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Cangrelor With and Without Glycoprotein IIb/IIIa Inhibitors in Patients Undergoing Percutaneous Coronary Intervention

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ABSTRACT

BACKGROUND Cangrelor, an intravenous, reversible $P2Y_{12}$ antagonist, is approved for use in patients undergoing percutaneous coronary intervention (PCI).

OBJECTIVES This study sought to evaluate the efficacy and safety of cangrelor compared with clopidogrel in subgroups that did and did not receive glycoprotein IIb/IIIa inhibitors (GPIs).

METHODS This pooled, patient-level analysis of the 3 CHAMPION (Cangrelor versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition) trials analyzed all randomized patients who underwent PCI and received the study drug (n = 24,902). Only bailout/rescue GPI use was permitted, except in CHAMPION PCI, in which routine or bailout/rescue GPI use was at the site investigator's discretion. The primary efficacy endpoint was the composite of all-cause mortality, myocardial infarction, ischemia-driven revascularization, or stent thrombosis at 48 h after randomization.

RESULTS Overall, 3,173 patients (12.7%) received a GPI, most commonly eptifibatide (69.4%). Despite variation in indications for GPIs, baseline characteristics were well balanced between the cangrelor and clopidogrel arms in subsets receiving and not receiving GPIs. Rates of the primary composite endpoint were lower with cangrelor compared with clopidogrel in patients who did (4.9% vs. 6.5%; odds ratio [OR]: 0.74; 95% confidence interval [CI]: 0.55 to 1.01) or did not receive a GPI (3.6% vs. 4.4%; OR: 0.82; 95% CI: 0.72 to 0.94; P_{int} = 0.55). Cangrelor did not increase the primary safety endpoint, GUSTO-defined severe/life-threatening bleeding, in patients who did (0.4% vs. 0.5%; OR: 0.71; 95% CI: 0.25 to 1.99) or did not receive GPIs (0.2% vs. 0.1%; OR: 1.56; 95% CI: 0.80 to 3.04; P_{int} = 0.21). GPI use was associated with increased risk of bleeding in both treatment arms.

CONCLUSIONS Cangrelor's efficacy in reducing ischemic complications in patients undergoing PCI was maintained irrespective of GPI administration. GPI use was associated with substantially higher bleeding rates, regardless of the randomization to cangrelor or clopidogrel. (A Clinical Trial to Demonstrate the Efficacy of Cangrelor [PCI]: NCT00305162; Cangrelor Versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition [PLATFORM]: NCT00385138; A Clinical Trial Comparing Cangrelor to Clopidogrel Standard Therapy in Subjects Who Require Percutaneous Coronary Intervention [PCI] [CHAMPION PHOENIX] [CHAMPION]: NCT01156571) (J Am Coll Cardiol 2017;69:176–85) © 2017 by the American College of Cardiology Foundation.

S tent thrombosis (ST) and other thrombotic complications present major challenges and continue to influence prognosis after percutaneous coronary intervention (PCI) (1). Despite contemporary advancements in the oral antiplatelet armamentarium, inability to tolerate oral intake, impaired gastrointestinal absorption, and high-risk presentations (2), including ST-segment elevation myocardial infarction (MI) (3), limit adequate drug bioavailability and effective attenuation of platelet activity with these agents. Furthermore, the long half-lives of available oral adenosine diphosphate $P2Y_{12}$ antagonists may delay necessary surgical interventions, including coronary artery bypass graft. As such, there is an enduring need for fast-onset, fast-offset, potent parenteral antiplatelet agents in clinical practice.

SEE PAGE 186

Intravenous glycoprotein IIb/IIIa inhibitors (GPIs) have been associated with reductions in certain post-PCI ischemic endpoints, and even mortality, in early randomized controlled trials (4) and more recent "real-world" registry studies (5). GPIs are used in up to one-third of patients during PCI for acute coronary syndromes in the United States (5), and maintain tempered support from national guidelines (6). Unfortunately, the routine use of GPIs has been limited by excess severe bleeding (4,5), related to their long-lasting biological effects and the lack of ready reversibility.

Cangrelor, an intravenous, rapidly reversible $P2Y_{12}$ antagonist, has been approved for use in the United States and Europe during PCI, and may offer a potent parenteral option with a potentially favorable safety profile. The consistency of the ischemic benefits of cangrelor in the context of contemporary selective or bailout/rescue GPI use is unclear. In this post hoc analysis, we evaluated the efficacy and safety of cangrelor compared with clopidogrel (or placebo) in subgroups that did and did not receive GPIs, using pooled, patient-level data from the 3 phase 3 CHAMPION (Cangrelor versus Standard Therapy to

Achieve Optimal Management of Platelet Inhibition) trials.

METHODS

STUDY POPULATION. The study designs (7) and primary results of the CHAMPION PCI (8), CHAMPION PLATFORM (9), and CHAMPION PHOENIX (10) trials have been reported previously. In these prospective, double-blind, double-dummy randomized trials, patients ≥18 years of age requiring elective or nonelective PCI were randomly assigned to receive cangrelor (30 μg/kg bolus followed by 4 μg/kg/min infusion for ≥2 h or the duration of PCI, whichever was longer) or clopidogrel. Timing of clopidogrel (300 mg or 600 mg) administration was variable across the 3 trials: at the beginning of PCI in CHAMPION PCI (8); at the end of PCI in CHAMPION PLATFORM (9); or at the start or end, on the basis of the site standard of care, in CHAMPION PHOENIX (10). Aspirin (75 to 325 mg) and clopidogrel 75 mg daily were administered to all patients in the first 48 h, after which, dual antiplatelet therapy was directed by the site investigators. Periprocedural anticoagulation strategy, choice of stent and access site, and sheath management protocol were left to the discretion of the treating clinician.

Exclusion criteria included receipt of fibrinolytic therapy or small-molecule GPIs (eptifibatide, tirofiban) within 12 h of randomization, or abciximab within 5 to 7 days of randomization. Patients who had received a $P2Y_{12}$ antagonist within 7 days of randomization were excluded from enrollment in CHAMPION PLATFORM and CHAMPION PHOENIX, but patients receiving clopidogrel at stable doses of ≤75 mg daily were permitted in CHAMPION PCI (8). Only bailout/rescue GPI use for the management of periprocedural thrombotic complications was permitted in CHAMPION PLATFORM and CHAMPION PHOENIX, whereas GPI use and indication was left to the discretion of the individual operators in CHAMPION PCI (8). The case report form required site investigators to specify the indication for GPI therapy. The institutional review boards or ethics committees at each enrolling site approved trial protocols, and all patients provided written informed consent to participate.

STUDY ENDPOINTS. Similar to the CHAMPION PHOENIX trial (10), the primary efficacy endpoint for this pooled subgroup analysis was the composite of all-cause mortality, MI, ischemia-driven revascularization, or ST at 48 h after randomization. The key secondary efficacy endpoint was ST at 48 h. The second universal definition of MI (11), used in the

CHAMPION PHOENIX trial (10), was retrospectively applied to adjudicated events in the other 2 trials. ST was defined according the Academic Research Consortium definition (12). In addition, intraprocedural ST was blindly adjudicated by a dedicated angiographic core laboratory (Cardiovascular Research Foundation, New York, New York) in CHAMPION PHOENIX (1). The efficacy endpoints were assessed in patients included in the modified intention-to-treat (mITT) population, as specified in the trial protocol, and independently adjudicated by a clinical events committee for each trial. The mITT cohort comprised patients who underwent PCI and received the study drug.

Safety was assessed with 3 bleeding scales (GUSTO [Global Use of Strategies to Open Occluded Coronary Arteries], Thrombolysis in Myocardial Infarction, and ACUITY [Acute Catheterization and Urgent Intervention Triage strategy]), and a requirement for blood transfusion at 48 h. GUSTO-defined noncoronary artery bypass graft severe/life-threatening bleeding was the primary overall safety endpoint in the CHAMPION trials. The safety endpoints were assessed in patients who underwent randomization and received at least 1 dose of the study drug and were not independently adjudicated.

STATISTICAL ANALYSIS. Baseline characteristics, and efficacy and safety endpoints were compared between the cangrelor and clopidogrel arms in subgroups that received and did not receive GPIs (administered for both routine and bailout/rescue purposes). Bailout/rescue use of GPIs is a treatment decision that occurs post-randomization, may be used to treat ischemic complications that constituted the primary endpoint, and is known to be reduced by cangrelor (7). As such, to address potential bias and confounding related to bailout/rescue GPI use, 2 dedicated sensitivity analyses were undertaken. First, comparisons of clinical endpoints were repeated after excluding patients requiring bailout/rescue GPI therapy altogether. Second, the efficacy and safety analyses were repeated in patients who did and did not receive GPIs as a planned upfront strategy at "baseline" determined by the individual operator. In this latter sensitivity analysis, bailout/rescue GPI use (which may have been required "post-baseline") was counted in the "no GPI" treatment strategy.

Continuous variables are summarized as mean ± SD or as median (interquartile range [Q1 to Q3]), and categorical variables as n (%). Binary comparisons were made using Student *t* tests, Wilcoxon rank sum tests, chi-square tests, or Fisher exact tests, as

appropriate. Heterogeneity across trials and appropriateness of pooling data were assessed using Breslow-Day tests and I^2 statistics. For within-group comparisons (cangrelor vs. clopidogrel), odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using logistic regression, with treatment by GPI interaction testing by the Breslow-Day method. Logistic regression models were further adjusted for key clinical parameters, including planned clopidogrel loading dose (300 mg vs. 600 mg), periprocedural anticoagulant choice, and stent type. For between-group comparisons (GPI vs. no GPI), separate logistic regression models were created for key safety endpoints. Kaplan-Meier failure curves were constructed for the primary efficacy endpoint, and the cangrelor and clopidogrel arms were compared using log-rank tests in 3 mutually exclusive cohorts: 1) patients not receiving GPIs; 2) patients receiving GPIs on a planned, routine basis; and 3) patients receiving GPIs for bailout/rescue purposes. All statistical tests were 2-tailed and 0.05 was considered statistically significant. All statistical analyses were performed using SAS software, version 9.3 (SAS Institute, Cary, North Carolina).

RESULTS

TREATMENT GROUP AND GPI USE. Of the 25,384 randomized patients in the CHAMPION trials (the intention-to-treat cohort), a minority (n = 482; 1.9%) ultimately did not receive the assigned study drug or undergo PCI. The remaining mITT population (n = 24,902), who underwent PCI and received the study drug, represented the pre-specified cohort for all primary analyses in the CHAMPION program and for this post hoc analysis. Of the mITT populations across the 3 CHAMPION trials, 21,729 patients (87.3%) did not receive GPIs and 3,173 patients (12.7%) received routine or bailout/rescue GPIs. Eptifibatide was used in 69.4% of patients, whereas abciximab was used in 19.4% and tirofiban in 10.8%. Of the GPI-treated patients, bailout/rescue use was in 745 patients (23.5%), whereas the remaining 2,428 (76.5%) received GPIs routinely as a part of site standard of care. Across the 3 CHAMPION trials, cangrelor significantly reduced the requirement for bailout/rescue GPIs compared with clopidogrel (2.6% vs. 3.4%; p < 0.001), but the proportion of patients receiving routine GPIs was similar in both treatment arms (9.8% vs. 9.7%; p = 0.96).

BASELINE CHARACTERISTICS. Table 1 highlights the major differences in baseline risk profiles of patients who did and did not receive GPIs in the CHAMPION program. Patients receiving routine or bailout/rescue GPIs were younger (60.6 ± 11.5 years vs. 63.4 ± 11.1 years), male (75.6% vs. 71.8%), enrolled from the United States (66.7% vs. 40.1%), and presented more frequently with non-ST-segment elevation acute coronary syndromes (67.8% vs. 56.2%) and ST-segment elevation MI (21.8% vs. 8.7%) (all comparisons p < 0.001). GPI users had higher rates of current smoking, but had consistently lower rates of cardiovascular comorbidities (diabetes mellitus, hypertension, hyperlipidemia) and established cardiovascular disease (prior stroke/transient ischemic attack, prior MI, prior PCI, peripheral artery disease, heart failure) (all comparisons p < 0.02). Patients who received GPIs were more likely to be administered clopidogrel loading doses of 600 mg (vs. 300 mg) and unfractionated heparin, and were less likely to receive bivalirudin (all comparisons p < 0.001). Drug-eluting stents were more frequently used during PCI of GPI users (63.2% vs. 51.7%; p < 0.001), whereas bare-metal stents were less frequently used (34.7% vs. 45.2%; p < 0.001) (Table 1). Despite variation in indications for GPIs, baseline characteristics were well balanced between the cangrelor and clopidogrel arms in subsets receiving and not receiving GPIs (Online Table 1).

HETEROGENEITY AND POOLING DATA. There was no heterogeneity detected across the 3 trials in cangrelor's effects on the primary efficacy endpoint in all CHAMPION mITT patients (Breslow-Day p = 0.45; I^2 = 0%), patients who received GPIs (Breslow-Day p = 0.98; I^2 = 0%), and patients who did not receive GPIs (Breslow-Day p = 0.44; I^2 = 0%). As such, pooling clinical outcome data from the 3 CHAMPION trials was considered appropriate.

EFFICACY ENDPOINTS. At 48 h, rates of the primary composite efficacy endpoint were lower with cangrelor compared with clopidogrel in patients who did (4.9% vs. 6.5%; OR: 0.74; 95% CI: 0.55 to 1.01) and did not receive GPIs (3.6% vs. 4.4%; OR: 0.82; 95% CI: 0.72 to 0.94) without heterogeneity by GPI use (p_{int} = 0.55) (Table 2). These treatment-related differences persisted even after adjusting for key clinical parameters in GPI-treated (adjusted OR: 0.76; 95% CI: 0.55 to 1.04) and GPI-naive subsets (adjusted OR: 0.81; 95% CI: 0.71 to 0.94). Similarly, cangrelor reduced the key secondary efficacy endpoint, ST, compared with clopidogrel in patients who did (1.5% vs. 2.2%; OR: 0.69; 95% CI: 0.41 to 1.18) and did not receive GPIs (0.4% vs. 0.6%; OR: 0.55; 95% CI: 0.37 to 0.81; p_{int} = 0.49). Kaplan-Meier estimates of the time to primary endpoint are shown in patients not receiving GPIs; patients receiving GPIs on a

TABLE 1   Baseline Characteristics in Patients Receiving and Not Receiving GPIs

	GPI (N = 3,173)	No GPI (N = 21,729)	p Value
Age, yrs			<0.001
Mean ± SD (n)	60.6 ± 11.5 (3,173)	63.4 ± 11.1 (21,729)	
Median (Q1-Q3)	60.0 (53-69)	63.0 (55-72)	
Range, min-max	23-93	26-95	
Female	24.4 (773/3,173)	28.2 (6,136/21,729)	<0.001
Race*			<0.001
White	84.8 (2,688/3,168)	86.1 (18,685/21,699)	
Asian	7.3 (230/3,168)	7.7 (1,680/21,699)	
Black	5.1 (163/3,168)	3.3 (717/21,699)	
Native Hawaiian/ Pacific Islander	0.3 (10/3,168)	0.4 (84/21,699)	
American Indian/ Alaskan native	0.2 (6/3,168)	0.1 (28/21,699)	
Hispanic or Latino	2.2 (71/3,168)	2.3 (505/21,699)	
Region			<0.001
United States	66.7 (2,117/3,173)	40.1 (8,721/21,729)	
Non-United States	33.3 (1,056/3,173)	59.9 (13,008/21,729)	
Weight			
Mean ± SD (n)	87.2 ± 19.4 (3,173)	84.4 ± 18.3 (21,729)	<0.001
Median (Q1-Q3)	85.0 (74-98)	83.0 (72-95)	
Range, min-max	35-190	29-223	
Diagnosis at presentation			<0.001
Stable angina	10.4 (330/3,173)	35.0 (7,611/21,729)	
NSTE-ACS	67.8 (2,151/3,173)	56.2 (12,219/21,729)	
STEMI	21.8 (692/3,173)	8.7 (1,899/21,729)	
Cardiac biomarker status†			<0.001
Normal	33.6 (1,039/3,088)	52.3 (11,209/21,441)	
Abnormal	66.4 (2,049/3,088)	47.7 (10,232/21,441)	
Medical history			
Diabetes mellitus	26.4 (836/3,168)	30.1 (6,530/21,710)	<0.001
Current smoker	33.1 (1,050/3,173)	28.1 (6,115/2,1729)	<0.001
Hypertension	66.6 (2,100/3,153)	77.1 (16,702/21,656)	<0.001
Hyperlipidemia	62.0 (1,894/3,056)	65.2 (12,935/19,845)	<0.001
Stroke or TIA	4.2 (134/3,162)	5.2 (1,136/21,646)	0.016
Myocardial infarction	20.7 (647/3,132)	23.4 (5,051/21,551)	<0.001
PCI	21.5 (679/3,163)	23.9 (5,180/21,671)	0.003
CABG	9.9 (314/3,170)	10.4 (2,267/21,710)	0.355
Congestive heart failure	5.0 (157/3,145)	9.4 (2,027/21,634)	<0.001
Peripheral artery disease	5.7 (179/3,120)	7.2 (1,541/21,394)	0.003

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planned, routine basis; and patients receiving GPIs for bailout/rescue purposes (**Central Illustration**).

SAFETY ENDPOINTS. Cangrelor did not increase the primary safety endpoint, GUSTO-defined severe/ life-threatening bleeding, across the 3 CHAMPION trials in patients who did (0.4% vs. 0.5%; OR: 0.71; 95% CI: 0.25 to 1.99) and did not receive GPIs (0.2% vs. 0.1%; OR 1.56; 95% CI: 0.80 to 3.04; p_{int} = 0.21). These treatment effects on the primary safety endpoint were largely unchanged after covariate adjustment in GPI-treated (adjusted OR: 0.70; 95% CI: 0.25 to 1.98) and GPI-naive patients (adjusted OR: 1.41; 95% CI: 0.67 to 2.96). Cangrelor did not

influence ACUITY-defined major bleeding compared with clopidogrel (5.7% vs. 5.5%; OR: 1.04; 95% CI: 0.77 to 1.41) in GPI-treated patients, but did increase ACUITY-defined major bleeding in patients not receiving GPIs (4.1% vs. 2.4%; OR: 1.71; 95% CI: 1.46 to 1.99; p_{int} = 0.004). Similarly, there was no increase in transfusion requirement in GPI-treated patients with cangrelor compared with clopidogrel (1.4% vs. 1.9%; OR: 0.75; 95% CI: 0.43 to 1.30), but there was an excess transfusion requirement with cangrelor in patients not receiving GPIs (0.6% vs. 0.4%; OR: 1.73; 95% CI: 1.17 to 2.57; p_{int} = 0.01) (**Table 2**).

SENSITIVITY ANALYSES. Even after exclusion of patients receiving bailout/rescue GPIs (Online Table 2), and when only upfront baseline decisions regarding GPI administration were considered (Online Table 3), cangrelor consistently reduced the primary composite efficacy endpoint and its components compared with clopidogrel. Similar patterns in safety endpoints were observed when bailout/rescue GPI use was entirely excluded (Online Table 2), and when GPI-related grouping was on the basis of whether or not site investigators planned to administer GPIs at baseline (Online Table 3).

GPI USE AND RISK OF BLEEDING. GPI use (routine or bailout/rescue) was associated with increased risk of major/severe bleeding, assessed by all 3 bleeding scales, compared with no GPI use, regardless of randomization to cangrelor or clopidogrel (**Table 2**). Patients receiving GPIs were at increased risk of GUSTO-defined severe/life-threatening bleeding (0.5% vs. 0.2%; OR: 2.87; 95% CI: 1.57 to 5.24; p < 0.001) and requirement for blood transfusions (1.7% vs. 0.5%; OR: 3.44; 95% CI: 2.47 to 4.79; p < 0.001) compared with patients not receiving GPIs in both treatment arms.

DISCUSSION

This large, patient-level, pooled analysis of the 3 phase 3 CHAMPION trials including almost 25,000 patients revealed several important findings: 1) GPI use varies substantially by geographic region, indication for PCI, and comorbidities; 2) cangrelor's efficacy in reducing ischemic complications at 48 h post-randomization in patients undergoing PCI was maintained irrespective of GPI use; 3) bailout/rescue GPI therapy is required in ~3% of contemporary elective and nonelective PCIs, and its requirement is reduced by periprocedural use of cangrelor; and 4) GPIs are associated with substantially higher bleeding rates, regardless of randomization to cangrelor or clopidogrel.

CLINICAL IMPLICATIONS. The ideal parenteral anti-platelet agent would provide rapid and robust periprocedural ischemic benefit without attendant excess bleeding risk (13,14). GPIs have been shown to reduce cardiovascular events after PCI compared with heparin alone (4), but their routine use has been met with an increase in severe bleeding complications (15), which, in turn, contribute to adverse clinical outcomes and increased PCI-related costs (16–18). Provisional use of GPIs, variation in GPI duration and delivery systems, and augmented use of radial access have improved the bleeding profile and tolerability of GPIs, although with relatively limited outcome data (14). Furthermore, recent advances in stent design, pharmacotherapy (including increased uptake of newer antithrombotic agents, such as bivalirudin), time to treatment, and overall quality and transitions in periprocedural care have led to stepwise improvements in PCI outcomes, potentially influencing the risk-benefit profile of GPIs (1,19,20). In this context, the optimal potent parenteral strategy requires reassessment.

In this contemporary trial-based experience, GPIs were used in lower-risk patients (e.g., younger patients with lower rates of established cardiovascular disease) with higher-risk presentations (e.g., biomarker-positive acute coronary syndromes). There was considerable regional variation in GPI use (21): site investigators in the United States prescribed two-thirds of GPIs in this experience. Our data support the consistency of cangrelor's clinical effects irrespective of background use of GPIs, thus providing reassurance of its therapeutic utility, even in regions of low GPI use (21).

Potent oral $P2Y_{12}$ antagonists, prasugrel (22) and ticagrelor (23), were previously demonstrated to exert clinical benefits, regardless of GPI use. Similarly, in the CHAMPION trials, cangrelor consistently reduced ischemic events after PCI compared with clopidogrel, without heterogeneity by GPI use. As such, in the CHAMPION experience, periprocedural administration of cangrelor not only reduced the requirement for bailout/rescue GPI therapy, but its clinical benefits were demonstrated regardless of background GPI therapy.

Similar to prior reports from randomized (4) and nonrandomized experiences (5), we found a high bleeding hazard associated with GPIs, when administered routinely or with bailout/rescue use. This bleeding risk may be overrepresented in our exploratory analysis, given that GPIs may have been preferentially administered in higher-risk patient scenarios and may be confounded by other patient- or procedure-specific factors, including concomitant

TABLE 1 Continued			
	GPI **(N = 3,173)**	**No GPI** **(N = 21,729)**	**p Value**
Family history of CAD	48.3 (1,382/2,861)	40.6 (8,208/20,195)	<0.001
Periprocedural medications			
Planned clopidogrel dose‡			<0.001
Clopidogrel, 300-mg loading dose	1.8 (57/3,173)	12.7 (2,749/21,729)	
Clopidogrel, 600-mg loading dose	98.2 (3,116/3,173)	87.3 (18,980/21,729)	
Bivalirudin	9.6 (305/3,172)	27.2 (5,901/21,725)	<0.001
UFH	68.6 (2,176/3,172)	62.4 (13,546/21,725)	<0.001
LMWH	8.4 (265/3,170)	8.9 (1,924/21,723)	0.356
Fondaparinux	1.0 (31/3,165)	0.6 (134/21,720)	0.019
Aspirin	93.0 (2,938/3,159)	93.8 (20,347/21,696)	0.09
≤100 mg	16.6 (486/2,920)	36.6 (7,336/20,048)	<0.001
>100 mg	83.4 (2,434/2,920)	63.4 (12,712/20,048)	
Number of vessels treated, index PCI			<0.001
0	0.1 (4/3,173)	0.5 (111/21,729)	
1	87 (2,760/3,173)	84.6 (18,391/21,729)	
2	11.6 (368/3,173)	13.5 (2,937/21,729)	
3	1.3 (40/3,173)	1.3 (273/21,729)	
4	0.03 (1/3,173)	0.1 (17/21,729)	
Time from hospital admission to PCI, h, median (Q1–Q3)	5.2 (2–21)	5.4 (3–23)	<0.001
Duration of PCI, min			
Mean ± SD (n)	33.9 ± 24.8 (3,171)	23.6 ± 19.3 (21,719)	0.02
Median (Q1–Q3)	28.0 (17–44)	19.0 (11–30)	
Range, min–max	2–229	0–359	
Drug-eluting stent	63.2 (2,004/3,173)	51.7 (11,243/21,729)	<0.001
Bare-metal stent	34.7 (1,102/3,173)	45.2 (9,829/21,729)	<0.001
Balloon angioplasty	77.4 (2,456/3,173)	41.7 (9,058/21,729)	<0.001

Values are % (n/N) unless otherwise indicated. Baseline characteristics describe patients included in the modified intention-to-treat cohort. Denominators exclude patients whose status was reported as unknown by the study center. *Race was self-reported. †Cardiac biomarker status was considered to be abnormal if, as determined by the local laboratory, at least 1 of the baseline troponin I or T levels obtained within 72 h before randomization or after randomization, but before initiation of the study drug, was greater than the upper limit of the normal range. If the baseline troponin level was not available, the baseline myocardial band fraction of creatine kinase was used. ‡Percentage of patients receiving each clopidogrel loading dose is on the basis of planned or intended use, declared at the time of stratification.

CABG = coronary artery bypass graft; CAD = coronary artery disease; GPI = glycoprotein IIb/IIIa inhibitor; IQR = interquartile range; LMWH = low-molecular-weight heparin; NSTE-ACS = non-ST-segment elevation acute coronary syndrome; PCI = percutaneous coronary intervention; Q = quartile; STEMI = ST-segment elevation myocardial infarction; TIA = transient ischemic attack; UFH = unfractionated heparin.

antithrombotic therapies. In GPI-treated patients, bleeding risk, measured by 3 validated and sensitive bleeding scales, and requirement for blood transfusion were not significantly increased by the use of cangrelor compared with clopidogrel. Similarly, in patients not receiving GPIs, cangrelor did not increase GUSTO-defined severe/life-threatening bleeding (the primary safety endpoint in the CHAMPION program) compared with clopidogrel. However, in this latter subgroup, cangrelor marginally increased bleeding risk, assessed by other bleeding scales, and requirement for blood transfusion compared with clopidogrel. This excess bleeding risk with cangrelor in GPI-naive patients may be related to selection of

TABLE 2 Efficacy and Safety Endpoints at 48 h After Randomization in Patients Receiving and Not Receiving GPIs

Endpoint	GPI			No GPI			p Value, Treatment By GPI Interaction
	Cangrelor	Clopidogrel	OR (95% CI)	Cangrelor	Clopidogrel	OR (95% CI)	
Efficacy	1,534	1,625		10,921	10,793		
Composite of death/MI/IDR/ST	75/1,534 (4.9)	105/1,625 (6.5)	0.74 (0.55–1.01)	398/10,921 (3.6)	474/10,793 (4.4)	0.82 (0.72–0.94)	0.55
Death	7/1,534 (0.5)	10/1,625 (0.6)	0.74 (0.28–1.95)	26/10,921 (0.2)	35/10,793 (0.3)	0.73 (0.44–1.22)	0.99
MI	51/1,534 (3.3)	71/1,625 (4.4)	0.75 (0.52–1.09)	336/10,921 (3.1)	382/10,793 (3.5)	0.87 (0.75–1.00)	0.49
IDR	20/1,534 (1.3)	26/1,625 (1.6)	0.81 (0.45–1.46)	46/10,921 (0.4)	66/10,793 (0.6)	0.69 (0.47–1.00)	0.64
ST	23/1,534 (1.5)	35/1,625 (2.2)	0.69 (0.41–1.18)	39/10,921 (0.4)	70/10,793 (0.6)	0.55 (0.37–0.81)	0.49
Q-wave MI	7/1,534 (0.5)	8/1,625 (0.5)	0.93 (0.34–2.56)	12/10,921 (0.1)	28/10,793 (0.3)	0.42 (0.21–0.83)	0.2
ARC-defined ST	13/1,534 (0.8)	15/1,625 (0.9)	0.92 (0.44–1.93)	15/10,921 (0.1)	38/10,793 (0.4)	0.39 (0.21–0.71)	0.08
Safety	1,549	1,643		11,012	10,894		
GUSTO							
Severe or LT*	6/1,549 (0.4)	9/1,643 (0.5)	0.71 (0.25–1.99)	22/11,012 (0.2)	14/10,894 (0.1)	1.56 (0.80–3.04)	0.21
Moderate	19/1,549 (1.2)	24/1,643 (1.5)	0.84 (0.46–1.54)	57/11,012 (0.5)	32/10,894 (0.3)	1.77 (1.14–2.73)	0.05
Severe or LT/moderate	25/1,549 (1.6)	33/1,643 (2.0)	0.80 (0.47–1.35)	78/11,012 (0.7)	46/10,894 (0.4)	1.68 (1.17–2.42)	0.02
TIMI							
Major	17/1,549 (1.1)	12/1,643 (0.7)	1.51 (0.72–3.17)	15/11,012 (0.1)	16/10,894 (0.1)	0.93 (0.46–1.88)	0.35
Minor	19/1,549 (1.2)	25/1,643 (1.5)	0.80 (0.44–1.47)	58/11,012 (0.5)	26/10,894 (0.2)	2.21 (1.39–3.52)	0.008
Major/minor	36/1,549 (2.3)	37/1,643 (2.3)	1.03 (0.65–1.64)	73/11,012 (0.7)	42/10,894 (0.4)	1.72 (1.18–2.52)	0.09
ACUITY							
Major	88/1,549 (5.7)	90/1,643 (5.5)	1.04 (0.77–1.41)	446/11,012 (4.1)	263/10,894 (2.4)	1.71 (1.46–1.99)	0.004
Minor	355/1,549 (22.9)	373/1,643 (22.7)	1.01 (0.86–1.19)	1,383/11,012 (12.6)	1,008/10,894 (9.3)	1.41 (1.29–1.53)	<0.001
Major/minor	422/1,549 (27.2)	447/1,643 (27.2)	1.00 (0.86–1.17)	1,774/11,012 (16.1)	1,249/10,894 (11.5)	1.48 (1.37–1.60)	<0.001
Blood transfusions	22/1,549 (1.4)	31/1,643 (1.9)	0.75 (0.43–1.30)	68/11,012 (0.6)	39/10,894 (0.4)	1.73 (1.17–2.57)	0.01
ICH	1/1,549 (0.1)	0/1,643 (0.0)	—	5/11,012 (0.0)	2/10,894 (0.0)	2.47 (0.48–12.75)	0.52

Values are N or n/N (rate) from patient-level pooled analysis from the 3 phase 3 CHAMPION trials (PCI, PLATFORM, and PHOENIX). The efficacy endpoints were assessed in patients included in the modified intention-to-treat population (which comprised patients who underwent PCI and received the study drug). The safety endpoints were assessed in patients who underwent randomization and received at least 1 dose of the study drug. *GUSTO-defined severe or life-threatening bleeding was the primary overall safety endpoint in the CHAMPION trials.

ACUITY = Acute Catheterization and Urgent Intervention Triage Strategy; ARC = Academic Research Consortium; CI = confidence interval; GUSTO = Global Use of Strategies to Open Occluded Coronary Arteries; ICH = intracranial hemorrhage; IDR = ischemia-driven revascularization; LT = life-threatening; MI = myocardial infarction; OR = odds ratio; ST = stent thrombosis; TIMI = Thrombolysis In Myocardial Infarction; other abbreviations as in Table 1.

low-risk patients and exclusion of certain patients who benefited from cangrelor therapy (i.e., cangrelor reduced the requirement for bailout/rescue GPIs across the CHAMPION trials). Furthermore, although both potent parenteral agents achieve near-maximal platelet inhibition, bleeding risk is more substantial with GPIs, given differential pharmacologic targets, lack of reversibility, and prolonged effects, even after cessation of infusion. The increased bleeding with GPIs seems to overshadow the relatively modest differences between more potent P2Y$_{12}$ inhibitors and clopidogrel. As such, the small increment in bleeding risk related to more potent P2Y$_{12}$ inhibition with cangrelor is only observed in GPI-naive patients.

Thus, cangrelor may be a promising potent alternative to GPIs, affording ischemic benefit with acceptable bleeding risk in patients undergoing PCI. Although the global use of and guideline support for GPIs seem to be declining, these agents continue to be used in up to one-third of patients undergoing PCI for acute coronary syndromes in the United States (5). As such, contextualizing the efficacy and safety of emerging therapies, such as cangrelor, in the background of GPIs remains clinically informative. At present, there are no randomized clinical trials comparing the utility of these 2 parenteral antithrombotic agents (cangrelor and GPIs). GPI use is expected to continue in bailout/rescue scenarios, but the introduction and uptake of cangrelor may limit their requirement in clinical practice.

Recent data have suggested a potential synergistic role of cangrelor with the direct thrombin inhibitor, bivalirudin (24). Cangrelor seems to reduce the requirement for bailout/rescue GPIs compared with clopidogrel, even in bivalirudin-treated patients (24), and the efficacy and safety of cangrelor in GPI-treated and GPI-naive subsets does not seem to be attenuated after accounting for bivalirudin use. However, a strategy of combination therapy with cangrelor and bivalirudin to determine if there is a synergistic benefit requires prospective, independent validation. **STUDY LIMITATIONS.** Our analysis is limited by its post hoc nature and indication bias. Planned and bailout/rescue GPI use was left to the discretion of the

CENTRAL ILLUSTRATION Cangrelor and Glycoprotein IIb/IIIa Inhibitors: Kaplan-Meier Failure Curves for the Primary Efficacy Endpoint
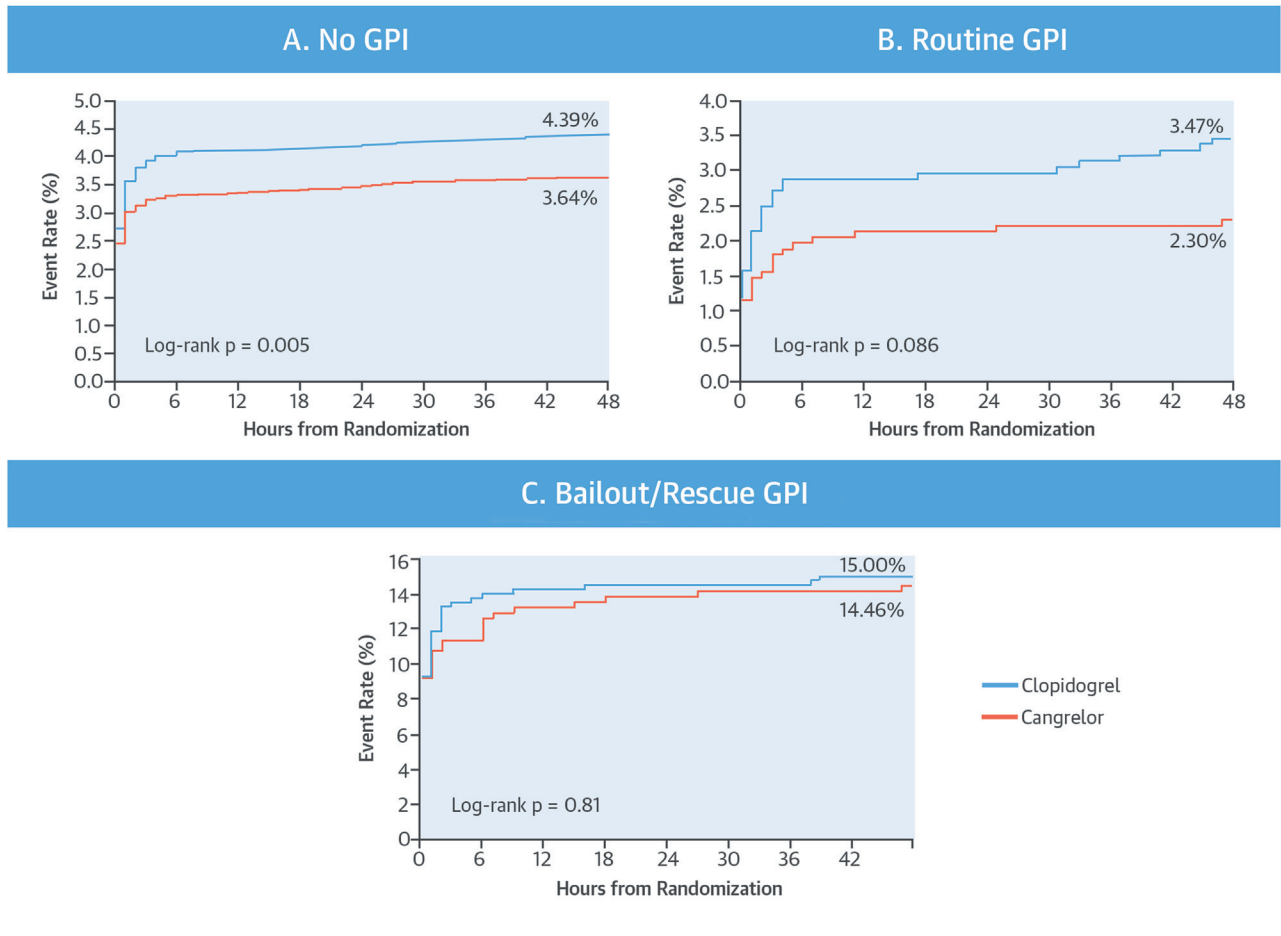
Vaduganathan, M. et al. J Am Coll Cardiol. 2017;69(2):176–85.

Event curves have been constructed in 3 separate, mutually exclusive subgroups: **(A)** patients not receiving GPIs; **(B)** patients receiving GPIs on a planned, routine basis; and **(C)** patients receiving GPIs for bailout/rescue purposes. The primary efficacy endpoint was the composite of death from any cause, myocardial infarction, ischemia-driven revascularization, or stent thrombosis assessed at 48 h after randomization in the modified intention-to-treat population (which comprised patients who underwent percutaneous coronary intervention and received the study drug). Failure functions were compared between the cangrelor and clopidogrel arms using the log-rank test. GPI = glycoprotein IIb/IIIa inhibitor.

treating clinician in CHAMPION PCI, and thus may have been influenced by baseline clinical risk, thrombotic burden, and periprocedural complications. Operator decision making surrounding use of GPI therapy for bailout/rescue purposes occurred "post-baseline," introducing the potential for bias. Unfortunately, we were unable to treat bailout/rescue GPI use as a time-varying covariate, given the lack of data regarding the specific timing of administration. To limit the influence of these "post-baseline" effects, we carried out dedicated sensitivity analyses, excluding the bailout/rescue GPI subgroup altogether

and grouping patients on the basis of upfront decision making regarding use of GPIs for routine purposes. The CHAMPION trials were not powered to test treatment differences in individual subsets, and bleeding endpoints were not specifically adjudicated. Although the access site is known to affect the periprocedural clinical course and bleeding risk (25), specific data regarding the access site were not routinely collected in CHAMPION PCI and CHAMPION PLATFORM. Similarly, more contemporary bleeding scales, such as that of the Bleeding Academic Research Consortium (26), were created after

CHAMPION PCI and CHAMPION PLATFORM were completed; as such, these studies lack essential data capture to algorithmically derive these bleeding indexes. Newer, more potent oral $P2Y_{12}$ antagonists, such as prasugrel or ticagrelor, were not used, and data regarding duration, timing, and costs of GPI therapy were not collected.

CONCLUSIONS

On the basis of a pooled, patient-level analysis from the 3 phase 3 CHAMPION trials, cangrelor's reduction in periprocedural ischemic complications compared with clopidogrel was maintained irrespective of GPI use. The use of GPIs was associated with substantially higher bleeding rates, regardless of randomization to cangrelor or clopidogrel. Cangrelor seems to be an attractive alternative to use of GPIs during PCI.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In patients undergoing PCI, use of GPIs is associated with high rates of major bleeding, and trials comparing cangrelor with clopidogrel found efficacy maintained, irrespective of coadministration of GPIs.

TRANSLATIONAL OUTLOOK: Further comparative effectiveness data are needed to assess the safety and efficacy of parenteral cangrelor as an alternative to GPIs in patients undergoing PCI.

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KEY WORDS antiplatelet therapy, bleeding, coronary artery disease, outcomes

APPENDIX For a full list of the CHAMPION Investigators as well as supplemental tables, please see the online version of this article.