The Heart Surgery Forum #2012-1103
16 (2), 2013 [Epub April 2013]
doi: 10.1532/HSF98.20121103

Online address: http://cardenjennings.metapress.com

Safety and Efficacy of Cangrelor, an Intravenous, Short-Acting Platelet Inhibitor in Patients Requiring Coronary Artery Bypass Surgery

Michael S. Firstenberg,[1] Cornelius M. Dyke,[2] Dominick J. Angiolillo,[3] Chandrashekhar Ramaiah,[4] Matthew Price,[5] Miroslav Brtko,[6] Ian Welsby,[7] Harish Chandna,[8] David R. Holmes,[9] Michele Voeltz,[2] Pradyumna Tummala,[10] Martin Hutyra,[11] Steven V. Manoukian,[12] Jayne Prats,[13] Meredith Todd,[13] Tiepu Liu,[13] Nicholas Chronos,[14] Markus Dietrich,[13] Gilles Montalescot,[15] Louis A. Cannon,[16] Eric J. Topol[5]

[1]Department of Surgery (Cardiothoracic), Akron City Hospital, Northeast Ohio Medical University, Akron Ohio, USA; [2]Department of Cardiovascular Surgery, Sanford Medical Center, Fargo, North Dakota, USA; [3]Department of Cardiology, University of Florida, Jacksonville, Florida, USA; [4]Department of Surgery, University of Kentucky, Lexington, Kentucky, USA; [5]Department of Cardiology, Scripps Clinic and Scripps Translational Science Institute, La Jolla, California, USA; [6]Department of Cardiac Surgery, University Hospital, Hradec Kralove, Czech Republic; [7]Duke University, Durham, North Carolina, USA; [8]Department of Cardiology, Detar Hospital, Victoria, Texas, USA; [9]Department of Cardiology, The Mayo Clinic, Rochester, Minnesota, USA; [10]Department of Cardiology, Northeast Georgia Heart Center, Gainesville, Georgia, USA; [11]1st Internal Clinic, Faculty Hospital Olomouc, Olomouc, Czech Republic; [12]Sarah Cannon Research Institute, Nashville, Tennessee, USA; [13]The Medicines Company, Parsippany, New Jersey, USA; [14]Saint Joseph's Translational Research Institute, Atlanta, Georgia, USA; [15]Department of Cardiology, Pitié-Salpétrière Hospital, Paris, France; [16]Cardiac and Vascular Research Center, Northern Michigan Hospital, Petoskey, Michigan, USA

ABSTRACT

Objective: Oral $P2Y_{12}$ platelet receptor inhibitors are a cornerstone of reducing complications in patients with acute coronary syndromes or coronary stents. Guidelines advocate discontinuing treatment with $P2Y_{12}$ platelet receptor inhibitors before surgery. Cangrelor, a short-acting, reversible, intravenously administered $P2Y_{12}$ platelet inhibitor is effective in achieving appropriate platelet inhibition in patients who are awaiting coronary artery bypass grafting (CABG) and require $P2Y_{12}$ inhibition. The objective of this study was to assess the effects of preoperative cangrelor on the incidence of perioperative complications, which are currently unknown.

Methods: Patients (n = 210) requiring preoperative clinical administration of thienopyridine therapy were randomized in a multicenter, double-blinded study to receive cangrelor or placebo while awaiting CABG after discontinuation of the thienopyridine. Optimal platelet reactivity, which was defined as <240 $P2Y_{12}$ platelet reaction units, was measured with serial point-of-care testing (VerifyNow). Pre- and postoperative outcomes, bleeding values, and transfusion rates were compared. To quantify potential risk factors for bleeding, we developed a multivariate logistic model.

Results: The differences between the groups in bleeding and perioperative transfusion rates were not significantly different. The rate of CABG-related bleeding was 11.8% (12/102) in cangrelor-treated patients and 10.4% (10/96) in the placebo group (P = .763). Transfusion rates for the groups were similar. Serious postoperative adverse events for the cangrelor and placebo groups were 7.8% (8/102) and 5.2% (5/96), respectively (P = .454).

Conclusions: Compared with placebo, bridging patients with cangrelor prior to CABG effectively maintains platelet inhibition without increasing post-CABG complications, including bleeding and the need for transfusions. These data suggest cangrelor treatment is a potential strategy for bridging patients requiring $P2Y_{12}$ receptor inhibition while they await surgery.

Received September 30, 2012; accepted March 21, 2013.

Correspondence: Michael S. Firstenberg, MD, Department of Surgery (Cardiothoracic), Akron City Hospital, Northeast Ohio Medical University, Akron Ohio 44309, USA; 1-614-366-7414; fax: 1-614-293-2200 (e-mail: Michael.firstenberg@osumc.edu).

INTRODUCTION

The use of dual antiplatelet therapy, specifically the combination of aspirin and an oral $P2Y_{12}$ receptor inhibitor such as clopidogrel, prasugrel, or ticagrelor, is the standard of care for patients who present with acute coronary syndromes (ACS) or who have recently placed coronary stents [Lewis 2005; Chen 2005; Sabatine 2005]. Early platelet inhibition with P2Y12 platelet receptor has been shown to reduce the risk of recurrent ischemic events inhibitors in these patients. Several large studies of patients presenting with ACS have shown, however, that 10% to 15% of patients require surgical intervention [Yusuf 2001]. Continuation of $P2Y_{12}$ inhibition up until the time of surgery reduces the risk of preoperative ischemic events, but it may also increase the risks of bleeding and bleeding-related complications. Although current guidelines recommend withholding thienopyridine therapy for at least 5 to 7 days for clopidogrel, 5 days for ticagrelor, and

7 days for prasugrel before planned coronary artery bypass grafting surgery (CABG), adherence to these guidelines still exposes patients to an increased risk of preoperative ischemic events [Wright 2011]. Although the risk is poorly defined, some investigators have suggested a 10% to 15% risk of major adverse events during the "washout" period in patients in whom thienopyridines are held prior to surgery [Sambu 2011]. Evidence also suggests that a "rebound" phenomenon with increased platelet reactivity could occur with an abrupt withdrawal, which might also predispose the patient to recurrent ischemic events [Collet 2004]. Optimal strategies are lacking for transitioning patients who are receiving platelet inhibition therapies and then require surgery.

Cangrelor is an intravenous, short-acting, reversible, platelet $P2Y_{12}$ inhibitor [Norgard 2009]. Its mechanism of action differs from oral, irreversible thienopyridines that are prodrugs and require metabolic activation and bind irreversibly to the receptor. In contrast, cangrelor directly and reversibly binds to the $P2Y_{12}$ receptor. Ticagrelor, another oral nonthienopyridine $P2Y_{12}$ inhibitor, also binds directly and reversibly. Its onset is slower (approximately 30 minutes to 1 hour, compared with immediately for cangrelor); however, the offset of effect is considerably longer (approximately 5 days) than for cangrelor. Pharmacodynamic studies have shown that platelet function returns to normal within 1 hour after cangrelor discontinuation. Our recently published report of a double-blind, placebo-controlled trial has demonstrated that a cangrelor infusion of 0.75 µg/kg per minute provided adequate platelet inhibition in 98.8% of patients awaiting CABG. This platelet inhibition was maintained throughout the duration of therapy [Angiolillo 2012]. The objective of the present study was to assess the effects of preoperative cangrelor on the incidence of perioperative complications in the BRIDGE trial.

METHODS

The design and protocol of the BRIDGE trial have already been described [Angiolillo 2012]. In brief, we conducted an open-label phase of the study to identify the cangrelor dose that produced a desired antiplatelet effect. We then identified 210 patients who had indications for thienopyridine therapy, because of either recent ACS or recent implantation of an intracoronary stent, and randomized them to an infusion of cangrelor or placebo. We used serial point-of-care testing (VerifyNow™; Accumetrics, San Diego, CA, USA) to measure platelet reactivity, which was defined as <240 platelet reaction units (PRU). Measurements were made before infusion, every day preoperatively, immediately before discontinuation of the study drug, and at the time of surgical incision. By protocol design, all patients received between 2 and 7 days of therapy with the study drug. This therapy was discontinued 1 to 6 hours before the planned CABG. All patients received aspirin during the study period. All other perioperative management decisions (ie, heparin infusions, transfusion decisions, need for reoperation, and surgical techniques) were at the discretion of the primary teams and were consistent with accepted standards of care. All events were site-reported and defined as any new complaint or diagnosis in the medical record, as reported by the treating physicians during the pre- and postoperative periods. The site-reported, protocol-defined end points of bleeding and major adverse cardiovascular/cerebrovascular end points/events (MACCE) were reported separately from other pre- and postsurgery complications (see Appendix A for definitions).

All patients provided written informed consent, and appropriate ethics committee and regulatory approval were obtained by each participating center. Study oversight was monitored by an executive committee chaired by the lead investigator (E.J.T.). The study was sponsored by The Medicines Company and was registered with ClinicialTrials.gov (http://www.clinicaltrials.gov; NCT00767507).

Statistical Analysis

The study randomized 210 patients. The safety-analysis population included the patients in the cangrelor group (n = 106) and the placebo group (n = 101) who had been randomized to receive any study drug. The patients were classified according to the actual treatment received for safety analysis. The intent-to-treat (ITT) population (cangrelor group, 93 patients; placebo group, 90 patients) was defined as all patients who were randomized to receive the study drug, except for the first 24 patients, whose data were unblinded for a planned review by the Data Safety Monitoring Board for dosing confirmation. The efficacy analysis was based on the patients in the ITT population who had valid PRU results (84 patients each in the cangrelor and placebo groups). The efficacy end point was the proportion (ie, percentage) of patients with a platelet reactivity of <240 PRU for all samples assessed during infusion of the study drug before surgery. In general, differences from baseline were compared with analysis of variance (ANOVA) for quantitative factors or with the chi-square test for proportions (or the Fisher exact test for rare events, as appropriate). The chi-square test was used to compare the differences between the 2 groups in the percentage of patients with platelet inhibition with regard to relative risk (RR) or odds ratio (OR), and their respective 95% confidence intervals (CI), which were estimated according to an approximation to normality. ANOVA was used to compare differences in PRU values. We did not apply any imputation to missing data or any αadjustment for multiple comparisons. To explore and quantify potential risk factors for bleeding, we developed a multivariate logistic model. First, we performed a univariate analysis with ANOVA or the chi-square test for each potential risk factor for bleeding. Bleeding risk was analyzed for protocol-defined excessive CABG-related bleeding and major or minor preprocedure bleeding. The ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy), GUSTO (Global Use of Strategies to Open Occluded Coronary Arteries), or TIMI (Thrombolysis in Myocardial Infarction) bleeding scale was used (separately and in combination for the cangrelor and placebo groups; see Appendix A). Potentially significant risk factors identified in the univariate analyses with *P* values <.15 were then included in a multivariate logistic model to quantify the adjusted risks and to control their potential confounding effect on the effect of cangrelor treatment for bleeding.

Table 1. Patient Demographic and Surgical-Procedure Characteristics (Safety Population)*

	Cangrelor (n = 106)	Placebo (n = 101)	*P*
Age, y	65.0 (42, 84)	62.0 (39, 89)	.260
Male, n (%)	80 (75.5)	74 (73.3)	.717
Race, n (%)			
White	93 (87.7)	94 (93.1)	.200
Asian	3 (2.8)	0 (0.0)	
Black	6 (5.7)	5 (5.0)	
Hispanic	4 (3.8)	2 (2.0)	
Weight, kg	88.0 (58, 154)	85.0 (51, 139)	.282
Height, cm	172.9 (152, 190)	172.7 (150, 193)	.756
Body mass index, kg/m^2	29.3 (20, 50)	28.2 (19, 47)	.262
STEMI, n (%)	16 (15.1)	12 (11.9)	.500
Medical history, n (%)			
Smoking	31/106 (29.2)	38/101 (37.6)	.202
Diabetes	49/106 (46.2)	47/101 (46.5)	.965
Hypertension	87/106 (82.1)	83/101 (82.2)	.985
Hyperlipidemia	76/104 (73.1)	77/100 (77.0)	.518
Stroke/TIA	9/106 (8.5)	4/101 (4.0)	.189
CAD	47/106 (44.3)	49/101 (48.5)	.547
Previous MI	46/106 (43.4)	36/101 (35.6)	.255
Previous PCI	53/106 (50.0)	46/101 (45.5)	.521
Previous CABG	3/106 (2.8)	1/101 (1.0)	.358
CHF	16/106 (15.1)	6/101 (5.9)	.039
Peripheral vascular disease	14/106 (13.2)	12/101 (11.9)	.775
Anemia	4/106 (3.8)	3/100 (3.0)	.760
Last thienopyridine therapy, n (%)			.040
Clopidogrel	105 (99.1)	93 (92.1)	
75 mg	88/105 (83.8)	65/93 (69.9)	
150 mg	1/105 (1.0)	2/93 (2.2)	
300 mg	4/105 (3.8)	12/93 (12.9)	
600 mg	12/105 (11.4)	13/93 (14.0)	
900 mg	0/105 (0.0)	1/93 (1.1)	
Prasugrel	1 (0.9)	8 (7.9)	
10 mg	1/1 (100)	6/8 (75.0)	
60 mg	0/1 (0.0)	1/8 (12.5)	
75 mg	0/1 (0.0)	1/8 (12.5)	
Other antithrombotic medications (presurgery), n (%)			
Aspirin	105 (99.1)	97 (96.0)	.193
Low molecular weight heparin	38 (35.8)	43 (42.6)	.322
Unfractionated heparin	51 (48.1)	49 (48.5)	.954
Bivalirudin	0 (0)	1 (1.0)	.488
Fondaparinux	3 (2.8)	4 (4.0)	.654
Time from last thienopyridine use to start of study drug, h	29.1 (1, 71)	29.5 (4, 111)	.684
Infusion duration, h	67.0 (1, 161)	82.7 (2, 306)	.010

CABG surgical characteristics			
CABG type			.2296
On pump	77/101 (76.2)	79/95 (83.2)	
Off pump	24/101 (23.8)	16/95 (16.8)	
CABG duration, h†	3.6 ± 1.2	3.8 ± 1.0	
No. of grafts, n (%)			.3591
1	8/101 (7.9)	7/95 (7.4)	
2	26/101 (25.7)	17/95 (17.9)	
3	35/101 (34.7)	44/95 (46.3)	
≥4	32/101 (31.7)	27/95 (28.4)	
Graft type used, n (%)			
LIMA	95/101 (94.1)	90/95 (94.7)	
Saphenous vein	90/101 (89.1)	81/95 (85.3)	
RIMA	8/101 (7.9)	11/95 (11.6)	
Any concomitant surgeries	4/102 (3.9)	6/96 (6.3)	.4443
Valvular (any)	2/102 (2.0)	4/96 (4.2)	
Aortic	0/102 (0.0)	0/96 (0.0)	
Mitral	2/102 (2.0)	2/96 (2.1)	
Tricuspid	0/102 (0.0)	0/96 (0.0)	
Other	2/102 (2.0)	2/96 (2.1)	
Chest tube output (4 h)			
Mean ± SD, mL	325.4 ± 265.6†	297.1 ± 200.2†	
Minimum, maximum, mL	35, 1500	20, 1250	
Chest tube output (24 h)			
No. of patients	101	93	
Mean ± SD, mL	830.4 ± 557.3	805.2 ± 440.4	
Minimum, maximum, mL	150, 4300	216, 2940	

*Variables are presented as the median (minimum, maximum) or as n (%). Differences were compared with analysis of variance for quantitative factors or with the chi-square test (or the Fisher exact test, as appropriate) for proportions. STEMI indicates ST-segment elevation myocardial infarction; TIA, transient ischemic attack; CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous intervention; CABG, coronary artery bypass grafting surgery; CHF, congestive heart failure; LIMA, left internal mammary artery; RIMA, right internal mammary artery.

†Data are presented as the mean ± SD.

RESULTS

The 2 groups were similar with respect to clinical characteristics, prestudy thienopyridine use, baseline demographics, and surgical procedure performed (Table 1). Aspirin was used in 99.1% of cangrelor-treated patients and in 96.0% of placebo patients (P = .158).

In the ITT population, values <240 PRU were observed during the entire preoperative infusion period in 98.8% (83/84) of cangrelor-treated patients and in 19.0% (16/84) of placebo patients (RR, 5.2; 95% CI, 3.3-8.1; P < .001), as previously reported. Values <240 PRU before discontinuation of the study drug prior to CABG were observed in 98.8% (83/84) of patients in the cangrelor-treated group, compared with 31.0% (26/84) of patients receiving placebo (P < .001). Immediately before surgery and after discontinuation of the study drug (1-6 hours before incision), values <240 PRU remained in 26.9% (21/78) of cangrelor-treated patients and in 20.0% (15/75) of patients receiving placebo (P = .313). The mean PRU value at the time of CABG (the median time from discontinuation of the study drug was 3.2 hours for both groups) was 279.7 PRU in the cangrelor-treated patients and 297.8 PRU in the placebo patients (P = .212). The efficacy end point (<240 PRU) was analyzed with the safety population as a sensitivity check. Results were very similar to those from the ITT analyses, thus indicating the robustness of the platelet inhibition result.

Bleeding/Transfusion

Of the randomized patients who received the study drug, 102 patients in the cangrelor group and 96 patients in the placebo group underwent surgery. There were no differences between the 2 groups with respect to excessive CABG-related bleeding (primary safety end point; see Appendix A): 11.8%

(12/102) in the cangrelor group versus 10.4% (10/96) in the placebo group (P = .763, Table 2). No difference was seen in bleeding according to the Bleeding Academic Research Consortium (BARC) scale (9.8% in the cangrelor group and 10.4% in the placebo group, P = .886). Major preoperative bleeding was rare in both groups. The rates of preoperative minor/mild bleeding were numerically higher in the cangrelor group than in the placebo group, but no statistically significant difference was seen on the ACUITY, GUSTO, or TIMI scale.

A univariate analysis evaluated the bleeding risk for protocol-defined excessive CABG-related bleeding and preprocedure major or minor bleeding, as defined according to the ACUITY, GUSTO, and TIMI scales (in combination and separately for the cangrelor and placebo groups; see Appendix B). For excessive CABG-related bleeding, the analysis also included surgery-specific factors (Appendix C). For excessive risk of CABG-related bleeding, the univariate analysis identified the following factors as potential predictors (ie, with P values <.15): age, body mass index, history of diabetes or hyperlipidemia, previous CABG, prior treatment with unfractionated heparin or low molecular weight heparin, and CABG duration. The data were fitted into a multivariate logistic regression model, together with the treatment term. Table 3 summarizes the results of the univariate analysis and presents the adjusted OR and 95% CI values for the effects on bleeding risk. The crude OR for cangrelor on excessive CABG-related bleeding was 1.15 (95% CI, 0.47-2.79). The adjusted OR was 1.42 (95% CI, 0.49-4.07; P = .520).

Multivariate analyses of major or minor bleeding risk were performed similarly for the preoperative ACUITY, GUSTO, or TIMI scale. Table 4 summarizes the univariate effects and the multivariate logistic model effect on bleeding risk. The crude OR for the effect of cangrelor on preoperative major and minor bleeding was 1.90 (95% CI, 0.86-4.20). The adjusted OR was 2.12 (95% CI, 0.78-5.76; P = .139). We also separately evaluated the relationships between potential risk factors and preoperative major or minor bleeding for the cangrelor and placebo groups. Although the risk profile for cangrelor is similar to that of the cangrelor and placebo groups combined, the only predictive factors in the placebo group were the last thienopyridine therapy dose and the baseline PRU value.

Table 2. Bleeding Events in the Safety Population*

	Cangrelor (n = 106)	Placebo (n = 101)	OR (95% CI)	P
Excessive CABG-related bleeding (primary safety end point) from CABG procedure through hospital discharge				
Protocol defined, n (%)	12/102 (11.8)	10/96 (10.4)	1.15 (0.47-2.79)	.763
Surgical reexploration	2/102 (2.0)	2/96 (2.1)	0.94 (0.13-6.81)	.951
Chest tube output (24 h) >1.5 L	8/102 (7.8)	5/96 (5.2)	1.55 (0.49-4.91)	.457
Incidence of PRBC transfusions >4 units	6/102 (5.9)	8/96 (8.3)	0.69 (0.23-2.06)	.503
BARC defined, n (%)	10/102 (9.8)	10/96 (10.4)	0.93 (0.37-2.36)	.886
Fatal bleeding	0/102 (0.0)	0/96 (0.0)	NA	NA
Perioperative intracranial bleeding within 48 h	0/102 (0.0)	0/96 (0.0)	NA	NA
Reoperation after sternotomy closure to control bleeding	2/102 (2.0)	2/96 (2.1)	0.94 (0.13-6.81)	.951
Transfusion of 5 units of whole blood or PRBC within 48-h period	7/102 (6.9)	8/ 96(8.3)	0.81 (0.28-2.33)	.696
Chest tube output 2 L within 24-h period	3/102 (2.9)	4/96 (4.2)	0.70 (0.15-3.20)	.642
Preoperative bleeding (from randomization until surgical incision)				
ACUITY, n (%)				
Major	3/106 (2.8)	1/101 (1.0)	2.91 (0.30-28.5)	.358
Minor	19/106 (17.9)	10/101 (9.9)	1.99 (0.88-4.51)	.101
GUSTO, n (%)				
Severe/life-threatening	0/106 (0.0)	0/101 (0.0)	NA	NA
Moderate	2/106 (1.9)	1/101 (1.0)	1.92 (0.17-21.5)	.596
Mild	19/106 (17.9)	10/101 (9.9)	1.99 (0.88-4.51)	.101
TIMI, n (%)				
Major	1/106 (0.9)	0/101 (0.0)	NA	>.999
Minor	1/106 (0.9)	0/101 (0.0)	NA	>.999

*OR indicates odds ratio; CI, confidence interval; CABG, coronary artery bypass graft surgery; BARC, Bleeding Academic Research Consortium; PRBC, packed red blood cells; NA, not applicable; ACUITY, Acute Catheterization and Urgent Intervention Triage Strategy (bleeding scale); GUSTO, Global Use of Strategies to Open Occluded Coronary Arteries (bleeding scale); TIMI, Thrombolysis in Myocardial Infarction (bleeding scale).

Table 3. Multivariate Analysis of Excessive CABG-Related Bleeding Risk*

Factor	Bleeding (n = 22)	Nonbleeding (n = 176)	Crude OR (95% CI)	Adjusted OR (95% CI)	*P*
Cangrelor versus placebo	12/22 (54.5)	90/176 (51.1)	1.15 (0.47-2.79)	1.42 (0.49-4.07)	.520
Age, y	67.14 ± 11.59	63.49 ± 10.43	NA	1.04 (0.99-1.10)	.090
Diabetes	6/22 (27.3)	84/176 (47.7)	0.41 (0.15-1.10)	0.63 (0.19-2.07)	.447
Hyperlipidemia	10/21 (47.6)	138/174 (79.3)	0.24 (0.09-0.60)	0.18 (0.06-0.54)	.002
Previous CABG	2/22 (9.1)	1/176 (0.6)	17.5 (1.52-202)	4.01 (0.26-61.96)	.320
Prior UFH	14/22 (63.6)	81/176 (46.0)	0.41 (0.14-1.15)	1.17 (0.36-3.82)	.797
Prior LMWH	5/22 (22.7)	74/176 (42.0)	1.35 (0.15-11.8)	0.44 (0.12-1.68)	.230
CABG duration, h	4.30 ± 1.59	3.62 ± 1.02	NA	1.78 (1.13-2.80)	.012

*Data are presented as n (%) or the mean SD, as indicated. For univariate analyses, the chi-square test was performed for proportions, and analysis of variance was used for continuous variables. A logistic model was fitted for adjusted odds ratios (ORs) including all factors listed. CABG indicates coronary artery bypass grafting surgery; NA, not applicable; UFH, unfractionated heparin; LMWH, low molecular weight heparin.

Table 4. Multivariate Analysis of Preoperative Major or Minor Bleeding Risk*

Factor	Bleeding (n = 31)	Nonbleeding (n = 176)	Crude OR (95% CI)	Adjusted OR (95% CI)	*P*
Cangrelor versus placebo	20/31 (64.5)	86/176 (48.9)	1.90 (0.86-4.20)	2.12 (0.78-5.76)	.139
Age, y	68.03 ± 10.91	63.30 ± 10.56	NA	1.05 (1.00-1.10)	.034
Height, cm	169.19 ± 9.17	172.51 ± 9.22	NA	0.97 (0.92-1.03)	.306
Stroke/TIA	4/31 (12.9)	9/176 (5.1)	2.75 (0.79-9.56)	5.13 (0.99-26.56)	.052
CAD	22/31 (71.0)	74/176 (42.0)	3.37 (1.47-7.74)	4.60 (1.57-13.45)	.005
Previous PCI	11/31 (35.5)	88/176 (50.0)	0.55 (0.25-1.22)	0.44 (0.15-1.30)	.139
Previous CABG	2/31 (6.5)	2/176 (1.1)	6.00 (0.81-44.3)	2.51 (0.24-26.19)	.442
Prior UFH	23/31 (74.2)	77/176 (43.8)	3.70 (1.57-8.72)	4.97 (1.49-16.62)	.009
Prior LMWH	10/31 (32.3)	71/176 (40.3)	0.70 (0.31-1.58)	1.75 (0.51-5.97)	.375
Last thienopyridine dose before surgery, h	225.00 ± 231.57	146.90 ± 172.57	NA	1.00 (1.00-1.00)	.230
Time of last thienopyridine dose to infusion, h	23.52 ± 15.37	30.32 ± 19.31	NA	0.96 (0.93-0.99)	.014
Baseline PRU	257.48 ± 91.02	210.77 ± 91.91	NA	1.01 (1.00-1.01)	.062

*Data are presented as n (%) or the mean ± SD, as indicated. For univariate analyses, the chi-square test was performed for proportions, and analysis of variance was used for continuous variables. A logistic model was fitted for adjusted odds ratios (ORs) including all factors listed. CI indicates confidence interval; NA, not applicable; TIA, transient ischemic attack; CAD, coronary artery disease; PCI, percutaneous intervention; CABG, coronary artery bypass grafting surgery; UFH, unfractionated heparin; LMWH, low molecular weight heparin; PRU, platelet reaction units.

Postbaseline PRU values were analyzed in various derivations in their relationship to bleeding (excessive CABG-related or major or minor preoperative bleeding). These values included last on-treatment PRU value, mean and median on-treatment PRU values, and posttreatment last pre-CABG PRU value. None of these PRU values were significantly related to either excessive CABG-related bleeding or preoperative major or minor bleeding.

Preoperatively, the cangrelor and placebo groups had similar blood transfusion rates: cangrelor group, 1.9% (2/106); placebo group, 1.0% (1/101) ($P > .999$). Similarly, in the cangrelor group 1 patient required transfusion with fresh frozen plasma, and 1 required pooled platelets. No patient in the placebo group required treatment with either plasma or platelets.

Postoperatively, the 2 groups were similar with respect to blood and blood product use. Overall, 32 of 106 patients in the cangrelor group required blood transfusion with at least 1 unit of packed red blood cells (PRBC), and 34 of 101 patients in the placebo group received at least 1 PRBC unit. The numbers of units of PRBC, platelets, and fresh frozen plasma were also similar (Table 5).

Thrombotic Events

The MACCE incidence was low. Preoperatively, 2.8% of cangrelor-treated patients and 4.0% of placebo-treated patients experienced an ischemic event. In the cangrelor group, 1 patient died, 2 patients experienced myocardial infarction (MI), and 1 patient had ischemic-driven revascularization (IDR). No preoperative strokes in the cangrelor group were reported; however, 3 deaths and 1 case of stroke during the preoperative period were reported in the placebo group. The incidence of these ischemic events remained low in the postoperative period, with 4 patients in each group experiencing a death, MI, IDR, or stroke from just after surgery

Table 5. Blood and Blood Product Use*

	Cangrelor (n =106)	Placebo (n =101)	*P*
No. of blood units†			
n	32	34	.495
Mean ± SD	3.44 ± 2.22	3.85 ± 2.57	
Minimum, maximum	1, 10	1, 10	
No. of platelet units			
n	16	13	.859
Mean ± SD	2.44 ± 2.68	2.62 ± 2.63	
Minimum, maximum	1, 12	1, 10	
No. of FFP units			
n	14	16	.406
Mean ± SD	3.79 ± 2.01	4.75 ± 3.84	
Minimum, maximum	2, 8	1, 17	

*FFP indicates fresh frozen plasma.

†Two patients in the cangrelor group and 1 patient in the placebo group received whole blood.

Table 6. Summary of Adverse Events (AE)

	Cangrelor (n = 106)	Placebo (n = 101)	*P*
Patients with any event, n (%)			
Preprocedure	32/106 (30.2)	29/101 (28.7)	.816
Postprocedure	59/102 (57.8)	57/96 (55.9)	.827
Patients with any serious AE, n (%)			
Preprocedure	5/106 (4.7)	4/101 (4.0)	.790
Postprocedure	8/102 (7.8)	5/96 (5.2)	.454
Pre- and postprocedure	11/106 (10.4)	9/101 (8.9)	.721
Patient deaths, n (%)			
Preprocedure	1/106 (0.9)	3/101 (3.0)	.360
Postprocedure	1/102 (1.0)	2/96 (2.1)	.612
Pre- and Postprocedure	2/106 (1.9)	5/101 (5.0)	.271
Patients discontinuing treatment owing to AE, n (%)			
Preprocedure	6/106 (5.7)	3/101 (3.0)	.499
Postprocedure	0/102 (0.0)	0/96 (0.0)	NA
Pre- and Postprocedure	6/106 (5.7)	3/101 (3.0)	.499

through 30 days postoperatively. In the cangrelor group, there were 2 MI, 2 IDR, 1 stroke, and 1 death (from systemic inflammatory response syndrome), whereas the placebo group had 1 MI, 1 stroke, and 2 deaths (1 cardiogenic shock and 1 multiorgan failure). All preoperative deaths were from cardiac causes.

Other Complications

The cangrelor-treated and placebo-treated groups had similar safety profiles. The incidence of any other complications was common in patients, both preoperatively (30.2% [32/106] and 28.7% [29/101], respectively; *P* = .816; see Table 6) and postoperatively (57.8% [59/102] and 55.9% [57/96], respectively; *P* = .827). The rates of individual complications for the cangrelor and placebo groups were not significantly different or clinically remarkable. They tended to be minor and rarely of any clinical significance. These complications were typically nonspecific or routine occurrences for the post-CABG patient (ie, electrolyte abnormalities, edema, and so on) and were unlikely to be drug related. Table 7 lists some of the more commonly encountered postoperative complications. Still, most events were infrequent, and the 2 groups had similar rates.

Complications that met serious adverse-event criteria were uncommon preoperatively (4.7% [5/106] and 4.0% [4/101] for the cangrelor and placebo groups, respectively; *P* = .790) and postoperatively (7.8% [8/102] and 5.2% [5/96], respectively; *P* = .454).

DISCUSSION

Our findings demonstrate that cangrelor was not associated with an increased risk of perioperative complications or reportable events (compared with placebo), despite preoperative platelet inhibition therapy. These findings, combined with those of our previous study, which demonstrated no increased risk of bleeding or transfusion rates [Angiolillo 2012], might have significant implications for the management of patients who are receiving thienopyridine therapy and require surgery.

Previously published trials have shown acceptable risk/benefit profiles for patients with coronary artery disease who are undergoing a percutaneous coronary intervention (PCI). In the randomized CHAMPION PCI trial of 8877 patients, cangrelor was not superior to a 600-mg loading dose of clopidogrel when administered 30 minutes prior to a planned PCI [Harrington 2009]. Although major bleeding complications did not increase, cangrelor showed a significant increase in minor bleeding complications on the ACUITY scale. More importantly, there was a trend toward a decrease in biomarker-independent study end points, which included death, Q-wave MI, or IDR (cangrelor, 0.6%; clopidogrel, 0.9%; OR, 0.67; 95% CI, 0.39-1.14; *P* = .14). A second CHAMPION trial (PLATFORM) randomized 5362 patients who were to undergo a PCI to either cangrelor or 600 mg clopidogrel, which was administered at the end of the PCI per the standard of care. Patients treated with cangrelor showed a slight increase in major bleeding, predominately from groin hematomas. This increased risk of bleeding did not involve an increased rate of transfusions, however, and there were decreased risks of acute stent thrombosis (cangrelor, 0.2%; placebo, 0.6%; OR, 0.31; 95% CI, 0.11-0.85; *P* = .02) and death (cangrelor, 0.2%; placebo, 0.7%; OR, 0.33; 95% CI, 0.13-0.83; *P* = .02) [Bhatt 2009].

Platelet inhibition is the standard of care in patients who present with ACS or have a recently implanted intracoronary stent. Continuation of thienopyridine treatment has been

Table 7. Summary of Commonly Encountered Postoperative Events*

	Cangrelor (n = 102)	Placebo (n = 96)	*P*
Patients with 1 event, n (%)	59 (57.8)	57 (59.4)	.827
Cardiac, n (%)			
Atrial fibrillation	13 (12.7)	16 (16.7)	.435
Bradycardia	1 (1.0)	0 (0.0)	>.999
Cardiogenic shock	3 (2.9)	2 (2.1)	>.999
VT/VF	2 (2.0)	0 (0.0)	.498
Other	4 (3.9)	8 (8.3)	.240
Gastrointestinal, n (%)			
Abdominal pain	2 (2.0)	0 (0.0)	.498
Constipation	4 (3.9)	1 (1.0)	.370
Nausea	6 (5.9)	1 (1.0)	.120
Vomiting	3 (2.9)	1 (1.0)	.622
Other	6 (5.9)	4 (4.2)	.749
Infections, n (%)			
Surgical site	2 (2.0)	0 (0.0)	.498
Nonsurgical site	3 (2.9)	2 (2.1)	>.999
Fever	1 (1.0)	2 (2.1)	.612
Pain, n (%)			
Incisional	11 (10.8)	8 (8.3)	.558
Musculoskeletal	6 (5.9)	4 (4.2)	.749
Psychiatric, n (%)			
Agitation	1 (1.0)	1 (1.0)	>.999
Anxiety	3 (2.9)	0 (0.0)	.247
Insomnia	4 (3.9)	0 (0.0)	.122
Other	6 (5.9)	1 (1.0)	.120
Renal, n (%)			
Oliguria	1 (1.0)	2 (2.1)	.612
Acute renal failure	1 (1.0)	3 (3.1)	.357
Acute renal insufficiency	1 (1.0)	0 (0.0)	>.999
Respiratory, n (%)			
Atelectasis	23 (22.5)	20 (20.8)	.770
Cough	1 (1.0)	0 (0.0)	>.999
Dyspnea	2 (2.0)	1 (1.0)	>.999
Hypoxemia	2 (2.0)	2 (2.1)	>.999
Pneumothorax	6 (5.9)	8 (8.3)	.501
Wheezing	2 (2.0)	1 (1.0)	>.999
Respiratory failure	3 (2.9)	2 (2.1)	>.999
Pulmonary edema	2 (2.0)	1 (1.0)	>.999
Pleural effusions	4 (3.9)	9 (9.4)	.122
Other	12 (11.8)	7 (7.3)	.286

*Many patients reported >1 event. VT indicates ventricular tachycardia; VF, ventricular fibrillation.

demonstrated to reduce the risk of recurrent ischemic events and acute coronary stent thrombosis. For the 10% to 15% of patients who present with ACS, however, current American College of Cardiology/American Heart Association (ACC/AHA) guidelines advocate that the optimal strategy for balancing the bleeding risks of discontinuing antiplatelet therapies is to discontinue clopidogrel or ticagrelor treatment for 5 to 7 days before surgery and to discontinue prasugrel 7 to 10 days before surgery [Wright 2011]. However, these guidelines may place patients at significant risks for ischemic or thrombotic complications while they are awaiting surgery, and it is clear that the risks and benefits need to be evaluated critically for each case [Biancari 2011]. Operative intervention in the setting of thienopyridine-induced platelet inhibition has been associated with an increased need for transfusions of blood and blood products, as well as with a significant increase in postoperative complications in some series. A recent meta-analysis of 34 studies with 22,584 patients conducted by Nijjer and colleagues has demonstrated the limitations of examining the effect of clopidogrel on major bleeding in patients who receive clopidogrel therapy up until the time of CABG [Nijjer 2011]. They observed significant increases in PRBC transfusions (by 1.1 units; 95% CI, 0.58-1.64 units; $P < .0001$), platelet transfusions (by 0.18 units; 95% CI, 0.14-0.21; $P = .006$), and fresh frozen plasma transfusions (by 0.49 units; 95% CI, 0.14-0.84; $P = .006$) in patients with recent exposure to clopidogrel. The rate of reoperation was also increased in the clopidogrel-exposed group, compared with patients without recent clopidogrel exposure (OR, 2.32; 95% CI, 1.76-3.06; $P < .001$), as was the mortality rate (OR, 1.6; 95% CI, 1.30-1.96; $P < .001$). The important clinical findings of this meta-analysis clearly illustrate not only the controversies surrounding the management of this patient population but also the need for an appropriate agent (such as cangrelor), protocol, and guidelines to assist in safely bridging patients to surgery, as outlined and demonstrated in this study.

Withholding antiplatelet therapy is also not without risk, despite current guidelines. The risks for recurrent ischemic or thrombotic events were statistically significant in the placebo arms of previous trials of thienopyridines for ACS. Furthermore, there is growing evidence that better describes the incidence and implications of acute stent thrombosis in patients who have thienopyridine therapy discontinued abruptly. Still unclear, however, are the actual risks to patients who require surgery after ACS presentation and have thienopyridine therapy withheld. Some have suggested the risk for recurrent ischemic or thrombotic complications in this perioperative "washout" period is as high as 15% [Sambu 2011]. Although that was not true in the present small study, it is nevertheless a significant concern in a potentially vulnerable patient population awaiting surgery. Clearly, urgent revascularization in the setting of recurrent or unstable symptoms increases the perioperative risks significantly. Conversely, recurrent symptoms, particularly if they are severe, may contraindicate or require postponement of surgical revascularization and therefore may limit the benefits of timely and comprehensive intervention. Unanticipated and potentially urgent changes in patient management may account for some of the differences in outcomes

and complications observed in patients who undergo CABG during the washout period.

Although the optimal strategy for transitioning patients to surgery has not been defined, several protocols are commonly used. Anticoagulation with intravenous heparin or a low molecular weight heparin is commonly used in symptomatic patients. Unfortunately, heparin-based agents have little effect on platelet inhibition, and evidence suggests that heparin could promote platelet aggregation [Gao 2011]. Similarly, continuous treatment with heparin and to a lesser extent low molecular weight heparins might increase the risk of operative complications or challenge the intraoperative management of anticoagulation owing to the development of heparin-induced thrombocytopenia or heparin resistance [Esposito 1983; Bennett-Guerrero 2005].

Preoperative platelet inhibition with glycoprotein IIb/IIIa receptor antagonists, such as abciximab, eptifibatide, or tirofiban has been proposed; however, studies involving these medications in the preoperative setting have demonstrated significantly increased risks of bleeding, bleeding-related complications, and costs [Aguirre 1995; Giugliano 2009]. In addition, these agents have longer half-lives, and therefore the timing of discontinuation before surgery can be difficult to determine—unlike cangrelor, in which platelet reactivity returns to baseline within 1 hour. Consequently, the use of these medications is typically discouraged in patients for whom surgery is indicated.

An additional challenge in managing patients who require antiplatelet therapy is determining efficacy. It is well known that patients taking oral platelet inhibitors such as clopidogrel demonstrate variable degrees of responsiveness [Gurbel 2003]. Recent evidence suggests, however, that residual platelet reactivity may be a better indication of thrombotic risk than the absolute response to a treatment. A consensus review of available data has identified 3 methods capable of measuring high platelet reactivity [Bonello 2010]. Adenosine diphosphate (ADP)-induced light transmittance aggregometry is the standard test, but it is time-consuming to perform and is nonspecific [Michelson 2004]. The vasodilator-stimulated phosphoprotein phosphorylation platelet reactivity index has also been used, but it is also a laboratory-based assay. VerifyNow testing, which was used for this study, is a commonly used point-of-care platelet inhibition test. This cartridge-based rapid assay directly measures ADP-induced inhibition of adenylyl cyclase, which is influenced directly by thienopyridine activity on the P2Y12 receptor. Platelet activity is measured as PRU, with lower levels correlating with increased platelet inhibition [Malinin 2006]. Previous studies have demonstrated that a value >240 PRU is correlated with increased short- and long-term mortality and with major adverse cardiocerebrovascular events after PCI and ACS [Patti 2008; Price 2008; Marcucci 2009]. Nevertheless, despite the evolving literature supporting the use of platelet testing, its value as a research tool, the complications associated with inadequate platelet inhibition, and the known individual variation in the response to therapies, the current ACC/AHA guidelines are not to recommend testing routinely, pending the results of trials in progress [Wright 2011].

Another implication of our findings is that a protocol of bridging patients with cangrelor would also be useful for patients who have undergone recent stenting and require noncardiac surgery. Although the goal of this study was to determine efficacy and safety in patients undergoing CABG, the findings suggest the lack of significant bleeding, bleeding-related, and other complications, compared with placebo. These results, combined with evidence for the normalization of platelet function before surgery, imply that such bridging might also be a reasonable approach for patients receiving a thienopyridine for coronary stents and who require elective noncardiac surgery.

Limitations

Our study has several limitations. First, although the patients were randomized to either cangrelor or placebo, other aspects of preoperative management were determined by the treating physicians; therefore, decisions regarding other anticoagulation therapy might have had a confounding effect on the outcomes. The small number of patients treated with various anticoagulation regimens was too small to determine whether any complications might subsequently predispose patients to additional risks. The fact that several patients in the placebo group still had evidence of platelet inhibition at the time of surgery suggests an incomplete washout or normalization of platelet function; therefore, the residual effects of prestudy thienopyridine therapy might have confounded the bleeding risks. In addition, although our results show a lower preoperative mortality in the cangrelor-treated group, this study was not designed to adequately evaluate the risks of limiting platelet inhibition in patients awaiting surgery—clearly a topic that needs further study. Conversely, there was a slightly increased incidence of minor preoperative bleeding in the cangrelor group, which is probably not surprising given the degree of platelet inhibition achieved in the treatment patients.

CONCLUSIONS

Bridging patients with cangrelor before CABG effectively maintains platelet inhibition without significantly increasing pre- or postoperative bleeding, thrombotic or other complications, or perioperative transfusions. Use of cangrelor appears to be a viable clinical strategy for balancing the need of sustained platelet inhibition with minimizing any undue risk of bleeding or postoperative complications in patients awaiting surgery.

REFERENCES

Aguirre FV, Topol EJ, Ferguson JJ, et al, for the EPIC Investigators. 1995. Bleeding complications with the chimeric antibody to platelet glycoprotein IIb/IIIa integrin in patients undergoing percutaneous coronary intervention. Circulation 91:2882-90.

Angiolillo DJ, Firstenberg MS, Price MJ, et al, for the BRIDGE Investigators. 2012. Bridging antiplatelet therapy with cangrelor in patients undergoing cardiac surgery: a randomized controlled trial. JAMA 307:265-74.

Bennett-Guerrero E, Slaughter TF, White WD, et al. 2005. Preoperative anti-PF4/heparin antibody level predicts adverse outcome after cardiac surgery. J Thorac Cardiovasc Surg 130:1567-72.

Bhatt DL, Lincoff AM, Gibson CM, et al, for the CHAMPION PLATFORM Investigators. 2009. Intravenous platelet blockade with cangrelor during PCI. N Engl J Med 361:2330-41.

Biancari F, Airaksinen KE, Lip GY. 2011. Benefits and risks of using clopidogrel before coronary artery bypass surgery: systematic review and meta-analysis of randomized trials and observational studies. J Thorac Cardiovasc Surg 143:665-75.e4.

Bonello L, Tantry US, Marcucci R, et al, Working Group on High On-Treatment Platelet Reactivity. 2010. Consensus and future directions on the definition of high on-treatment platelet reactivity to adenosine diphosphate. J Am Coll Cardiol 56:919-33.

Chen ZM, Jiang LX, Chen YP, et al; COMMIT (Clopidogrel and Metoprolol in Myocardial Infarction Trial) collaborative group. 2005. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. Lancet 366:1607-21.

Collet JP, Montalescot G, Blanchet B, et al. 2004. Impact of prior use or recent withdrawal of oral antiplatelet agents on acute coronary syndromes. Circulation 110:2361-7.

Esposito RA, Culliford AT, Colvin SB, Thomas SJ, Lackner H, Spencer FC. 1983. Heparin resistance during cardiopulmonary bypass. The role of heparin pretreatment. J Thorac Cardiovasc Surg 85:346-53.

Gao C, Boylan B, Fang J, Wilcox DA, Newman DK, Newman PJ. 2011. Heparin promotes platelet responsiveness by potentiating αIIbβ3-mediated outside-in signaling. Blood 117:4946-52.

Giugliano RP, White JA, Bode C, et al, for the EARLY ACS Investigators. 2009. Early versus delayed, provisional eptifibatide in acute coronary syndromes. N Engl J Med 360:2176-90.

Gurbel PA, Bliden KP, Hiatt BL, O'Connor CM. 2003. Clopidogrel for coronary stenting: response variability, drug resistance, and the effect of pretreatment platelet reactivity. Circulation 107:2908-13.

Harrington RA, Stone GW, McNulty S, et al. 2009. Platelet inhibition with cangrelor in patients undergoing PCI. N Engl J Med 361:2318-29.

Lewis BS, Mehta SR, Fox KA, et al, for the CURE trial investigators. 2005. Benefit of clopidogrel according to timing of percutaneous coronary intervention in patients with acute coronary syndromes: further results from the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) study. Am Heart J 150:1177-84.

Malinin A, Pokov A, Swaim L, Kotob M, Serebruany V. 2006. Validation of a VerifyNow-P2Y12 cartridge for monitoring platelet inhibition with clopidogrel. Methods Find Exp Clin Pharmacol 28:315-22.

Marcucci R, Gori AM, Paniccia R, et al. 2009. Cardiovascular death and nonfatal myocardial infarction in acute coronary syndrome patients receiving coronary stenting are predicted by residual platelet reactivity to ADP detected by a point-of-care assay: a 12-month follow-up. Circulation 119:237-42.

Michelson AD. 2004. Platelet function testing in cardiovascular diseases. Circulation 110:489-93.

Nijjer SS, Watson G, Athanasiou T, Malik IS. 2011. Safety of clopidogrel being continued until the time of coronary artery bypass grafting in patients with acute coronary syndrome: a meta-analysis of 34 studies. Eur Heart J 32:2970-88.

Norgard NB. 2009. Cangrelor: a novel P2Y12 receptor antagonist. Expert Opin Investig Drugs 18:1219-30.

Patti G, Nusca A, Mangiacapra F, Gatto L, D'Ambrosio A, Di Sciascio G. 2008. Point-of-care measurement of clopidogrel responsiveness predicts clinical outcome in patients undergoing percutaneous coronary intervention results of the ARMYDA-PRO (Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty-Platelet Reactivity Predicts Outcome) study. J Am Coll Cardiol 52:1128-33.

Price MJ, Endemann S, Gollapudi RR, et al. 2008. Prognostic significance of post-clopidogrel platelet reactivity assessed by a point-of-care assay on thrombotic events after drug-eluting stent implantation. Eur Heart J 29:992-1000.

Sabatine MS, Cannon CP, Gibson CM, et al, for the Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY)-Thrombolysis in Myocardial Infarction (TIMI) 28 Investigators. 2005. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. N Engl J Med 352:1179-89.

Sambu N, Warner T, Curzen N. 2011. Clopidogrel withdrawal: is there a "rebound" phenomenon? Thromb Haemost 105:211-20.

Wright RS, Anderson JL, Adams CD, et al. 2011. ACCF/AHA focused update incorporated into the ACC/AHA 2007 Guidelines for the Management of Patients with Unstable Angina/Non-ST-Elevation Myocardial Infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines developed in collaboration with the American Academy of Family Physicians, Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons. J Am Coll Cardiol 57:e215-367.

Yusuf S, Zhao F, Mehta SR, et al; Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. 2001. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 345:494-502.