ORIGINAL ARTICLE

Effect of Platelet Inhibition with Cangrelor during PCI on Ischemic Events

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ABSTRACT

BACKGROUND

The intensity of antiplatelet therapy during percutaneous coronary intervention (PCI) is an important determinant of PCI-related ischemic complications. Cangrelor is a potent intravenous adenosine diphosphate (ADP)–receptor antagonist that acts rapidly and has quickly reversible effects.

METHODS

In a double-blind, placebo-controlled trial, we randomly assigned 11,145 patients who were undergoing either urgent or elective PCI and were receiving guideline-recommended therapy to receive a bolus and infusion of cangrelor or to receive a loading dose of 600 mg or 300 mg of clopidogrel. The primary efficacy end point was a composite of death, myocardial infarction, ischemia-driven revascularization, or stent thrombosis at 48 hours after randomization; the key secondary end point was stent thrombosis at 48 hours. The primary safety end point was severe bleeding at 48 hours.

RESULTS

The rate of the primary efficacy end point was 4.7% in the cangrelor group and 5.9% in the clopidogrel group (adjusted odds ratio with cangrelor, 0.78; 95% confidence interval [CI], 0.66 to 0.93; P=0.005). The rate of the primary safety end point was 0.16% in the cangrelor group and 0.11% in the clopidogrel group (odds ratio, 1.50; 95% CI, 0.53 to 4.22; P=0.44). Stent thrombosis developed in 0.8% of the patients in the cangrelor group and in 1.4% in the clopidogrel group (odds ratio, 0.62; 95% CI, 0.43 to 0.90; P=0.01). The rates of adverse events related to the study treatment were low in both groups, though transient dyspnea occurred significantly more frequently with cangrelor than with clopidogrel (1.2% vs. 0.3%). The benefit from cangrelor with respect to the primary end point was consistent across multiple prespecified subgroups.

CONCLUSIONS

Cangrelor significantly reduced the rate of ischemic events, including stent thrombosis, during PCI, with no significant increase in severe bleeding. (Funded by the Medicines Company; CHAMPION PHOENIX ClinicalTrials.gov number, NCT01156571.)

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Percutaneous coronary intervention (PCI) with stent implantation is widely used to reduce the risk of death or myocardial infarction in patients with acute coronary syndromes and to reduce the burden of angina and improve the quality of life in patients with stable angina.[1-5] Despite advances in adjunctive pharmacotherapy, thrombotic complications during PCI remain a major concern.[6] Antiplatelet therapies, including the $P2Y_{12}$-receptor inhibitors, reduce the risk of ischemic events, particularly stent thrombosis.[7-10] To date, only oral $P2Y_{12}$ inhibitors have been available. There are several limitations of these drugs when they are used for urgent or periprocedural treatment of patients with cardiovascular disease who may undergo PCI, including a delayed onset of action.

Patients in the acute phase of cardiovascular illness may have conditions such as nausea, impaired absorption, or impaired perfusion that can limit drug bioavailability, and in such patients, the antiplatelet effect of the oral antiplatelet agent clopidogrel may not be sufficient.[11,12] In addition, multiple sources of variation in the pharmacokinetic and pharmacodynamic response to clopidogrel have been described.[13] More potent oral agents such as prasugrel and ticagrelor are also subject to some of these limitations.[14-16] Intravenous glycoprotein IIb/IIIa inhibitors can be effective in reducing the incidence of ischemic events, but their effects last for at least several hours and cannot be quickly reversed.[17] A potent, intravenous, fast-acting, reversible antiplatelet agent could address this unmet clinical need.

Cangrelor is an intravenous, fast-acting, potent, and direct-acting platelet adenosine diphosphate (ADP) $P2Y_{12}$ inhibitor that has rapidly reversible effects. When a bolus of cangrelor is administered, the antiplatelet effect is immediate, and the effect can be maintained with a continuous infusion. The plasma half-life of cangrelor is approximately 3 to 5 minutes, and platelet function is restored within 1 hour after cessation of the infusion.[18] The use of cangrelor in patients undergoing PCI was studied in two phase 3 trials, the Cangrelor versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition (CHAMPION) PCI and CHAMPION PLATFORM studies. Cangrelor was not associated with a significant reduction in the primary efficacy end point in either of these trials but was associated with reductions in secondary end points, including the rate of stent thrombosis, with no excess in severe bleeding.[19-22] The CHAMPION PHOENIX trial was designed to evaluate prospectively whether cangrelor does indeed reduce ischemic complications of PCI.

Methods

Study Oversight

The design of the CHAMPION PHOENIX trial has been published previously[23] and is summarized in Figure S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org. The trial was designed by an academic executive committee (see the Supplementary Appendix) and the sponsor (the Medicines Company). The data were collected by the sponsor. The Duke Clinical Research Institute received regular transfers of data from the sponsor and was responsible for coordinating activities and analyses for the independent data and safety monitoring board. At the end of the trial, the full database was transferred to the Duke Clinical Research Institute for primary and secondary analyses. These analyses were performed independently; the results were subsequently compared with the results obtained by the sponsor, and discrepancies were resolved collaboratively. The first author prepared the first draft of the manuscript, which was then reviewed and edited by the executive committee and other coauthors. The sponsor had the right to review but not approve the final manuscript. The first and last authors accept full responsibility for the accuracy and completeness of the reported analyses and interpretations of the data, as well as for the fidelity of this report to the protocol (which is available at NEJM.org), and made the decision to submit the manuscript for publication.

Study Patients

We intended this trial to be a large, generalizable study. Eligible patients were men or nonpregnant women 18 years of age or older with coronary atherosclerosis who required PCI for stable angina, a non–ST-segment elevation acute coronary syndrome, or ST-segment elevation myocardial infarction (STEMI) and who did not receive pretreatment with platelet inhibitors. Patients were required to provide written informed consent. Major exclusion criteria were receipt of a $P2Y_{12}$ inhibitor or abciximab at any time in the 7 days before randomization and receipt of eptifibatide or tirofiban or fibrinolytic therapy in the 12 hours before randomization.

STUDY TREATMENT

Patients were randomly assigned, in a double-dummy, double-blind manner, to receive cangrelor or clopidogrel before PCI. Randomization was performed with the use of an interactive voice-response or Web-response system, with stratification according to site, baseline status (normal or abnormal, as defined by a combination of biomarker levels, electrocardiographic changes, and symptoms), and intended loading dose of clopidogrel (600 mg or 300 mg). After randomization, patients received an infusion of cangrelor or matching placebo and the first set of capsules containing either 600 mg or 300 mg of clopidogrel (with the dose determined at the discretion of the site investigator) or matching placebo. At the end of the infusion, patients received a second set of capsules containing either 600 mg of clopidogrel (cangrelor group) or matching placebo (clopidogrel group) (Fig. S1 in the Supplementary Appendix). Cangrelor or matching placebo was administered as a bolus of 30 μg per kilogram of body weight followed by an infusion of 4 μg per kilogram per minute for at least 2 hours or the duration of the procedure, whichever was longer. The protocol called for aspirin (75 to 325 mg) to be administered to all patients. The protocol also called for clopidogrel (75 mg) to be administered during the first 48 hours; thereafter, clopidogrel or another $P2Y_{12}$ inhibitor could be administered at the discretion of the investigator, according to local guidelines. The choice of a periprocedural anticoagulant (bivalirudin, unfractionated heparin, low-molecular-weight heparin, or fondaparinux) was also at the discretion of the investigator. Glycoprotein IIb/IIIa inhibitors were allowed only as rescue therapy during PCI to treat new or persistent thrombus formation, slow or no reflow, side-branch compromise, dissection, or distal embolization. The investigator at the site determined the protocol for management of the arterial sheath.

END POINTS

The primary efficacy end point was the composite rate of death from any cause, myocardial infarction, ischemia-driven revascularization, or stent thrombosis in the 48 hours after randomization in the modified intention-to-treat population (which comprised patients who actually underwent PCI and received the study drug). The protocol specified that if more than 15% of the patients received a 300-mg loading dose of clopidogrel (as compared with a 600-mg dose) at the time of randomization, the primary analysis was to be adjusted for loading dose in addition to baseline status. The key secondary end point was the incidence of stent thrombosis at 48 hours; this end point included definite stent thrombosis, defined according to the criteria of the Academic Research Consortium, or intraprocedural stent thrombosis, which was assessed, with group assignments concealed, at an angiographic core laboratory (Cardiovascular Research Foundation).[24] Intraprocedural stent thrombosis was defined as any new or worsened thrombus related to the stent procedure that was confirmed angiographically. Events of death, myocardial infarction, ischemia-driven revascularization, and stent thrombosis that occurred during the first 30 days after randomization were adjudicated by the clinical events committee at the Duke Clinical Research Institute. The criteria that the clinical events committee used to define myocardial infarction are provided in Table S1 in the Supplementary Appendix.

The primary safety end point was severe bleeding not related to coronary-artery bypass grafting, according to the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) criteria, at 48 hours. Several other bleeding definitions were also applied. Bleeding end points were not adjudicated.

STATISTICAL ANALYSIS

On the basis of prior studies, we assumed that the rate of the composite primary end point would be 5.1% in the clopidogrel group and 3.9% in the cangrelor group, representing a 24.5% reduction in the odds ratio with cangrelor. We estimated that we would need to enroll approximately 10,900 patients for the study to have 85% power to detect that reduction. A two-sided overall alpha level of 0.05 was used for all analyses. This study had an adaptive design with conditional power calculation and potential for reestimation of the sample size, if necessary, after the interim analysis that was scheduled to be performed after 70% of the patients were enrolled.[25]

The numbers and percentages of patients within each analysis population (modified intention-to-treat, intention-to-treat, and safety) were summarized according to treatment group. The primary efficacy analysis of the rate of the composite end point of death from any cause, myocardial infarction, ischemia-driven revascularization, or stent thrombosis (with all events adjudicated by the clinical events committee) in the 48 hours after

randomization was conducted in the modified intention-to-treat population. The primary safety analysis was conducted in the safety population, which comprised all patients who underwent randomization and received at least one dose of the study drug; patients were classified according to the actual treatment received. All calculations and statistical analyses were performed with the use of SAS software, version 9.2.

RESULTS

PATIENTS

A total of 11,145 patients underwent randomization at 153 sites from September 30, 2010, to October 3, 2012. Of the patients who were randomly assigned to a study group, 203 did not undergo PCI or did not receive a study drug; therefore, the modified intention-to-treat population comprised 10,942 patients (Fig. S2 in the Supplementary Appendix). The baseline characteristics were well balanced between the two groups (Table 1). The average age of the patients was 64 years, and 28% were women. The diagnosis at presentation was stable angina in 56.1% of the patients, non–ST-segment elevation acute coronary syndrome in 25.7% (5.7% had unstable angina), and STEMI in 18.2%. Overall, the median time from hospital admission to PCI was 4.4 hours (interquartile range, 1.9 to 21.0). The characteristics of the pro-

Table 1. Baseline Characteristics of the Patients and Characteristics of the Procedure in the Modified Intention-to-Treat Population, According to Treatment Group.*

Characteristic	Cangrelor (N=5472)	Clopidogrel (N=5470)
Age — yr		
Median	64.0	64.0
Interquartile range	56–72	56–72
Female sex — no. (%)	1558 (28.5)	1493 (27.3)
White race — no./total no. (%)†	5132/5469 (93.8)	5120/5463 (93.7)
Weight — kg		
Median	84.0	84.0
Interquartile range	73–95	74–96
Diagnosis at presentation — no. (%)		
Stable angina	3121 (57.0)	3019 (55.2)
NSTE-ACS	1389 (25.4)	1421 (26.0)
STEMI	962 (17.6)	1030 (18.8)
Region — no. (%)		
United States	2048 (37.4)	2049 (37.5)
Other countries	3424 (62.6)	3421 (62.5)
Cardiac-biomarker status — no./total no. (%)‡		
Normal	3520/5467 (64.4)	3432/5466 (62.8)
Abnormal	1947/5467 (35.6)	2034/5466 (37.2)
Medical history — no./total no. (%)		
Diabetes mellitus	1519/5464 (27.8)	1536/5463 (28.1)
Current smoker	1504/5339 (28.2)	1549/5339 (29.0)
Hypertension	4374/5459 (80.1)	4332/5454 (79.4)
Hyperlipidemia	3363/4851 (69.3)	3338/4836 (69.0)
Prior stroke or TIA	271/5455 (5.0)	244/5452 (4.5)
Prior myocardial infarction	1092/5441 (20.1)	1175/5431 (21.6)
PTCA or PCI	1268/5462 (23.2)	1333/5461 (24.4)
CABG	578/5466 (10.6)	500/5464 (9.2)
Congestive heart failure	552/5460 (10.1)	584/5456 (10.7)
Peripheral-artery disease	447/5407 (8.3)	385/5419 (7.1)

Table 1. (Continued.)

Characteristic	Cangrelor (N=5472)	Clopidogrel (N=5470)
Periprocedural medications — no./total no. (%)		
Clopidogrel, 300-mg loading dose	1405/5472 (25.7)	1401/5470 (25.6)
Clopidogrel, 600-mg loading dose	4067/5472 (74.3)	4069/5470 (74.4)
Bivalirudin	1252/5472 (22.9)	1269/5468 (23.2)
Unfractionated heparin	4272/5472 (78.1)	4276/5469 (78.2)
Low-molecular-weight heparin	732/5472 (13.4)	753/5468 (13.8)
Fondaparinux	156/5471 (2.9)	135/5470 (2.5)
Aspirin	5164/5469 (94.4)	5148/5465 (94.2)
Duration of PCI — min		
Median	18	17
Interquartile range	10–30	10–30
Drug-eluting stent — no. (%)	3061 (55.9)	3020 (55.2)
Bare-metal stent — no. (%)	2308 (42.2)	2344 (42.9)
Balloon angioplasty — no. (%)	292 (5.3)	273 (5.0)

* Denominators exclude patients in whom the status was reported as unknown by the study center. There were no significant differences between the two groups, except for a history of coronary-artery bypass grafting (CABG) (P=0.01), prior myocardial infarction (P=0.04), and peripheral-artery disease (P=0.02). NSTE-ACS denotes non–ST-segment elevation acute coronary syndrome, PCI percutaneous coronary intervention, PTCA percutaneous transluminal coronary angioplasty, STEMI ST-segment elevation myocardial infarction, and TIA transient ischemic attack.
† Race was self-reported.
‡ Cardiac biomarker status was considered to be abnormal if at least one of the baseline troponin I or T levels, obtained within 72 hours before randomization or after randomization but before initiation of the study drug, was greater than the upper limit of the normal range, as determined by the local laboratory. If the baseline troponin level was not available, the baseline MB fraction of creatine kinase was used.

cedure are shown in Table 1. A total of 55.6% of the patients received drug-eluting stents and 42.4% received bare-metal stents. Additional baseline characteristics of the patients and characteristics of the procedure are provided in Table S2 in the Supplementary Appendix.

END POINTS

The rate of the primary composite efficacy end point of death from any cause, myocardial infarction, ischemia-driven revascularization, or stent thrombosis at 48 hours was significantly lower in the cangrelor group than in the clopidogrel group (4.7% vs. 5.9%; odds ratio, 0.78; 95% confidence interval [CI], 0.66 to 0.93; P=0.005), on the basis of the prespecified logistic-regression analysis, which adjusted for baseline status (normal vs. abnormal) and clopidogrel loading dose (600 mg vs. 300 mg). The result of the crude analysis was similar (odds ratio, 0.79; 95% CI, 0.67 to 0.93; P=0.006). Figure 1 shows the Kaplan–Meier estimates of the time-to-event distributions for the primary end point. The number needed to treat with cangrelor to prevent one primary end-point event is 84 (95% CI, 49 to 285). The results of analyses of the components of the primary end point and other composite end points are provided in Table 2 and in Tables S3 and S4 in the Supplementary Appendix. The rate of the key secondary efficacy end point of stent thrombosis at 48 hours was also lower in the cangrelor group than in the clopidogrel group (0.8% vs. 1.4%; odds ratio, 0.62; 95% CI, 0.43 to 0.90; P=0.01) (Table 2 and Fig. 2). At 30 days, the rate of the composite efficacy end point remained significantly lower in the cangrelor group than in the clopidogrel group (6.0% vs. 7.0%; odds ratio, 0.85; 95% CI, 0.73 to 0.99; P=0.03); the relative reduction in stent thrombosis also persisted (1.3% vs. 1.9%; odds ratio, 0.68; 95% CI, 0.50 to 0.92; P=0.01).

The rate of intraprocedural stent thrombosis was lower in the cangrelor group than in the clopidogrel group (0.6% vs. 1.0%; odds ratio, 0.65; 95% CI, 0.42 to 0.99; P=0.04). The use of rescue therapy with a glycoprotein IIb/IIIa inhibitor was 2.3% with cangrelor as compared

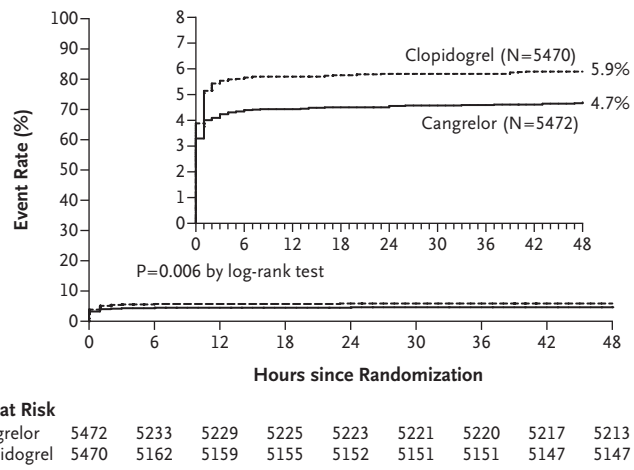


Figure 1. Kaplan–Meier Curves for the Primary Efficacy End Point.

The primary efficacy end point was a composite of death from any cause, myocardial infarction, ischemia-driven revascularization, or stent thrombosis at 48 hours after randomization, in the modified intention-to-treat population (which comprised patients who underwent percutaneous coronary intervention and received the study drug). The P value shown here was calculated with the use of a log-rank test. The P value calculated with the use of adjusted logistic regression was 0.005. The inset shows the same data on an enlarged y axis.

with 3.5% with clopidogrel (odds ratio, 0.65; 95% CI, 0.52 to 0.82; P<0.001). The rate of procedural complications was lower with cangrelor than with clopidogrel (3.4% vs. 4.5%; odds ratio, 0.74; 95% CI, 0.61 to 0.90; P=0.002).

The rate of the primary safety end point, GUSTO-defined severe bleeding, was 0.16% in the cangrelor group as compared with 0.11% in the clopidogrel group (odds ratio, 1.50; 95% CI, 0.53 to 4.22; P=0.44). Bleeding events according to several other bleeding definitions were also examined (Table S4 in the Supplementary Appendix). In a post hoc analysis, the primary efficacy end point and the primary safety end point were combined to provide a composite end point of the net rate of adverse clinical events, which was 4.8% in the cangrelor group as compared with 6.0% in the clopidogrel group (odds ratio, 0.80; 95% CI, 0.68 to 0.94; P=0.008).

ADVERSE EVENTS

The rate of adverse events related to treatment (Table S5 in the Supplementary Appendix) was similar in the cangrelor and clopidogrel groups (20.2% and 19.1%, respectively; P=0.13); 0.5% of these adverse events in the cangrelor group and 0.4% of those in the clopidogrel group led to discontinuation of the study drug (P=0.21). There were significantly more cases of transient dyspnea with cangrelor than with clopidogrel (1.2% vs. 0.3%, P<0.001).

SUBGROUP ANALYSES

The reduction in the primary efficacy end point with cangrelor was consistent across multiple subgroups, with no significant interactions with baseline variables except for status with respect to a history of peripheral-artery disease (Fig. 3). The benefit with cangrelor was similar among patients presenting with STEMI, those presenting with non–ST-segment elevation acute coronary syndrome, and those presenting with stable angina. There was no heterogeneity of treatment effect between patients in the United States and those in other countries (P=0.26).

According to the protocol, patients received a loading dose of clopidogrel or placebo after their coronary anatomy was delineated. The majority of patients received the loading dose before PCI was started (63.4%). The rest of the patients received the loading dose in the catheterization laboratory before PCI was completed (6.4%), within 1 hour after PCI was completed (30.1%), or more than 1 hour after PCI was completed (0.1%). There was no significant difference in the effect of cangrelor on the primary end point between patients who received the loading dose immediately before PCI (odds ratio, 0.80; 95% CI, 0.64 to 0.98) and those who received it during or after PCI (odds ratio, 0.79; 95% CI, 0.59 to 1.06) (P=0.99 for interaction). Similarly, there was no significant difference in the effect of cangrelor on the primary end point between patients who received a 600-mg loading dose of clopidogrel (74.4% of the population) and those who received a 300-mg loading dose (25.6% of the population): the odds ratio for the primary end point with cangrelor was 0.77 (95% CI, 0.63 to 0.94) with the 600-mg loading dose and 0.84 (95% CI, 0.62 to 1.14) with the 300-mg loading dose (P=0.62 for interaction). The protocol required at least 2 hours of study-drug infusion; the median duration of infusion in the cangrelor group was 129 minutes (interquartile range, 120 to 146); the duration of infusion was similar in the clopidogrel group (in which patients received a placebo infusion). A subgroup analysis showed a similar effect of cangrelor among patients who received the infusion for 129 minutes or less

Table 2. Efficacy and Safety End Points at 48 Hours after Randomization.*

End Point	Cangrelor	Clopidogrel	Odds Ratio (95% CI)	P Value
	number/total number (percent)			
Efficacy				
No. of patients in modified intention-to-treat population	5472	5470		
Primary end point: death from any cause, myocardial infarction, ischemia-driven revascularization, or stent thrombosis†	257/5470 (4.7)	322/5469 (5.9)	0.78 (0.66–0.93)	0.005
Key secondary end point: stent thrombosis	46/5470 (0.8)	74/5469 (1.4)	0.62 (0.43–0.90)	0.01
Myocardial infarction	207/5470 (3.8)	255/5469 (4.7)	0.80 (0.67–0.97)	0.02
Q-wave myocardial infarction	11/5470 (0.2)	18/5469 (0.3)	0.61 (0.29–1.29)	0.19
Ischemia-driven revascularization	28/5470 (0.5)	38/5469 (0.7)	0.74 (0.45–1.20)	0.22
Death from any cause	18/5470 (0.3)	18/5469 (0.3)	1.00 (0.52–1.92)	>0.999
Death from cardiovascular causes	18/5470 (0.3)	18/5469 (0.3)	1.00 (0.52–1.92)	>0.999
Death or stent thrombosis	59/5470 (1.1)	87/5469 (1.6)	0.67 (0.48–0.94)	0.02
Death, Q-wave myocardial infarction, or ischemia-driven revascularization	49/5470 (0.9)	64/5469 (1.2)	0.76 (0.53–1.11)	0.16
Safety: non-CABG–related bleeding				
No. of patients in safety population	5529	5527		
GUSTO-defined bleeding				
Primary safety end point: severe or life-threatening bleeding	9/5529 (0.2)	6/5527 (0.1)	1.50 (0.53–4.22)	0.44
Moderate bleeding	22/5529 (0.4)	13/5527 (0.2)	1.69 (0.85–3.37)	0.13
Severe or moderate bleeding	31/5529 (0.6)	19/5527 (0.3)	1.63 (0.92–2.90)	0.09
TIMI-defined bleeding				
Major bleeding	5/5529 (0.1)	5/5527 (0.1)	1.00 (0.29–3.45)	>0.999
Minor bleeding	9/5529 (0.2)	3/5527 (0.1)	3.00 (0.81–11.10)	0.08
Major or minor bleeding	14/5529 (0.3)	8/5527 (0.1)	1.75 (0.73–4.18)	0.20
Any blood transfusion	25/5529 (0.5)	16/5527 (0.3)	1.56 (0.83–2.93)	0.16
Efficacy and safety: net adverse clinical events‡				
Death, myocardial infarction, ischemia-driven revascularization, stent thrombosis, or GUSTO-defined severe bleeding	264/5470 (4.8)	327/5469 (6.0)	0.80 (0.68–0.94)	0.008

* GUSTO denotes Global Use of Strategies to Open Occluded Coronary Arteries, and TIMI Thrombolysis in Myocardial Infarction.
† The prespecified logistic-regression analysis was adjusted for baseline status (normal vs. abnormal) and clopidogrel loading dose (600 mg vs. 300 mg).
‡ The primary efficacy and primary safety end points were combined to provide a composite end point of net adverse clinical events in the modified intention-to-treat population.

(odds ratio, 0.85; 95% CI, 0.68 to 1.07) and those who received the infusion for more than 129 minutes (odds ratio, 0.72; 95% CI, 0.56 to 0.92) (P=0.31 for interaction).

Since the rate of the primary safety end point, GUSTO-defined severe bleeding, was very low, severe bleeding according to GUSTO criteria was combined with moderate bleeding to provide a larger number of events for an analysis of potential subgroup interactions. There were no interactions at P<0.05 (Fig. S3 in the Supplementary Appendix).

DISCUSSION

As compared with clopidogrel administered immediately before or after PCI, intravenous ADP-receptor blockade with cangrelor significantly reduced the rate of periprocedural complications of PCI, including stent thrombosis. A reduction in the rate of acute periprocedural myocardial infarction accounted for most of the benefit. The odds of an ischemic event were 22% lower with cangrelor than with clopidogrel, and this benefit was not accompanied by a significant increase in

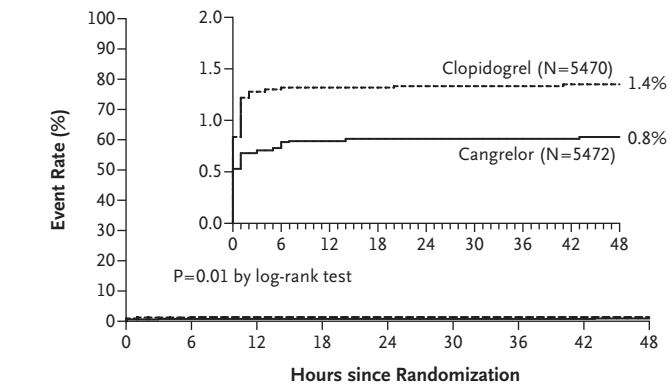


Figure 2. Kaplan–Meier Curves for the Key Secondary End Point.

The key secondary end point was stent thrombosis at 48 hours after randomization, in the modified intention-to-treat population. The inset shows the same data on an enlarged y axis.

Figure 3 (facing page). Subgroup Analysis of the Primary Efficacy End Point.

Race was self-reported. CHF denotes congestive heart failure, MI myocardial infarction, NSTE-ACS non–ST-segment elevation acute coronary syndrome, PAD peripheral-artery disease, PCI percutaneous coronary intervention, STEMI ST-segment elevation myocardial infarction, and TIA transient ischemic attack.

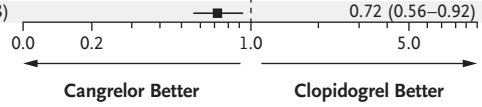
severe bleeding or in the need for transfusions. More sensitive measures did show an increase in bleeding with cangrelor, as would be expected with a potent antithrombotic agent. The rates of transient dyspnea were very low but were higher with cangrelor than with clopidogrel, a finding that was also observed in the prior CHAMPION studies. The use of cangrelor resulted in a reduction in ischemic complications across the full spectrum of patients undergoing contemporary PCI, with a consistent benefit in major subgroups.

The previous CHAMPION studies of cangrelor during PCI had suggested a clinical benefit, including a significant reduction in the secondary end point of stent thrombosis.[19,22] However, the rate of the primary end point was not reduced in the previous studies, probably because the definition of periprocedural myocardial infarction in those studies did not allow discrimination of reinfarction in patients presenting for PCI soon after admission with a biomarker-positive acute coronary syndrome.[21] In the CHAMPION PHOENIX trial, the definition of periprocedural myocardial infarction required careful assessment of patients' baseline biomarker status.[23] In addition, the use of an angiographic core laboratory allowed objective determination of intraprocedural complications. Table S6 in the Supplementary Appendix lists the differences between the CHAMPION PHOENIX trial and the CHAMPION PLATFORM and CHAMPION PCI trials.

Beyond its role in reducing ischemic complications of PCI, cangrelor may be useful in clinical situations in which ADP-receptor blockade is needed but a short-acting intravenous agent would be preferred. For example, in patients waiting to undergo open-heart surgery, cangrelor (at a lower dose than that used in this study) has been shown to result in consistent platelet inhibition without a significant increase in bleeding.[26]

There are some limitations of the current study. A 600-mg loading dose of clopidogrel is known to be superior to a 300-mg dose in some, though not all, patients undergoing PCI.[27-29] However, the results of the CHAMPION PHOENIX trial were similar after adjustment for loading dose and in each loading-dose subgroup. It is possible that the results observed here would have been attenuated if the duration of oral antiplatelet pretreatment had been longer, though both a drug and a strategy were being tested in the CHAMPION PHOENIX trial. Furthermore, although pretreatment with clopidogrel before coronary angiography has been shown in some, though not all, studies to reduce ischemic events,[30-32] it does necessitate treatment before delineation of the coronary anatomy, which might then be problematic if emergency cardiac surgery is required or intraprocedural complications such as perforation of the coronary artery occur. In addition, in patients with nausea or emesis, in those who are intubated or receiving hypothermic therapy, or in those with impaired perfusion (e.g., patients with a large myocardial infarction), adequate absorption of oral medications cannot be ensured.[11,12] Studies show that administration of even the more potent oral antiplatelet agents prasugrel and ticagrelor may not result in maximal platelet inhibition in high-risk patients undergoing PCI.[14,16] Future studies are needed to determine the most effective way to transition patients from cangrelor to prasugrel or

Subgroup	Total No. of Patients	Cangrelor	Clopidogrel	Odds Ratio (95% CI)	P Value for Interaction
		no. of events/total no. (%)			
Overall	10,939	257/5470 (4.7)	322/5469 (5.9)	0.79 (0.67–0.93)	
Age					0.55
≥75 yr	2,008	55/1021 (5.4)	73/987 (7.4)	0.71 (0.50–1.02)	
<75 yr	8,931	202/4449 (4.5)	249/4482 (5.6)	0.81 (0.67–0.98)	
Sex					0.23
Male	7,889	183/3913 (4.7)	219/3976 (5.5)	0.84 (0.69–1.03)	
Female	3,050	74/1557 (4.8)	103/1493 (6.9)	0.67 (0.50–0.92)	
Race					0.72
White	10,249	243/5130 (4.7)	300/5119 (5.9)	0.80 (0.67–0.95)	
Nonwhite	680	14/337 (4.2)	20/343 (5.8)	0.70 (0.35–1.41)	
Region					0.26
United States	4,097	93/2048 (4.5)	131/2049 (6.4)	0.70 (0.53–0.92)	
Other countries	6,842	164/3422 (4.8)	191/3420 (5.6)	0.85 (0.69–1.05)	
Diagnosis at presentation					0.98
Stable angina	6,138	181/3120 (5.8)	222/3018 (7.4)	0.78 (0.63–0.95)	
NSTE-ACS	2,810	49/1389 (3.5)	62/1421 (4.4)	0.80 (0.55–1.17)	
STEMI	1,991	27/961 (2.8)	38/1030 (3.7)	0.75 (0.46–1.25)	
Weight					0.89
≥60 kg	10,356	239/5155 (4.6)	302/5201 (5.8)	0.79 (0.66–0.94)	
<60 kg	583	18/315 (5.7)	20/268 (7.5)	0.75 (0.39–1.45)	
Biomarker status					0.35
Positive	3,980	63/1946 (3.2)	73/2034 (3.6)	0.90 (0.64–1.27)	
Negative	6,950	194/3519 (5.5)	249/3431 (7.3)	0.75 (0.61–0.91)	
Diabetes					0.26
No	7,870	181/3943 (4.6)	240/3927 (6.1)	0.74 (0.61–0.90)	
Yes	3,054	75/1519 (4.9)	82/1535 (5.3)	0.92 (0.67–1.27)	
Insulin-dependent diabetes					0.82
Yes	863	23/459 (5.0)	27/404 (6.7)	0.74 (0.42–1.31)	
No	10,061	233/5003 (4.7)	295/5058 (5.8)	0.79 (0.66–0.94)	
Previous myocardial infarction					0.30
Yes	2,267	52/1092 (4.8)	81/1175 (6.9)	0.68 (0.47–0.97)	
No	8,602	203/4347 (4.7)	235/4255 (5.5)	0.84 (0.69–1.02)	
Previous TIA or stroke					0.97
Yes	515	14/271 (5.2)	16/244 (6.6)	0.78 (0.37–1.63)	
No	10,389	242/5182 (4.7)	305/5207 (5.9)	0.79 (0.66–0.94)	
History of PAD					0.003
Yes	832	20/447 (4.5)	44/385 (11.4)	0.36 (0.21–0.63)	
No	9,991	235/4958 (4.7)	276/5033 (5.5)	0.86 (0.72–1.03)	
History of CHF					0.74
Yes	1,136	29/552 (5.3)	41/584 (7.0)	0.73 (0.45–1.20)	
No	9,777	228/4906 (4.6)	279/4871 (5.7)	0.80 (0.67–0.96)	
Clopidogrel dose					0.62
300 mg	2,806	81/1405 (5.8)	95/1401 (6.8)	0.84 (0.62–1.14)	
600 mg	8,133	176/4065 (4.3)	227/4068 (5.6)	0.77 (0.63–0.94)	
Periprocedural anticoagulant					0.51
Bivalirudin only	2,059	48/1014 (4.7)	70/1045 (6.7)	0.69 (0.47–1.01)	
Heparin only	7,566	183/3800 (4.8)	224/3766 (5.9)	0.80 (0.65–0.98)	
Arterial access					0.83
Femoral	8,064	193/4053 (4.8)	239/4011 (6.0)	0.79 (0.65–0.96)	
Radial	2,852	62/1408 (4.4)	83/1444 (5.7)	0.76 (0.54–1.06)	
No. of vessels					0.51
1	9,146	190/4543 (4.2)	239/4603 (5.2)	0.80 (0.66–0.97)	
≥2	1,695	61/878 (6.9)	79/817 (9.7)	0.70 (0.49–0.99)	
Stent type					0.79
Drug-eluting	6,080	146/3061 (4.8)	177/3019 (5.9)	0.80 (0.64–1.01)	
Bare-metal	4,859	111/2409 (4.6)	145/2450 (5.9)	0.77 (0.60–0.99)	
Aspirin dose					0.49
≤100 mg	5,387	141/2709 (5.2)	173/2678 (6.5)	0.80 (0.63–1.00)	
>100 mg	4,209	77/2082 (3.7)	111/2127 (5.2)	0.70 (0.52–0.94)	
Timing of clopidogrel loading dose					0.99
Before PCI	6,902	166/3460 (4.8)	205/3442 (6.0)	0.80 (0.64–0.98)	
After PCI	3,976	86/1980 (4.3)	108/1996 (5.4)	0.79 (0.59–1.06)	
Duration of study-drug infusion					0.31
≤129 min	5,597	145/2818 (5.1)	166/2779 (6.0)	0.85 (0.68–1.07)	
>129 min	5,331	112/2647 (4.2)	156/2684 (5.8)	0.72 (0.56–0.92)	



ticagrelor. Intravenous glycoprotein IIb/IIIa inhibitors are effective antiplatelet agents, but their antiplatelet effect does not stop quickly after cessation of the infusion, and they have been associated with an excess in episodes of major bleeding.[17]

In conclusion, intravenous ADP-receptor inhibition with cangrelor significantly reduced the rate of ischemic events across the entire spectrum of patients undergoing PCI, with a consistent benefit in all major subgroups.

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APPENDIX

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