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

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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, 1270 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.[1–3] The majority of periprocedural strokes are ischemic in nature, with an embolic pattern and often involving the middle cerebral artery.[4,5] Stroke during PCI is associated with a substantial increase in both in-hospital and 30-day mortality.[6,7] Risk factors for periprocedural stroke include known cerebrovascular disease, older age, coronary atherosclerosis, and intra-aortic balloon pump use.[1–3] A history of prior cerebrovascular event also increases the risk of intracerebral hemorrhage related to PCI.[8]

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.[9–12] 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).[10,13] The recently approved thrombin receptor antagonist vorapaxar is also contraindicated

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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.[14–16]

Cangrelor is a potent intravenous adenosine diphosphate–receptor antagonist that directly and reversibly blocks platelet aggregation.[17] Cangrelor has been compared directly with clopidogrel, the most widely used oral $P2Y_{12}$ 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.[18–23] 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).[18–20,24] 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 $P2Y_{12}$-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 $P2Y_{12}$-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 χ^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 24 910 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,

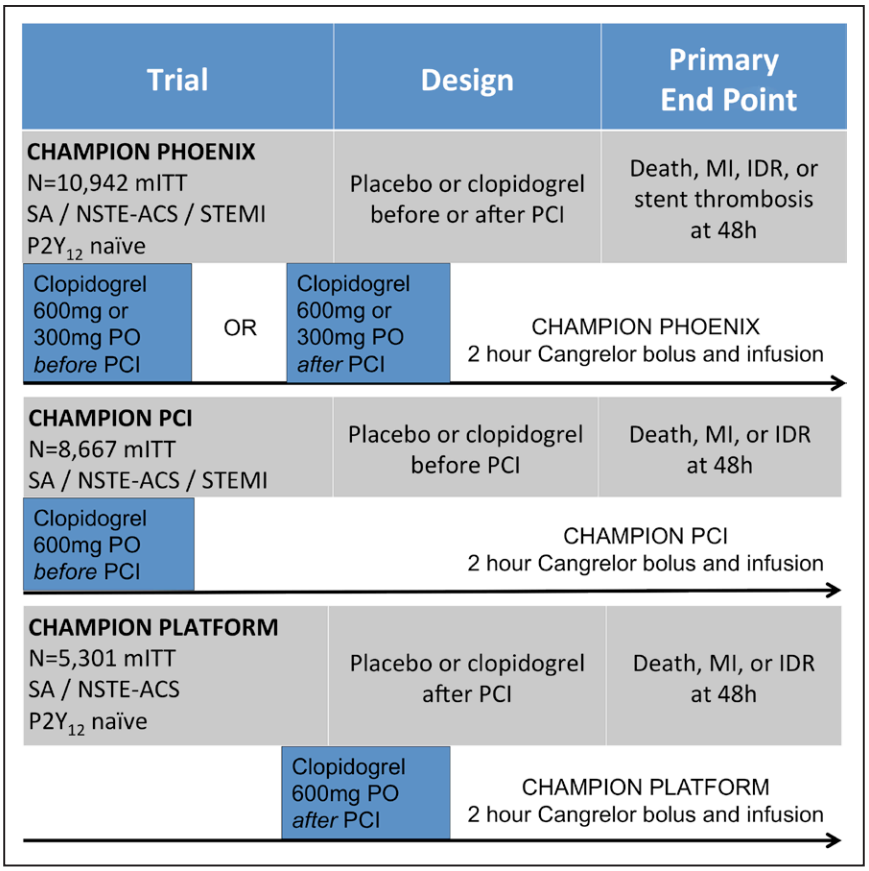

Figure 1. Trial designs and drug administration. CHAMPION PCI indicates A Clinical Trial to Demonstrate the Efficacy of Cangrelor; CHAMPION PHOENIX, A Clinical Trial Comparing Cangrelor to Clopidogrel Standard Therapy in Subjects Who Require Percutaneous Coronary Intervention; CHAMPION PLATFORM, Cangrelor Versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition; IDR, ischemia-driven revascularization; MI, myocardial infarction; mITT, modified intention to treat; NSTE-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.[25–27] This benefit extends to cases of shock and patients with endotracheal intubation in whom oral drug delivery is uncertain.[17] 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.[17,28]

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.[7] 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.[10]

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

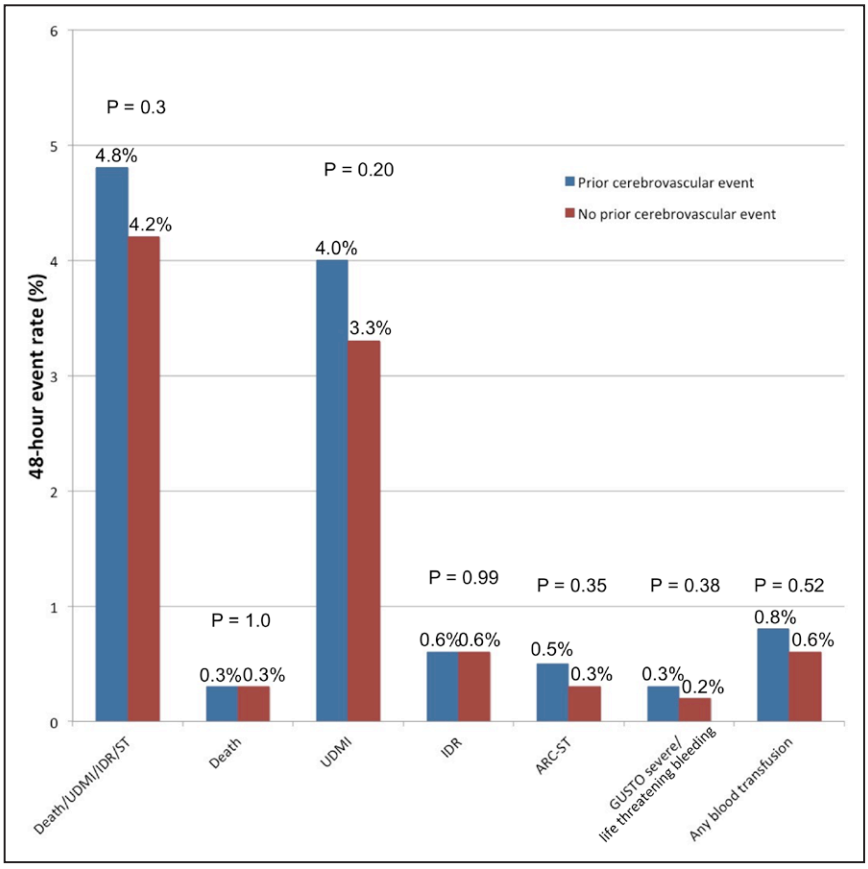

Figure 2. Primary efficacy and safety end points at 48 hours. ARC-ST indicates Academic Research Consortium definite or probable stent thrombosis; IDR, ischemia-driven revascularization; ST, stent thrombosis; and UDMI, Universal Definition Myocardial Infarction.

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				
	Cangrelor (N=650)	Clopidogrel (N=620)	OR (95% CI)	*P* Value	Cangrelor (N=11 763)	Clopidogrel (N=11 755)	OR (95% CI)	*P* Value	Interaction *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				
	Cangrelor (n=650)	Clopidogrel (n=620)	OR (95% CI)	*P* Value	Cangrelor (n=11 763)	Clopidogrel (n=11 755)	OR (95% CI)	*P* Value	Interaction *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				
	Cangrelor (n=655)	Clopidogrel (n=631)	OR (95% CI)	*P* Value	Cangrelor (n=11 862)	Clopidogrel (n=11 863)	OR (95% CI)	*P* Value	Interaction *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

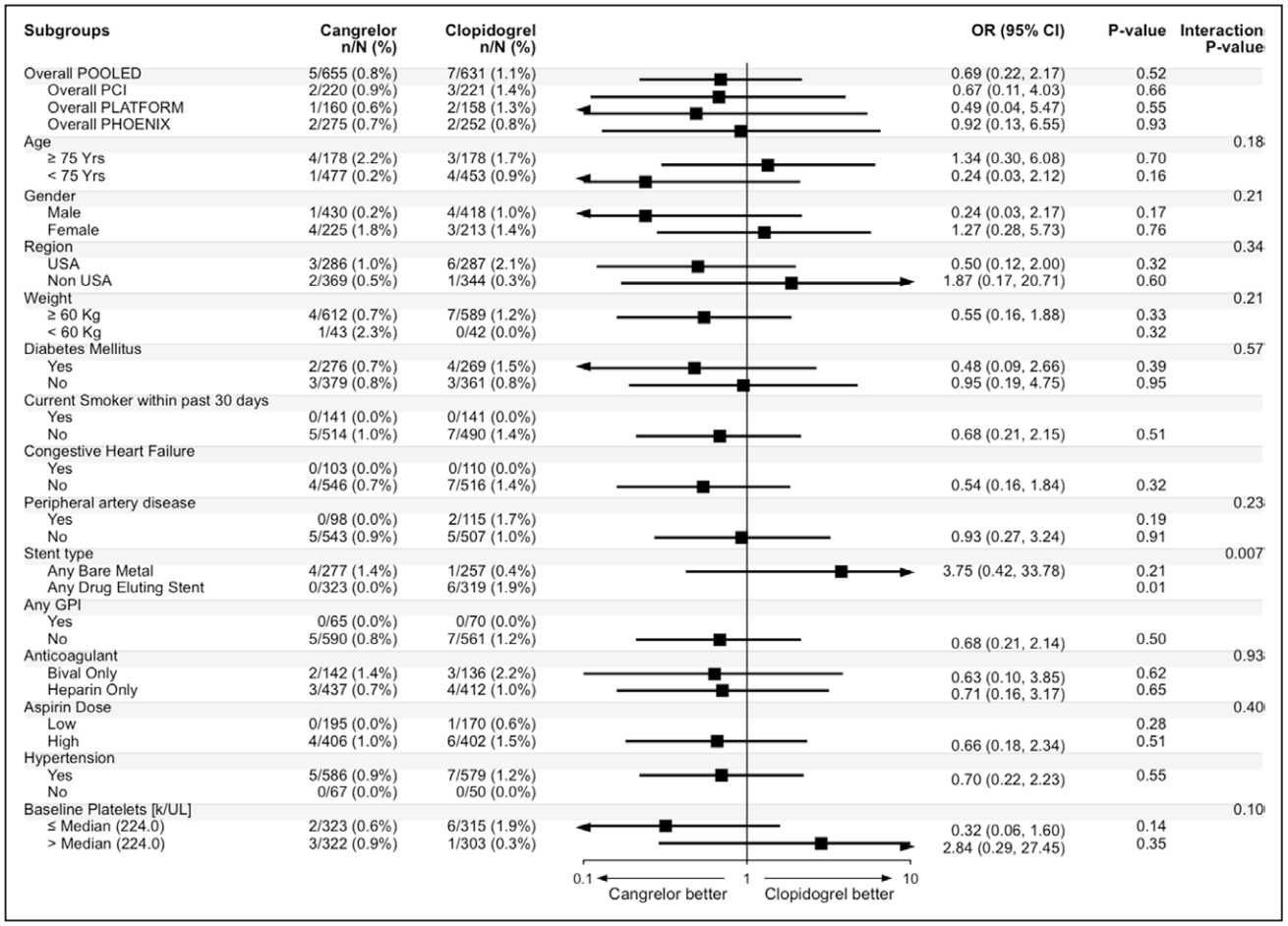

Figure 3. Forest plot for GUSTO severe and moderate bleeding in subjects with a history of cerebrovascular event >1 year undergoing PCI and randomization to either cangrelor or clopidogrel. CI indicates confidence interval; GUSTO, Global Use of Strategies to Open Occluded Coronary Arteries; OR, odds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

of intracerebral hemorrhage was low with both cangrelor and clopidogrel.

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

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Supplemental Table 1

Supplementary Table 1. Baseline clinical and procedural characteristics

	Prior Cerebrovascular Event* (N=1,270)	**No Prior Cerebrovascular Event (N=23,546)**	p value
Age, y, mean ± SD	67·7 ± 10·3	62·8 ± 11·2	<0.0001
Male gender, n (%)	834 (65·7)	17,099 (72·6)	<0.0001
Weight, kg, mean ± SD	83·5±17·8	84·9 ± 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.