with the investigational treatment allocation, qualifying atherosclerosis (MI or PAD), and planned use of a thienopyridine as covariates. The Kaplan-Meier method was used to calculate cumulative event rates at 3 years. Efficacy data were analyzed on an intention-to-treat basis. 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. Outcomes of interest for this analysis after a first ischemic stroke were death and hemorrhagic conversion. Analyses were performed using Stata version 12.1 (Stata Corp., College Station, Texas).

**RESULTS**

**BASELINE CHARACTERISTICS.** A total of 20,170 patients qualified for the trial with MI or PAD and had no history of CVD (Online Figure 1). Median follow-up in this cohort was 31 months, representing over 52,000 patient-years of observation. Their baseline characteristics are shown in Table 1. Background treatment included aspirin in 97%, thienopyridine in 71%, and dual antiplatelet therapy (DAPT) in 69%. Experimental treatment allocation was well balanced (Table 1). There was frequent use of statin therapy (93% in those on vorapaxar and 94% in those on placebo) and angiotensin-converting enzyme inhibitor or angiotensin receptor blocker therapy (76% overall).

**VORAPAXAR AND TOTAL STROKE (ISCHEMIC AND HEMORRHAGIC).** During follow-up, there were 243 new strokes occurring at a median of 507 days following randomization. Median follow-up was 358 days after a first stroke occurring during participation in the trial. The majority of new strokes were ischemic strokes without hemorrhagic conversion (n = 187). Ischemic stroke with hemorrhagic conversion occurred in 20 patients, primary hemorrhagic stroke in 19 patients, and nonclassified stroke in 23 patients. Compared with placebo, vorapaxar led to a significant reduction in new stroke in patients with MI or PAD and no prior stroke or TIA (1.20% vs. 1.65%, hazard ratio [HR]: 0.67, 95% confidence interval [CI]: 0.52 to 0.87; p = 0.002) (Figure 1).

**ISCHEMIC STROKE.** Vorapaxar reduced ischemic stroke (74 vs. 130, 0.88% vs. 1.47%, HR: 0.57, 95% CI: 0.43 – 0.75, P<0.001) (Figure 2).
TABLE 2 Efficacy and Bleeding Endpoints

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Vorapaxar (n = 10,080)</th>
<th>Placebo (n = 10,080)</th>
<th>HR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall efficacy</td>
<td>688 (7.9)</td>
<td>851 (9.5)</td>
<td>0.80 (0.73-0.89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CVD/MI/stroke</td>
<td>69 (0.8)</td>
<td>118 (1.3)</td>
<td>0.58 (0.43-0.78)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GUSTO moderate/severe bleed</td>
<td>14 (0.1)</td>
<td>12 (0.1)</td>
<td>0.67 (0.27-1.63)</td>
<td>0.38</td>
</tr>
<tr>
<td>GUSTO severe bleed†</td>
<td>10 (0.1)</td>
<td>7 (0.1)</td>
<td>1.22 (0.92-1.62)</td>
<td>0.16</td>
</tr>
<tr>
<td>Fatal bleed</td>
<td>17 (0.3)</td>
<td>14 (0.2)</td>
<td>1.23 (0.60-2.49)</td>
<td>0.57</td>
</tr>
</tbody>
</table>

Values are n (%) except as indicated. *Any stroke includes 23 strokes of unknown subtype. **Includes fatal bleeding.

CI = confidence interval; CVD = cardiovascular disease; GUSTO = Global Utilization Of Streptokinase and tPA for Occluded arteries; HR = hazard ratio; MI = myocardial infarction.

therapy and the effect of vorapaxar on the development of ischemic stroke with hemorrhagic conversion (p for interaction = 0.56). In addition, there was no detectable increase in the hazard of death during follow-up after a first ischemic stroke with vorapaxar compared with placebo (HR: 1.09, 95% CI: 0.57 to 2.07; p = 0.79) (Figure 4).

At the time of a first ischemic stroke, 72% (53 of 74) of patients randomized to vorapaxar and 70% (91 of 130) of patients randomized to placebo were on study treatment. When restricting the analysis to those patients taking study treatment at the time of their first ischemic stroke, there was no increase in subsequent hemorrhagic conversion with vorapaxar compared with placebo, whether or not the study drug was stopped within 30 days after the stroke (3 of 20 with vorapaxar vs. 5 of 39 on placebo) or continued for 30 days or longer (3 of 33 with vorapaxar vs. 3 of 52 on placebo).

HEMORRHAGIC STROKE. When considering all patients with MI or PAD and no prior stroke or TIA, the rate of ischemic stroke with hemorrhagic conversion was similar with vorapaxar compared with placebo (0.10% with vorapaxar vs. 0.14% with placebo, HR: 0.67, 95% CI: 0.27 to 1.63; p = 0.38) (Table 2, Figure 3). Primary hemorrhagic stroke was increased with vorapaxar (0.17% vs. 0.06%, HR: 2.79; 95% CI: 1.00 to 7.74; p = 0.049) (Table 2, Figure 3). Rates of fatal bleeding of any kind (0.3% vs. 0.2%; p = 0.57) were similar with vorapaxar compared with placebo (Table 2).

These findings with respect to new ischemic stroke were similar among patients who entered the trial on the basis of MI or PAD (Table 3). In particular, among patients who qualified with prior MI, vorapaxar reduced the risk of any stroke by 38% and of ischemic stroke by 49% (Table 3). In patients enrolled with MI who we previously identified as at particularly low risk for bleeding complications (age <75 years, weight ≥60 kg, no history of stroke or TIA; n = 14,909) (10), vorapaxar reduced the occurrence of any stroke by 40% and ischemic stroke by 53% (Online Table 1).

OUTCOMES AFTER ISCHEMIC STROKE. In those patients who experienced a first ischemic stroke during the trial, there was no significant increase in the hazard of hemorrhagic conversion with vorapaxar compared with placebo (8 of 66 with vorapaxar vs. 12 of 118 with placebo, HR: 1.19, 95% CI: 0.49 to 2.91; p = 0.70). Moreover, there was no statistically significant interaction between planned thienopyridine

![Figure 3 - First Strokes Occurring During Follow-Up by Stroke Type and Treatment Allocation](image-url)
**MRS AFTER STROKE WITH VORAPAXAR.** In patients who experienced an ischemic stroke during trial follow-up, there was no difference in the mean MRS after stroke (90 days or last observation carried forward) with vorapaxar versus placebo (2.7 vs. 2.3; p = 0.21). The overall reduction in ischemic stroke was similar across all MRS categories (Figure 5A), and was consistent for ischemic stroke with and without hemorrhagic conversion (Online Figures 2 and 3). The hazard of a moderate-to-severely disabling ischemic stroke of any kind was reduced with vorapaxar, both for nonfatal events (MRS 3 to 5, HR: 0.51 95% CI: 0.30 to 0.87; p = 0.013) and for all events, including fatal strokes (MRS 3 to 6, HR: 0.55 95% CI: 0.35 to 0.87; p = 0.011) (Online Figure 4). Hemorrhagic stroke was increased with vorapaxar across MRS, including those that were fatal (score of 6) (Online Figure 5).

When evaluating all strokes (ischemic and hemorrhagic), vorapaxar reduced stroke across MRS categories, with the exception of a greater number of fatal strokes (MRS 6) with vorapaxar (20 vs. 15) (Figure 5B). The hazard of a moderately to severely disabling nonfatal stroke was reduced with vorapaxar (MRS 3 to 5, HR: 0.51 95% CI: 0.30 to 0.87; p = 0.013), with a consistent trend when including fatal events (MRS 3 to 6, HR: 0.73 95% CI: 0.50 to 1.08; p = 0.11) (Online Figure 5).

**INFLUENCE OF BACKGROUND THIENOPYRIDINE THERAPY.** The majority of patients receiving a thienopyridine were also administered aspirin as DAPT (Table 1). The reduction in a new stroke of any kind with vorapaxar compared with placebo was similar in both patients planned for thienopyridine therapy (n = 13,452, HR: 0.65, 95% CI: 0.46 to 0.93; p = 0.018), as well as those not planned for thienopyridine therapy (n = 6,718, HR: 0.70, 95% CI: 0.48 to 1.01; p = 0.022; p for interaction = 0.79) (Figure 6). Findings were similar for new ischemic stroke (planned thienopyridine therapy HR: 0.54, 95% CI: 0.37 to 0.80; p = 0.002 vs. no planned thienopyridine therapy HR: 0.60, 95% CI: 0.39 to 0.91; p = 0.016; p for interaction = 0.75) (Figure 6). Vorapaxar was associated with increased rates of hemorrhagic stroke, regardless of background thienopyridine (Online Figure 4).

**DISCUSSION**

Vorapaxar significantly reduced the risk of stroke in patients with a history of MI or PAD and no prior history of stroke or TIA, the patient group approved for use by the U.S. Food and Drug Administration (Central Illustration). This benefit with vorapaxar was mediated through a significant reduction in ischemic stroke, which represented the majority of new strokes occurring in this cohort (84%). Vorapaxar increased the risk of primary hemorrhagic stroke; however, due to the infrequency of this event relative to ischemic stroke, the overall incidence of stroke was reduced. Importantly, in patients who experienced a first ischemic stroke while taking vorapaxar, there was no significant increase in the risk of hemorrhagic conversion or death during follow-up. The reduction in ischemic stroke was consistent across MRS, including severely disabling and fatal events.

**ANTIPLATELET THERAPY AND STROKE.** New treatments that prevent stroke are needed (15). Stroke is the leading cause of long-term disability in the United States, with about a quarter of patients who

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**TABLE 3** Vorapaxar Compared With Placebo for Stroke by Qualifying Disease State

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>MI (n = 16,897)</th>
<th>PAD (n = 3,273)</th>
<th>p Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any stroke</td>
<td>0.62 (0.45-0.85)</td>
<td>0.80 (0.51-1.25)</td>
<td>0.35</td>
</tr>
<tr>
<td>All ischemic stroke</td>
<td>0.51 (0.36-0.72)</td>
<td>0.71 (0.44-1.14)</td>
<td>0.28</td>
</tr>
<tr>
<td>Ischemic stroke without hemorrhagic conversion</td>
<td>0.51 (0.35-0.74)</td>
<td>0.76 (0.46-1.25)</td>
<td>0.21</td>
</tr>
<tr>
<td>Ischemic stroke with hemorrhagic conversion</td>
<td>0.75 (0.26-2.16)</td>
<td>0.51 (0.093-2.76)</td>
<td>0.70</td>
</tr>
</tbody>
</table>

Values are HR (95% CI). HR = hazard ratio; PAD = peripheral artery disease; other abbreviations in Table 2.
experience a stroke remaining institutionalized 6 months after the event (11). Every year, 15 million people worldwide experience a stroke (16), with the majority being ischemic strokes (83%) (11). Although the strongest predictor of ischemic stroke is prior stroke, the majority of strokes each year occur in patients with no history of prior stroke (77%) because of the prevalence of other risk factors, such as established atherosclerotic vascular disease (11). It is recognized that patients with coronary artery disease and PAD are at a heightened risk of a first stroke, and account for a significant proportion of patients presenting each year with a new stroke (11,17).

The accumulated evidence regarding antiplatelet therapy to reduce the risk of stroke suggested a complicated balance between its potential benefits for primary stroke prevention and its potential for harm because of excess bleeding with high-intensity regimens for secondary stroke prevention (4,7,18). Meta-analyses by the Antithrombotic Trialists’ Collaboration showed a >20% reduction in stroke in high-risk patients with antiplatelet monotherapy, supporting this strategy for both primary and secondary stroke prevention (18,19). The efficacy of monotherapy with clopidogrel compared with aspirin was investigated in the CAPRIE (Clopidogrel Versus Aspirin in Patients at Risk of Ischaemic
Events) trial, which showed a numeric, but not statistically significant, reduction in ischemic stroke with clopidogrel, primarily in those patients who qualified for the trial with stroke, rather than with MI or PAD (20). Although DAPT with aspirin and clopidogrel appeared potentially effective for the reduction of all stroke and ischemic stroke in a post hoc analysis of the CHARISMA (Clopidogrel for High Atherothrombotic Risk, Ischemic Stabilization, Management, and Avoidance) trial, in several large dedicated trials of long-term secondary stroke prevention, DAPT showed either lack of benefit or overall harm in multiple well-powered studies (2-4,7,8).

This complicated balance may stem from the heterogeneous etiologies of stroke events (e.g., cardioembolic, lacunar, hemorrhagic, or atherothrombotic) and whether all causes of ischemic stroke are equally modifiable with antiplatelet therapy. Indeed, outcomes with intensive antiplatelet therapy appear to differ among subsets of stroke patients, including harm in patients enrolled in a trial with entry criteria of lacunar stroke, and benefit in a trial of patients enrolled with minor acute ischemic stroke (8,21). It is plausible that antiplatelet therapy would carry the greatest benefit in preventing atherothrombotic strokes, and those at the greatest risk of this stroke subtype are those with established atherosclerotic vascular disease (15).

**FINDINGS WITH VORAPAXAR.** The main results from the TRA 2° P-TIMI 50 trial show a significant reduction in overall ischemic events with vorapaxar when added to background antiplatelet therapy (2) (Central Illustration). On the basis of these results, vorapaxar was recommended for approval in patients with prior MI or symptomatic PAD (9), but because of an excess risk of intracranial hemorrhage, it should not be administered to patients with a history of stroke or TIA. In the present analysis, we described the incidence and subtypes of first stroke in this population, and demonstrated a significant 33% reduction in strokes of any kind and a 43% reduction in ischemic stroke with vorapaxar. This benefit of vorapaxar was on the background of aspirin therapy, and was observed whether or not a thienopyridine was also used. The reduction in ischemic stroke was also consistent at all levels of severity, as measured by MRS. At the same time, vorapaxar increased the risk of primary hemorrhagic stroke, but the frequency was significantly lower than the ischemic stroke frequency, resulting in a significant reduction in all strokes. In addition, we found an overall decreased risk of ischemic stroke with hemorrhagic conversion with vorapaxar compared with placebo, which was due to a significant reduction in ischemic stroke. Importantly, we did not find a significant increase in the risk of hemorrhagic conversion or death in patients who had an ischemic stroke on vorapaxar.

**STUDY LIMITATIONS.** In TRA 2° P-TIMI 50, vorapaxar was studied in addition to background antiplatelet therapy and, therefore, the efficacy and safety of vorapaxar as monotherapy for stroke prevention cannot be evaluated.

**CONCLUSIONS.** In stable patients with atherosclerotic vascular disease and no history of stroke or TIA, chronic therapy with vorapaxar reduces the risk of ischemic stroke. Although primary hemorrhagic stroke was increased with vorapaxar, stroke of any kind was significantly reduced. This benefit of vorapaxar is consistent when given with aspirin or aspirin and a thienopyridine. Patients who suffer a first ischemic stroke on vorapaxar were not at a detectable increased risk of subsequent intracranial hemorrhage or death when vorapaxar was discontinued.

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COMPETENCY IN MEDICAL KNOWLEDGE: The risk of first ischemic stroke and subsequent outcomes in patients with stable atherothrombotic vascular disease (history of myocardial infarction or symptomatic peripheral artery disease) and no history of stroke or transient ischemic attack treated with the recently approved novel PAR-1 antagonist vorapaxar are unknown. The objectives were to investigate both whether PAR-1 antagonism modifies the risk of ischemic stroke and whether patients who experience a first ischemic stroke on vorapaxar are at increased risk of hemorrhagic conversion or death. PAR-1 antagonism with vorapaxar significantly reduced all strokes in this population by 33% and ischemic stroke by 43%. No statistically significant increase in the risk of hemorrhagic conversion or death was observed with vorapaxar when the agent was stopped after a first ischemic stroke.

REFERENCES


KEY WORDS antiplatelet therapy, intracranial hemorrhage, PAR-1, platelet aggregation inhibitors, secondary prevention, thrombin receptor

APPENDIX For a supplemental table and figures, please see the online version of this article.