DOI: 10.1161/CIRCULATIONAHA.112.000679

Vorapaxar in Patients with Peripheral Artery Disease: Results from TRA2°P-TIMI 50

Running title: *Bonaca et al.; Vorapaxar in patients with PAD*

Marc P. Bonaca, MD, MPH[1]; Benjamin M. Scirica, MD[1]; Mark A. Creager, MD[1]; Jeffrey Olin, MD[2]; Henri Bounameaux, MD[3]; Mikael Dellborg, MD[4]; Jessica M. Lamp, BA[1]; Sabina A. Murphy, MPH[1]; Eugene Braunwald, MD[1]; David A. Morrow, MD, MPH[1]

[1]TIMI Study Group, Cardiovascular Division, Dept of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA; [2]Wiener Cardiovascular Institute and Marie-Jose and Henry R. Kravis Ctr for Cardiovascular Health, Mount Sinai School of Medicine, New York, NY; [3]Faculty of Medicine of Geneva, Division of Angiology and Hemostasis, Dept of Medical Specialties, University Hospitals of Geneva, Geneva, Switzerland; [4]Institute of Medicine, Sahlgrenska Academy at University of Gothenburg and Sahlgrenska University Hospital – Östra, Gothenburg, Sweden

Address for Correspondence:

Marc P. Bonaca, MD

TIMI Study Group, Cardiovascular Division

Brigham and Women's Hospital

75 Francis Street

Boston, MA 02115

Tel: 617-278-0071

Fax: 617-734-7329

E-mail: mbonaca@partners.org

Journal Subject Codes: Hypertension:[17] Peripheral vascular disease, Treatment:[118] Cardiovascular pharmacology, Myocardial biology:[93] Receptor pharmacology, Thrombosis:[172] Arterial thrombosis, Thrombosis:[176] Thrombin

DOI: 10.1161/CIRCULATIONAHA.112.000679

Abstract:

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

Methods and Results—The TRA2°P-TIMI 50 trial was a randomized, double-blind, placebo controlled trial of vorapaxar in 26,449 patients with stable atherosclerotic vascular disease (MI, stroke, or PAD). Patients with qualifying PAD (N= 3,787) had a history of claudication and ABI of <0.85 or prior revascularization for limb ischemia. The primary efficacy endpoint was cardiovascular death, MI, or stroke and the principal safety endpoint was GUSTO bleeding. In the PAD cohort, the primary endpoint did not differ significantly with vorapaxar (11.3% vs. 11.9%, HR 0.94, 95% CI 0.78–1.14, p=0.53). However, rates of hospitalization for acute limb ischemia (2.3% vs. 3.9%, HR 0.58, 95% CI 0.39–0.86, p=0.006) and peripheral artery revascularization (18.4% vs. 22.2%, HR 0.84, 95% CI 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% vs. 4.5%, HR 1.62, 95% CI 1.21–2.18, p=0.001).

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

Clinical Trial Registration Information—http://www.clinicaltrials.gov; Identifier: NCT00526474.

Key words: antiplatelet therapy, ischemia, peripheral artery disease, limb ischemia, vorapaxar

DOI: 10.1161/CIRCULATIONAHA.112.000679

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 circulations, subclinical atherosclerosis is often present and puts them at risk for adverse cardiovascular outcomes.[1, 2] This risk is exacerbated by under-diagnosis and under-treatment, even of patients with recognized disease.[4] Accordingly, secondary preventive strategies in patients with PAD have been targeted primarily at reduction of major cardiovascular outcomes. Nonetheless, the need for peripheral revascularization for claudication and acute and chronic critical limb ischemia are a significant source 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 remains a topic of debate, as some trials have shown no conclusive benefit of antiplatelet therapy in PAD.[7, 8]

Vorapaxar is a novel oral antiplatelet agent that antagonizes activation of the protease activated receptor (PAR)-1 by thrombin. Thrombin's action on PAR-1 on the platelet surface leads to activation while thrombin's interaction with PAR-1 on endothelial and smooth muscle cells is mitogenic.[9] The Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events (TRA 2°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 as well as peripheral vascular outcomes in patients who qualified for TRA 2°P-TIMI 50 with symptomatic PAD.

DOI: 10.1161/CIRCULATIONAHA.112.000679

Methods

Study Population and Procedures

TRA 2°P-TIMI 50 was a multinational, randomized, double-blind, placebo-controlled trial among 26,449 subjects with stable atherosclerotic vascular disease. The details of the trial design have been previously reported.[10, 11] The PAD cohort was planned to enroll to approximately 15% of the overall trial cohort.[10] In order 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 (ABI) <0.85 or previous revascularization for limb ischemia. Qualifying and follow up ABIs 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 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 ~2 years of follow-up, the data and safety monitoring board reported an excess of intarcranial 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]

DOI: 10.1161/CIRCULATIONAHA.112.000679

Endpoints

In the hierarchical analysis of efficacy endpoints, the first endpoint 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 endpoint was GUSTO moderate or severe bleeding. Bleeding events were also classified according to the TIMI bleeding definition. Definitions of these endpoints have been previously reported.[10]

Pre-specified limb efficacy endpoints 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, intra-operative findings, or pathological evaluation. Peripheral revascularization was defined as any arterial vascular intervention done to treat ischemia or prevent major ischemic events including percutaneous or surgical interventions and categorized as either urgent or elective. The additional pre-specified composite endpoint 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.(Online Supplement) All elements of this endpoint were adjudicated by a clinical events committee (CEC) comprised 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.

DOI: 10.1161/CIRCULATIONAHA.112.000679

Statistical Methods

Data were analyzed on an intention-to-treat basis with all randomized patients including PAD patients with history of stroke. Baseline characteristics were compared using the chi-square test for categorical variables and the Wilcoxon rank-sum test for continuous ones. The efficacy analyses were performed using 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 one 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 using Stata v12.1 (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 **Table 1**. Compared to 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 1a**). 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% on dual antiplatelet therapy, and 11% were on cilostazol (**Table 1a**). Drug discontinuation rates at three years in the PAD cohort were higher than those in the overall trial population (33% PAD vs. 23% overall). The rates by treatment allocation in the PAD group were similar (34% vorapaxar

vs. 32% 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 TIA) (**Table 1b**) with 8% having a history of stroke. Most patients had a history of peripheral artery revascularization (62%) and about 10% had history of carotid artery intervention. Overall 68% of patients had a baseline ABI of <0.85. The majority (75%) of patients 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 1b**).

Major Efficacy Endpoints

Among patients in the PAD cohort, vorapaxar did not significantly reduce the composite of CV death, MI, or stroke compared to placebo (11.3% vs. 11.9%, HR 0.94 95% CI 0.78 – 1.14, p=0.53, **Figure 1**) or CV death, MI, stroke, or urgent coronary revascularization (p=0.57) (**Table 2**). The individual components of the primary endpoint are shown in **Supplemental Table 1**. However, formal testing for a difference in the effect of vorapaxar in the PAD stratum compared with that observed the remainder of the trial cohort was not significant (p-interaction 0.35), including comparison with the MI group alone, in which there was a clear benefit of vorapaxar[11] (p-interaction 0.16).

Peripheral Vascular Endpoints

Focusing on manifestations of peripheral vascular disease, vorapaxar significantly reduced the risk of limb ischemic events including hospitalization for acute limb ischemia (2.3% vs. 3.9%, HR 0.58, 95% CI 0.39 – 0.86, p=0.006) (**Table 2**, **Figure 2a**) and peripheral revascularization (18.4% vs. 22.2%, HR 0.84, 95% CI 0.73 – 0.97, p = 0.017) (**Table 2**, **Figure 2b**). This

DOI: 10.1161/CIRCULATIONAHA.112.000679

reduction was consistent for both urgent peripheral revascularization (3.1% vs. 4.7%, HR 0.65, 95% CI 0.46 – 0.91, p=0.012) and elective peripheral revascularization (16.5% vs. 19.5%, HR 0.86, 95% CI 0.74 – 0.9995. p=0.049)

The reduction in acute limb ischemia was evident by 30 days (0% vs 0.4; p=0.008) and continued through the duration of follow up (2.3% vs 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 also include events involving the coronary and cerebral circulation both urgent vascular hospitalization (5.8% vs. 8.0%, HR 0.72, 95% CI 0.56 – 0.93, p=0.011; **Table 2**, **Figure 3**) and the need for any arterial revascularization (26.2% vs. 30.3%, HR 0.88, 95% CI 0.78 – 0.99, p=0.036) were also both significantly reduced with vorapaxar compared to placebo. Moreover, the pre-specified composite endpoint combining CV death, MI, or stroke with the broader vascular elements of any arterial revascularization and urgent vascular hospitalization was significantly reduced with vorapaxar compared to placebo (32.7% vs 38.0%, HR 0.87, 95% CI 0.78 – 0.97, p=0.009; **Table 2**, **Figure 4**).

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

A total of 3,483 (92%) of the PAD cohort had no history of stroke. When restricting analyses to this cohort, efficacy findings were similar. In this cohort, vorapaxar did not reduce CV death, MI, or stroke (p=0.43) but did significantly reduce limb ischemic events including

DOI: 10.1161/CIRCULATIONAHA.112.000679

hospitalization for acute limb ischemia (2.2% vs. 4.1%, HR 0.53, 95% CI 0.35 – 0.80, p=0.002) and peripheral revascularization (18.1% vs. 22.0%, HR 0.83, 95% CI 0.72 – 0.97, p= 0.018) as well as the broader endpoint of urgent vascular hospitalization (2.3% vs. 8.1%, HR 0.66, 95% CI 0.51 – 0.86, p=0.002).

Safety End Points

Compared to placebo, in the PAD cohort vorapaxar increased the risk of bleeding including GUSTO moderate or severe bleeding (7.4% vs. 4.5%, HR 1.62, 95% CI 1.21 – 2.18, p=0.001, **Table 2**, **Supplemental Figure 1**). The rates of intracranial hemorrhages with vorapaxar compared with placebo were 0.9% vs. 0.4%, HR 2.03, 95% CI 0.82 – 5.02, p=0.13 (**Supplemental Figure 2**). We found no difference in the risk of ICH in the PAD cohort compared with those who qualified with MI or stroke (p-interaction = 0.91) or those who qualified with MI (p-interaction = 0.60). There was no difference in fatal bleeding (**Table 2**, **Supplemental Figure 3**). When excluding patients with a history of cerebrovascular disease, rates of ICH were lower (0.7% vorapaxar vs. 0.4% 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 to those not on thienopyridine at baseline (HR 1.63, 95% CI 1.1 – 2.42, p=0.016) with no significant interaction for bleeding (p-interaction 0.98 for GUSTO moderate/severe bleeding, p=NS for all other safety endpoints reported). The risk of bleeding also did not differ based on the use of aspirin at baseline (p-interaction 0.20 for GUSTO moderate/severe bleeding) or with background dual antiplatelet therapy (p-interaction 0.403 for GUSTO moderate/severe bleeding).

Discussion

DOI: 10.1161/CIRCULATIONAHA.112.000679

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 there are 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 ABI (<0.99 and ≤0.95), have shown no benefit [7, 8] In addition, a meta-analysis of aspirin for 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 vs. asymptomatic PAD, the type and intensity of antiplatelet therapy administered and concomitant background therapies. In a subgroup analysis of the 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 to aspirin monotherapy.[13] Notably, the PAD cohort in the CAPRIE trial was defined as symptomatic PAD, requiring an ABI ≤ 0.85 and claudication or a history of claudication and revascularization.[13] However, in the

CHARISMA trial, dual antiplatelet therapy with clopidogrel and aspirin compared with aspirin alone did not reduce cardiovascular events in the 2,838 patients with symptomatic PAD (p=0.28) or in the broader group of 3,096 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 pooling five trials of patients with intermittent claudication, four studying ticlopidine and one with picotamide; 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 using 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 prior year (p-interaction=0.16 for PAD vs. MI qualifying cohorts). However, taken together with findings in the CHARISMA trial, we find that these data suggest a more modest, if any, reduction in CV death, MI, or stroke with potent multi-agent 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; with the latter two treatments currently recommended by professional society guidelines.[18, 19]

A novel finding of this study was that vorapaxar reduced acute limb ischemia, a complex

DOI: 10.1161/CIRCULATIONAHA.112.000679

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 while acute events are most likely reduced through direct anti-platelet activity, the significant reduction in all peripheral revascularizations including non-urgent 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 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 that 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.

There were several limitations to the current study that should be noted. Although there was a numerical reduction in the primary endpoint in the PAD group and no statistical difference from the significant reduction observed in the overall trial, the current cohort was not sufficiently sized to show a significant reduction in the primary endpoint with vorapaxar. In addition, while 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 (e.g. cilostazol). In addition, the current 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. While annualized treatment discontinuation was similar to other trials of antiplatelet therapies in stable populations, premature cessation and treatment non-adherence 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 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.

Sources of Funding: This study was supported by a grant from Merck and Co.

Conflict of Interest Disclosures: The TIMI Study Group has received significant research grant support from Accumetrics, Amgen, AstraZeneca, Beckman Coulter, Bristol-Myers Squibb, CV Therapeutics, Daiichi Sankyo Co Ltd, Eli Lilly and Co, GlaxoSmithKline, Integrated Therapeutics, Merck and Co, Nanosphere, Novartis Pharmaceuticals, Nuvelo, Ortho-Clinical Diagnostics, Pfizer, Roche Diagnostics, Sanofi-Aventis, Sanofi-Synthelabo, Siemens Medical Solutions, and Singulex. Dr. Bonaca was supported by a Research Career Development Award (K12 HL083786) from the NHLBI. Dr. Scirica has received consulting fees from Lexicon, Arena, Gilead, and Eisai. Dr. Creager has received consulting fees from Aastrom Biosciences, Astra Zeneca, Baxter Healthcare, and Genzyme. Dr. Olin has received consulting fees from Merck and

Plurestem. Dr. Bounameaux has received research support, consulting fees and/or honoraria for lectures from the Swiss National Foundation, Bayer-Schering Pharma, Schering-Plough, Daiichi-Sankyo, Bristol-Myers-Squibb, GlaxoSmithKline, Pfizer, Boehringer-Ingelheim and sanofi-aventis. Dr. Dellborg has received consulting fees and/or honoraria for lectures from Schering-Plough, Pfizer, Merck, Boehringer-Ingelheim and Actelion. Ms. Murphy has received consulting fees from Eli Lilly and Amarin Pharmaceuticals. Dr. Braunwald has served as a consultant for Merck (no compensation), Amorcyte, Daiichi Sankyo, Medicines Co, Ikaria, CardioRentis, Sanofi-Aventis, and CVRx (no compensation). Dr. Morrow has received consulting fees from Beckman-Coulter, Boehringher Ingelheim, Critical Diagnostics, Genentech, Gilead, Instrumentation Laboratory, Merck, Novartis, Roche Diagnostics, and Servier. The other authors report no conflicts.

References:

1. Bhatt DL, Eagle KA, Ohman EM, Hirsch AT, Goto S, Mahoney EM, Wilson PW, Alberts MJ, D'Agostino R, Liau CS, Mas JL, Rother J, Smith SC,Jr, Salette G, Contant CF, Massaro JM, Steg PG, REACH Registry Investigators. Comparative determinants of 4-year cardiovascular event rates in stable outpatients at risk of or with atherothrombosis. *JAMA.* 2010;304:1350-1357.

2. Criqui MH, Denenberg JO, Langer RD, Fronek A. The epidemiology of peripheral arterial disease: importance of identifying the population at risk. *Vasc Med.* 1997;2 221-226.

3. Criqui MH, Langer RD, Fronek A, Feigelson HS, Klauber MR, McCann TJ, Browner D. Mortality over a period of 10 years in patients with peripheral arterial disease. *N Engl J Med.* 1992;326:381-386.

4. Pande RL, Perlstein TS, Beckman JA, Creager MA. Secondary prevention and mortality in peripheral artery disease: National Health and Nutrition Examination Study, 1999 to 2004. *Circulation.* 2011;124:17-23.

5. Mahoney EM, Wang K, Keo HH, Duval S, Smolderen KG, Cohen DJ, Steg G, Bhatt DL, Hirsch AT, Reduction of Atherothrombosis for Continued Health (REACH) Registry Investigators. Vascular hospitalization rates and costs in patients with peripheral artery disease in the United States. *Circ Cardiovasc Qual Outcomes.* 2010;3:642-651.

6. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ.* 2002;324:71-86.

7. Belch J, MacCuish A, Campbell I, Cobbe S, Taylor R, Prescott R, Lee R, Bancroft J, MacEwan S, Shepherd J, Macfarlane P, Morris A, Jung R, Kelly C, Connacher A, Peden N,

Jamieson A, Matthews D, Leese G, McKnight J, O'Brien I, Semple C, Petrie J, Gordon D, Pringle S, MacWalter R, Prevention of Progression of Arterial Disease and Diabetes Study Group, Diabetes Registry Group, Royal College of Physicians Edinburgh. The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. *BMJ.* 2008;337:a1840.

8. Fowkes FG, Price JF, Stewart MC, Butcher I, Leng GC, Pell AC, Sandercock PA, Fox KA, Lowe GD, Murray GD, Aspirin for Asymptomatic Atherosclerosis Trialists. Aspirin for prevention of cardiovascular events in a general population screened for a low ankle brachial index: a randomized controlled trial. *JAMA.* 2010;303:841-848.

9. Patterson C, Stouffer GA, Madamanchi N, Runge MS. New tricks for old dogs: nonthrombotic effects of thrombin in vessel wall biology. *Circ Res.* 2001;88:987-997.

10. Morrow DA, Scirica BM, Fox KA, Berman G, Strony J, Veltri E, Bonaca MP, Fish P, McCabe CH, Braunwald E, TRA 2(o)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 degrees P)-TIMI 50 trial. *Am Heart J.* 2009;158:335-341.e3.

11. 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 2P-TIMI 50 Steering Committee and Investigators. Vorapaxar in the secondary prevention of atherothrombotic events. *N Engl J Med.* 2012;366:1404-1413.

12. Berger JS, Krantz MJ, Kittelson JM, Hiatt WR. Aspirin for the prevention of cardiovascular events in patients with peripheral artery disease: a meta-analysis of randomized trials. *JAMA.* 2009;301:1909-1919.

13. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. *Lancet.* 1996;348:1329-1339.

14. Bhatt DL, Fox KA, Hacke W, Berger PB, Black HR, Boden WE, Cacoub P, Cohen EA, Creager MA, Easton JD, Flather MD, Haffner SM, Hamm CW, Hankey GJ, Johnston SC, Mak KH, Mas JL, Montalescot G, Pearson TA, Steg PG, Steinhubl SR, Weber MA, Brennan DM, Fabry-Ribaudo L, Booth J, Topol EJ, CHARISMA Investigators. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med.* 2006;354:1706-1717.

15. Bhatt DL, Flather MD, Hacke W, Berger PB, Black HR, Boden WE, Cacoub P, Cohen EA, Creager MA, Easton JD, Hamm CW, Hankey GJ, Johnston SC, Mak KH, Mas JL, Montalescot G, Pearson TA, Steg PG, Steinhubl SR, Weber MA, Fabry-Ribaudo L, Hu T, Topol EJ, Fox KA, CHARISMA Investigators. Patients with prior myocardial infarction, stroke, or symptomatic peripheral arterial disease in the CHARISMA trial. *J Am Coll Cardiol.* 2007;49:1982-1988.

16. Cacoub PP, Bhatt DL, Steg PG, Topol EJ, Creager MA, CHARISMA Investigators. Patients

with peripheral arterial disease in the CHARISMA trial. *Eur Heart J.* 2009;30:192-201.

17. Wong PF, Chong LY, Mikhailidis DP, Robless P, Stansby G. Antiplatelet agents for intermittent claudication. *Cochrane Database Syst Rev.* 2011: CD001272.

18. Rooke TW, Hirsch AT, Misra S, Sidawy AN, Beckman JA, Findeiss LK, Golzarian J, Gornik HL, Halperin JL, Jaff MR, Moneta GL, Olin JW, Stanley JC, White CJ, White JV, Zierler RE, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society for Vascular Medicine, Society for Vascular Surgery. 2011 ACCF/AHA Focused Update of the Guideline for the Management of Patients With Peripheral Artery Disease (updating the 2005 guideline): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2011;58:2020-2045.

19. Alonso-Coello P, Bellmunt S, McGorrian C, Anand SS, Guzman R, Criqui MH, Akl EA, Olav Vandvik P, Lansberg MG, Guyatt GH, Spencer FA, American College of Chest Physicians. Antithrombotic therapy in peripheral artery disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012;141:e669S-90S.

20. Davi G, Patrono C. Platelet activation and atherothrombosis. *N Engl J Med.* 2007;357:2482-2494.

21. Coughlin SR. Protease-activated receptors in hemostasis, thrombosis and vascular biology. *J Thromb Haemost.* 2005;3:1800-1814.

22. Achterberg S, Visseren FL, Kappelle LJ, Pruissen DM, Van Der Graaf Y, Algra A, Smart Study Group. Differential propensity for major hemorrhagic events in patients with different types of arterial disease. *J Thromb Haemost.* 2011;9:1724-1729.

DOI: 10.1161/CIRCULATIONAHA.112.000679

Table 1a. Baseline Characteristics (Comparison of Qualifying Disease Cohorts).

Variable	PAD Cohort N=3787	MI/Stroke Cohorts N=22662	p-value
Demographics			
Age, median(IQR)	66 (60 – 73)	60 (52 - 68)	< 0.001
Female (%)	1115 (29)	5211 (23)	< 0.001
White race (%)	3425 (90)	19661 (87)	< 0.001
Weight<60 kg (%)	370 (10)	1482 (7)	< 0.001
Clinical Characteristics			
Diabetes mellitus (%)	1358 (36)	5366 (24)	< 0.001
Hypertension (%)	3157 (83)	15017 (66)	< 0.001
Hyperlipidemia (%)	3312 (87)	18682 (82)	< 0.001
Current smoker (%)	1167 (31)	4331 (19)	< 0.001
Any coronary artery disease (%)	2155 (57)	18536 (82)	< 0.001
Previous cerebrovascular event (%)	513 (14)	5755 (25)	< 0.001
Prior coronary revascularization (%)	1592 (42)	15669 (69)	< 0.001
eGFR <60ml/min/1.73 m2 (%)	1082 (29)	3002 (13)	< 0.001
Medical Therapy			
No aspirin or thienopyridine (%)	128 (3.4)	218 (1.0)	< 0.001
Aspirin (%)	3332 (88)	21402 (94)	< 0.001
Thienopyridine (%)	1394 (37)	15048 (66)	< 0.001
Cilostazol (%)	420 (11)	182 (1)	< 0.001
Aspirin and thienopyridine therapy (%)	1067 (28)	14006 (62)	< 0.001
Statin therapy (%)	3098 (82)	20639 (91)	< 0.001

DOI: 10.1161/CIRCULATIONAHA.112.000679

Table 1b. Baseline Characteristics (Randomized Treatment Allocation in PAD Cohort).

Variable	Vorapaxar N=1892	Placebo N=1895	p-value
Demographics			
Age, median(IQR)	66 (60 – 73)	66 (60 – 73)	0.90
Female (%)	546 (29)	569 (30)	0.43
White race (%)	1706 (90)	1719 (91)	0.60
Weight<60 kg (%)	185 (10)	185 (10)	0.996
Clinical Characteristics			
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 <60ml/min/1.73 m2 (%)	537 (29)	545 (29)	0.88
Pervious cerebrovascular event (%)	269 (14)	244 (13)	0.23
Peripheral Arterial Disease Details			
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			
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

Table 2. Efficacy and Bleeding End Points.

End Point	Vorapaxar N=1892	Placebo N=1895	Hazard Ratio (95% CI)	P Value
	Number (%)			
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

*Includes vascular events involving the coronary, cerebral, or peripheral vasculature
** excluding patients with cerebrovascular disease

Figure Legends:

Figure 1. Kaplan-Meier rates of the composite of cardiovascular death, myocardial infarction, or stroke by treatment allocation in the PAD cohort.

Figure 2. A Kaplan-Meier rates of hospitalization for limb ischemia by treatment allocation in the PAD cohort. **B.** Kaplan-Meier rates peripheral revascularization by treatment allocation in the PAD cohort.

Figure 3. Kaplan-Meier rates for urgent hospitalization for vascular cause of an ischemic nature stratified by treatment allocation in the PAD cohort.

Figure 4. Kaplan-Meier rates of 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 PAD cohort.

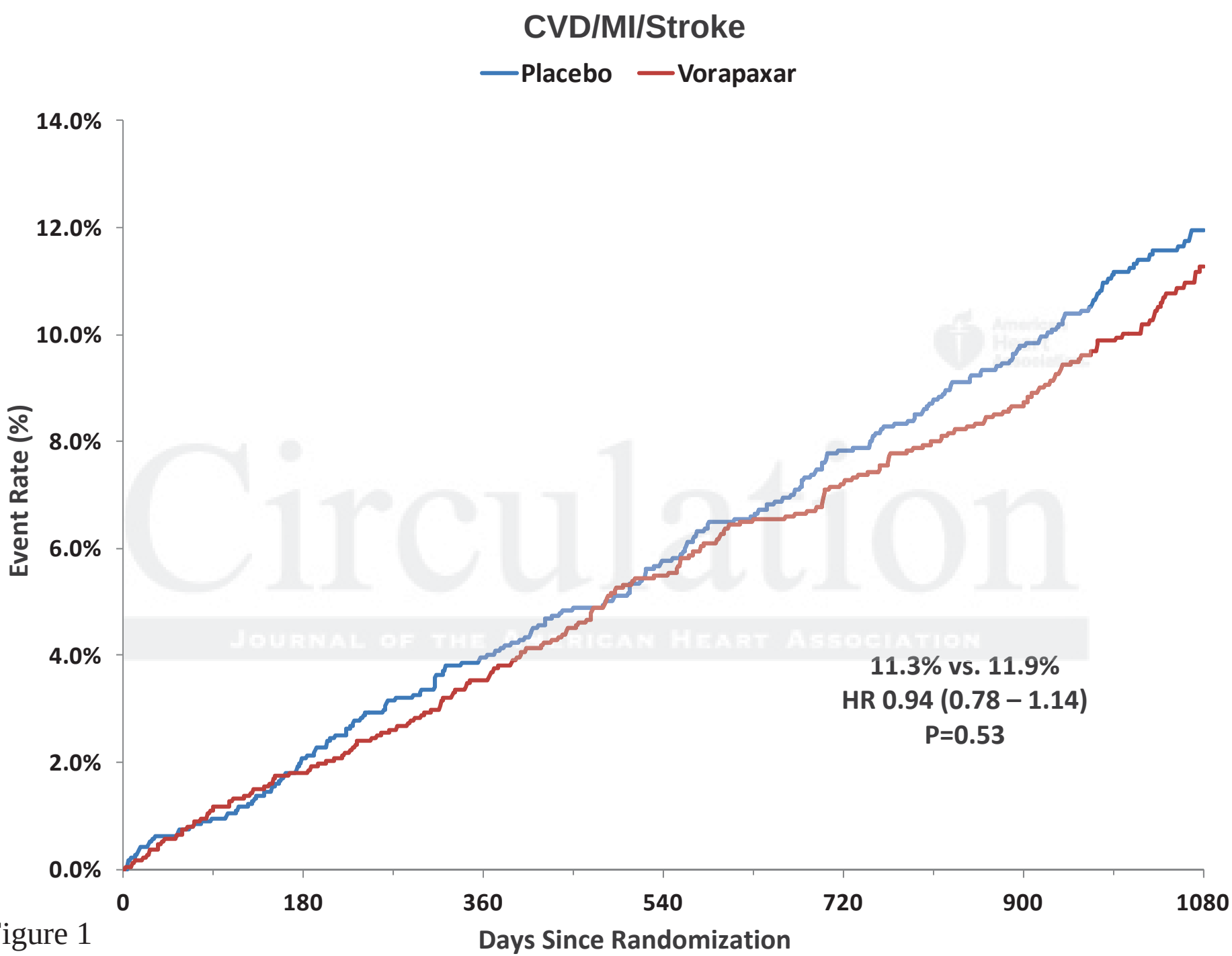


Figure 1

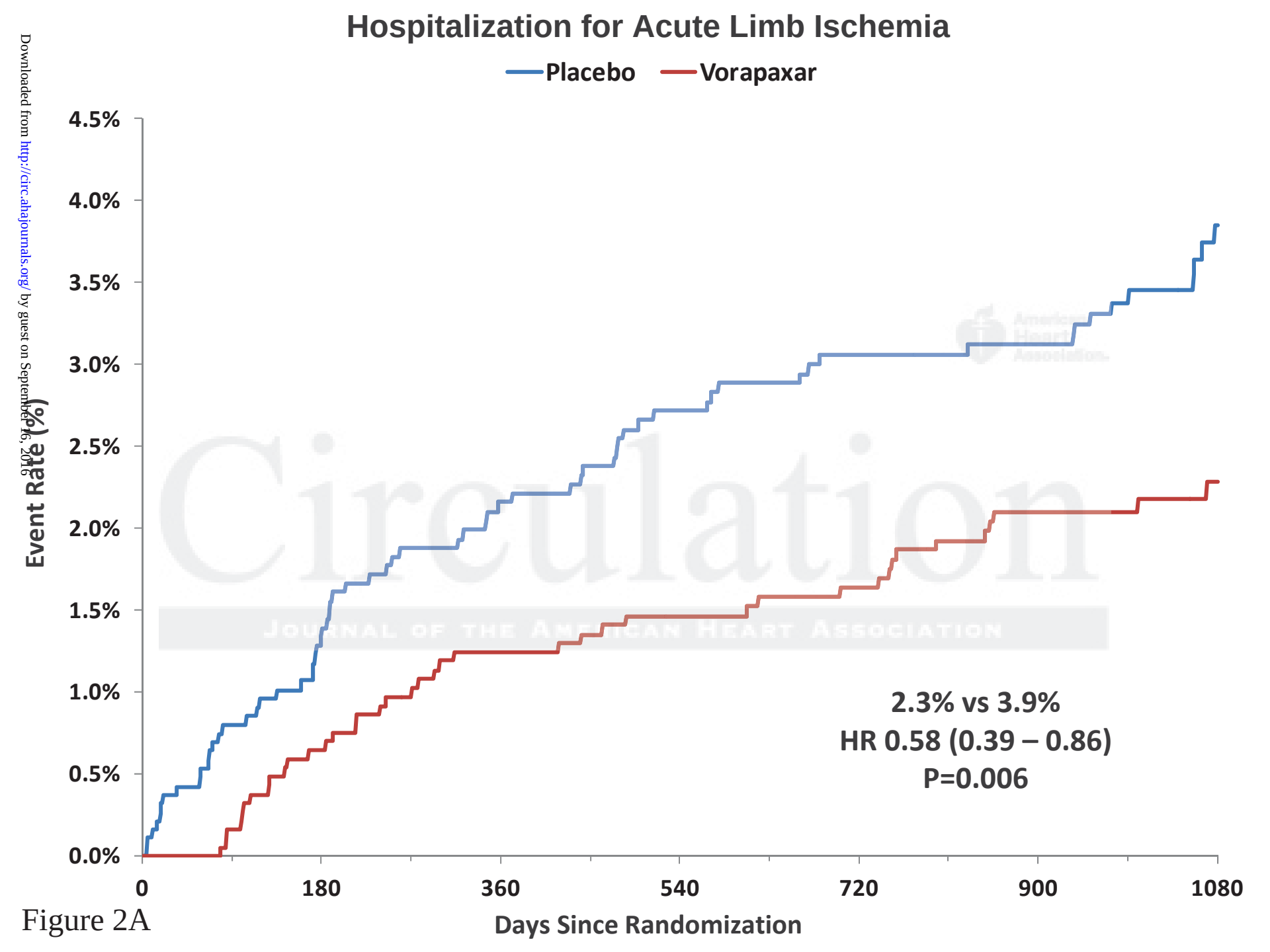


Figure 2A

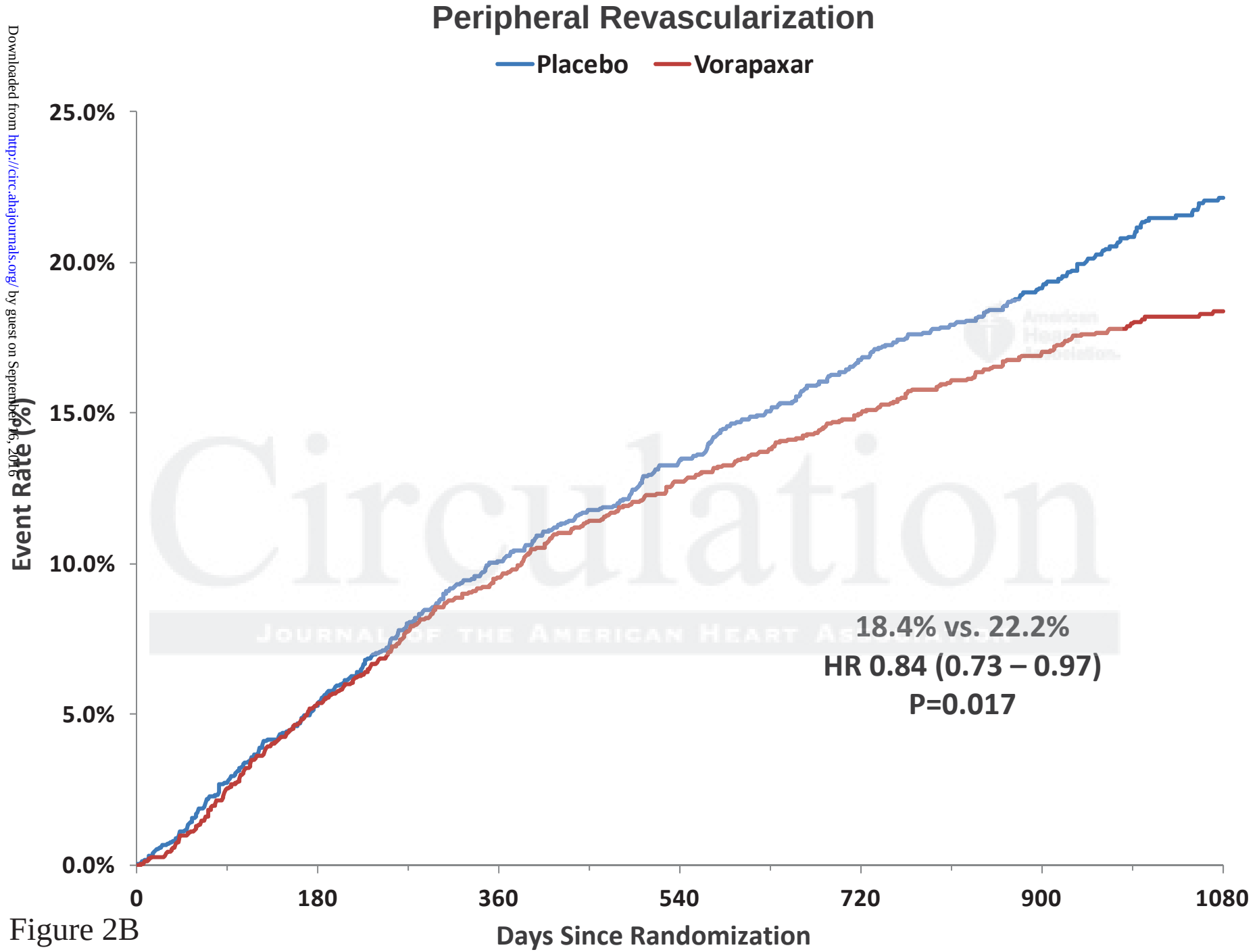


Figure 2B

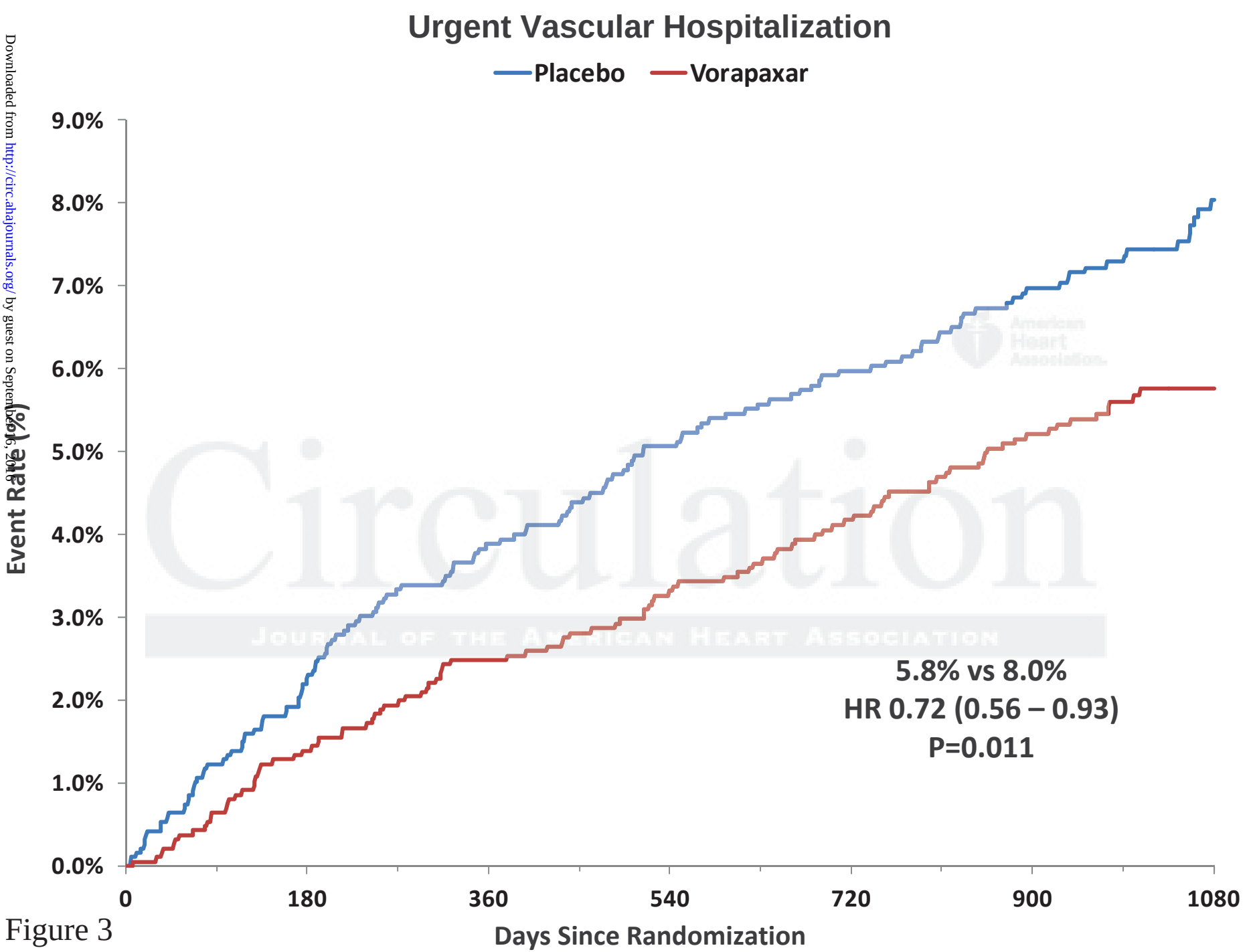


Figure 3

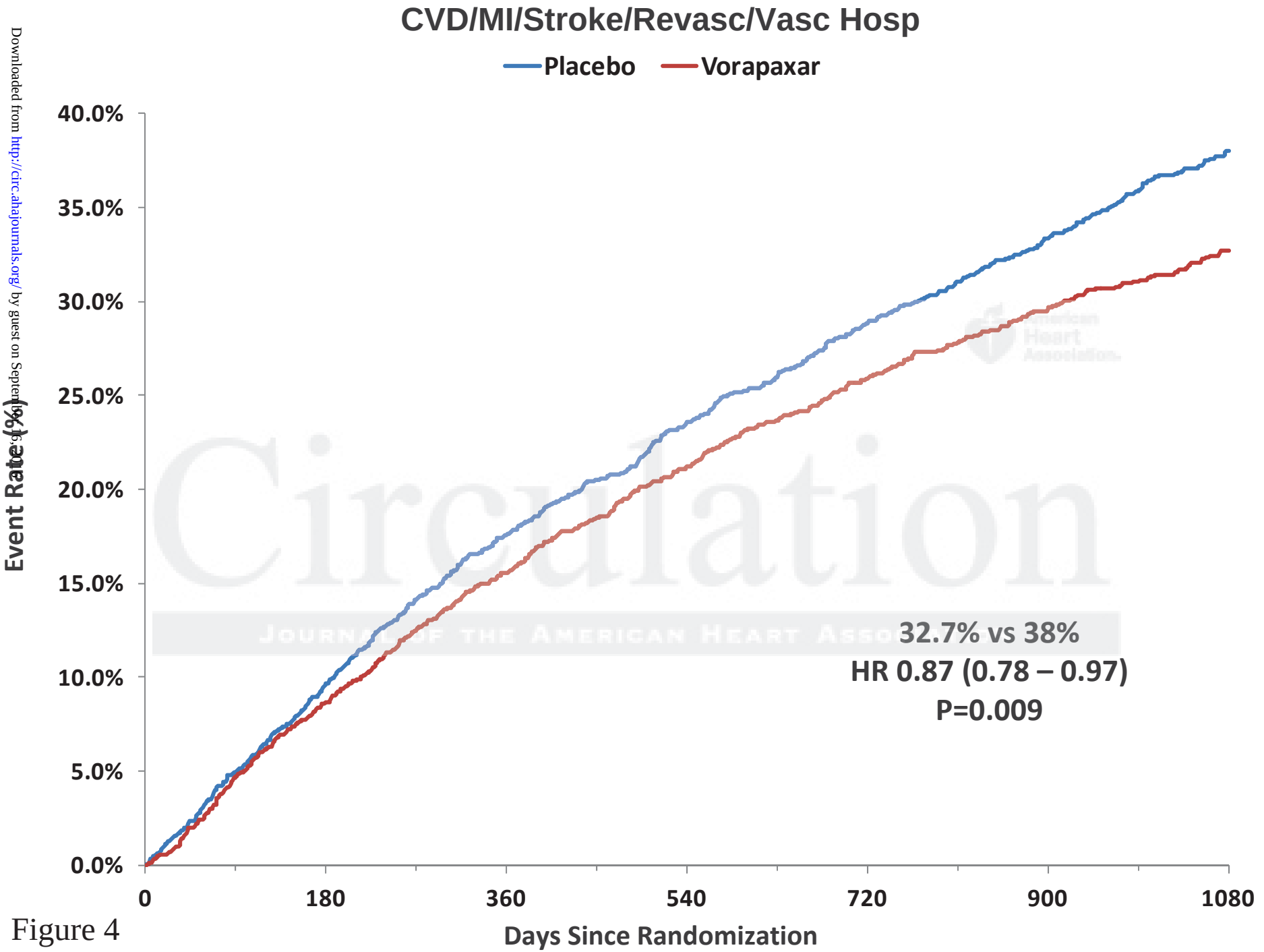


Figure 4

Vorapaxar in Patients with Peripheral Artery Disease: Results from TRA2°P-TIMI 50

Marc P. Bonaca, Benjamin M. Scirica, Mark A. Creager, Jeffrey W. Olin, Henri Bounameaux, Mikael Dellborg, Jessica M. Lamp, Sabina A. Murphy, Eugene Braunwald and David A. Morrow

Circulation. published online March 15, 2013;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539

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

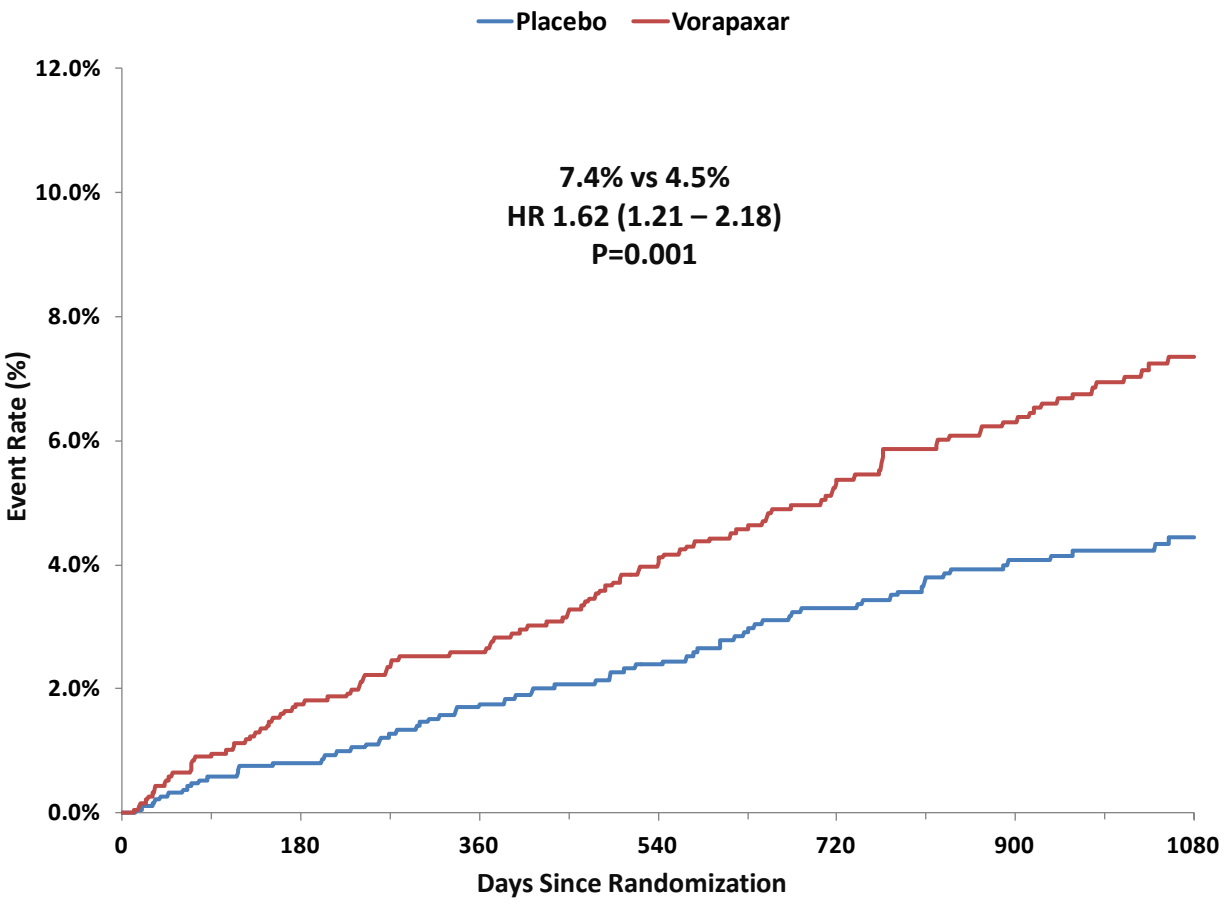
This is defined as any unplanned hospitalization for a new coronary, cerebrovascular or peripheral arterial ischemic event. This definition includes patients with:

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

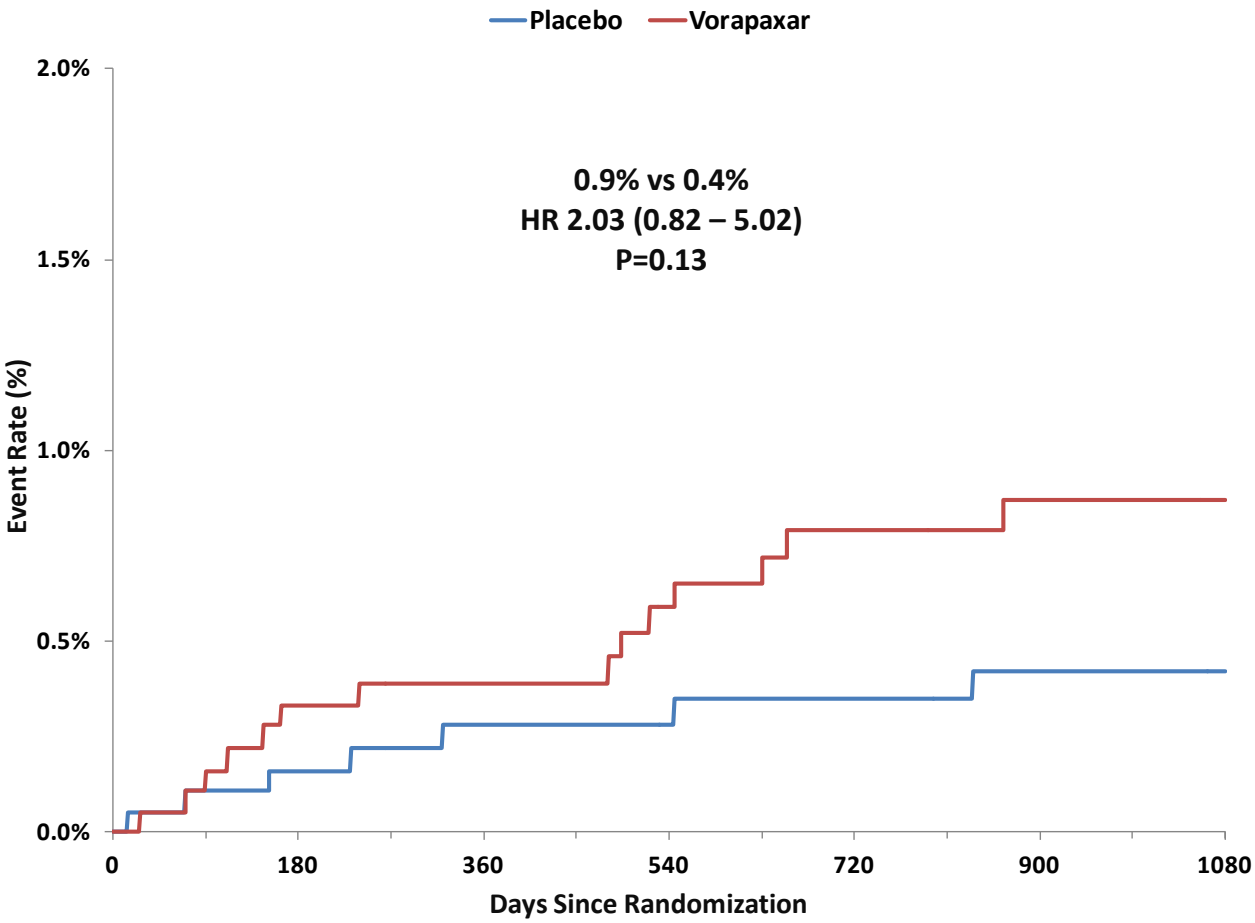
Table 1. Individual Efficacy Components

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