ORIGINAL ARTICLE

Platelet Inhibition with Cangrelor in Patients Undergoing PCI

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ABSTRACT

BACKGROUND

Cangrelor, a nonthienopyridine adenosine triphosphate analogue, is an intravenous blocker of the adenosine diphosphate receptor $P2Y_{12}$. This agent might have a role in the treatment of patients who require rapid, predictable, and profound but reversible platelet inhibition.

METHODS

We performed a large-scale international trial comparing cangrelor with 600 mg of oral clopidogrel administered before percutaneous coronary intervention (PCI) in patients with acute coronary syndromes. The primary efficacy end point was a composite of death from any cause, myocardial infarction, or ischemia-driven revascularization at 48 hours.

RESULTS

We enrolled 8877 patients, and 8716 underwent PCI. At 48 hours, cangrelor was not superior to clopidogrel with respect to the primary composite end point, which occurred in 7.5% of patients in the cangrelor group and 7.1% of patients in the clopidogrel group (odds ratio, 1.05; 95% confidence interval [CI], 0.88 to 1.24; P=0.59). Likewise, cangrelor was not superior at 30 days. The rate of major bleeding (according to Acute Catheterization and Urgent Intervention Triage Strategy criteria) was higher with cangrelor, a difference that approached statistical significance (3.6% vs. 2.9%; odds ratio, 1.26; 95% CI, 0.99 to 1.60; P=0.06), but this was not the case with major bleeding (according to the Thrombolysis in Myocardial Infarction criteria) or severe or life-threatening bleeding (according to Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries criteria). A secondary exploratory end point of death from any cause, Q-wave myocardial infarction, or ischemia-driven revascularization showed a trend toward a reduction with cangrelor, but it was not significant (0.6% vs. 0.9%; odds ratio, 0.67; 95% CI, 0.39 to 1.14; P=0.14).

CONCLUSIONS

Cangrelor, when administered intravenously 30 minutes before PCI and continued for 2 hours after PCI, was not superior to an oral loading dose of 600 mg of clopidogrel, administered 30 minutes before PCI, in reducing the composite end point of death from any cause, myocardial infarction, or ischemia-driven revascularization at 48 hours. (ClinicalTrials.gov number, NCT00305162.)

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Percutaneous coronary intervention (PCI) may be complicated by adverse cardiac events including death, myocardial infarction, a need for urgent revascularization, and acute, subacute, or late stent thrombosis, regardless of whether bare-metal or drug-eluting stents are used.[1-3] As a result, antithrombotic therapy is an important adjunct to PCI.[4] Clinical practice guidelines recommend treatment with antiplatelet agents, including clopidogrel, during and after PCI, although the optimal timing, loading dose, and duration of therapy have not been definitively established by randomized clinical trials.[5,6] Current guidelines recommend an oral loading dose of 300 to 600 mg of clopidogrel (preferably before PCI) followed by 75 mg daily.

The pharmacokinetic and pharmacodynamic effects of clopidogrel are highly variable[7,8] and may be influenced by genetic polymorphisms,[9] which translate into differential pharmacodynamic and therapeutic responses, leading to the notion of clopidogrel "nonresponders."[10] Two newer oral adenosine diphosphate (ADP) blockers, prasugrel and ticagrelor, have been associated with less interpatient variability and a more potent platelet-aggregation response.[11,12] Ticagrelor was superior to clopidogrel in patients with acute coronary syndromes, and prasugrel was superior to clopidogrel in patients with acute coronary syndromes who were undergoing PCI.[13,14]

Cangrelor, a nonthienopyridine adenosine triphosphate analogue, is in a class of intravenous blockers of the ADP receptor $P2Y_{12}$ that might have a role in the treatment of patients who require rapid, predictable, and profound but reversible platelet inhibition.[15] A direct-acting, selective, and specific $P2Y_{12}$ inhibitor, cangrelor is metabolized through dephosphorylation pathways and has a plasma half-life of 3 to 6 minutes. Platelet function normalizes within 30 to 60 minutes after discontinuation.[15] Cangrelor has an additional antiplatelet effect when added in vitro to the platelets of patients receiving long-term treatment with clopidogrel.[16,17] A phase 2 trial involving patients undergoing PCI showed dose-dependent platelet inhibition similar to that of abciximab, less prolongation of bleeding time, and a more rapid return to platelet function.[18]

We performed two large, phase 3, randomized clinical trials comparing cangrelor with clopidogrel, administered before PCI (Cangrelor versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition [CHAMPION] PCI) or after PCI (CHAMPION PLATFORM; ClinicalTrials.gov number, NCT00385138). This article describes the outcomes of the CHAMPION PCI trial. The outcomes of the CHAMPION PLATFORM trial are reported elsewhere in this issue of the *Journal*.[19]

Methods

Study Design

CHAMPION PCI was a randomized, double-blind, double-dummy, active-control trial comparing cangrelor with 600 mg of clopidogrel in patients undergoing PCI. The study was sponsored by the Medicines Company. The trial was designed by an executive committee, which included the sponsor, in consultation with a steering committee. The Duke Clinical Research Institute performed primary and secondary analyses in collaboration with the sponsor. The sponsor had the right to review but not approve the final manuscript. One of the principal investigators drafted the manuscript, and both principal investigators accept full responsibility for the analyses and interpretation of the data.

Patients

Patients were eligible for enrollment in the study if they had stable angina, unstable angina, or non–ST-segment–elevation myocardial infarction with obstructive coronary artery disease and were scheduled to undergo PCI. An additional 1000 patients with ST-segment–elevation myocardial infarction for whom primary PCI was planned were also eligible. A protocol amendment issued in May 2007 required definite features of an acute coronary syndrome (ST-segment–elevation myocardial infarction in patients undergoing planned primary PCI, a non–ST-segment–elevation acute coronary syndrome with positive cardiac biomarkers, or chest pain with dynamic electrocardiographic changes in patients 65 years of age or older or with diabetes).

Patients could not have received fibrinolytic agents or glycoprotein IIb/IIIa inhibitors within the previous 12 hours or clopidogrel at a dose of more than 75 mg per day in the previous 5 days. All patients provided written informed consent.

Treatments

Patients were randomly assigned to either cangrelor or clopidogrel in a 1:1 double-blind, double-dummy design with the use of an interactive voice-response system. All patients received cangrelor (in an intravenous bolus of 30 μg per kilo-

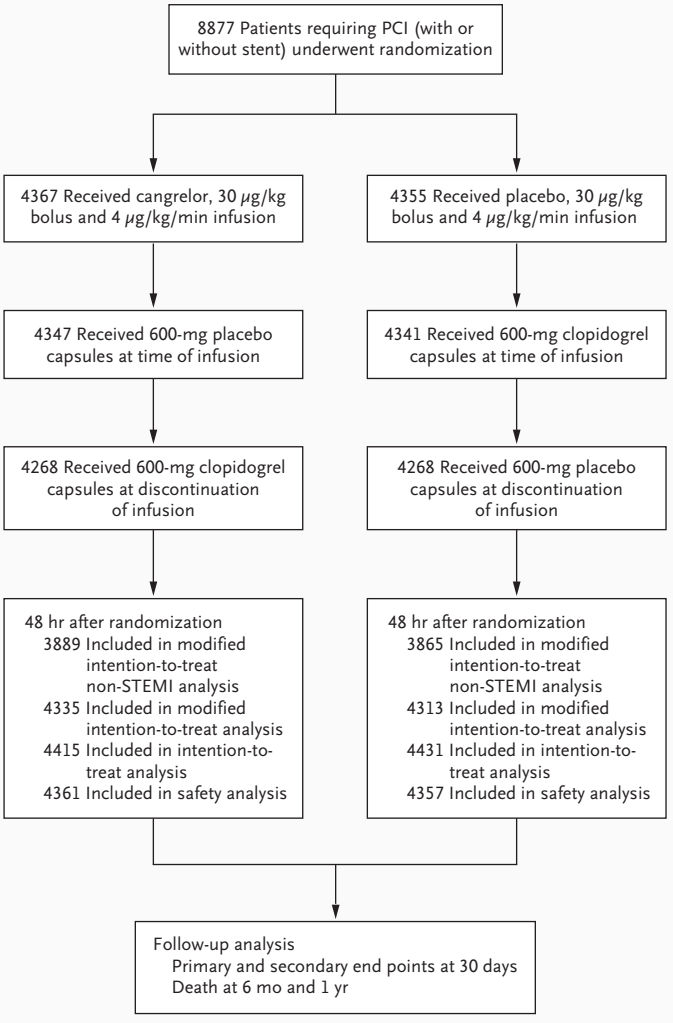

Figure 1. Randomization, Treatment, and Follow-up.

PCI denotes percutaneous coronary intervention, and STEMI ST-segment–elevation myocardial infarction.

gram of body weight and an intravenous infusion of 4 μg per kilogram per minute) or a placebo bolus and infusion (Fig. 1). The infusion began within 30 minutes before PCI and continued for at least 2 hours or until the conclusion of the index procedure, whichever was longer. At the treating physician's discretion, the infusion could be continued for 4 hours. Patients received 600 mg of clopidogrel (in four 150-mg capsules) or placebo at the time of infusion. To allow the transition from intravenous cangrelor to oral clopidogrel, patients received another four capsules (either clopidogrel in patients receiving cangrelor or placebo in patients receiving clopidogrel) at the discontinuation of the study-drug infusion. The duration of daily clopidogrel after the procedure was left to the discretion of the treating physician, although additional clopidogrel beyond the prescribed study medication was not allowed until the day after the index procedure.

All patients received 75 to 325 mg of aspirin according to local-site standards. Decisions about the use of adjunctive anticoagulants (unfractionated heparin, low-molecular-weight heparin, bivalirudin, or fondaparinux) and the procedural use of glycoprotein IIb/IIIa inhibitors were made by the treating physician.

EFFICACY END POINTS

The primary efficacy end point of the study was the composite of death from any cause, myocardial infarction, or ischemia-driven revascularization at 48 hours. Prespecified secondary efficacy end points included the composite end point of death or myocardial infarction at 48 hours and at 30 days; the composite end point of death, myocardial infarction, or ischemia-driven revascularization at 30 days; the components of the composite end points at 48 hours and at 30 days; stroke at 48 hours; abrupt vessel closure; threatened abrupt vessel closure; the need for urgent coronary-artery bypass grafting or an unsuccessful procedure during the index PCI; acute stent thrombosis (at 24 hours) and subacute stent thrombosis (at 48 hours); and death from any cause at 6 months and at 1 year.

Rates of myocardial infarction and ischemia-driven revascularization up to 30 days after the index procedure were assessed. Ischemia-driven revascularization was defined as symptoms of myocardial ischemia leading to urgent revascularization (within 24 hours after the last episode of ischemia), which must have occurred after the conclusion of the index procedure (i.e., guidewire removal). New electrocardiographic changes, acute pulmonary edema, ventricular arrhythmias, or hemodynamic instability could also constitute evidence of ischemia.

Myocardial infarction was defined by a new Q wave lasting longer than 0.03 seconds in two contiguous electrocardiographic leads or elevations in creatine kinase and the MB fraction of creatine kinase (CK-MB), including an increase in the CK-MB level that was three or more times the local upper limit of the normal range and, when biomarkers were elevated before PCI, an additional

50% above baseline.[20] One baseline troponin measurement was required in patients undergoing urgent PCI. Measurements of CK-MB were obtained 2, 10, 17, and 24 hours after PCI. Stent thrombosis was defined according to the Academic Research Consortium criteria.[21]

SAFETY END POINTS

Bleeding was assessed for up to 48 hours. Multiple clinical and laboratory definitions of bleeding were used for full assessment of the risk of bleeding associated with cangrelor. These definitions were based on criteria from the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) trial[22] (mild, moderate, or severe or life-threatening bleeding on the basis of use or nonuse of transfusions and the presence or absence of hemodynamic compromise), the Thrombolysis in Myocardial Infarction (TIMI) trial[23] (minor or major bleeding on the basis of clinical and laboratory findings), and the Acute Catheterization and Urgent Intervention Triage Strategy trial (ACUITY; NCT00093158)[24] (major bleeding on the basis of detailed clinical assessment, changes in the hemoglobin level, hematomas >5 cm, and the need for blood transfusion). Investigators reported adverse and serious adverse events according to International Conference on Harmonization guidelines.[25]

Suspected myocardial infarction, ischemia-driven revascularization, stent thrombosis, and stroke were reviewed and adjudicated by an independent clinical events committee whose members were unaware of the treatment-group assignments.[26]

EXPLORATORY EFFICACY END POINTS

Determination of periprocedural myocardial infarction can be challenging when most patients have elevated biomarkers and a single baseline sample. After the initial analyses were completed and reviewed, additional post hoc analyses were performed to better understand the potential effect of the drug on periprocedural outcomes that were less reliant on biomarkers (e.g., death, stent thrombosis, and Q-wave myocardial infarction).

STATISTICAL ANALYSIS

The sample size was based on the estimated composite incidence of death from any cause, myocardial infarction, and ischemia-driven revascularization at 48 hours. Since there was no previous information about the use of cangrelor in the patients with ST-segment–elevation myocardial infarction who were undergoing primary PCI, and given the challenge of measuring reinfarction in the early hours of ST-segment–elevation myocardial infarction, the primary efficacy end point excluded these patients from the analysis, though they were included in analyses of safety. The composite event rate was estimated at 7% in the control clopidogrel group. The trial was designed to demonstrate the superiority of cangrelor over 600 mg of clopidogrel. Assuming a 22% relative risk reduction, we estimated that a sample size of 8000 patients would provide approximately 82% power with an alpha level of 0.05. The plan was to include up to 1000 patients with ST-segment–elevation myocardial infarction, increasing the sample size to 9000 patients.

The primary efficacy analysis was to be determined in the modified intention-to-treat population, defined as all patients who underwent randomization (excluding the ST-segment–elevation myocardial infarction cohort), received at least one dose of a study drug, and underwent the index PCI.[27,28] The safety population consisted of all patients who underwent randomization and who received any study drug. Patients in the safety analyses were assigned to a treatment group on the basis of the treatment received, not on the basis of the assigned treatment. We report the results of the intention-to-treat analysis with and without the ST-segment–elevation myocardial infarction cohort.

Two interim analyses were planned after 50% and 70% of planned enrollment in the modified intention-to-treat efficacy cohort. These analyses used O'Brien–Fleming methods for stopping and protection of the type I error. Two independent monitoring committees guided the executive committee and sponsor. The data and safety monitoring board was responsible for review and oversight of patient safety. After the trial began and after the data and safety monitoring board met to review interim trial data, the executive committee and the sponsor decided to perform interim efficacy analyses to ensure that assumptions about event rates and treatment effects remained valid. The goal was to use interim data to make decisions about the need to modify the trial (i.e., increase the sample size or increase enrollment in certain subgroups) or discontinue

Table 1. Baseline Characteristics of the Patients, According to Study Population.*

Variable	Intention-to-Treat		Intention-to-Treat without ST-segment–Elevation Myocardial Infarction		Intention-to-Treat with ST-segment–Elevation Myocardial Infarction	
	Cangrelor (N=4433)	Clopidogrel (N=4444)	Cangrelor (N=3946)	Clopidogrel (N=3935)	Cangrelor (N=487)	Clopidogrel (N=509)
Age — yr						
Median	62.0	62.0	63.0	62.0	58.0	61.0
Interquartile range	54.0–70.0	54.0–71.0	55.0–71.0	54.0–71.0	51.0–67.0	52.0–70.0
Sex — no. (%)						
Male	3275 (73.9)	3209 (72.2)	2891 (73.3)	2831 (71.9)	384 (78.9)	378 (74.3)
Female	1158 (26.1)	1235 (27.8)	1055 (26.7)	1104 (28.1)	103 (21.1)	131 (25.7)
Race or ethnic group — no./total no. (%)†						
White	3658/4428 (82.6)	3626/4438 (81.7)	3229/3941 (81.9)	3184/3930 (81.0)	429/487 (88.1)	442/508 (87.0)
Asian	311/4428 (7.0)	313/4438 (7.1)	294/3941 (7.5)	300/3930 (7.6)	17/487 (3.5)	13/508 (2.6)
Black	215/4428 (4.9)	239/4438 (5.4)	190/3941 (4.8)	208/3930 (5.3)	25/487 (5.1)	31/508 (6.1)
Hispanic	209/4428 (4.7)	218/4438 (4.9)	197/3941 (5.0)	204/3930 (5.2)	12/487 (2.5)	14/508 (2.8)
Other	35/4428 (0.8)	42/4438 (1.0)	31/3941 (0.8)	34/3930 (0.9)	4/487 (0.8)	8/508 (1.6)
Weight — kg						
Median	84.0	84.0	84.0	84.0	83.0	82.0
Interquartile range	73.0–97.0	73.0–97.0	73.0–97.0	73.0–98.0	72.0–95.0	72.0–95.0
Height — cm						
Median	172.0	172.0	172.0	172.0	173.0	172.0
Interquartile range	165.0–178.0	165.0–178.0	165.0–178.0	165.0–178.0	167.6–178.0	165.0–178.0
Stable angina — no. (%)	668 (15.1)	665 (15.0)	668 (16.9)	665 (16.9)	0	0
Unstable angina — no. (%)	1097 (24.7)	1088 (24.5)	1097 (27.8)	1088 (27.6)	0	0
Myocardial infarction without ST-segment elevation — no. (%)	2181 (49.2)	2182 (49.1)	2181 (55.3)	2182 (55.5)	0	0
ST-segment–elevation myocardial infarction — no. (%)	487 (11.0)	509 (11.5)	0	0	487 (100.0)	509 (100.0)
Other medical history — no./total no. (%)						
Diabetes mellitus	1350/4431 (30.5)	1352/4440 (30.5)	1248/3944 (31.6)	1263/3931 (32.1)	102/487 (20.9)	89/509 (17.5)
Current smoker	1247/4383 (28.5)	1283/4408 (29.1)	1035/3898 (26.6)	1076/3905 (27.6)	212/485 (43.7)	207/503 (41.2)
Hypertension	3181/4413 (72.1)	3139/4421 (71.0)	2900/3929 (73.8)	2839/3921 (72.4)	281/484 (58.1)	300/500 (60.0)
Hyperlipidemia	2825/4244 (66.6)	2777/4239 (65.5)	2590/3788 (68.4)	2536/3765 (67.4)	235/456 (51.5)	241/474 (50.8)
Stroke or transient ischemic attack	223/4415 (5.1)	227/4420 (5.1)	208/3928 (5.3)	205/3916 (5.2)	15/487 (3.1)	22/504 (4.4)
Family history of coronary artery disease	1843/4018 (45.9)	1873/4025 (46.5)	1656/3590 (46.1)	1686/3576 (47.1)	187/428 (43.7)	187/449 (41.6)
Myocardial infarction	1075/4364 (24.6)	1089/4385 (24.8)	1003/3880 (25.9)	1007/3879 (26.0)	72/484 (14.9)	82/506 (16.2)

PTCA or PCI	1266/4419 (28.6)	1261/4428 (28.5)	1193/3933 (30.3)	1198/3921 (30.6)	73/486 (15.0)	63/507 (12.4)
Coronary-artery bypass grafting	557/4428 (12.6)	552/4441 (12.4)	541/3941 (13.7)	532/3932 (13.5)	16/487 (3.3)	20/509 (3.9)
Congestive heart failure	333/4392 (7.6)	338/4403 (7.7)	319/3908 (8.2)	322/3897 (8.3)	14/484 (2.9)	16/506 (3.2)
Peripheral artery disease	323/4344 (7.4)	315/4351 (7.2)	294/3863 (7.6)	290/3852 (7.5)	29/481 (6.0)	25/499 (5.0)
Periprocedural medications — no./total no. (%)						
Bivalirudin	1313/4429 (29.6)	1337/4439 (30.1)	1244/3943 (31.5)	1250/3931 (31.8)	69/486 (14.2)	87/508 (17.1)
Unfractionated heparin	2437/4429 (55.0)	2452/4438 (55.3)	2154/3943 (54.6)	2155/3930 (54.8)	283/486 (58.2)	297/508 (58.5)
Low-molecular-weight heparin	368/4427 (8.3)	340/4438 (7.7)	322/3941 (8.2)	298/3930 (7.6)	46/486 (9.5)	42/508 (8.3)
Glycoprotein IIb/IIIa inhibitors	1163/4430 (26.3)	1183/4438 (26.7)	909/3944 (23.0)	927/3930 (23.6)	254/486 (52.3)	256/508 (50.4)
Study treatment — no./total no. (%)						
No. of target vessels						
1	3836/4359 (88.0)	3796/4342 (87.4)	3406/3902 (87.3)	3360/3884 (86.5)	430/457 (94.1)	436/458 (95.2)
2	484/4359 (11.1)	509/4342 (11.7)	457/3902 (11.7)	488/3884 (12.6)	27/457 (5.9)	21/458 (4.6)
3	38/4359 (0.9)	36/4342 (0.8)	38/3902 (1.0)	35/3884 (0.9)	0/457	1/458 (0.2)
Drug-eluting stent	2581/4359 (59.2)	2560/4342 (59.0)	2422/3902 (62.1)	2383/3884 (61.4)	159/457 (34.8)	177/458 (38.6)
Non–drug-eluting stent	1640/4359 (37.6)	1635/4342 (37.7)	1367/3902 (35.0)	1380/3884 (35.5)	273/457 (59.7)	255/458 (55.7)
Angiographic complications, site-reported — no./total no. (%)						
Threatened abrupt vessel closure	13/4359 (0.3)	12/4342 (0.3)	9/3902 (0.2)	10/3884 (0.3)	4/457 (0.9)	2/458 (0.4)
Unsuccessful procedure	90/4359 (2.1)	103/4342 (2.4)	81/3902 (2.1)	92/3884 (2.4)	9/457 (2.0)	11/458 (2.4)
Abrupt vessel closure	24/4359 (0.6)	22/4342 (0.5)	20/3902 (0.5)	19/3884 (0.5)	4/457 (0.9)	3/458 (0.7)
New or suspected thrombus	17/4359 (0.4)	23/4342 (0.5)	16/3902 (0.4)	16/3884 (0.4)	1/457 (0.2)	7/458 (1.5)
Acute stent thrombosis	2/4359 (<0.1)	5/4342 (0.1)	2/3902 (0.1)	5/3884 (0.1)	0/457	0/458
Need for urgent coronary-artery bypass grafting	10/4359 (0.2)	7/4342 (0.2)	8/3902 (0.2)	7/3884 (0.2)	2/457 (0.4)	0/458
Intravenous study drug administered — no. (%)	4367/4432 (98.5)	4355/4444 (98.0)	3904/3945 (99.0)	3883/3935 (98.7)	463/487 (95.1)	472/509 (92.7)
Bolus administered — no. (%)	4367/4432 (98.5)	4354/4444 (98.0)	3904/3945 (99.0)	3883/3935 (98.7)	463/487 (95.1)	471/509 (92.5)
Infusion administered — no./total no. (%)	4364/4432 (98.5)	4353/4444 (98.0)	3901/3945 (98.9)	3882/3935 (98.7)	463/487 (95.1)	471/509 (92.5)
Duration of infusion — hr						
Median	2.1	2.1	2.1	2.1	2.0	2.1
Interquartile range	2.0–2.2	2.0–2.2	2.0–2.2	2.0–2.2	2.0–2.2	2.0–2.2
Oral study drug administered — no./total no. (%)	4351/4432 (98.2)	4345/4444 (97.8)	3896/3945 (98.8)	3882/3935 (98.7)	455/487 (93.4)	463/509 (91.0)

* Percentages may not total 100 because of rounding. PCI denotes percutaneous coronary intervention, and PTCA percutaneous transluminal coronary angioplasty.
† Race or ethnic group was self-reported.

Table 2. Major End Points at 48 Hours in the Modified Intention-to-Treat Population without ST-Segment–Elevation Myocardial Infarction.

End Point	Cangrelor Group (N=3889)	Clopidogrel Group (N=3865)	Odds Ratio (95% CI)	P Value
	no. (%)			
Adjudicated end points				
Primary end point: death, myocardial infarction, or ischemia-driven revascularization	290 (7.5)	276 (7.1)	1.05 (0.88–1.24)	0.59
Myocardial infarction	278 (7.1)	256 (6.6)	1.09 (0.91–1.29)	0.36
Ischemia-driven revascularization	13 (0.3)	23 (0.6)	0.56 (0.28–1.11)	0.10
Death from any cause	8 (0.2)	5 (0.1)	1.59 (0.52–4.87)	0.42
Stent thrombosis	7 (0.2)	11 (0.3)	0.63 (0.25–1.63)	0.34
Stroke	6 (0.2)	7 (0.2)	0.85 (0.29–2.54)	0.77
Q-wave myocardial infarction	4 (0.1)	10 (0.3)	0.40 (0.12–1.27)	0.12
Exploratory end points				
Death, Q-wave myocardial infarction, or ischemia-driven revascularization	23 (0.6)	34 (0.9)	0.67 (0.39–1.14)	0.14
Death, Q-wave myocardial infarction, or stent thrombosis	18 (0.5)	23 (0.6)	0.78 (0.42–1.44)	0.42

it for futility. Because the data and safety monitoring board had knowledge of the treatment differences based on the 50% interim analysis, after discussion with the Food and Drug Administration, it was decided to convene a separate group, the interim-analysis review committee, to conduct and review the 70% interim analysis and make recommendations based on predefined algorithms that allowed an increase in the sample size up to a maximum of 15,000 patients.[29] Possible additional groups of eligible patients included patients with diabetes, those with positive troponin levels before enrollment, and those who had not previously received clopidogrel. The interim-analysis review committee received guidance from the executive committee regarding stopping rules for efficacy or futility on the basis of estimates of conditional power. The interim-analysis review committee considered the interim results of CHAMPION PCI and the companion trial, CHAMPION PLATFORM,[19] when making recommendations to the executive committee and sponsor.

All statistical tests were two-tailed and used a level of significance of 0.05. The primary endpoint comparison between the cangrelor and placebo groups was performed by calculating an odds ratio, with accompanying 95% confidence intervals, with the use of logistic regression. Logistic regression was used to analyze the majority of the remaining secondary end points. Continuous variables are reported as medians and interquartile ranges. Categorical variables are reported as frequencies and percentages. In the secondary efficacy analyses, there was no attempt to adjust the P values for multiple comparisons. These analyses were considered exploratory and hypothesis-generating.

RESULTS

PATIENT ENROLLMENT

At the 70% interim analysis, the interim-analysis review committee reported that the estimated conditional power to demonstrate superiority was low. The data and safety monitoring board reported no safety concerns, so the executive committee and sponsor elected to continue the trial until the companion trial, CHAMPION PLATFORM,[19] underwent its 70% interim analysis. At that time, the interim-analysis review committee and the data and safety monitoring board reported that the estimated conditional power in CHAMPION PLATFORM was also low and recommended discontinuation of enrollment into both trials. The sponsor, in consultation with the executive committee, terminated enrollment on May 13, 2009, at which point 8877 of the expected 9000 patients (98.6%) had been enrolled in CHAMPION PCI at 268 sites across 14 countries. For the end points at 48 hours and 30 days, the vital-status follow-up was 99.7% and 98.6% complete, respectively.

PATIENT CHARACTERISTICS AND TREATMENTS

Baseline demographic characteristics of the patients in the intention-to-treat population are shown in Table 1. Baseline demographic characteristics of the patients in the modified intention-to-treat and safety populations are shown in Tables 1 and 2 of the Supplementary Appendix, available with the full text of this article at NEJM.org. There were no significant differences between the groups with respect to baseline characteristics. Enrolled patients were typical of a contemporary PCI population; most were men, and the median age was 62.0 years (interquartile range, 54.0 to 71.0). Diabetes was diagnosed in 30.5% of the patients, and hypertension or hyperlipidemia was present in the majority of patients. Previous cardiac events included myocardial infarction in 24.7% of the patients and revascularization in 34.1% (PCI in 28.6% and bypass grafting in 12.5%). Almost half the enrolled patients (49.1%) had myocardial infarction without ST-segment elevation at baseline, whereas stable angina and unstable angina were the baseline diagnoses in 15.0% and 24.6%, respectively. The cohort with ST-segment–elevation myocardial infarction included 996 patients (11.2%).

During the index procedure, a majority of patients (55.1%) received unfractionated heparin, and 29.9% received bivalirudin. Glycoprotein IIb/IIIa inhibitors were used in 26.5% of patients, with most receiving eptifibatide (75.0%). Almost all patients in the intention-to-treat population (98.5%) received a study drug. Sites were instructed to start PCI within 30 minutes after patients received clopidogrel capsules.

PCI was attempted in all but 161 patients (1.8%), 65 in the cangrelor group (1.5%) and 96 in the clopidogrel group (2.2%). The median duration of PCI was 0.4 hours (range, 0.2 to 0.6), and the median time from hospital admission to PCI was 6.3 hours (range, 2.6 to 23.7). Most procedures involved single-vessel or two-vessel PCI (87.7% and 11.4%, respectively). Drug-eluting stents were used in the majority of interventions (59.1%), and bare-metal stents were used in 37.6%.

EFFICACY END POINTS

Cangrelor was not superior to 600 mg of clopidogrel with respect to the primary composite end point of death from any cause, myocardial infarction, or ischemia-driven revascularization at 48 hours. This primary end point occurred in 7.5% of patients receiving cangrelor and 7.1% of patients receiving clopidogrel (odds ratio, 1.05; 95% CI, 0.88 to 1.24; P=0.59) (Table 2). The primary composite efficacy end point did not differ significantly between the two groups at 30 days (Table 3 of the Supplementary Appendix). Figure 2, as well as Figure 1 in the Supplementary Appendix, shows odds-ratio data for the primary end point in key subgroups. Additional data on end points are included in the Supplementary Appendix.

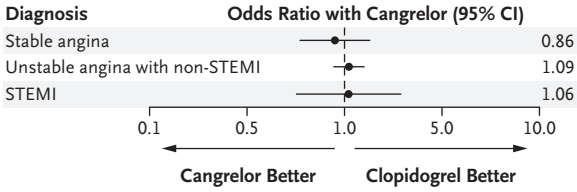

Figure 2. Odds Ratios for the Primary End Point, According to Diagnosis at Enrollment, in the Modified Intention-to-Treat Population.

Data for the primary end point — a composite of death from any cause, myocardial infarction, or ischemia-driven revascularization at 48 hours — are shown. For each subgroup, the circle represents the estimated odds ratio for the treatment effect. The horizontal lines indicate 95% confidence intervals. STEMI denotes ST-segment–elevation myocardial infarction.

SAFETY END POINTS

Bleeding events at 48 hours as observed in the safety population (including patients with ST-segment–elevation myocardial infarction) are listed in Table 3. Reported adverse events occurred in similar proportions of patients in the two groups (in 26.4% of patients in the cangrelor group and in 25.7% of patients in the clopidogrel group), and discontinuation of the study drug because of an adverse event was unusual in both groups (0.5% in both). Serious adverse events were infrequent and occurred in similar proportions of patients in the two groups (2.7% in both). Dyspnea was reported in 1.0% of patients who received cangrelor, as compared with 0.4% of patients who received clopidogrel (P=0.001).

EXPLORATORY CLINICAL EFFICACY END POINTS

Key secondary and composite exploratory (post hoc) end points are shown in Table 2, and in Table 4 of the Supplementary Appendix. Additional data on exploratory end points are included in the Supplementary Appendix.

Table 3. Bleeding Events at 48 Hours in the Safety Population.

Variable	Cangrelor Group (N=4374)	Clopidogrel Group (N=4365)	Odds Ratio (95% CI)	P Value
	no. (%)			
Event				
Access-site bleeding requiring radiologic or surgical intervention	6 (0.1)	10 (0.2)	0.60 (0.22–1.65)	0.32
Hematoma at puncture site				
≥5 cm	85 (1.9)	76 (1.7)	1.12 (0.82–1.53)	0.48
<5 cm	251 (5.7)	222 (5.1)	1.14 (0.94–1.37)	0.18
Intracranial hemorrhage	1 (<0.1)	0 (0.0)		
Intraocular hemorrhage	2 (<0.1)	0 (0.0)		
Bleeding requiring surgery	1 (<0.1)	1 (<0.1)	1.00 (0.06–15.96)	1.00
Retroperitoneal hemorrhage	15 (0.3)	10 (0.2)	1.50 (0.67–3.34)	0.32
Ecchymosis	284 (6.5)	234 (5.4)	1.23 (1.03–1.47)	0.03
Epistaxis	9 (0.2)	22 (0.5)	0.41 (0.19–0.89)	0.02
Oozing at puncture site	400 (9.1)	319 (7.3)	1.28 (1.10–1.49)	0.002
Thrombocytopenia	6 (0.1)	7 (0.2)	0.86 (0.29–2.55)	0.78
Hemodynamic compromise	9 (0.2)	11 (0.3)	0.82 (0.34–1.97)	0.65
Transfusion				
Any blood	46 (1.1)	42 (1.0)	1.09 (0.72–1.67)	0.68
Any platelet	6 (0.1)	5 (0.1)	1.20 (0.37–3.93)	0.77
Decrease in level of hemoglobin, hematocrit, or both*	91 (2.1)	63 (1.4)	1.45 (1.05–2.01)	0.02
Category of bleeding†				
ACUITY criteria				
Minor bleeding	768 (17.6)	663 (15.2)	1.19 (1.06–1.33)	0.003
Major bleeding	158 (3.6)	126 (2.9)	1.26 (0.99–1.60)	0.06
GUSTO criteria				
Mild bleeding	858 (19.6)	739 (16.9)	1.20 (1.07–1.34)	0.001
Moderate bleeding	41 (0.9)	34 (0.8)	1.21 (0.76–1.90)	0.42
Severe or life-threatening bleeding	10 (0.2)	11 (0.3)	0.91 (0.39–2.14)	0.82
TIMI criteria				
Minor bleeding	36 (0.8)	26 (0.6)	1.39 (0.84–2.30)	0.21
Major bleeding	19 (0.4)	14 (0.3)	1.36 (0.68–2.71)	0.39

* A drop in hemoglobin or hematocrit was defined as a decrease of at least 3 g per deciliter in hemoglobin or a 9% decrease in hematocrit after treatment, as compared with baseline, as reported by investigators.

† The bleeding categories for each set of criteria are not mutually exclusive. For example, a patient may have had clinically significant bleeding and minor bleeding according to the criteria from the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial, if more than one bleeding episode occurred. For each set of criteria, a patient was counted once for each category of bleeding, regardless of the number of bleeding episodes identified in that category. GUSTO denotes Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries, and TIMI Thrombolysis in Myocardial Infarction.

DISCUSSION

There is little question that blockade of the platelet $P2Y_{12}$ receptor confers a benefit in reducing the risk of ischemia in multiple acute cardiac care settings. Clopidogrel reduces the composite risk of death or myocardial infarction among patients presenting with acute coronary syndromes

(with or without ST-segment elevation), regardless of whether they are undergoing PCI.[30-33] Recently, prasugrel was shown to be superior to a 300-mg loading dose, followed by a 75-mg dose of clopidogrel, in reducing both short- and long-term rates of myocardial infarction among patients with acute coronary syndromes who were undergoing PCI.[14] Prasugrel reduced the risk of stent thrombosis by more than 50% as compared with clopidogrel.[34] These observations were extended in a trial of ticagrelor, a reversible nonthienopyridine inhibitor of $P2Y_{12}$, which significantly reduced the composite end point of cardiovascular death, myocardial infarction, or stroke, as compared with the standard dose of clopidogrel, among patients with acute coronary syndromes who were treated invasively and medically.[13] The recently presented Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events/Optimal Antiplatelet Strategy for Interventions (CURRENT/OASIS 7) study (NCT00335452) showed reduced rates of myocardial infarction at 30 days among patients undergoing PCI when a loading dose of 600 mg of clopidogrel, followed by 150 mg per day for 1 week, was compared with standard clopidogrel dosing.[35]

On the basis of these observations as well as others that address the pharmacodynamic limitations of clopidogrel, it was unexpected that a cangrelor infusion was not superior to 600 mg of clopidogrel in this trial with the use of the predefined primary end point, especially since significantly higher levels of periprocedural platelet inhibition were achieved with cangrelor. These results raise questions about the most appropriate end-point selection and definition as well as the best trial design to test the efficacy and safety of a short-acting antiplatelet agent in patients who have myocardial infarction without ST-segment elevation, when short times from admission to PCI prevent clear delineation between myocardial infarction occurring before and that occurring after randomization.

Analyses that concentrate on end points that are less dependent on a biomarker-defined myocardial infarction, such as Q-wave myocardial infarction and stent thrombosis, were performed. The odds ratio for a benefit of cangrelor in reducing the composite end point of death from any cause, Q-wave myocardial infarction, or ischemia-driven revascularization was 0.66, but it was not significant (95% CI, 0.42 to 1.05). As an exploratory (post hoc) analysis, this observation should be viewed as hypothesis-generating until it is addressed in an adequately powered randomized clinical trial. In addition, a longer duration of more potent platelet inhibition with cangrelor may be worth testing. Other potential uses for a short-acting $P2Y_{12}$ inhibitor such as cangrelor, which include a bridging strategy when patients require platelet blockade but cannot receive oral therapy, are also worthy of investigation.

In conclusion, in the CHAMPION PCI trial, intravenous cangrelor was not superior to a 600-mg loading dose of clopidogrel, administered 30 minutes before PCI, in reducing the composite end point of death from any cause, myocardial infarction, or ischemia-driven revascularization at 48 hours. Minor bleeding was more common in patients who received cangrelor, and one measure of major bleeding (based on criteria from the ACUITY trial) showed a trend toward an increase in bleeding with cangrelor as compared with clopidogrel. Post hoc secondary analyses raise the possibility that further clinical investigation of cangrelor may be worthwhile.

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