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EDITORIAL COMMENT

Vorapaxar, Combination Antiplatelet Therapy, and Stroke*

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Drugs that inhibit platelet activation and aggregation reduce vascular events, notably myocardial infarction (MI) and ischemic stroke, and are generally associated with low rates of bleeding (1). Available agents inhibit platelets via distinct mechanisms (**Table 1**) (2), and combining antiplatelet drugs with different mechanisms of action should enhance net antithrombotic activity. For over a decade, the standard of care in patients with acute coronary syndromes, particularly those undergoing coronary stent implantation, has been dual antiplatelet therapy with aspirin plus an adenosine diphosphate receptor antagonist. When administered to selected patients with acute brain ischemia, a 21-day course of dual antiplatelet therapy with aspirin and clopidogrel reduced the ischemic stroke risk compared with aspirin alone (3). However, there is a price to pay with dual antiplatelet therapy: the lower risk of ischemic events cannot be dissociated from an increased bleeding risk, and, ironically, the most lethal toxicity of dual antiplatelet therapy for prevention of ischemic stroke is an increase in hemorrhagic stroke (4–6).

In contrast to the advantage of dual antiplatelet therapy in patients with acute coronary syndromes, particularly those with potentially thrombogenic coronary stents, the net clinical benefit of combination antiplatelet therapy in patients with stable atherosclerotic vascular disease is less clear. In available trials, unexpected patient subgroups appear to benefit or not in complicated, sometimes confusing ways (7,8). Compounding this conundrum are subgroup results from the large, double-blind 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), which compared vorapaxar with placebo in 26,449 patients with recent myocardial infarction (MI) (66% of participants), recent ischemic stroke (18%), or peripheral arterial disease (PAD) (14%) on a background of single (40% of participants, usually taking aspirin) or dual antiplatelet therapy (60% of participants, taking aspirin plus a thienopyridine) (9).

Vorapaxar is a potent oral inhibitor of protease-activated receptor (PAR)-1, the predominant thrombin receptor on platelets. Vorapaxar is U.S. Food and Drug Administration approved for reducing the risk of MI, stroke, cardiovascular death, and the need for revascularization in patients with a history of MI or PAD (10).

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In this issue of the *Journal*, Bonaca et al. (11,12) present 2 subgroup analyses of TRA°2P-TIMI 50. The first analysis reports substantially reduced ischemic stroke with vorapaxar compared with placebo (hazard ratio [HR]: 0.57, 95% confidence interval [CI]: 0.43 to 0.75; $p < 0.001$) in participants without prior stroke or transient ischemic attack (TIA), most of whom (69%) were already receiving dual antiplatelet therapy with aspirin and a thienopyridine (11). The second analysis reports reduced incidence of coronary stent thrombosis when vorapaxar was added to standard antiplatelet therapy (12). During the main trial, treatment of participants with a history

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TABLE 1 Categories of Oral Antiplatelet Drugs According to Mechanism of Platelet Inhibition*

Mechanism	Agent(s)	Comments
Thromboxane A2 inhibition	Aspirin	Irreversible acetylation of cyclooxygenase-1
Thromboxane-prostaglandin receptor antagonism	Terutroban	Reversible inhibitor of platelet activation by thromboxane A2 and prostaglandin intermediates.
Irreversible $P2Y_{12}$ blockade	Clopidogrel and prasugrel	Active metabolites irreversibly inhibit $P2Y_{12}$
Reversible $P2Y_{12}$ blockade	Ticagrelor	Binds reversibly to $P2Y_{12}$; additional adenosine-like effects
Phosphodiesterase inhibition	Dipyridamole and cilostazol	Additional vasodilatory effects
PAR-1 antagonism	Vorapaxar and atopaxar	Long-acting PAR-1 inhibition

*Antiplatelet agents used clinically to prevent thrombosis.

of ischemic stroke was terminated early because of a higher intracranial hemorrhage rate (HR: 2.6; $p < 0.001$) among those assigned vorapaxar (9). A similar increase in hemorrhagic stroke was evident in patients without a history of ischemic stroke or TIA (HR: 2.8; $p = 0.05$) given vorapaxar (11), but the absolute rate of intracranial bleeding was over 10-fold higher in those with prior ischemic stroke, regardless of assigned therapy. These findings are not surprising in a trial in which at least one-half of previous ischemic strokes were of presumed lacunar origin and without special attention to blood pressure control (13,14).

To us, the most remarkable subgroup result of TRA°2P-TIMI 50 was vorapaxar's failure to reduce recurrent ischemic stroke among participants with prior ischemic stroke. There were 137 ischemic strokes in those randomized to vorapaxar versus 140 in the placebo group (HR: 0.99, 95% CI: 0.78 to 1.25) (13), contrasting sharply with the results for participants without prior ischemic stroke or TIA (11). What accounts for this difference? Among those with prior ischemic stroke as the qualifying event, 27% were receiving dual antiplatelet therapy in addition to voraxapar or placebo, in contrast to 69% of other participants. Treatment with triple instead of dual antiplatelet therapy (including vorapaxar) is unlikely to account for the lack of effect on ischemic stroke. Could PAR-1 inhibition be more effective for primary than secondary prevention? Although possible, this is an unlikely explanation. The type of stroke seems a more plausible explanation for these findings. In a cohort with a high prevalence of previous lacunar strokes, recurrent strokes are overwhelmingly likely to have lacunar mechanisms, and lacunar ischemic stroke may be less responsive to dual antiplatelet therapy (4,5). In those without prior ischemic stroke or TIA, who had clinical manifestations of atherosclerosis, vorapaxar prevented ischemic strokes, with only a minority likely to be lacunar. To verify this possibility, and to better understand the underlying mechanisms, more information is needed about the proportion of lacunar and nonlacunar ischemic strokes. Such details about ischemic stroke subtypes and associated risk factors are important to identify patients who would benefit most from vorapaxar, considering the risk of hemorrhage associated with this agent.

Treatment with vorapaxar was associated with a lower risk of MI among patients with prior MI (HR: 0.79; $p = 0.003$) (15), and a lower risk of coronary stent thrombosis (12), but there was no decrease in MI among those with prior ischemic stroke or PAD. Do these curious results reflect the play of chance (the bane of multiple subgroup analyses) or provide evidence that vorapaxar's effects extend beyond platelet inhibition? PAR-1 is not only expressed on platelets, but is also found on endothelial and vascular smooth muscle cells, where its activation has mitogenic effects. By inhibiting vascular PAR-1, vorapaxar may attenuate arterial remodeling, contributing to its beneficial effects in reducing late stent thrombosis.

The major disadvantage of vorapaxar is its associated risk of intracranial bleeding, a complication shared with other potent antiplatelet drugs, such as prasugrel and ticagrelor. Does vorapaxar increase the risk of intracranial bleeding more than antiplatelet drugs with other mechanisms of action? The relative risk of intracranial hemorrhage with PAR-1 antagonists added to single or dual antiplatelet therapy is 2.0 (95% CI: 1.5 to 2.7) (16), higher than that for major extracranial hemorrhage with vorapaxar (odds ratio [OR]: about 1.4) or when clopidogrel is added to aspirin monotherapy (OR: 1.12, 95% CI: 0.9 to 1.5) (17). Data regarding vorapaxar and intracranial hemorrhage are derived mainly from 2 trials in which triple antiplatelet therapy was employed, patients with lacunar stroke were overrepresented, and confidence intervals were wide (9,16,18). Oral anticoagulant drugs with different mechanisms of action carry strikingly different risks of intracranial bleeding (19), and further studies are needed to determine whether PAR-1 antagonists are associated with a higher risk of intracranial bleeding than other antiplatelet agents.

The TRA°2P-TIMI 50 trial may have been confounded by the inclusion of patients with prior lacunar stroke who sustained high rates of intracerebral hemorrhage when vorapaxar was added to therapy with 1 or 2 other antiplatelet drugs. Despite this limitation and those inherent to a subgroup analysis

that was not pre-specified, the investigators' conclusion that addition of vorapaxar to background antiplatelet therapies reduces all stroke and ischemic stroke in patients with prior MI or PAD and no history of stroke or TIA appears warranted. It is intriguing that triple antiplatelet therapy reduced ischemic stroke more than dual antiplatelet therapy, an observation that raises the possibility that even 2 antiplatelet agents with differing mechanisms of action provide submaximal protection against ischemic stroke. Like the results of all subsidiary analyses of trials, this finding must be considered exploratory, requiring independent validation before addition of vorapaxar to standard antiplatelet drug therapy for stroke prevention can be recommended with confidence.

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