

## Impact of Cerebrovascular Events Older Than One Year on Ischemic and Bleeding Outcomes With Cangrelor in Percutaneous Coronary Intervention

Neal N. Sawlani, MD, MPH; Robert A. Harrington, MD; Gregg W. Stone, MD; Ph. Gabriel Steg, MD; C. Michael Gibson, MD; Christian W. Hamm, MD; Matthew J. Price, MD; Jayne Prats, PhD; Efthymios N. Deliargyris, MD; Kenneth W. Mahaffey, MD; Harvey D. White, DSc; Deepak L. Bhatt, MD, MPH

**Background**—Cangrelor is a potent intravenous adenosine diphosphate–receptor antagonist that in the CHAMPION trials reduced the 48-hour and 30-day rates of ischemic events during percutaneous coronary intervention without an increase in severe bleeding.

**Methods and Results**—CHAMPION PCI (A Clinical Trial to Demonstrate the Efficacy of Cangrelor), CHAMPION PLATFORM (Cangrelor Versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition), and CHAMPION PHOENIX (A Clinical Trial Comparing Cangrelor to Clopidogrel Standard Therapy in Subjects Who Require Percutaneous Coronary Intervention) were 3 randomized, double-blind, double-dummy trials in which cangrelor was compared with clopidogrel during percutaneous coronary intervention. The effect of cangrelor on ischemic events and bleeding was analyzed in the subgroup of patients with a history of cerebrovascular events at least 1 year prior to randomization; the Breslow–Day test was used to test for interaction of treatment effect in subgroups with and without such a history. The primary efficacy end point was a composite of death, myocardial infarction, ischemia-driven revascularization, or stent thrombosis at 48 hours. Among 24 910 randomized patients, 1 270 patients (5.1%) had a cerebrovascular event >1 year old, including 650 assigned to cangrelor and 620 assigned to clopidogrel. Consistent with the overall trial results, the rate of the primary efficacy end point was 4.3% in the cangrelor group versus 5.3% in the clopidogrel group (odds ratio 0.80; 95% confidence interval 0.48–1.34;  $P=0.40$ ;  $P$  for interaction =0.97), and the rate of GUSTO (Global Use of Strategies to Open Occluded Coronary Arteries) severe bleeding was 0.3% in both groups ( $P=0.97$ ;  $P$  for interaction =0.81).

**Conclusions**—Among patients in the CHAMPION trials with a prior cerebrovascular event at least 1 year before the percutaneous coronary intervention, the efficacy and bleeding profile of cangrelor compared with clopidogrel was similar to that in the overall trial. (*Circ Cardiovasc Interv.* 2017;10:e004380. DOI: 10.1161/CIRCINTERVENTIONS.116.004380.)

**Key Words:** blood platelets ■ cangrelor ■ cerebrovascular event ■ percutaneous coronary intervention ■ stroke

The incidence of stroke after percutaneous coronary intervention (PCI) is ≈0.33% and has remained largely unchanged in recent years, despite advances in cardiac catheterization techniques, equipment, and pharmacology.<sup>1–3</sup> The majority of periprocedural strokes are ischemic in nature, with an embolic pattern and often involving the middle cerebral artery.<sup>4,5</sup> Stroke during PCI is associated with a substantial increase in both in-hospital and 30-day mortality.<sup>6,7</sup> Risk factors for periprocedural stroke include known cerebrovascular disease, older age, coronary atherosclerosis, and intra-aortic balloon pump use.<sup>1–3</sup> A

history of prior cerebrovascular event also increases the risk of intracerebral hemorrhage related to PCI.<sup>8</sup>

Utilization of platelet aggregation antagonists in addition to aspirin at the time of PCI has significantly reduced periprocedural ischemic events and has been adopted as the standard of care.<sup>9–12</sup> Dual antiplatelet therapy with aspirin and prasugrel (compared with aspirin and clopidogrel) increases the risk of hemorrhagic stroke in patients with a history of prior stroke or transient ischemic attack (TIA).<sup>10,13</sup> The recently approved thrombin receptor antagonist vorapaxar is also contraindicated

Received August 5, 2016; accepted November 22, 2016.

From the Brigham and Women's Hospital Heart & Vascular Center and Harvard Medical School, Boston, MA (N.N.S., D.L.B.); Stanford University Medical School, CA (R.A.H., K.W.M.); Columbia University Medical Center and the Cardiovascular Research Foundation, New York, NY (G.W.S.); FACT (French Alliance for Cardiovascular clinical Trials), DHU FIRE, INSERM Unité 1148, Université Paris-Diderot, and Hôpital Bichat, Assistance-Publique-Hôpitaux de Paris, Paris, France and NHLI, Imperial College, Royal Brompton Hospital, London, United Kingdom (P.G.S.); Beth Israel Deaconess Medical Center, Division of Cardiology, Boston, MA (C.M.G.); Kerckhoff Heart and Thorax Center, Bad Nauheim, Germany (C.W.H.); Scripps Clinic and Scripps Translational Science Institute, La Jolla, CA (M.J.P.); The Medicines Company, Parsippany, NJ (J.P., E.N.D.); and Green Lane Cardiovascular Service, Auckland City Hospital, New Zealand (H.D.W.).

Guest Editor for this article was Sunil V. Rao, MD.

The Data Supplement is available at <http://circinterventions.ahajournals.org/lookup/suppl/doi:10.1161/CIRCINTERVENTIONS.116.004380/-DC1>.

Correspondence to Deepak L. Bhatt, MD, MPH, Brigham and Women's Hospital Heart & Vascular Center, 75 Francis St, Boston, MA 02115. E-mail dlbhattmd@post.harvard.edu

© 2016 American Heart Association, Inc.

*Circ Cardiovasc Interv* is available at <http://circinterventions.ahajournals.org>

DOI: 10.1161/CIRCINTERVENTIONS.116.004380

### WHAT IS KNOWN

- Prior stroke or transient ischemic attack is a risk factor for stroke at the time of percutaneous coronary intervention.
- Cangrelor reduces ischemic events after percutaneous coronary intervention without an increase in severe bleeding compared with clopidogrel.
- In patients with a prior stroke or transient ischemic attack, dual antiplatelet therapy with aspirin and prasugrel increases the risk of hemorrhagic stroke compared with aspirin and clopidogrel.

### WHAT THE STUDY ADDS

- In patients with a prior stroke or transient ischemic attack undergoing percutaneous coronary intervention with cangrelor, there is no difference in the rate of severe bleeding compared with clopidogrel.
- In patients with a stroke or transient ischemic attack >1 year prior who are undergoing percutaneous coronary intervention with cangrelor or clopidogrel, the rate of intracerebral hemorrhage is low.

in those with a history of prior stroke because of an increased risk of intracranial hemorrhage.<sup>14–16</sup>

Cangrelor is a potent intravenous adenosine diphosphate-receptor antagonist that directly and reversibly blocks platelet aggregation.<sup>17</sup> Cangrelor has been compared directly with clopidogrel, the most widely used oral P2Y<sub>12</sub> receptor antagonist, for its ability to prevent ischemic events at the time of PCI in 3 randomized, double-blind, placebo-controlled trials: CHAMPION PCI (A Clinical Trial to Demonstrate the Efficacy of Cangrelor), CHAMPION PLATFORM (Cangrelor Versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition), and CHAMPION PHOENIX (A Clinical Trial Comparing Cangrelor to Clopidogrel Standard Therapy in Subjects Who Require Percutaneous Coronary Intervention). Overall, cangrelor reduced the 48-hour rate of ischemic events during PCI without an increase in severe bleeding.<sup>18–23</sup> However, the safety of cangrelor in patients with cerebrovascular events >1 year old is unknown. We, therefore, sought to evaluate the benefits and risks of cangrelor within the subgroup of patients with prior ischemic stroke or TIA in the CHAMPION trials.

### Methods

The 3 CHAMPION trials were randomized, double-blind, double-dummy studies comparing cangrelor with clopidogrel during PCI (Figure 1).<sup>18–20,24</sup> Men and nonpregnant women were eligible if they were ≥18 years of age and required PCI. Patients with stable angina, unstable angina, and non-ST-segment-elevation myocardial infarction (MI) were enrolled in CHAMPION PLATFORM. CHAMPION PCI and CHAMPION PHOENIX included the same categories of patients, as well as those with ST-segment-elevation MI. Randomized treatment was given in addition to aspirin 75 to 325 mg. Patients with a history of stroke or TIA within 1 year of study enrollment, any history of hemorrhagic stroke, cerebral arteriovenous malformation,

intracranial aneurysm, or current warfarin use were excluded from the trials. Patients with a history of stroke or TIA at least 1 year prior to randomization were actively recruited, however. Patients were also excluded if they had received a P2Y<sub>12</sub>-receptor inhibitor or abciximab within 7 days or eptifibatide, tirofiban, or fibrinolytic therapy within 12 hours of randomization. The exception was CHAMPION PCI, in which patients could be enrolled if they had received a P2Y<sub>12</sub>-receptor inhibitor within 7 days. In CHAMPION PLATFORM, clopidogrel 600 mg was loaded at the end of the PCI procedure; in CHAMPION PCI, clopidogrel 600 mg was loaded at the start of the PCI procedure; and in CHAMPION PHOENIX, 300 mg or 600 mg of clopidogrel could be loaded at the start or at the end of the procedure.

Patients undergoing PCI were randomized to receive a loading dose of clopidogrel or a bolus and infusion of cangrelor (30 μg/kg bolus and then 4 μg/kg thereafter) for at least 2 hours or the duration of the PCI procedure, whichever was longer. Commensurate with a double-dummy study design, the comparator group received either a placebo infusion or placebo oral study drug, respectively. The choice of anticoagulant for the procedure was left to the operator's discretion. The institutional review boards or ethics committees at each enrolling site approved trial protocols, and all patients provided written informed consent to participate.

The primary efficacy end point in CHAMPION PCI and PLATFORM was a composite of death, MI, or ischemia-driven revascularization at 48 hours after randomization. In CHAMPION PHOENIX, the primary efficacy composite end point included a fourth component of stent thrombosis. The end point of death included all-cause death, encompassing death from stroke. The clinical events committee adjudicated the composite end point events, including stroke in CHAMPION PCI and PLATFORM. Severe bleeding unrelated to coronary artery bypass graft surgery was defined according to the GUSTO (Global Use of Strategies to Open Occluded Coronary Arteries) criteria at 48 hours after randomization. Bleeding end points were derived from investigator-reported data and were not prospectively adjudicated.

### Statistical Analysis

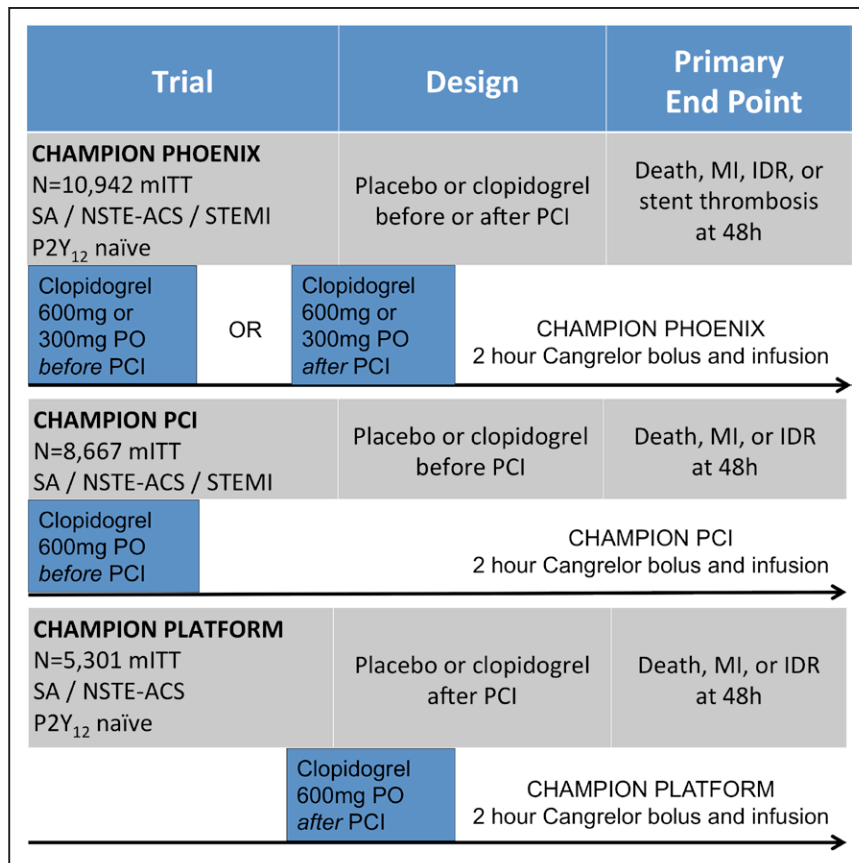
To determine the benefits and risks of cangrelor in patients with ischemic events >1 year old, the present post hoc analysis was performed on the subgroup of patients with a history of stroke or TIA at least 1 year prior to randomization. The primary and secondary efficacy end points were analyzed in the modified intention-to-treat population, defined as those patients who underwent PCI and received the study drug. The safety analysis of bleeding end points was performed in the safety population comprising all patients who received study drug.

Logistic regression was used to estimate effect size, expressed as odds ratios and 95% confidence intervals (CIs) for all efficacy and bleeding end points. Treatment differences among all end points were analyzed with the  $\chi^2$  test. Interaction effects between study treatment and clinically meaningful baseline and procedural characteristics were tested using the Breslow–Day method. No adjustments were made for multiple comparisons. *P* values ≤0.05 were considered to be statistically significant.

Continuous variables are presented as mean±standard deviation. Categorical variables are presented as n (%). All statistical analyses were performed using SAS software, version 9.3 (SAS Institute, Cary, NC).

### Results

Among 24910 randomized patients in the modified intention-to-treat analysis, 1270 (5.1%) had a history of stroke or TIA >1 year old, including 650 assigned to cangrelor and 620 assigned to clopidogrel. Baseline patient and procedural characteristics according to whether there was a history of cerebrovascular event >1 year old and also according to the treatment allocation within the group of patients with a prior cerebrovascular event are shown in Table 1. Overall, those with a history of cerebrovascular event >1 year ago were older and had a higher proportion of diabetes mellitus, hypertension, dyslipidemia,



**Figure 1.** Trial designs and drug administration. CHAMPION PCI indicates A Clinical Trial to Demonstrate the Efficacy of Cangrelor; CHAMPION PHOENIX, A Clinical Trial Comparing Cangrelor to Clopidogrel Standard Therapy in Subjects Who Require Percutaneous Coronary Intervention; CHAMPION PLATFORM, Cangrelor Versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition; IDR, ischemia-driven revascularization; MI, myocardial infarction; mITT, modified intention to treat; NSTEMI-ACS, non-ST-elevation acute coronary syndrome; PCI, percutaneous coronary intervention; SA, stable angina; and STEMI, ST-segment-elevation myocardial infarction.

congestive heart failure, MI, peripheral arterial disease, and coronary artery bypass surgery compared with those without a history of prior cerebrovascular event (Table I in the [Data Supplement](#)). Of those with a history of stroke or TIA, the mean age was 67.7 years, with 27.9% of patients over the age of 75 years. A total of 65.7% were men, and the mean weight was 83.5 kg, with 6.7% weighing <60 kg. Diabetes mellitus was present in 42.4% patients, 21.7% were current smokers, 16.8% had peripheral arterial disease, and 34.6% had a history of prior MI. A total of 54.6% of patients received a drug-eluting stent during PCI.

As shown in Table 2, there was no statistically significant difference in the 48-hour primary efficacy outcome between patients who had a history of cerebrovascular event >1 year old compared with those without a cerebrovascular event (4.8% versus 4.2%, respectively; odds ratio [OR] 1.14, 95% CI 0.89–1.47;  $P=1.15$ ). In patients with a history of prior stroke or TIA, the 48-hour rate of any GUSTO bleeding was 17.1% compared with 15.4% in the remainder of the pooled population (OR 1.13; 95% CI 0.98–1.32;  $P=0.10$ ). There was also no statistically significant difference in the rate of blood transfusion between the groups with and without a history of prior stroke or TIA (Figure 2). For both those with and without a history of prior cerebrovascular events, net adverse clinical events defined as the composite primary efficacy outcome or GUSTO severe bleeding demonstrated a consistent benefit of cangrelor compared with clopidogrel (Table 3).

Efficacy outcomes among patients with a history of cerebrovascular event were consistent with the overall trial results

(Table 4). Specifically, the primary efficacy end point of death, MI, ischemia-driven revascularization, or stent thrombosis at 48 hours occurred in 4.3% of patients treated with cangrelor versus 5.3% treated with clopidogrel (OR 0.80; 95% CI 0.48–1.34;  $P=0.40$ ;  $P$  for interaction =0.97). Stent thrombosis defined by the Academic Research Consortium occurred in 0.3% of cangrelor-treated patients and in 0.6% of clopidogrel-treated patients (OR 0.48; 95% CI 0.09–2.60;  $P=0.38$ ;  $P$  for interaction =0.91).

The 48-hour rate of the primary safety end point of GUSTO severe bleeding in the subgroup with a cerebrovascular event >1 year old was 0.3% in both the clopidogrel and cangrelor arms ( $P=0.97$ ;  $P$  for interaction =0.81; Table 5). Nor were significant differences in GUSTO moderate or severe bleeding observed in patients with prior cerebrovascular event randomized to cangrelor versus clopidogrel (Figure 3), including subgroups over the age of 75 years and those weighing <60 kg. Furthermore, there was no significant difference in the rate of any blood product transfusion in patients with prior cerebrovascular event randomized to cangrelor versus clopidogrel (0.6% versus 1.0%, respectively; OR 0.64; 95% CI 0.18–2.28;  $P=0.49$ ;  $P$  for interaction =0.26). There were 2 episodes (0.31%) of intracranial hemorrhage in the cangrelor group and 1 episode (0.16%) in the clopidogrel group ( $P=0.59$ ).

## Discussion

In patients enrolled in the CHAMPION trials, cangrelor reduced the 48-hour and 30-day rates of ischemic events after PCI, without an increase in GUSTO severe bleeding when

**Table 1. Baseline Clinical and Procedural Characteristics**

	Cangrelor (N=650)	Clopidogrel (N=620)	Prior Cerebrovascular Event* (N=1270)	No Prior Cerebrovascular Event (N=23 546)
Age, y, mean±SD	67.8±10.0	67.6±10.6	67.7±10.3	62.8±11.2
Age ≤75 y, n (%)	178 (27.4)	176 (28.4)	354 (27.9)	3849 (16.3)
Male sex, n (%)	426 (65.5)	408 (65.8)	834 (65.7)	17 099 (72.6)
Weight, kg, mean±SD	83.3±17.5	83.7±18.1	83.5±17.8	84.9±18.5
Weight <60 kg, n (%)	43 (6.6)	42 (6.8)	85 (6.7)	1463 (6.2)
Stable angina, n (%)	195 (30.0)	181 (29.2)	376 (29.6)	7531 (32.0)
Non-ST-segment-elevation acute coronary syndrome, n (%)	409 (62.9)	401 (64.7)	810 (63.8)	13 518 (57.4)
ST-segment-elevation MI, n (%)	46 (7.1)	38 (6.1)	84 (6.6)	2497 (10.6)
Diabetes mellitus, n (%)	274 (42.2)	264 (42.6)	538/1269 (42.4)	6797 (28.9)
Current smoker, n (%)	139 (21.4)	137 (22.1)	276 (21.7)	6867 (29.2)
Hypertension, n (%)	581/648 (89.7)	568/618 (91.9)	1149/1266 (90.8)	17 587/23 467 (74.9)
Hyperlipidemia, n (%)	444/612 (72.5)	424/585 (72.5)	868/1197 (72.5)	13 908/21 642 (64.3)
Prior MI, n (%)	222/643 (34.5)	213/614 (34.7)	435/1257 (34.6)	5241 (22.4)
Congestive heart failure, n (%)	101 (15.7)	107 (17.4)	208/1259 (16.5)	1967 (8.4)
Peripheral artery disease, n (%)	97/636 (15.3)	113/611 (18.5)	210/1247 (16.8)	1506 (6.5)
Prior CABG, n (%)	120 (18.5)	107 (17.3)	227/1269 (17.9)	2343/23 531 (10.0)
Procedural anticoagulant				
Bivalirudin, n (%)	166 (25.5)	156 (25.2)	322 (25.4)	5855/23 541 (24.9)
Unfractionated heparin, n (%)	431 (66.3)	397/619 (64.1)	828/1269 (65.2)	14 849/23 542 (63.1)
LMWH, n (%)	57 (8.8)	58 (9.4)	115 (9.1)	2066/23 538 (8.8)
Fondaparinux, n (%)	5 (0.8)	3 (0.5)	8 (0.6)	155/23 529 (0.7)
Aspirin, n (%)	599/647 (92.6)	578/619 (93.4)	1177/1266 (93.0)	22 036/23 506 (93.7)
Prior thienopyridine use, n (%)	113 (17.4)	103 (16.6)	216 (17.0)	2749 (11.7)
Any drug-eluting stent, n/N (%)	323/600 (53.8)	319/576 (55.4)	642/1176 (54.6)	12 559/22 240 (56.5)
Only bare metal stent, n/N (%)	277/600 (46.2)	257/576 (44.6)	534/1176(45.4)	9681/22 240 (43.5)

CABG indicates coronary artery bypass grafting; LMWH, low molecular weight heparin; and MI, myocardial infarction.

\*Prior stroke column comprises all patients with cerebrovascular event over 1 year ago treated with either cangrelor or clopidogrel. Of those with a history of prior cerebrovascular event, there were no statistically significant differences between those randomized to cangrelor or clopidogrel.

compared with clopidogrel. The present study demonstrates that these results were consistent in a large randomized cohort of patients with a history of cerebrovascular event at least 12 months prior to PCI. There was no increase in GUSTO severe or life-threatening bleeding with cangrelor compared with clopidogrel in these high-risk patients, and the rate of intracerebral hemorrhage was low with both cangrelor and clopidogrel.

Cangrelor's parenteral administration at the time of PCI offers unique advantages over oral adenosine diphosphate receptor antagonists that are limited by reduced oral absorption and poor bioavailability at the time of PCI, particularly in patients with ST-segment-elevation MI.<sup>25–27</sup> This benefit extends to cases of shock and patients with endotracheal intubation in whom oral drug delivery is uncertain.<sup>17</sup> Cangrelor is rapidly metabolized and has a small volume of distribution with prompt reversal on discontinuation (≈60 minutes), a favorable attribute if urgent surgery is required.<sup>17,28</sup>

In the studies from the CHAMPION trials, the 48-hour incidence of stroke was low at 0.05%, similar to that observed in prior PCI studies.<sup>7</sup> The rate of stroke was not increased in patients with cerebrovascular events >1 year, either compared with those without cerebrovascular events, and in those treated with cangrelor compared with clopidogrel. Thus, despite the potency of cangrelor (near 100% inhibition of adenosine diphosphate induced platelet aggregation), these data are consistent with the overall safety profile of cangrelor in the periprocedural period, reflecting its short half-life and rapid elimination.

There was no difference in the primary efficacy outcome between those who had a history of cerebrovascular event >1 year old compared with those who did not. Similarly, the rate of net adverse clinical events was not significantly different between those with and without a history of cerebrovascular event >1 year old. Of note, the CHAMPION trials were not designed to elucidate differences in safety or efficacy

**Table 2. Primary Efficacy and Safety End Points at 48 Hours Overall**

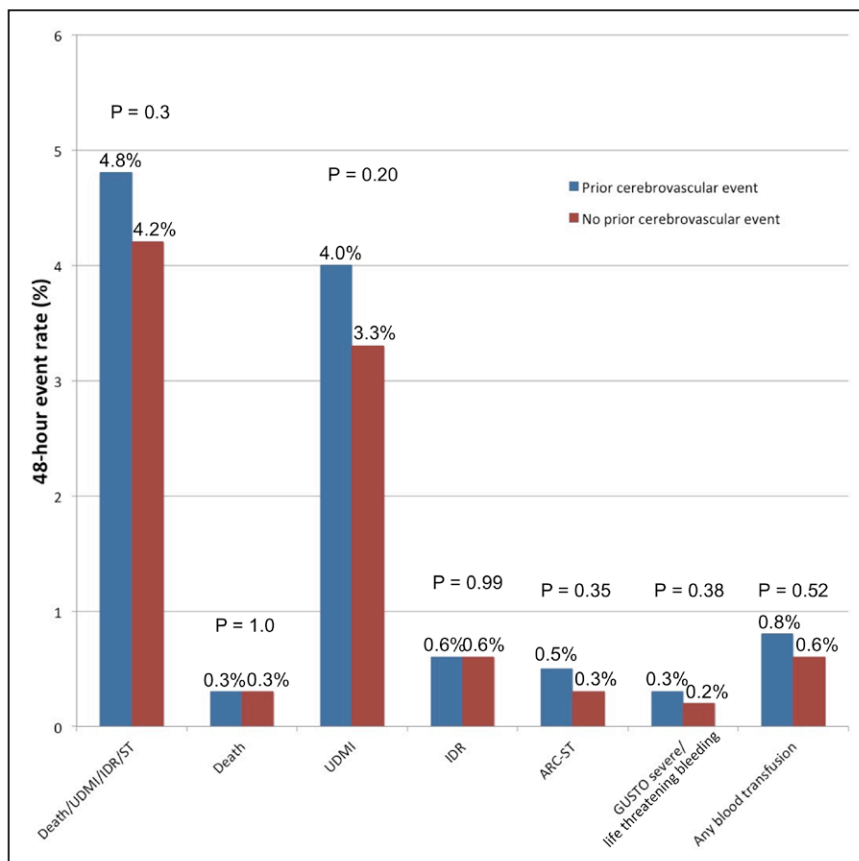
	Prior Cerebrovascular Event (N=1270)	No Prior Cerebrovascular Event (N=23 546)	OR (95% CI)	P Value
Death/UDMI/IDR/ST	61 (4.8)	988/23 518 (4.2)	1.15 (0.88–1.50)	0.30
Death	4 (0.3)	74 (0.3)	1.00 (0.37–2.74)	1.00
UDMI	51 (4.0)	787 (3.3)	1.21 (0.91–1.61)	0.20
IDR	8 (0.6)	149 (0.6)	0.99 (0.49–2.03)	0.99
ST	10 (0.8)	157 (0.7)	1.18 (0.62–2.24)	0.61
ARC-ST	6 (0.5)	75 (0.3)	1.48 (0.64–3.41)	0.35
Any GUSTO bleeding	220/1286 (17.1)	3653/23725 (15.4)	1.13 (0.98–1.32)	0.10
Severe/life threatening	4 (0.3)	47 (0.2)	1.57 (0.57–4.37)	0.38
Any blood transfusion	10/1286 (0.8)	150/23 725 (0.6)	1.23 (0.65–2.34)	0.52

ARC-ST indicates Academic Research Consortium stent definite or probable stent thrombosis; CI, confidence interval; GUSTO, Global Use of Strategies to Open Occluded Coronary Arteries; IDR, ischemia-driven revascularization; OR, odds ratio; ST, stent thrombosis; and UDMI, Universal Definition Myocardial Infarction.

within the subgroup of patients with prior cerebrovascular events. Nevertheless, by combining the data of all 3 trials, a relatively large subgroup of patients were enrolled (1270 patients) who were randomized to cangrelor versus clopidogrel. Although the small sample size likely precludes sufficient statistical power, it seems that the safety of cangrelor compared with clopidogrel persists in this high-risk subgroup, including those above the age of 75 years and weighing <60 kg. Furthermore, in this subgroup with a history of cerebrovascular events, the rate of any GUSTO bleeding was not significantly different in those treated with cangrelor or

clopidogrel. This contrasts with the findings in the TRITON-TIMI 38 study (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction) in patients with prior stroke or TIA in whom Thrombolysis in Myocardial Infarction major bleeding ( $P=0.05$ ) and intracerebral hemorrhage ( $P=0.02$ ) were increased at 15 months with prasugrel compared with clopidogrel.<sup>10</sup>

Importantly, hemorrhagic stroke was uncommon in the present study in patients with cerebrovascular events >1 year old, with 2 episodes in the cangrelor group and 1 episode in



**Figure 2.** Primary efficacy and safety end points at 48 hours. ARC-ST indicates Academic Research Consortium definite or probable stent thrombosis; IDR, ischemia-driven revascularization; ST, stent thrombosis; and UDMI, Universal Definition Myocardial Infarction.

**Table 3. Net Adverse Clinical Events at 48 Hours in Patients With and Without Cerebrovascular Events >1 Year Old**

	Prior Cerebrovascular Event				No Prior Cerebrovascular Event				Interaction P Value
	Cangrelor (N=650)	Clopidogrel (N=620)	OR (95% CI)	P Value	Cangrelor (N=11 763)	Clopidogrel (N=11 755)	OR (95% CI)	P Value	
Net adverse clinical events	30 (4.6)	35 (5.6)	0.81 (0.49–1.33)	0.41	465 (4.0)	559 (4.8)	0.82 (0.73–0.93)	0.003	0.94

CI indicates confidence interval; and OR, odds ratio.

the clopidogrel group. The 2 patients with intracranial hemorrhage in the cangrelor arm were 75 and 76 years old. Both patients were treated with aspirin, one received periprocedural heparin while the other received bivalirudin, and neither patient was treated with a glycoprotein IIb/IIIa inhibitor. The one patient with intracranial hemorrhage in the clopidogrel arm was 81 years old and similarly received aspirin and heparin without any periprocedural glycoprotein IIb/IIIa inhibitor. All 3 patients weighed between 84 and 94 kg, and all 3 strokes occurred within 36 hours. Thus, no clear predictors of these rare events were identified. While these 3 events preclude stating with certainty whether there is absolutely no increased risk of intracranial hemorrhage with cangrelor compared with clopidogrel in this high-risk subgroup, this complication would appear to be uncommon with both agents as long as the enrollment criteria of the present trials are respected (exclusion of patients with a history of stroke or TIA within 1 year, any history of hemorrhagic stroke,

cerebral arteriovenous malformation, intracranial aneurysm, or current warfarin use and by extension use of other chronic oral anticoagulants).

There are several limitations to this study. There were differences in the study design of the 3 CHAMPION trials. All 3 trials enrolled patients with acute coronary syndromes, while CHAMPION PLATFORM was the only trial that excluded patients with ST-segment–elevation MI, a group at higher risk of ischemic stroke. The loading dose and timing of administration of clopidogrel during the procedure varied in all 3 CHAMPION trials. However, this difference in timing is unlikely to have affected the outcomes of stroke because every patient received clopidogrel by the end of the procedure. Finally, given the small size of some of the subgroups of the prior cerebrovascular event cohort (eg, patients >75 years of age or <60 kg in body weight), we cannot exclude some increase in hemorrhagic risk with cangrelor, particularly, in high-risk groups.

**Table 4. Primary Efficacy End Points at 48 Hours in Patients With and Without Prior Cerebrovascular Events >1 Year**

	Prior Cerebrovascular Event				No Prior Cerebrovascular Event				Interaction P Value
	Cangrelor (n=650)	Clopidogrel (n=620)	OR (95% CI)	P Value	Cangrelor (n=11 763)	Clopidogrel (n=11 755)	OR (95% CI)	P Value	
48-Hour death/UMI/IDR/ST	28 (4.3)	33 (5.3)	0.80 (0.48–1.34)	0.40	444 (3.8)	544 (4.6)	0.81 (0.71–0.92)	0.001	0.97
ST	3 (0.5)	7 (1.1)	0.41 (0.10–1.58)	0.18	59 (0.5)	98 (0.8)	0.60 (0.43–0.83)	0.002	0.58
Death/UMI/IDR/ARC-ST	27 (4.2)	32 (5.2)	0.80 (0.47–1.35)	0.39	418 (3.6)	509 (4.3)	0.81 (0.71–0.93)	0.002	0.94
ARC-ST	2 (0.3)	4 (0.6)	0.48 (0.09–2.60)	0.38	26 (0.2)	49 (0.4)	0.53 (0.33–0.85)	0.008	0.91
Death	2 (0.3)	2 (0.3)	0.95 (0.13–6.79)	0.96	31 (0.3)	43 (0.4)	0.72 (0.45–1.14)	0.16	0.78
UMI	24 (3.7)	27 (4.4)	0.84 (0.48–1.48)	0.55	362 (3.1)	425 (3.6)	0.85 (0.73–0.98)	0.02	0.99
IDR	3 (0.5)	5 (0.8)	0.57 (0.14–2.40)	0.44	63 (0.5)	86 (0.7)	0.73 (0.53–1.01)	0.06	0.74
30-Day death/UMI/IDR/ST	45/646 (7.0)	48/618 (7.8)	0.89 (0.58–1.36)	0.59	608/11 715 (5.2)	695/11 692 (5.9)	0.87 (0.77–0.97)	0.01	0.91
ST	7 (1.1)	13 (2.1)	0.51 (0.20–1.29)	0.15	106 (0.9)	148 (1.3)	0.71 (0.55–0.92)	0.07	0.50
Death/UMI/IDR/ARC-ST	44/646 (6.8)	47/618 (7.6)	0.89 (0.58–1.36)	0.59	584 (5.0)	660 (5.6)	0.88 (0.78–0.98)	0.02	0.96
ARC-ST	6 (0.9)	10 (1.6)	0.57 (0.21–1.58)	0.27	75 (0.6)	99 (0.8)	0.75 (0.56–1.02)	0.07	0.98
Death	14 (2.2)	14 (2.3)	0.96 (0.45–2.02)	0.91	121 (1.0)	125 (1.1)	0.97 (0.75–1.24)	0.79	0.98
UMI	25 (3.9)	29 (4.7)	0.82 (0.47–1.41)	0.47	392 (3.3)	457 (3.9)	0.85 (0.74–0.98)	0.02	0.89
IDR	8 (1.2)	13 (2.1)	0.58 (0.24–1.42)	0.23	144 (1.2)	163 (1.4)	0.88 (0.70–1.10)	0.27	0.38
1-Year death	30/373 (8.0)	31/372 (8.3)	0.96 (0.57–1.62)	0.89	197/6522 (3.0)	223/6480 (3.4)	0.87 (0.72–1.06)	0.17	0.74

ARC-ST indicates Academic Research Consortium stent definite or probable stent thrombosis; CI, confidence interval; GUSTO, Global Use of Strategies to Open Occluded Coronary Arteries; IDR, ischemia-driven revascularization; OR, odds ratio; ST, stent thrombosis; and UDMI, Universal Definition Myocardial Infarction.

**Table 5. Safety End Points of Bleeding at 48 Hours in Subgroup With and Without Prior Cerebrovascular Event >1 Year**

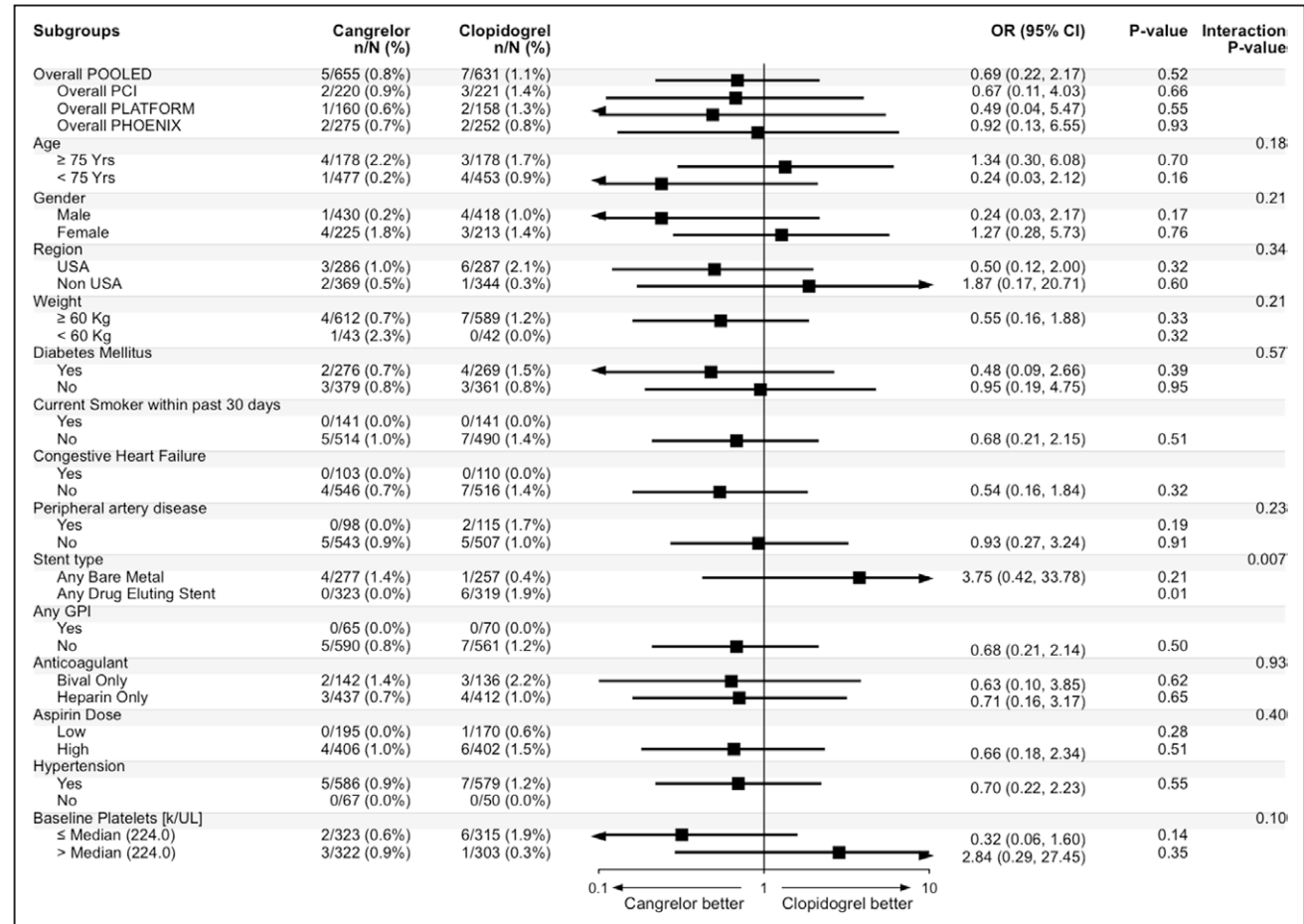
	Prior Cerebrovascular Event				No Prior Cerebrovascular Event				Interaction P Value
	Cangrelor (n=655)	Clopidogrel (n=631)	OR (95% CI)	P Value	Cangrelor (n=11 862)	Clopidogrel (n=11 863)	OR (95% CI)	P Value	
Any GUSTO bleeding	112 (17.1)	108 (17.1)	1.00 (0.75–1.34)	0.99	2074 (17.5)	1579 (13.3)	1.38 (1.29–1.48)	<0.001	0.03
Severe/life threatening	2 (0.3)	2 (0.3)	0.96 (0.14–6.86)	0.97	26 (0.2)	21 (0.2)	1.24 (0.70–2.20)	0.47	0.81
Moderate	4 (0.6)	5 (0.8)	0.77 (0.21–2.88)	0.70	72 (0.6)	51 (0.4)	1.41 (0.99–2.03)	0.06	0.38
Mild	109 (16.6)	101 (16.0)	1.05 (0.78–1.41)	0.76	1990 (16.8)	1517 (12.8)	1.37 (1.28–1.48)	<0.001	0.08
TIMI major/minor bleeding	6 (0.9)	5 (0.8)	1.16 (0.35–3.81)	0.81	103 (0.9)	73 (0.6)	1.41 (1.05–1.91)	0.02	0.75
Major	3 (0.5)	3 (0.5)	0.96 (0.19–4.79)	0.96	29 (0.2)	25 (0.2)	1.16 (0.68–1.98)	0.59	0.83
Any ACUITY bleeding	112 (17.1)	108 (17.1)	1.00 (0.75–1.34)	0.99	2074 (17.5)	1579 (13.3)	1.38 (1.29–1.48)	<0.001	0.03
Major	33 (5.0)	31 (4.9)	1.03 (0.62–1.70)	0.92	499 (4.2)	318 (2.7)	1.59 (1.38–1.84)	<0.001	0.10
Blood transfusion	4 (0.6)	6 (1.0)	0.64 (0.18–2.28)	0.49	86 (0.7)	64 (0.5)	1.35 (0.97–1.86)	0.07	0.26
Intracerebral hemorrhage	2 (0.3)	1 (0.2)	1.93 (0.17–21.33)	0.59	4 (0.03)	1 (0.008)	4.00 (0.45–35.8)	0.18	0.66

ACUITY indicates Acute Catheterization and Urgent Intervention Triage Strategy; CI, confidence interval; GUSTO, Global Use of Strategies to Open Occluded Coronary Arteries; OR, odds ratio; and TIMI, Thrombolysis in Myocardial Infarction.

### Conclusions

Among high-risk patients in the CHAMPION trials with a prior cerebrovascular event at least 1 year before the PCI, the efficacy and bleeding profile of cangrelor compared with

clopidogrel was similar to that in the overall trial, though the relatively small sample size of this subgroup precludes sufficient statistical power to be completely definitive. Efficacy was preserved, severe bleeding was not increased, and the rate



**Figure 3.** Forest plot for GUSTO severe and moderate bleeding in subjects with a history of cerebrovascular event >1 year undergoing PCI and randomization to either cangrelor or clopidogrel. CI indicates confidence interval; GUSTO, Global Use of Strategies to Open Occluded Coronary Arteries; OR, odds ratio; and PCI, percutaneous coronary intervention.

of intracerebral hemorrhage was low with both cangrelor and clopidogrel.

### Acknowledgments

Steve Elkin, MS, from The Medicines Company performed the initial analyses. Yuyin Liu, MS, and Xiaohua Chen, MS, from Harvard Clinical Research Institute performed independent verification of the analyses. Harvard Clinical Research Institute received funding from The Medicines Company and Chiesi for these analyses.

### Sources of Funding

This study was supported by The Medicines Company.

### Disclosures

Dr Stone discloses the following relationships: personal fees from Velomedix, personal fees from Toray, personal fees from Vascular Dynamics, personal fees from Miracor, personal fees from TherOx, personal fees from Reva, personal fees from V-wave, personal fees from Matrizyme, personal fees from Ablative Solutions, personal fees from Neovasc, personal fees from Medical Development Technologies, other from MedFocus family of funds, other from Guided Delivery Systems, other from Micardia, other from Vascular Nanotransfer Technologies, other from Cagent, other from Qool Therapeutics, other from Caliber, other from Aria, other from Biostar family of funds, outside the submitted work, and Consultant on prasugrel patent litigation paid for by Lupin Pharmaceuticals. Dr Bhatt discloses the following relationships: Advisory Board—Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, Regado Biosciences; Board of Directors—Boston VA Research Institute, Society of Cardiovascular Patient Care; Chair—American Heart Association Quality Oversight Committee; Data Monitoring Committees—Duke Clinical Research Institute, Harvard Clinical Research Institute, Mayo Clinic, Population Health Research Institute; Honoraria—American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees), Harvard Clinical Research Institute (clinical trial steering committee), HMP Communications (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Guest Editor; Associate Editor), Population Health Research Institute (clinical trial steering committee), Slack Publications (Chief Medical Editor, Cardiology Today's Intervention), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees); Other—Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), VA CART Research and Publications Committee (Chair); Research Funding—Amarin, Amgen, AstraZeneca, Bristol-Myers Squibb, Eisai, Ethicon, Forest Laboratories, Ischemix, Lilly, Medtronic, Pfizer, Roche, Sanofi Aventis, The Medicines Company (including for his role as co-Chair of the CHAMPION trials); Royalties—Elsevier (Editor, Cardiovascular Intervention: A Companion to Braunwald's Heart Disease); Site Co-Investigator—Biotronik, Boston Scientific, St. Jude Medical; Trustee—American College of Cardiology; Unfunded Research—FlowCo, PLx Pharma, Takeda.

### References

- Shivaraju A, Yu C, Kattan MW, Xie H, Shroff AR, Vidovich MI. Temporal trends in percutaneous coronary intervention-associated acute cerebrovascular accident (from the 1998 to 2008 Nationwide Inpatient Sample Database). *Am J Cardiol* 2014;114:206–213.
- Aggarwal A, Dai D, Rumsfeld JS, Klein LW, Roe MT; American College of Cardiology National Cardiovascular Data Registry. Incidence and predictors of stroke associated with percutaneous coronary intervention. *Am J Cardiol*. 2009;104:349–353. doi: 10.1016/j.amjcard.2009.03.046.
- Wong SC, Minutello R, Hong MK. Neurological complications following percutaneous coronary interventions (a report from the 2000-2001 New York State Angioplasty Registry). *Am J Cardiol*. 2005;96:1248–1250. doi: 10.1016/j.amjcard.2005.06.065.
- Hoffman SJ, Yee AH, Slusser JP, Rihal CS, Holmes DR Jr, Rabinstein AA, Gulati R. Neuroimaging patterns of ischemic stroke after percutaneous

coronary intervention. *Catheter Cardiovasc Interv*. 2015;85:1033–1040. doi: 10.1002/ccd.25678.

- Guptill JT, Mehta RH, Armstrong PW, Horton J, Laskowitz D, James S, Granger CB, Lopes RD. Stroke after primary percutaneous coronary intervention in patients with ST-segment elevation myocardial infarction: timing, characteristics, and clinical outcomes. *Circ Cardiovasc Interv*. 2013;6:176–183. doi: 10.1161/CIRCINTERVENTIONS.112.000159.
- Werner N, Bauer T, Hochadel M, Zahn R, Weidinger F, Marco J, Hamm C, Gitt AK, Zeymer U. Incidence and clinical impact of stroke complicating percutaneous coronary intervention: results of the Euro heart survey percutaneous coronary interventions registry. *Circ Cardiovasc Interv*. 2013;6:362–369. doi: 10.1161/CIRCINTERVENTIONS.112.000170.
- Kwok CS, Kontopantelis E, Myint PK, Zaman A, Berry C, Keavney B, Nolan J, Ludman PF, de Belder MA, Buchan I, Mamas MA; British Cardiovascular Intervention Society; National Institute for Cardiovascular Outcomes Research. Stroke following percutaneous coronary intervention: type-specific incidence, outcomes and determinants seen by the British Cardiovascular Intervention Society 2007-12. *Eur Heart J*. 2015;36:1618–1628. doi: 10.1093/eurheartj/ehv113.
- Mahaffey KW, Hager R, Wojdyla D, White HD, Armstrong PW, Alexander JH, Tricoci P, Lopes RD, Ohman EM, Roe MT, Harrington RA, Wallentin L. Meta-analysis of intracranial hemorrhage in acute coronary syndromes: incidence, predictors, and clinical outcomes. *J Am Heart Assoc*. 2015;4:e001512. doi: 10.1161/JAHA.114.001512.
- Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK; Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med*. 2001;345:494–502. doi: 10.1056/NEJMoa010746.
- 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. doi: 10.1056/NEJMoa0706482.
- Cannon CP, Harrington RA, James S, Ardissino D, Becker RC, Emanuelsson H, Husted S, Katus H, Keltai M, Khurmi NS, Kontny F, Lewis BS, Steg PG, Storey RF, Wojdyla D, Wallentin L; Platelet Inhibition and Patient Outcomes Investigators. Comparison of ticagrelor with clopidogrel in patients with a planned invasive strategy for acute coronary syndromes (PLATO): a randomised double-blind study. *Lancet*. 2010;375:283–293. doi: 10.1016/S0140-6736(09)62191-7.
- Amsterdam EA, Wenger NK, Brindis RG, Casey DE Jr, Ganiats TG, Holmes DR Jr, Jaffe AS, Jneid H, Kelly RF, Kontos MC, Levine GN, Liebson PR, Mukherjee D, Peterson ED, Sabatine MS, Smalling RW, Zieman SJ; ACC/AHA Task Force Members. 2014 AHA/ACC Guideline for the Management of Patients with Non-ST-Elevation Acute Coronary Syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;130:e344–e426. doi: 10.1161/CIR.0000000000000134.
- Ducrocq G, Amarencio P, Labreuche J, Alberts MJ, Mas JL, Ohman EM, Goto S, Lavallée P, Bhatt DL, Steg PG. A history of stroke/transient ischemic attack indicates high risks of cardiovascular event and hemorrhagic stroke in patients with coronary artery disease. *Circulation*. 2013;127:730–738. doi: 10.1161/CIRCULATIONAHA.112.141572.
- 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. doi: 10.1056/NEJMoa1200933.
- 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, Rorick 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. doi: 10.1056/NEJMoa1109719.
- Bonaca MP, Scirica BM, Braunwald E, Wiviott SD, Goto S, Nilsen DW, Bonarjee V, Murphy SA, Morrow DA. New ischemic stroke and outcomes with vorapaxar versus placebo: results from the TRA 2 °P-TIMI 50 trial. *J Am Coll Cardiol*. 2014;64:2318–2326. doi: 10.1016/j.jacc.2014.07.997.



17. Akers WS, Oh JJ, Oestreich JH, Ferraris S, Wethington M, Steinhubl SR. Pharmacokinetics and pharmacodynamics of a bolus and infusion of cangrelor: a direct, parenteral P2Y<sub>12</sub> receptor antagonist. *J Clin Pharmacol*. 2010;50:27–35. doi: 10.1177/0091270009344986.
18. Harrington RA, Stone GW, McNulty S, White HD, Lincoff AM, Gibson CM, Pollack CV Jr, Montalescot G, Mahaffey KW, Kleiman NS, Goodman SG, Amine M, Angiolillo DJ, Becker RC, Chew DP, French WJ, Leisch F, Parikh KH, Skerjanec S, Bhatt DL. Platelet inhibition with cangrelor in patients undergoing PCI. *N Engl J Med*. 2009;361:2318–2329. doi: 10.1056/NEJMoa0908628.
19. Bhatt DL, Lincoff AM, Gibson CM, Stone GW, McNulty S, Montalescot G, Kleiman NS, Goodman SG, White HD, Mahaffey KW, Pollack CV Jr, Manoukian SV, Widimsky P, Chew DP, Cura F, Manukov I, Tousek F, Jafar MZ, Arneja J, Skerjanec S, Harrington RA; CHAMPION PLATFORM Investigators. Intravenous platelet blockade with cangrelor during PCI. *N Engl J Med*. 2009;361:2330–2341. doi: 10.1056/NEJMoa0908629.
20. Bhatt DL, Stone GW, Mahaffey KW, Gibson CM, Steg PG, Hamm CW, Price MJ, Leonardi S, Gallup D, Bramucci E, Radke PW, Widimsky P, Tousek F, Tauth J, Spriggs D, McLaurin BT, Angiolillo DJ, Généreux P, Liu T, Prats J, Todd M, Skerjanec S, White HD, Harrington RA; CHAMPION PHOENIX Investigators. Effect of platelet inhibition with cangrelor during PCI on ischemic events. *N Engl J Med*. 2013;368:1303–1313. doi: 10.1056/NEJMoa1300815.
21. White HD, Chew DP, Dauerman HL, Mahaffey KW, Gibson CM, Stone GW, Gruberg L, Harrington RA, Bhatt DL. Reduced immediate ischemic events with cangrelor in PCI: a pooled analysis of the CHAMPION trials using the universal definition of myocardial infarction. *Am Heart J*. 2012;163:182–190.e4. doi: 10.1016/j.ahj.2011.11.001.
22. Steg PG, Bhatt DL, Hamm CW, Stone GW, Gibson CM, Mahaffey KW, Leonardi S, Liu T, Skerjanec S, Day JR, Iwaoka RS, Stuckey TD, Gogia HS, Gruberg L, French WJ, White HD, Harrington RA; CHAMPION Investigators. Effect of cangrelor on periprocedural outcomes in percutaneous coronary interventions: a pooled analysis of patient-level data. *Lancet*. 2013;382:1981–1992. doi: 10.1016/S0140-6736(13)61615-3.
23. Thygesen K, Alpert JS, White HD; Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. Universal definition of myocardial infarction. *J Am Coll Cardiol*. 2007;50:2173–2195. doi: 10.1016/j.jacc.2007.09.011.
24. Leonardi S, Mahaffey KW, White HD, Gibson CM, Stone GW, Steg GW, Hamm CW, Price MJ, Todd M, Dietrich M, Gallup D, Liu T, Skerjanec S, Harrington RA, Bhatt DL. Rationale and design of the Cangrelor Versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition PHOENIX trial. *Am Heart J*. 2012;163:768–776.e2. doi: 10.1016/j.ahj.2012.02.018.
25. Alexopoulos D, Xanthopoulou I, Gkizas V, Kassimis G, Theodoropoulos KC, Makris G, Koutsogiannis N, Damelou A, Tsigkas G, Davlouros P, Hahalis G. Randomized assessment of ticagrelor versus prasugrel antiplatelet effects in patients with ST-segment-elevation myocardial infarction. *Circ Cardiovasc Interv*. 2012;5:797–804. doi: 10.1161/CIRCINTERVENTIONS.112.972323.
26. Angiolillo DJ, Franchi F, Waksman R, Sweeny JM, Raveendran G, Teng R, Zhao Y, Carlson G, Khan N, Mehran R. Effects of ticagrelor versus clopidogrel in troponin-negative patients with low-risk ACS undergoing ad hoc PCI. *J Am Coll Cardiol*. 2016;67:603–613. doi: 10.1016/j.jacc.2015.11.044.
27. Alexopoulos D, Bhatt DL, Hamm CW, Steg PG, Stone GW. Early P2Y<sub>12</sub> inhibition in ST-segment elevation myocardial infarction: Bridging the gap. *Am Heart J*. 2015;170:3–12. doi: 10.1016/j.ahj.2015.04.012.
28. Angiolillo DJ, Firstenberg MS, Price MJ, Tummala PE, Hutyra M, Welsby IJ, Voeltz MD, Chandna H, Ramaiah C, Brtko M, Cannon L, Dyke C, Liu T, Montalescot G, Manoukian SV, Prats J, Topol EJ; BRIDGE Investigators. Bridging antiplatelet therapy with cangrelor in patients undergoing cardiac surgery: a randomized controlled trial. *JAMA*. 2012;307:265–274. doi: 10.1001/jama.2011.2002.

## Impact of Cerebrovascular Events Older Than One Year on Ischemic and Bleeding Outcomes With Cangrelor in Percutaneous Coronary Intervention

Neal N. Sawlani, Robert A. Harrington, Gregg W. Stone, Ph. Gabriel Steg, C. Michael Gibson, Christian W. Hamm, Matthew J. Price, Jayne Prats, Efthymios N. Deliargyris, Kenneth W. Mahaffey, Harvey D. White and Deepak L. Bhatt

*Circ Cardiovasc Interv.* 2017;10:

doi: 10.1161/CIRCINTERVENTIONS.116.004380

*Circulation: Cardiovascular Interventions* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Copyright © 2016 American Heart Association, Inc. All rights reserved.

Print ISSN: 1941-7640. Online ISSN: 1941-7632

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://circinterventions.ahajournals.org/content/10/1/e004380>

Data Supplement (unedited) at:

<http://circinterventions.ahajournals.org/content/suppl/2017/01/16/CIRCINTERVENTIONS.116.004380.DC1>

**Permissions:** Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation: Cardiovascular Interventions* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the [Permissions and Rights Question and Answer](#) document.

**Reprints:** Information about reprints can be found online at:  
<http://www.lww.com/reprints>

**Subscriptions:** Information about subscribing to *Circulation: Cardiovascular Interventions* is online at:  
<http://circinterventions.ahajournals.org/subscriptions/>

Supplemental Table 1

**Supplementary Table 1.** Baseline clinical and procedural characteristics

	<b>Prior Cerebrovascular Event* (N=1,270)</b>	<b>No Prior Cerebrovascular Event (N=23,546)</b>	p value
Age, y, mean $\pm$ SD	67.7 $\pm$ 10.3	62.8 $\pm$ 11.2	<0.0001
Male gender, n (%)	834 (65.7)	17,099 (72.6)	<0.0001
Weight, kg, mean $\pm$ SD	83.5 $\pm$ 17.8	84.9 $\pm$ 18.5	0.0105
Stable angina, n (%)	376 (29.6)	7,531 (32.0)	0.0765
Non-ST-segment elevation acute coronary syndrome, n (%)	810 (63.8)	13,518 (57.4)	<0.0001
ST-segment elevation MI, n (%)	84 (6.6)	2,497 (10.6)	<0.0001
Diabetes, n (%)	538/1269 (42.4)	6,797 (28.9)	<0.0001
Current smoker, n (%)	276 (21.7)	6867 (29.2)	<0.0001
Hypertension, n (%)	1149/1266 (90.8)	17587/23467 (74.9)	<0.0001
Hyperlipidemia, n (%)	868/1197 (72.5)	13908/21642 (64.3)	<0.0001
Prior MI, n (%)	435/1257 (34.6)	5,241 (22.4)	<0.0001
Congestive heart failure, n (%)	208/1259 (16.5)	1,967 (8.4)	<0.0001
Peripheral artery disease, n (%)	210/1247 (16.8)	1,506 (6.5)	<0.0001
Prior CABG	227/1269 (17.9)	2343/23531 (10.0)	<0.0001
Procedural anticoagulant			
Bivalirudin, n (%)	322 (25.4)	5,855/23541 (24.9)	0.6983
Unfractionated Heparin, n (%)	828/1269 (65.2)	14,849/23542 (63.1)	0.1178
LMWH, n (%)	115 (9.1)	2,066/ 23538 (8.8)	0.7334
Fondaparinux, n (%)	8 (0.6)	155/ 23529 (0.7)	0.9014
Aspirin, n (%)	1177/1266 (93.0)	22,036/23506 (93.7%)	0.2679
Prior thienopyridine use, n (%)	216 (17.0)	2,749 (11.7)	<0.0001
Any drug eluting stent, n/N (%)	642/1176 (54.6)	12559/22240 (56.5)	0.2055
Only bare metal stent, n/N (%)	534/1176(45.4)	9681/22240 (43.5)	0.2055

MI=myocardial infarction. LMWH=low molecular weight heparin.

\*Prior stroke column comprises all patients with cerebrovascular event older than one year treated with either cangrelor or clopidogrel.