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# Efficacy and Safety of Vorapaxar as Approved for Clinical Use in the United States

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**Background**—Vorapaxar is a protease-activated receptor-1 antagonist approved by the U.S. Food and Drug Administration (FDA) for the reduction of thrombotic cardiovascular (CV) events in patients with a history of myocardial infarction (MI) and peripheral artery disease (PAD), without a previous stroke or transient ischemic attack (TIA).

**Methods and Results**—We examined the efficacy and safety of vorapaxar in the intended use population, considering 20 170 patients randomized in the multinational, double-blinded, placebo-controlled TRA 2°P-TIMI 50 trial. Of these, 16 897 qualified with a history of MI in the prior 2 weeks to 1 year and 3273 with PAD. At baseline 97% of the patients were treated with aspirin, 71% with a thienopyridine, and 93% a statin. At 3 years, the endpoint of CV death, MI, or stroke was significantly reduced with vorapaxar compared with placebo (7.9% versus 9.5%, HR, 0.80; 95% CI 0.73 to 0.89;  $P<0.001$ ). Vorapaxar also significantly reduced the composite of CV death, MI, stroke, and urgent coronary revascularization (10.1% versus 11.8%, HR, 0.83; 95% CI 0.76 to 0.90;  $P<0.001$ ), as well as the rate of CV death or MI ( $P<0.001$ ). The safety endpoint of GUSTO moderate or severe bleeding, was increased in the vorapaxar group (3.7 versus 2.4, HR, 1.55; 95% CI 1.30 to 1.86,  $P<0.001$ ). Intracranial bleeding (ICH) was 0.6% versus 0.4%,  $P=0.10$  with vorapaxar versus placebo, with fatal bleeding 0.2% versus 0.2%;  $P=0.70$ .

**Conclusions**—In patients with prior MI or PAD who have not had a previous stroke or TIA, vorapaxar added to standard therapy is effective for long-term secondary prevention of thrombotic CV events, while increasing moderate or severe bleeding.

**Clinical Trial Registration**—URL: [clinicaltrials.gov](http://clinicaltrials.gov) Unique Identifier: NCT00526474. (*J Am Heart Assoc.* 2015;4:e001505 doi: 10.1161/JAHA.114.001505)

**Key Words:** antiplatelet therapy • atherosclerosis • myocardial infarction • peripheral arterial disease • secondary prevention • vorapaxar

Vorapaxar is a first-in-class oral protease-activated receptor (PAR)-1 antagonist, which inhibits thrombin-induced platelet activation<sup>1</sup> and is effective in the secondary prevention of atherothrombosis.<sup>2–4</sup> We previously reported the

primary results of the Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events (TRA 2°P)-TIMI 50 trial. Vorapaxar was compared with placebo in patients receiving standard cardiovascular care and found to significantly reduce the occurrence of cardiovascular (CV) death, myocardial infarction (MI), or stroke among 26 449 stable patients with established atherosclerosis, manifested as prior MI, ischemic stroke, or peripheral artery disease (PAD).<sup>2</sup> This improvement in thrombotic outcomes with vorapaxar was accompanied by an increase in the incidence of moderate or severe bleeding and intracranial hemorrhage (ICH)<sup>2</sup>; the latter was increased primarily in patients with prior stroke.<sup>5</sup> For this reason, upon recommendation by the Data and Safety Monitoring Board, study therapy was discontinued during the course of the trial in all patients with a history of stroke.

Based on the results of the trial, in May 2014, the U.S. Food and Drug Administration (FDA) approved vorapaxar for the reduction of thrombotic cardiovascular events in patients with prior MI or with PAD. Because of the above-mentioned

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**Table 1.** Baseline Characteristics

Characteristic	Vorapaxar (N=10 080)	Placebo (N=10 090)
Demographic characteristics		
Age (y), median (25th to 75th percentiles)	60 (52 to 67)	60 (52 to 67)
Age ≥75 years, n (%)	929 (9.2)	925 (9.2)
Female, n (%)	2204 (21.9)	2165 (21.5)
White race, n (%)	8939 (88.7)	8924 (88.5)
Qualifying type of atherosclerosis, n (%)		
Myocardial infarction	8458 (83.9)	8439 (83.6)
Peripheral artery disease	1622 (16.1)	1651 (16.4)
Selected clinical characteristics, n (%)		
Diabetes mellitus	2385 (23.7)	2377 (23.6)
Hypertension	6520 (64.7)	6564 (65.1)
Hyperlipidemia	8554 (84.9)	8573 (85.0)
Current smoker	2143 (21.3)	2214 (21.9)
Prior coronary revascularization	7953 (78.9)	7954 (78.8)
Prior PCI	7125 (70.7)	7153 (70.9)
Prior CABG	1471 (14.6)	1471 (14.6)
Peripheral revascularization	1200 (11.9)	1231 (12.2)
Any established coronary artery disease	9341 (92.7)	9377 (93.0)
Any established peripheral arterial disease	2313 (22.9)	2364 (23.4)
Estimated glomerular filtration rate <60 mL/min per 1.73 m <sup>2</sup>	1476 (14.8)	1383 (13.9)
Concomitant medications, n (%)		
Antiplatelet therapy		
Aspirin	9746 (96.7)	9756 (96.7)
Thienopyridine	7177 (71.2)	7215 (71.5)
ACE inhibitors or ARB	7584 (75.2)	7713 (76.4)
Lipid-lowering medications	9486 (94.1)	9604 (95.2)

ACE indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.

observations, vorapaxar's contraindications include a prior history of stroke or transient ischemic attack (TIA). We have previously reported the findings of TRA 2°P-TIMI 50 among the separate cohorts with MI and with PAD, *inclusive* of

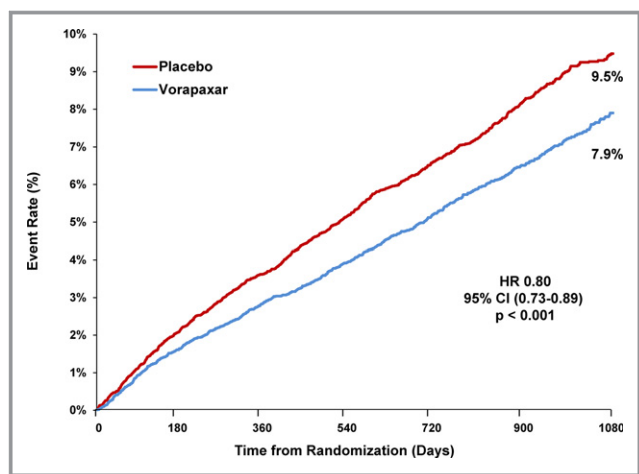
patients with prior stroke or TIA<sup>3-5</sup>; however, the findings in the specific population for whom the FDA approved vorapaxar for clinical use have not been published previously.

**Table 2.** Distribution of CV deaths, MI, and Strokes in Placebo-treated Patients With and Without a History of Stroke/TIA

	KM% at 3 Years		
	MI+PAD Without Prior Stroke/TIA	MI or PAD With Prior Stroke/TIA	All Prior Stroke/TIA*
Number of patients	10 090	683	3129
CV death	2.8	6.4	4.3
MI	6.4	12.9	5.8
Any stroke	1.6	5.4	7.4
Ischemic stroke	1.5	4.3	6.7

CV indicates cardiovascular; KM, Kaplan–Meier failure rates; MI, myocardial infarction; PAD, peripheral artery disease; TIA, transient ischemic attack.

\*Includes patients who qualified for the trial with ischemic stroke.



**Figure 1.** Kaplan–Meier estimated occurrence of CV death, MI, or stroke. CI indicates confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction.

Accordingly, in the present analysis, we report for the first time the efficacy and safety of vorapaxar versus placebo in the large cohort of patients who qualified for TRA 2°P-TIMI 50 with MI or PAD, who had no history of stroke or TIA, and who form the population relevant to the intended clinical use of vorapaxar in the United States.

## Methods

### Study Population

TRA 2°P-TIMI 50 was a multinational, double-blind, randomized, placebo-controlled trial. The design<sup>6</sup> and primary results of the trial have been published.<sup>2</sup> Patients who qualified for the trial on the basis of a history of MI had a history of spontaneous MI within the prior 2 weeks to 12 months and those with symptomatic PAD had a history of intermittent

claudication, in conjunction with either an ankle-brachial index of <0.85 or previous revascularization for limb ischemia.<sup>2</sup> Details of the full eligibility criteria have been reported.<sup>6</sup> The protocol was approved by the relevant ethics committee at all participating centers. Written informed consent was obtained from all patients.

### Study Protocol

Eligible patients were randomly assigned in a 1:1 ratio to receive either vorapaxar sulfate 2.5 mg (vorapaxar 2.08 mg) daily or placebo, stratified according to the qualifying atherosclerosis (previous MI or PAD), and the responsible physician's intent to administer a thienopyridine. All concomitant medical therapy, including the use of other anti-platelet agents, was managed by the responsible clinicians according to local standards of care.

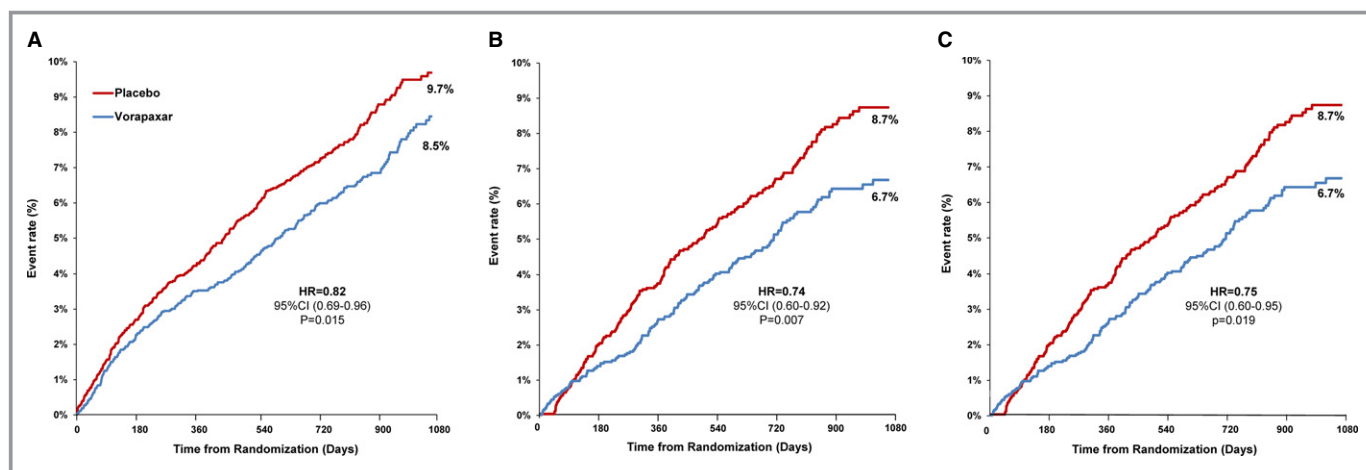
### Endpoints

The composite endpoints of CV death, MI, or stroke, and CV death, MI, stroke, or recurrent ischemia leading to urgent coronary revascularization were tested hierarchically as previously described.<sup>2</sup> The principal safety endpoint 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.<sup>6</sup> Exploratory composite endpoints of net clinical outcome were pre-specified in the Data and Analysis Plan developed by the TIMI Study Group and finalized before database lock. All elements of the composite efficacy endpoints, and bleeding were adjudicated according to standardized definitions by a Clinical Events Committee blinded to treatment allocation.<sup>6</sup>

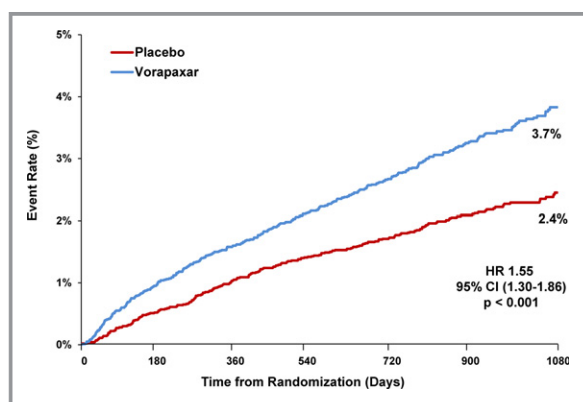
**Table 3.** Efficacy Endpoints at 3 Years

Efficacy Endpoints	Vorapaxar no. (3-Year KM%)	Placebo no. (3-Year KM%)	Hazard Ratio (95% CI)	P Value
Number of patients	10 080	10 090		
CV death, MI, or stroke	688 (7.9)	851 (9.5)	0.80 (0.73 to 0.89)	<0.001
CV death, MI, stroke, or urgent coronary revascularization	896 (10.1)	1073 (11.8)	0.83 (0.76 to 0.90)	<0.001
CV death or MI	626 (7.2)	747 (8.3)	0.83 (0.75 to 0.93)	<0.001
CV death	205 (2.4)	239 (2.8)	0.86 (0.71 to 1.03)	0.11
MI	470 (5.4)	569 (6.4)	0.82 (0.73 to 0.93)	0.002
Any stroke	98 (1.2)	145 (1.6)	0.67 (0.52 to 0.87)	0.002
Ischemic stroke	74 (0.9)	130 (1.5)	0.57 (0.43 to 0.75)	<0.001
Urgent coronary revascularization	249 (2.8)	283 (3.0)	0.88 (0.74 to 1.04)	0.13

CI indicates confidence interval; CV, cardiovascular; KM, Kaplan–Meier failure rates; MI, myocardial infarction.



**Figure 2.** Kaplan–Meier estimates of CV death, MI, or stroke according to time from qualifying MI to randomization; (A) <3 months (N=7456), (B) 3 to 6 months (N=4907), and (C) >6 months (N=4462) in the population with no history of stroke or TIA and a nonmissing date. CI indicates confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction; TIA, transient ischemic attack.



**Figure 3.** Kaplan–Meier estimated occurrence of GUSTO moderate or severe bleeding. CI indicates confidence interval; GUSTO, Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries; HR, hazard ratio.

## Statistical Considerations

All analyses comparing vorapaxar versus placebo for efficacy were conducted on an intent-to-treat basis from randomization to each subject's last visit using a Cox proportional-hazard model, with the investigational treatment allocation, qualifying atherosclerotic disease, and planned use of a thienopyridine as covariates. Event rates are presented as Kaplan–Meier failure rates at 3 years. Safety analyses were performed according to the censoring approach employed by the FDA among patients who received one or more doses of study medication and included events through 30 days after the last dose of study therapy. As for the overall trial population, 23% of patients prematurely discontinued study drug. Only 0.1% patients were lost to any follow-up and 1.9% withdrew consent for follow-up. All randomized subjects in this cohort were included in the intention-to-treat efficacy analysis.

## Results

### Study Participants

A total of 20 170 patients (76% of the overall trial population) were eligible for the present analysis. Of these, 16 897 patients qualified with a history of MI, and 3273 qualified with PAD. Baseline characteristics of the patients are shown in Table 1. At enrollment, 97% of the patients were treated with aspirin and 71% were receiving a thienopyridine, with nearly all (70.5%) receiving clopidogrel. Lipid-lowering medications were administered to 95% of patients, and angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers to 76%. The majority (79%) of the patients had a history of a coronary revascularization prior to randomization. Of those who qualified with PAD, 12% had undergone a peripheral intervention. The median follow-up was 30 months (interquartile range 24 to 36). Table 2 details the distribution of CV deaths, MIs, and strokes in placebo-treated patients with and without a history of stroke/TIA. Patients with cerebrovascular disease were at high CV risk compared with those without a history of stroke/TIA and had a higher burden of recurrent stroke.

### Efficacy Analyses

The 3-year Kaplan–Meier event rate of CV death, MI, or stroke was 7.9% in patients receiving vorapaxar compared with 9.5% in patients receiving placebo (HR, 0.80; 95% CI 0.73 to 0.89;  $P<0.001$ , Figure 1, Table 3). The rate of CV death, MI, stroke, or urgent coronary revascularization was 10.1% in the vorapaxar group, as compared with 11.8% in the placebo group (HR, 0.83; 95% CI 0.76 to 0.90;  $P<0.001$ ). Moreover, CV death or MI was significantly reduced (7.2%

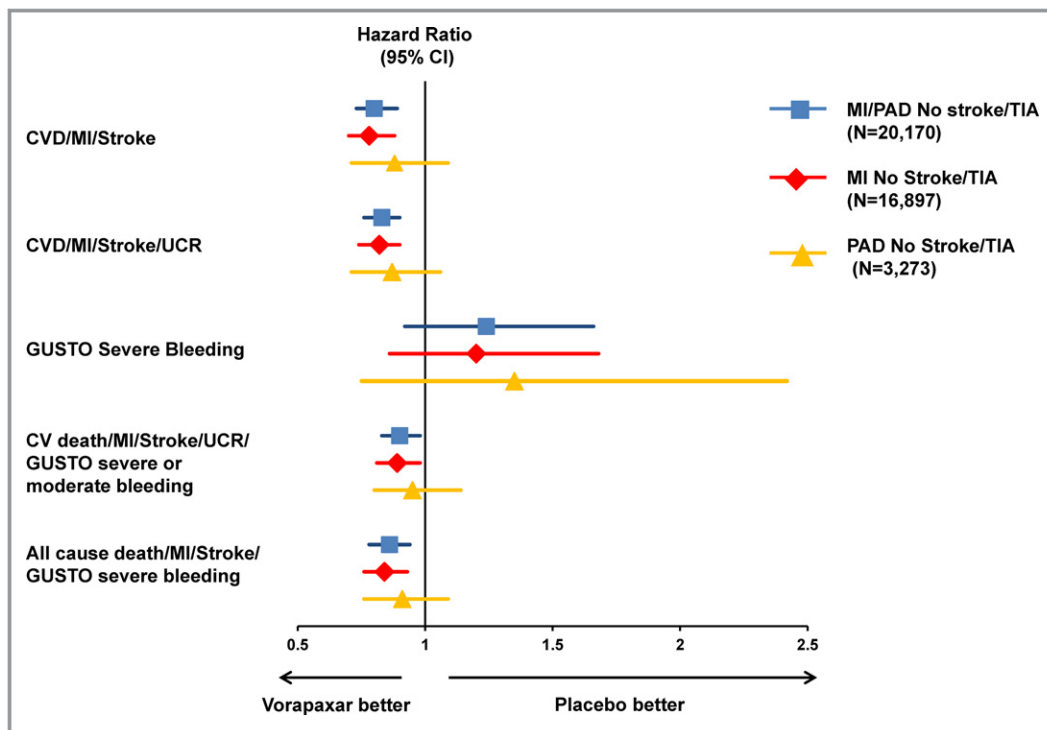
**Table 4.** Safety Endpoints and Net Clinical Outcome at 3 Years

	Vorapaxar no. (3-Year KM%)	Placebo no. (3-Year KM%)	Hazard Ratio (95% CI)	P Value
Number of patients	10 059	10 049		
<b>Safety endpoints</b>				
GUSTO moderate or severe bleeding	303 (3.7)	199 (2.4)	1.55 (1.30 to 1.86)	<0.001
GUSTO severe bleeding	100 (1.3)	82 (1.0)	1.24 (0.92 to 1.66)	0.16
GUSTO moderate	208 (2.6)	119 (1.4)	1.79 (1.43 to 2.24)	<0.001
Fatal bleeding	16 (0.2)	14 (0.2)	1.15 (0.56 to 2.36)	0.70
Intracranial hemorrhage	45 (0.6)	31 (0.4)	1.46 (0.92 to 2.31)	0.10
Death from any cause	382 (4.5)	415 (4.8)	0.92 (0.80 to 1.06)	0.25
<b>Net clinical outcome (prespecified)</b>				
CV death, MI, stroke, urgent coronary revascularization, GUSTO moderate or severe bleeding	1096 (12.2)	1208 (13.3)	0.90 (0.83 to 0.98)	0.015
All-cause death, MI, stroke, GUSTO severe bleeding	902 (10.3)	1046 (11.7)	0.86 (0.79 to 0.94)	<0.001

CI indicates confidence interval; CV, cardiovascular; GUSTO, Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries; KM, Kaplan–Meier failure rates; MI, myocardial infarction.

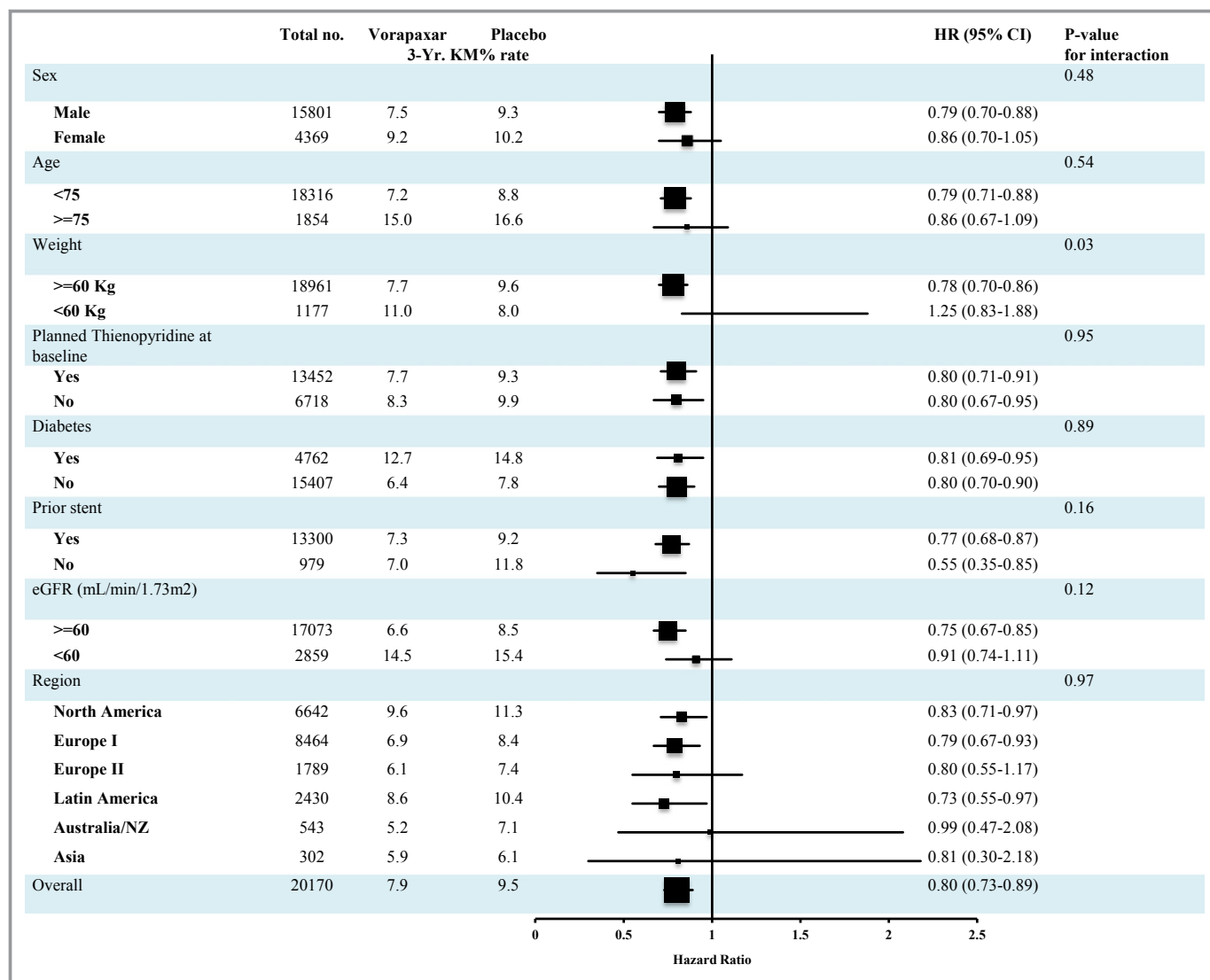
versus 8.3%, HR 0.83, 95% CI 0.75 to 0.93,  $P<0.001$ , Table 3). As well, vorapaxar reduced the rate of MI (5.4% versus 6.4%,  $P<0.001$ ) and stroke (1.2% versus 1.6%,  $P=0.002$ ) individually. Although the rate of CV death was numerically lower in the active treatment group than in the

placebo group (2.4% versus 2.8%), this trend did not achieve statistical significance ( $P=0.11$ , Table 3). The effect of vorapaxar on the risk of CV death, MI, or stroke was similar irrespective of the timing of the qualifying MI relative to randomization (Figure 2).



**Figure 4.** Efficacy, safety, and net clinical outcomes according to the qualifying atherosclerosis (MI or PAD). CI indicates confidence interval; CVD, cardiovascular disease; MI, myocardial infarction; PAD, peripheral artery disease; TIA, transient ischemic attack; UCR, urgent coronary revascularization.





**Figure 5.** CV death, MI, or stroke in major subgroups. CI indicates confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HR, hazard ratio; MI, myocardial infarction.

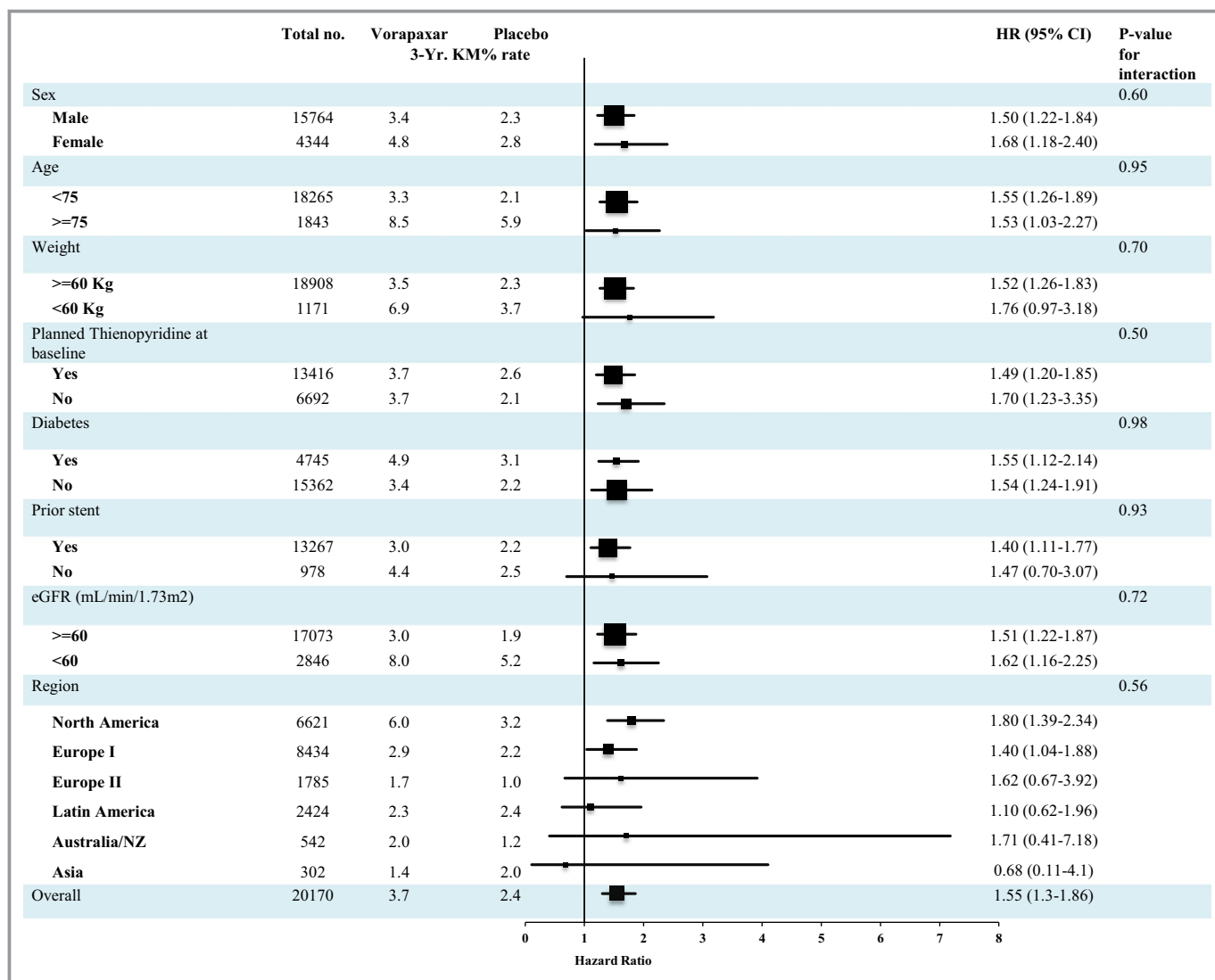
## Safety Endpoints

The rate of combined severe or moderate GUSTO bleeding criteria was 3.7% with vorapaxar and 2.4% in the placebo group (HR, 1.55; 95% CI 1.30 to 1.86,  $P<0.001$ , Figure 3). This difference was driven by an increase of GUSTO moderate bleeding (2.6% versus 1.4%,  $P<0.001$ ). The rate of GUSTO severe bleeding was 1.3% with vorapaxar versus 1.0% with placebo (HR 1.22; 95% CI 0.92 to 1.62,  $P=0.16$ ). The rate of TIMI major bleeding was increased in the vorapaxar group compared with placebo (2.5% versus 1.9%;  $P=0.015$ ), as was TIMI minor bleeding (1.7% versus 0.8%,  $P<0.001$ ). ICH occurred in 0.6% in the vorapaxar group, as compared with 0.4% in the placebo group (HR, 1.46; 95% CI 0.92 to 2.31). The rate of fatal bleeding was 0.2% in both the vorapaxar and placebo groups as shown in Table 4.

## Subgroup Analyses

The efficacy and safety of vorapaxar were consistent in the subgroups defined by qualifying MI or PAD (Figure 4). There was no significant heterogeneity for the benefit of vorapaxar on the rate of CV death, MI, or stroke across most of the major subgroups examined, including those defined according to the use or nonuse of a thienopyridine at the time of randomization.

The efficacy and bleeding risk with vorapaxar were also consistent in the subgroup of patients enrolled in the United States compared with the non-US population, without heterogeneity (all  $P$ -interaction  $>0.1$ ) across any of the major efficacy or safety endpoints examined. However, among the small proportion of patients who weighed  $<60$  kg, the use of vorapaxar did not appear to have a favorable influence on



**Figure 6.** GUSTO moderate or severe bleeding in major subgroups. CI indicates confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; GUSTO, Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries; HR, hazard ratio; MI, myocardial infarction.

major CV events (nominal *P*-interaction=0.03) (Figure 5). There was no evidence of heterogeneity in the effect of vorapaxar on GUSTO moderate or severe bleeding in major subgroups, including weight and age (Figure 6).

### Net Clinical Outcome

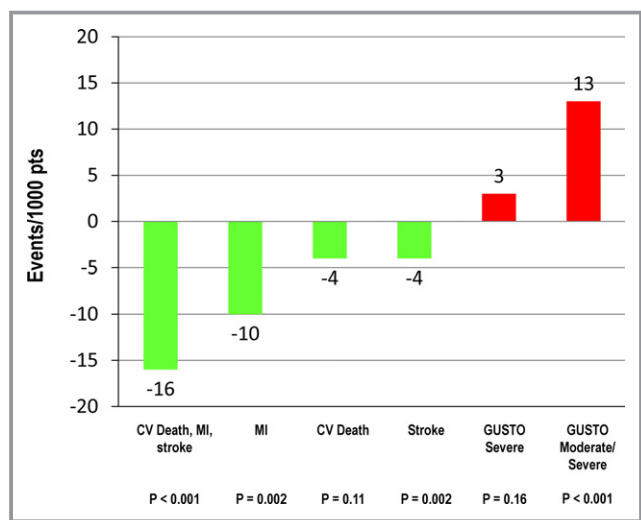
The composite of CV death, MI, stroke, urgent coronary revascularization, or GUSTO moderate or severe bleeding was reduced with vorapaxar compared with placebo (12.2% versus 13.3%; HR 0.90; 95% CI 0.83 to 0.98, *P*=0.015; Table 4). Similarly, the composite of all-cause death, MI, stroke, or GUSTO severe bleeding was influenced favorably by vorapaxar (10.3% versus 11.7%; HR 0.86; 95% CI 0.78 to 0.94, *P*<0.001). Considering major CV outcomes in long-term secondary

prevention, for every 1000 patients treated for 3 years, treatment with vorapaxar resulted in 16 fewer major CV events, at the cost of 3 GUSTO severe bleeds (Figure 7).

### Discussion

An incremental value of prolonged antiplatelet therapy in addition to aspirin has been shown in patients with acute coronary syndromes (ACS) and coronary stenting;<sup>7</sup> however, a benefit of additional antiplatelet therapy in stable patients post MI or with chronic PAD had been uncertain. TRA 2°P-TIMI 50 provided definitive evidence for a benefit of the novel PAR-1 antagonist vorapaxar for long-term secondary prevention in such patients.<sup>2</sup> In the present analysis, we have reported for the first time the efficacy





**Figure 7.** Outcomes for every 1000 patients treated for 3 years. The net clinical outcome of CV death, MI, stroke, or GUSTO severe bleeding was 8.55% with vorapaxar versus 10.08% with placebo (HR 0.82; 95% CI 0.75 to 0.91). The *P* values below each column are those generated by the Cox proportional model over the duration of follow-up in the trial. CI indicates confidence interval; CV, cardiovascular; GUSTO, Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries; HR, hazard ratio; MI, myocardial infarction.

and safety of vorapaxar in patients with MI or PAD, who had no history of stroke or TIA, who represent the population in which the agent has been approved for clinical use in the United States. These findings demonstrate a 20% relative reduction (1.6% absolute) in the “hard” outcome of CV death, MI, or stroke that is accompanied by a 0.3% absolute increase in GUSTO severe bleeding compared with placebo in a population of >20 000 patients. Two pre-specified net clinical outcomes were also improved significantly with vorapaxar, including one based on events associated with irreversible tissue damage (death, MI, stroke, and GUSTO severe bleeding).

These findings were consistent when vorapaxar was added to aspirin alone or when added to dual antiplatelet therapy with aspirin and clopidogrel. In addition, the incremental benefit of vorapaxar was observed in conjunction with a high adherence to guideline-based medical therapy, with 97% of the patients treated with aspirin, 71% on a thienopyridine (usually clopidogrel), and 93% receiving a statin. Furthermore, the majority of the patients had undergone successful prior coronary revascularization. Despite these standard therapies for secondary prevention, the patients in the trial had 3-year risk of recurrent major vascular events of 9.5%; a finding that shows that patients with stable atherosclerosis continue to remain at risk for recurrent atherothrombosis.

As observed with other potent antiplatelet drugs,<sup>8,9</sup> the reduction in ischemic events that we observed with vorapaxar was associated with a significant increase in GUSTO moderate or severe bleeding. This increase in the bleeding risk with vorapaxar was driven primarily by a higher rate of GUSTO moderate bleeding. We have previously demonstrated that patients with known cerebrovascular disease are at substantially increased risk of ICH with vorapaxar.<sup>5</sup> This finding led to the conclusion of the Sponsor and FDA that patients with a history of a prior cerebrovascular event do not have a suitable benefit-risk balance for treatment with vorapaxar and is consistent with our prior observations with prasugrel.<sup>8</sup> In addition, an excess of bleeding, including hemorrhagic stroke, without clear efficacy for secondary prevention has been observed in multiple randomized trials of dual antiplatelet therapy in patients with ischemic stroke.<sup>10–12</sup> We speculate that this difference in the risk-to-benefit profile of combination antiplatelet therapy relates to the substantially more broad pathobiology of stroke, inclusive of hypertensive and embolic etiologies, that plausibly are not modified by more potent antiplatelet regimens. Recurrent strokes contribute a greater proportion of the recurrent cardiovascular events in such patients with cerebrovascular disease (Table 2). At the same time, prior cerebrovascular disease is associated with a higher risk of intracranial bleeding. Together, these factors may considerably and unfavorably shift the potential for benefit versus risk in such patients. Although the etiology of recurrent ischemic strokes (large vessel, lacunar, or other) might offer additional insight with respect to the balance of efficacy and safety in patients with prior stroke, these data were not captured in this trial.

Overall our findings presented in this report indicate a favorable benefit-risk profile for vorapaxar in patients with stable atherosclerosis following MI or with PAD and without previous stroke or TIA. Notably, the overall pattern of efficacy and safety was similar among patients who qualified with PAD versus those who qualified with MI. Vorapaxar is not approved for use in the acute management of ACS,<sup>13</sup> and may be initiated in stable patients on antiplatelet therapy after an MI. Vorapaxar has not been studied in patients receiving prasugrel or ticagrelor. Underlying bleeding risk should be considered when initiating any antiplatelet agent in patients with low body weight and older age.<sup>5,8</sup>

## Conclusion

In patients with prior MI or PAD who have not had a previous stroke or TIA, vorapaxar added to standard therapy is effective for long-term secondary prevention of thrombotic CV events, while increasing moderate or severe bleeding.

## Sources of Funding

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## Disclosures

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## References

- Bonaca MP, Morrow DA. SCH 530348: a novel oral thrombin receptor antagonist. *Future Cardiol*. 2009;5:435–442.
- Morrow DA, Braunwald E, Bonaca MP, Ameriso SF, Dalby AJ, Fish MP, Fox KA, Lipka LJ, Liu X, Nicolau JC, Ophuis AJ, Paolasso E, Scirica BM, Spinar J, Theroux P, Wiviott SD, Strony J, Murphy SA; TRA 2°P-TIMI 50 Steering Committee and Investigators. Vorapaxar in the secondary prevention of atherothrombotic events. *N Engl J Med*. 2012;366:1404–1413.
- Scirica BM, Bonaca MP, Braunwald E, De Ferrari GM, Isaza D, Lewis BS, Mehrhof F, Merlini PA, Murphy SA, Sabatine MS, Tendera M, Van de Werf F, Wicox R, Morrow DA; TRA 2°P-TIMI 50 Steering Committee Investigators. Vorapaxar for secondary prevention of thrombotic events for patients with previous myocardial infarction: a prespecified subgroup analysis of the TRA 2°P-TIMI 50 trial. *Lancet*. 2012;380:1317–1324.
- Bonaca MP, Scirica BM, Creager MA, Olin J, Bounameaux H, Dellborg M, Lamp JM, Murphy SA, Braunwald EB, Morrow DA. Vorapaxar in patients with peripheral artery disease: results from TRA 2°P-TIMI 50. *Circulation*. 2013;127:1522–1529.
- Morrow DA, Alberts MJ, Mohr JP, Ameriso SF, Bonaca MP, Goto S, Hankey GJ, Murphy SA, Scirica BM, Braunwald E; TRA 2°P-TIMI 50 Steering Committee and Investigators. Efficacy and safety of vorapaxar in patients with prior ischemic stroke. *Stroke*. 2013;44:691–698.
- Morrow DA, Scirica BM, Fox KA, Berman G, Strony J, Veltri E, Bonaca MP, Fish P, McCabe CH, Braunwald E; TRA 2°P-TIMI 50 Investigators. Evaluation of a novel antiplatelet agent for secondary prevention in patients with a history of atherosclerotic disease: design and rationale for the Thrombin-Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events (TRA 2°P)-TIMI 50 trial. *Am Heart J*. 2009;158:335–341.e3.
- Hamm CW, Bassand JP, Agewall S, Bax J, Boersma E, Bueno H, Caso P, Dudek D, Gielen S, Huber K, Ohman M, Petrie MC, Sonntag F, Uva MS, Storey RF, Wijns W, Zaher D; ESC Committee for Practice Guidelines. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: the Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2011;32:2999–3054.
- Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, Neumann FJ, Ardissino D, De Servi S, Murphy SA, Riesmeyer J, Weerakkody G, Gibson CM, Antman EM; TRITON TIMI 38 Investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2007;357:2001–2015.
- Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Skene A, Steg PG, Storey SF, Harrington RA; PLATO Investigators. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009;361:1045–1057.
- Diener HC, Bogousslavsky J, Brass LM, Cimminiello C, Csiba L, Kaste M, Leys D, Matias-Guiu J, Rupprecht HJ; MATCH Investigators. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. *Lancet*. 2004;364:331–337.
- SPS3 Investigators, Benavente OR, Hart RG, McClure LA, Szychowski JM, Coffey CS, Pearce LA. Effects of clopidogrel added to aspirin in patients with recent lacunar stroke. *N Engl J Med*. 2012;367:817–825.
- Sacco RL, Diener HC, Yusuf S, Cotton D, Ounpuu S, Lawton WA, Palesch Y, Martin RH, Albers GW, Bath P, Bornstein N, Chan BP, Chen ST, Cunha L, Dahlöf B, De Keyser J, Donnan GA, Estol C, Gorelick P, Gu V, Hermansson K, Hilbrich L, Kaste M, Lu C, Machnig T, Pais P, Roberts R, Skvortsova V, Teal P, Toni D, Vandermaelen C, Voigt T, Weber M, Yoon BW; PRoFESS Study Group. Aspirin and extended-release dipyridamole versus clopidogrel for recurrent stroke. *N Engl J Med*. 2008;359:1238–1251.
- Tricoci P, Huang Z, Held C, Moliterno DJ, Armstrong PW, Van de Werf F, White HD, Aylward PE, Wallentin L, Chen E, Likhnygina Y, Pei J, Leonardi S, Sorick TL, Kilian AM, Jennings LH, Ambrosio G, Bode C, Cequier A, Cornel JH, Diaz R, Erkan A, Huber K, Hudson MP, Jiang L, Jukema JW, Lewis BS, Lincoff AM, Montalescot G, Nicolau JC, Ogawa H, Pfisterer M, Prieto JC, Ruzyllo W, Sinnaeve PR, Storey RF, Valgimigli M, Whellan DJ, Widimsky P, Strony J, Harrington RA, Mahaffey KW; TRACER Investigators. Thrombin-receptor antagonist vorapaxar in acute coronary syndromes. *N Engl J Med*. 2012;366:20–33.