Platelet Function Measurement–Based Strategy to Reduce Bleeding and Waiting Time in Clopidogrel-Treated Patients Undergoing Coronary Artery Bypass Graft Surgery

The Timing Based on Platelet Function Strategy to Reduce Clopidogrel-Associated Bleeding Related to CABG (TARGET-CABG) Study

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Background—Aspirin and clopidogrel therapy is associated with a variable bleeding risk in patients undergoing coronary artery bypass graft surgery (CABG). We evaluated the role of platelet function testing in clopidogrel-treated patients undergoing CABG.

Methods and Results—One hundred eighty patients on background aspirin with/without clopidogrel therapy undergoing elective first time isolated on-pump CABG were enrolled in a prospective single-center, nonrandomized, unblinded investigation (Timing Based on Platelet Function Strategy to Reduce Clopidogrel-Associated Bleeding Related to CABG [TARGET-CABG] study) between September 2008 and January 2011. Clopidogrel responsiveness (ADP-induced platelet-fibrin clot strength [MA_{ADP}]) was determined by thrombelastography; CABG was done within 1 day, 3–5 days, and >5 days in patients with an MA_{ADP} >50 mm, 35–50 mm, and <35 mm, respectively. The primary end point was 24-hour chest tube drainage and key secondary end point was total number of transfused red blood cells. Equivalence was defined as ≤25% difference between groups. ANCOVA was used to adjust for confounders. Mean 24-hour chest tube drainage in clopidogrel-treated patients was 93% (95% confidence interval, 81–107%) of the amount observed in clopidogrel-naive patients, and the total amount of red blood cells transfused did not differ between groups (1.80 U versus 2.08 U, respectively, $P=0.540$). The total waiting period in clopidogrel-treated patients was 233 days (mean, 2.7 days per patient).

Conclusions—A strategy based on preoperative platelet function testing to determine the timing of CABG in clopidogrel-treated patients was associated with the same amount of bleeding observed in clopidogrel-naive patients and ≈50% shorter waiting time than recommended in the current guidelines.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00857155.

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Key Words: cardiopulmonary bypass ■ antiplatelet therapy ■ bleeding

Treatment with aspirin and a thienopyridine is a well-established strategy to prevent ischemic event occurrence in patients with high-risk coronary artery disease.[1,2] Irreversible inhibition of platelet function associated with thienopyridine therapy carries a substantial risk of bleeding, particularly in patients undergoing coronary artery bypass graft surgery (CABG).[3–5] Up to 15% of patients presenting with acute coronary syndromes will require CABG,[6,7] and bleeding complications and transfusion of red blood cells in these patients have been associated with adverse outcomes.[8–11]

The *2011 ACCF/AHA Guidelines for the Management of Patients with Unstable Angina/Non-ST-Elevation Myocardial Infarction* has a class I recommendation for withdrawing clopidogrel for 5 days and prasugrel for 7 days to allow for recovery of platelet function before planned CABG.[12] The antiplatelet response to clopidogrel is highly variable and is negligible in up to ≈30% of patients.[13] Clopidogrel is also associated with a slow and variable offset of pharmacodynamic effect. In selected patients, platelet function may recover before the recommended 5-day discontinuation period.[14,15]

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Despite some evidence of less bleeding events associated with off-pump CABG, the recent literature yields heterogeneous results with increased as well as similar bleeding events in patients receiving clopidogrel ≤5 days and >5 days before CABG, respectively.[5–7,16–20] Therefore, a recommended 5-day waiting period may not benefit selected patients and will be associated with increased costs of hospitalization. Notably, the *2011 Update to the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists' Blood Conservation Clinical Practice Guidelines* gave a class IIb recommendation for platelet function testing to determine the timing of surgery in patients on clopidogrel therapy (level of evidence C).[21] However, thus far, no prospective study using platelet function testing has been performed to determine timing of surgery in clopidogrel-treated patients. We hypothesized that clopidogrel-treated patients will have the same bleeding outcomes as clopidogrel-naive patients when the timing of elective first time isolated on-pump CABG in the former patients is based on platelet function testing.

WHAT IS KNOWN

- The antiplatelet effect of clopidogrel is highly variable and is negligible in up to 30% of patients;10–15% of patients with acute coronary syndrome require coronary artery bypass graft surgery (CABG).
- The recent literature yields heterogeneous results with increased as well as similar bleeding events in patients on clopidogrel therapy clopidogrel before CABG.

WHAT THE STUDY ADDS

- In patients on dual antiplatelet therapy needing CABG, targeted waiting based on preoperative platelet function monitoring shortens the recommended preoperative waiting period and results in similar bleeding as compared with clopidogrel-naive patients.

Methods

Study Design and Treatment Strategies

Timing Based on Platelet Function Strategy to Reduce Clopidogrel-Associated Bleeding Related to CABG (TARGET-CABG) was a prospective, single-center, unblinded study. After institutional review board approval and written informed consent, consecutive patients scheduled for elective, first-time, isolated on-pump CABG at the Sinai Hospital of Baltimore were enrolled between September 2008 and January 2011. Patients between the ages of 18–85 were included if they were on aspirin therapy (81–325 mg/d). Patients were excluded for any of the following criteria: emergency surgery after failed percutaneous coronary intervention (PCI), redo sternotomy, concomitant valve repair or replacement, anemia (hematocrit <30%), low platelet count (<120 000/mm^3), coagulopathy (history of bleeding diathesis, exposure to coumadin), renal insufficiency (creatinine clearance <30 mL/min), and known active hepatic disease.

The study flow diagram is presented in Figure 1. Eligible patients were categorized as either clopidogrel-treated or clopidogrel-naive. The clopidogrel-treated group consisted of patients treated with a clopidogrel loading dose or patients on 75 mg daily maintenance therapy for at least 5 days. Platelet function testing was determined by ADP-induced platelet-fibrin clot strength (MA_{ADP}) measured by thrombelastography after a minimum of 8 hours after loading and at least 1 hour after maintenance dosing. Patients were stratified into 3 groups according to on-treatment platelet reactivity. Surgery was scheduled within 1 day in those with an MA_{ADP} >50 mm (high reactivity), within 3–5 days in those with an MA_{ADP} 35–50 mm (intermediate reactivity), and after 5 days in those with an MA_{ADP} <35 mm (low reactivity). In the absence of a validated cutoff to predict on-pump CABG related bleeding, we chose these above expert opinion–based thrombelastography (TEG, Haemonetics Corporation Braintree, MA) cutoffs for targeted waiting based on a prior study demonstrating that an MA_{ADP} >47 was associated with short- and long- term ischemic event occurrence in patients with coronary artery disease undergoing stenting. Therefore, these findings served as the rationale for scheduling surgery with no delay in patients with an MA_{ADP} >50 mm. We speculated that an MA_{ADP} cutoff associated with ischemia in patients with coronary artery disease undergoing stenting could potentially serve as a surrogate for adequate hemostasis in surgical patients.[22] The rationale for the delayed groups was established by using a calculation for MA_{ADP} recovery based on platelet turnover rate of 10 days and 5–95th percentile range for MA_{ADP} in patients on aspirin and clopidogrel.[3,22]

Patients in the clopidogrel-naive group also had postcatheterization MA_{ADP} assessed and were scheduled for surgery at the discretion of the treating physician. Platelet function testing was repeated immediately before CABG, on arrival in the cardiac surgical intensive care unit (ICU), and at 24 hours after CABG. Troponin I was measured before surgery and serially after surgery in patients with signs and symptoms suggestive of myocardial ischemia. Postoperative bleeding was assessed by 24-hour chest tube drainage and total amount of transfused red blood cells. Duration of intubation, length of ICU stay, postoperative complications including redo sternotomy rates, and length of hospital stay were recorded. Patient data were collected by source document review and telephone interviews at 30 days after CABG to monitor the development of major adverse cardiac events (MACE).

The perioperative care of the patients was at the discretion of the attending physician. Apart from the preoperative MA_{ADP} values, the investigators were blinded to the results of platelet function testing. Aspirin therapy was continued until the day before surgery. In patients on preoperative heparin therapy for acute coronary syndromes, treatment was continued until surgery. Glycoprotein IIb/IIIa inhibitor therapy (eptifibatide only) was discontinued at least 4 hours before surgery.

Three surgeons performed all of the operations. Hemodynamics were monitored in all patients by pulmonary and systemic arterial catheters. Lorazepam (0.5–1.0 mg) was given orally 60 minutes before surgery. Anesthesia was induced with parenteral fentanyl (4–12 μg/kg), etomidate (0.2–0.4 mg/kg), and pancuronium bromide (0.1 mg/kg) and maintained with isoflurane (1.0–1.9%) in oxygen. During cardiopulmonary bypass additional doses of fentanyl (1–4 μg/kg) and pancuronium bromide (0.05–0.1 mg/kg) or atracurium besylate (0.2–0.4 mg/kg) were administered as needed. Nitroglycerin (0.1–0.2 μg/kg per minute) was administered for vasodilatation, dobutamine (1–4 μg/kg per minute) or epinephrine (0.02–0.1 μg/kg per minute) for inotropic support, and norepinephrine (0.02–0.1 μg/kg per minute) as a vasopressor. All patients were treated with 5 g intravenous ε-aminocapronic acid at induction of anesthesia and 5 g in the pump prime solution. Before aortic cannulation, systemic anticoagulation was established by an initial loading dose of 300 IU/kg unfractionated heparin to obtain an activated clotting time ≥480 seconds that was maintained during bypass by supplemental administration. On completion of cardiopulmonary bypass, anticoagulation was reversed by protamine chloride in a 1:1 ratio; additional protamine was given as required to achieve an activated clotting time <140 seconds. A centrifugal pump (Sorin Group, Deutschland GMBH, Lindberghstrasse 25, Munich, Germany) was used for bypass. The oxygenator was primed with 800 mL of lactated ringers solution and 200 mL of solution containing 50 g mannitol and

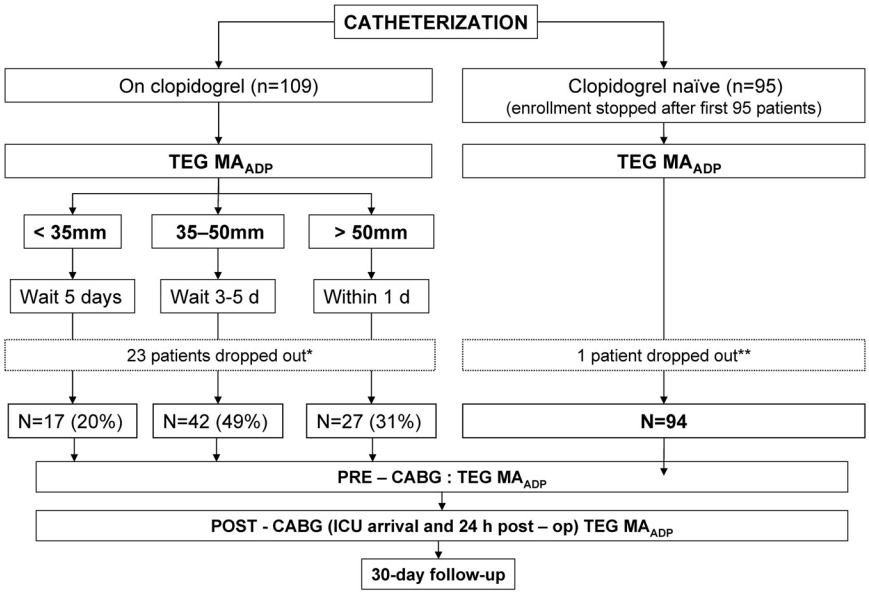

Figure 1. Study design and patient flow diagram. TEG indicates thrombelastography; MA_{ADP}, adenosine-diphosphate–induced platelet-fibrin clot strength; CABG, coronary artery bypass graft surgery; ICU, intensive care unit. *Reasons for dropout: refusal of surgery after consenting (n=4); declined by the surgeons due to poorly graftable veins (n=4) or serious comorbidity (n=3), combined procedures (n=2), scheduling problems (n=4), acute hemodynamic compromise needing urgent CABG (n=2), protocol violation (n=4). **Reason for dropout: refusal of surgery after screening (n=1).

5000 IU heparin. During bypass, nonpulsatile flow was maintained at 2.2–2.6 L/m^2, and hypothermia (31–33°C) was established in all patients.

After surgery, patients were transferred to the ICU and weaned from the ventilator after exhibiting complete recovery from anesthesia, hemodynamic stability with no evidence of significant bleeding, adequate blood gas values, and a core temperature >36°C. The perioperative transfusion trigger was set to a hematocrit of 21% on pump and 25% thereafter, unless active bleeding, low cardiac output, poor left ventricular function, or other clinical variables suggested a need to increase this level. Platelets were administered in bleeding patients with a platelet count of <70 000/mL. Fresh frozen plasma and cryoprecipitate were administered in bleeding patients with an activated partial thromboplastin time >1.75×normal. Surgical reexploration was indicated when chest tube drainage was >1200 mL in first 3 hours after surgery.

After surgery, patients received 300 mg aspirin per rectum 6 hours after surgery and 162 mg/d orally thereafter unless contraindicated by a platelet count <70 000/mL or active bleeding as indicated by the necessity of administrating platelets, fresh frozen plasma, or cryoprecipitate. Deep vein thrombosis prophylaxis was achieved with enoxaparin (Lovenox, Sanofi-Aventis, LLC, US) administered subcutaneously (40 mg/d and 30 mg/d in patients with a creatinine clearance <40 mL/min, respectively) starting on postoperative day 1, unless contraindicated by a platelet count <70 000/mL or a platelet count decrease suggestive of heparin-induced thrombocytopenia.

Blood Sampling

Postcatheterization blood samples were taken from an indwelling femoral arterial sheath in the cardiac catheterization laboratory. Subsequent blood samples were obtained from an indwelling radial arterial line and after its removal, from the central venous line. Blood samples were transferred to one Vacutainer tube (Becton-Dickinson, Becton-Dickinson; Franklin Lakes, NJ) containing 3.8% trisodium citrate and 1 tube containing 45 USP lithium heparin (Becton-Dickinson, Becton-Dickinson; Franklin Lakes, NJ). The blood tubes were filled to capacity and gently inverted 3–5 times to ensure complete mixing of the respective anticoagulant.

Thrombelastography Platelet Mapping Assay

The TEG technology is described elsewhere.[23] Briefly, a stationary pin is suspended into an oscillating cup that contains the whole blood sample. As the blood clots, it links the pin to the cup. Clot strength is determined by measuring the amplitude of the rotation of the pin, which increases proportionally with clot strength. Maximum amplitude represents maximum clot strength, expressed as the MA parameter. Reptilase and factor XIIIa (activator F) are used to generate a cross-linked fibrin clot to isolate the contribution of fibrin to clot strength. The $P2Y_{12}$ receptor contribution to clot formation is measured by the addition of ADP.

One milliliter of citrated blood was transferred to a vial containing kaolin and mixed by inversion. Three hundred forty microliters of the activated blood was then transferred to the cup. Twenty microliters of 0.2 mol/L calcium chloride were added to this cup and assayed in the TEG analyzer to measure thrombin-induced clot strength ($MA_{thrombin}$). Three hundred forty microliters heparinized blood were added to another cup containing reptilase and activator F to determine the tensile strength of the fibrin clot (MA_{fibrin}) in the absence of thrombin generation or platelet stimulation. A third sample of heparinized blood (340 μL) was added to the cup in the presence of the activator F and ADP (2 μmol/L) to determine the tensile strength of the platelet-fibrin clot induced by ADP (MA_{ADP}). A final sample of heparinized blood (340 μL) was added to the cup in the presence of activator F and arachidonic acid (AA) (1 mmol/L) to determine the tensile strength of the platelet-fibrin clot (MA_{AA}) due to cyclooxygenase activity as a measure of aspirin responsiveness. Percent inhibition of arachidonic acid-induced aggregation was calculated by the formula $100\%-[(MA_{AA}-MA_{fibrin})/(MA_{thrombin}-MA_{fibrin})]\times 100\%$.

Troponin I

Troponin I levels were determined according to manufacturer's specifications (Siemens Dimension Vista 1500, Deerfield, IL). The upper level of normal is 0.9 ng/mL.

End Points

The primary and secondary end points were the volume of chest tube drainage at 24 hours after CABG and the total number of transfused packed red blood cells, respectively. Tertiary end points were MACE (cardiac death, nonfatal myocardial infarction, and revascularization), rethoracotomy, and all-cause mortality within 30 days after the index surgery. The diagnosis of myocardial infarction required either the development of new Q waves or new persistent ST-segment or T-wave changes associated with an increase of troponin I (>5 times upper limits of normal) or autopsy evidence of acute myocardial infarction.[24] Cardiac death was defined as death related to myocardial infarction, heart failure, or arrhythmia.

Statistical Analysis

Based on a review of 50 consecutive clopidogrel-naive patients undergoing on-pump CABG between April and June 2008, the mean

24-hour chest tube drainage was 1000±500 mL. Assuming an α risk of 0.05 and a power of 0.90, we estimated that 85 patients were required per group to demonstrate equivalent bleeding (no more than 25% difference) in patients on clopidogrel therapy as compared with clopidogrel-naive patients, based on 2 1-sided tests (NCSS software, Kaysville, UT). Due to an expected dropout rate of up to 20%, a total of 200 patients (100 per group) was required. For safety reasons, we performed an interim analysis after the first 50 clopidogrel-treated patients were enrolled.

Data were tested for normal distribution by Shapiro-Wilk test. Results are presented as mean±SD, medians, and interquartile range (25–75th percentile), as appropriate. Categorical variables were compared by Fisher exact or Mann-Whitney *U* test, as appropriate. Continuous variables were compared by *t* test or Mann-Whitney *U* test as appropriate. Equivalence of 24-hours chest output (after log transformation due to log-normal distribution) and total number of transfused packed blood cells was tested using 2 1-sided *t* tests and 2 1-sided Mann-Whitney *U* tests, respectively. In addition, analysis of covariance (ANCOVA) was performed to correct for potential confounders. Demographic variables and intraoperative characteristics with a $P<0.05$ as well as the following preoperative and postoperative clinical and laboratory parameters were entered into the model: 24-hour preoperative unfractionated heparin, low-molecular-weight heparin or eptifibatide therapy, dose of aspirin (81 mg, 162 mg, or 325 mg), preoperative hemoglobin, preoperative $MA_{thrombin}$, MA_{fibrin}, and activated partial thromboplastin time; and $MA_{thrombin}$, MA_{fibrin}, and MA_{ADP} on ICU arrival. Confidence intervals were calculated from the ANCOVA according to Tukey-Kramer. The perioperative change of platelet function, platelet count, and hemoglobin were compared by 2-way ANOVA for repeated measurements with post hoc testing according to Tukey-Kramer in case of significant time and interaction effects. The level of significance was set at 0.05. The statistical software package NCSS 2007 (NCSS, Kaysville, UT) was used for analysis.

Results

Interim Analysis

Interim analysis revealed numerically less 24-hour chest tube drainage in the first 50 clopidogrel-treated as compared with 90 clopidogrel-naive patients (777±516 versus 846±414 mL, respectively).[25] In the absence of safety concerns, the study protocol continued.

Study Population

A total of 204 patients eligible for the study underwent post–cardiac catheterization screening of platelet function (Figure 1). Twenty-four patients (23 clopidogrel-treated and 1 clopidogrel-naive) dropped out due to protocol deviations, leaving 180 patients for the final analysis.

Baseline characteristics are presented in Table 1. More frequent male sex, a lower body mass index, a less frequent history of myocardial infarction and coronary artery stenting, less β-blocker usage, and treatment with lower aspirin doses were observed in the clopidogrel-naive group. More patients treated with clopidogrel presented with acute coronary syndrome. The EURO score[26] and the percentage of patients receiving anticoagulants within the last 24 hours preoperatively were similar between the groups.

Preoperative Waiting Period

Based on screening MA_{ADP}, 27, 42, and 17 clopidogrel-treated patients were scheduled to undergo CABG within 1 day, 3–5 days, and after 5 days of clopidogrel withdrawal, respectively (Figure 1). The total preoperative waiting period of clopidogrel-treated patients was 233 days (mean, 2.7 days per patient). The actual median waiting period according to preoperative screening MA_{ADP} values in the 3 groups is shown in Figure 2. Although actual and predefined waiting periods corresponded well in 59% of the patients scheduled to undergo CABG after 5 days, 35% underwent surgery earlier. Likewise, in the group of patients scheduled to wait for 3–5 days, actual and predefined waiting periods corresponded in 62%, and 33% went earlier. Eighty-two percent of the patients scheduled to undergo CABG within 1 day underwent surgery within 24 hours.

Table 1. Baseline Characteristics of Study Patients

	Total (n=180)	Clopidogrel-Treated (n=86)	Clopidogrel-Naive (n=94)	*P* Value
Age, y, mean±SD	65.2±10	65.1±10	65.3±11	0.893
Male, n (%)	113 (63)	45 (52)	68 (72)	0.008
BMI, mean±SD	31±6.4	32±6.3	30±6.2	0.033
Hypertension, n (%)	153 (85)	78 (91)	75 (80)	0.059
Diabetes, n (%)	74 (41)	39 (45)	35 (37)	0.291
History of MI, n (%)	60 (33)	42 (49)	18 (19)	<0.001
History of stent, n (%)	53 (29)	46 (54)	7 (7)	<0.001
Preoperative ACS, n (%)	81 (45)	46 (54)	35 (37)	0.036
Ejection fraction, %, mean±SD	50±12	50±12	50±12	0.977
EURO score, median (IQR)	4 (2–5)	4 (2–5)	3.5 (1.8–5)	0.230
Unfractionated heparin, 24 h preoperative, n (%)	40 (22)	24 (28)	16 (17)	0.106
LMW heparin, 24 h preoperative, n (%)	2 (1)	2 (2)	0	0.227
Eptifibatide, 24 h preoperative, n (%)	9 (5)	5 (6)	4 (4)	0.739
Aspirin dose				<0.001
81 mg, n (%)	78 (43)	28 (32)	50 (53)	
162 mg, n (%)	12 (7)	5 (6)	7 (8)	
325 mg, n (%)	90 (50)	53 (62)	37 (39)	
ACEIs/ARBs, n (%)	118 (66)	62 (72)	56 (60)	0.086
β-blockers, n (%)	111 (62)	62 (72)	49 (52)	0.008
Statins, n (%)	125 (69)	66 (77)	59 (63)	0.052
PPIs, n (%)	42 (23)	17 (20)	25 (27)	0.296

Data are expressed as n (percentage), mean±SD, or median and interquartile range (IQR); *P* values indicate differences between clopidogrel-treated patients and clopidogrel-naive patients.

BMI indicates body mass index; MI, myocardial infarction; ACS, acute coronary syndrome; EURO score, European System for Cardiac Operative Risk Evaluation; LMW, low molecular weight; ACEIs, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; PPIs, proton pump inhibitors.

Perioperative Patient Characteristics

The intraoperative characteristics of patients are presented in Table 2. Clopidogrel-naive patients received more grafts, had longer cardiopulmonary bypass and cross-clamp times, and received more salvaged blood.

Perioperative Laboratory Measurements

Percent inhibition of arachidonic acid–induced aggregation did not differ between clopidogrel-naive and clopidogrel-

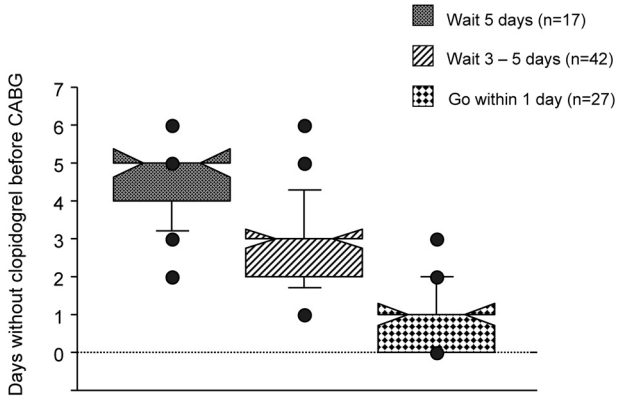

Figure 2. Stratification according to screening adenosine-diphosphate–induced platelet-fibrin clot strength (MA_{ADP}). Actual days without clopidogrel before coronary artery bypass graft surgery (CABG) in the 3 groups of clopidogrel-treated patients according to screening MA_{ADP} depicted as box-and-whisker plots. Line in the box indicates the median and the box reaches from the 25th and the 75th percentiles. Whiskers range from the 10–90th percentile. Circles are outliers.

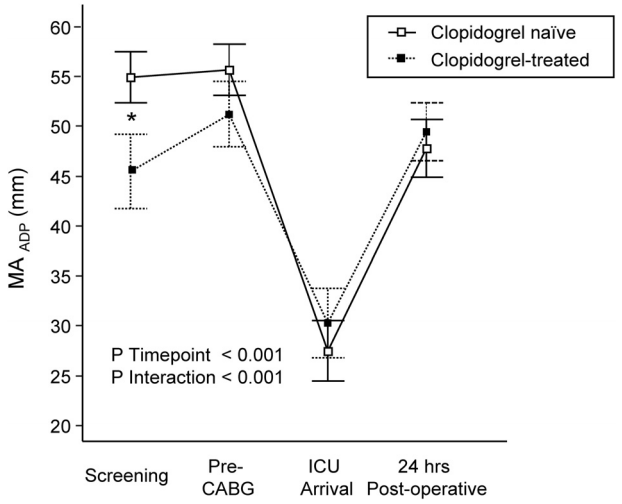

Figure 3. Perioperative change in platelet function. Platelet function (mean; 95% confidence interval) assessed by thrombelastography platelet mapping in clopidogrel-naive patients (**open rectangles, solid line**) as compared with clopidogrel-treated patients.(**closed rectangles, dotted line**). *Significant group difference ($P<0.05$) in post hoc Tukey-Kramer multiple comparison test. CABG indicates coronary artery bypass graft surgery; ICU, intensive care unit; and MA_{ADP}, adenosine-diphosphate–induced platelet-fibrin clot strength.

treated patients (86±17% versus 89±16%, P=NS). Prespecified waiting was associated with an increase in MA_{ADP} in clopidogrel-treated patients ([44.6 (95% CI: 42.0–47.2) to 50.6 (95% CI: 48.1–53.1)], Figure 3). However, after surgery there was a similar trend in the MA_{ADP} in both groups, with a decrease on ICU arrival and a recovery 24 hours after surgery ($P<0.001$ for trend; Figure 3). The perioperative trend of MA_{fibrin} was similar between the 2 treatment groups, with an immediate postoperative decrease and a recovery at 24 hours after surgery ($P<0.001$ for trend; data not shown). Despite a slightly higher preoperative hemoglobin level in clopidogrel-naive patients, postoperative and discharge levels

Table 2. Intraoperative Characteristics and Outcome Data

	Total (n=180)	Clopidogrel-Treated (n=86)	Clopidogrel-Naive (n=94)	*P* Value
Intraoperative characteristics				
CPB time, min, mean±SD	88±32	82±27	93±35	0.014
Cross-clamp time, min, mean±SD	72±25	68±26	76±23	0.033
Duration of surgery, min, median (IQR)	240 (190–280)	235 (185–250)	240 (194–300)	0.077
Peripheral grafts, n, mean±SD	3.0±1.1	2.6±1.0	3.3±1.0	<0.001
Arterial grafts				0.810
1, n (%)	156 (87)	76 (88)	80 (85)	
2, n (%)	5 (3)	2 (2)	3 (3)	
Heparin, ×1000 units, mean±SD	42±10	43±11	41±9	0.234
Protamine, ×1000 units, mean±SD	49±12	49±13	49±12	0.700
Cell salvage, mL, median (IQR)	1000 (750–1000)	750 (500–1000)	1000 (750–1000)	<0.001
Saline, mL, mean±SD	1605±842	1598±887	1611±804	0.921
Albumin, mL, mean±SD	632±276	608±267	654±284	0.257
Outcome				
24-h chest tube drainage, median (IQR)	750 (520–970)	650 (480–1010)	780 (570–953)	0.080
RBCs total, median (IQR)	2 (0–3)	2 (0–3)	2 (0–3)	0.539
Intubation, h, median (IQR)	7 (5–12)	7 (5–11)	7 (4–14)	0.460
ICU stay, d, median (IQR)	2 (2–3)	2 (2–3)	2 (2–3)	0.456
LOS, d, median (IQR)	7 (6–9)	8 (7–11)	6 (5–8)	<0.001
Re-thoracotomy, n (%)	3 (2)	1 (1)	2 (2)	1.000
30-d mortality, n (%)	2 (1)	1 (1)	1 (1)	1.000
30-d readmission rate, n (%)	12 (7)	5 (6)	7 (7)	0.769

P values are for clopidogrel-treated versus clopidogrel-naive patients.

CPB indicates cardiopulmonary bypass; IQR, interquartile range; RBCs total, total number of transfused red blood cells; ICU, intensive care unit; LOS, length of hospital stay.

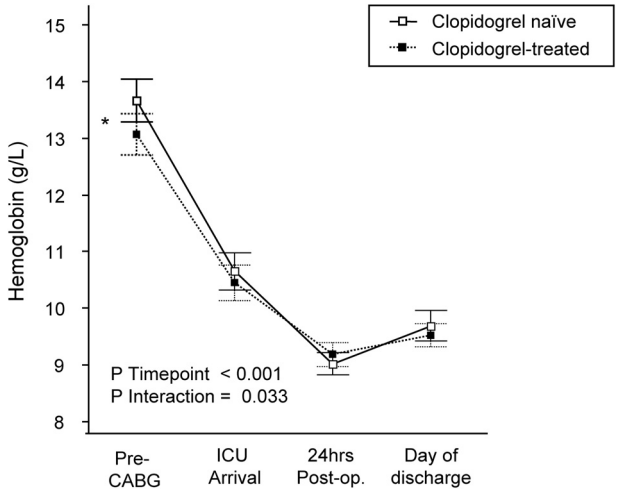

Figure 4. Perioperative change in hemoglobin. Hemoglobin levels (mean; 95% confidence interval) in clopidogrel-naive patients (**open rectangles, solid line**) as compared with clopidogrel-treated patients (**closed rectangles, dotted line**). CABG indicates coronary artery bypass graft surgery; ICU, intensive care unit.*Significant group difference ($P<0.05$) in post hoc Tukey-Kramer multiple comparison test.

were similar in both groups ($P<0.001$ for trend; Figure 4). Perioperative platelet count was similar in both groups (Figure 5), although a numerically lower platelet count was observed in clopidogrel-naive patients on ICU arrival and 24 hours after surgery.

Perioperative Bleeding

Median chest tube drainage was similar between clopidogrel-treated and clopidogrel-naive patients (Figure 6). The mean chest tube drainage (log data) was 730 mL, 692 mL, and 766 mL after back-transformation in all patients, in clopidogrel-treated, and in clopidogrel-naive patients, respectively. ANCOVA yielded 728 mL, 703 mL and 753 mL.

Both 1-sided *t* tests were highly significant (upper boundary: $P<0.001$, lower boundary: $P=0.005$), thus equivalence was established.

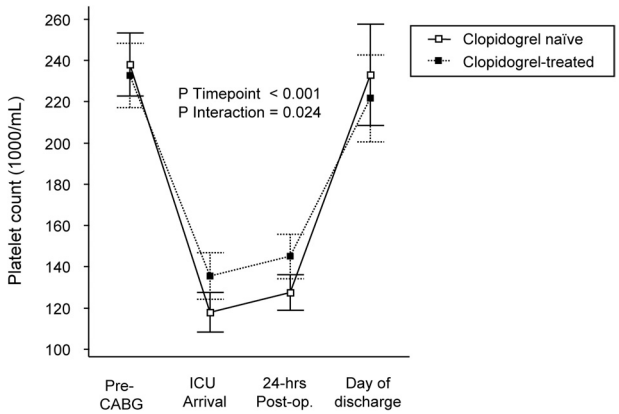

Figure 5. Perioperative change in platelet count. Platelet count (mean; 95% confidence interval) in clopidogrel-naive patients (**open rectangles, solid line**) as compared with clopidogrel-treated patients (**closed rectangles, dotted line**). CABG indicates coronary artery bypass graft surgery; ICU, intensive care unit; and Post-op, postoperative.

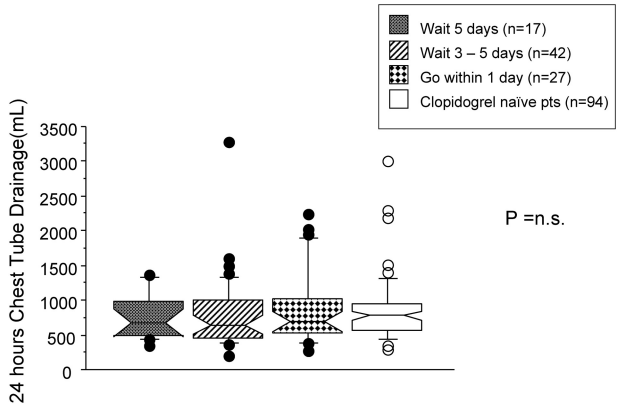

Figure 6. Twenty-four–hour postoperative chest tube drainage. Chest tube drainage in clopidogrel-treated patients (3 waiting groups) and clopidogrel-naive patients presented as box-and-whisker plots. The line in the box indicates the median and the box reaches from the 25th and the 75th percentile. The whiskers range from the 10–90th percentile. Circles are outliers; n.s. indicates not significant between the groups.

Correcting for potential confounders by covariate analysis also demonstrated that there was no difference in blood loss between clopidogrel-treated and clopidogrel-naive patients ($P=0.496$) and there was no difference across the 3 categories of clopidogrel-treated patients ($P=0.27$). Chest tube drainage in clopidogrel-treated patients was 93.3% (95% confidence interval [CI], 81.0–107.4%) that of clopidogrel-naive patients.

The mean total amount of red blood cells transfused was 1.98, 1.81, and 2.14 in all patients, in clopidogrel-treated, and in clopidogrel-naive patients, respectively. ANCOVA yielded 1.94, 1.80, and 2.08. For the upper boundary, the 1-sided *U* test was highly significant ($P<0.001$), whereas the test for the lower boundary showed no significance ($P=0.31$). Therefore, noninferiority was established but not equivalence.

ANCOVA yielded no difference in the total amount of red blood cells transfused to clopidogrel-treated patients as compared with clopidogrel-naive patients ($P=0.540$). Clopidogrel-treated patients received 86.6% (95% CI, 56.3–116.9%) of the amount of red blood cells transfused to clopidogrel-naive patients.

Clinical Outcomes

One clopidogrel-treated patient had a preoperative myocardial infarction during clopidogrel withdrawal. Median length of hospital stay was significantly higher in the clopidogrel-treated patients as compared with clopidogrel-naive patients (8 days versus 6 days, $P<0.001$). However, there was no difference in duration of intubation, ICU stay, rethoracotomy rates, 30-day mortality, and 30-day readmission rate between the 2 groups (Table 2). Two patients underwent recatheterization for clinical signs of ischemia: 1 clopidogrel-treated and 1 clopidogrel-naive patient.

Discussion

To the best of our knowledge, this is the first prospective investigation of a platelet function measurement–based strategy to reduce bleeding and waiting time in clopidogrel-treated patients undergoing on-pump CABG. Our study

demonstrated that the strategy of platelet function measurement by thrombelastography shortened the waiting period of clopidogrel-treated patients without increasing CABG-related bleeding. Our strategy resulted in an overall 46% shortening of the guideline recommended preoperative waiting period for clopidogrel-treated patients (mean 2.7 days versus 5 days per patient).[12] The aspirin response did not differ between groups and therefore a differential response to aspirin cannot serve as an explanation for our findings.

The reduction in waiting time was largely due to the high prevalence of patients with high platelet reactivity during clopidogrel therapy who underwent CABG within 1 day of platelet function testing. Overall, chest tube drainage and the transfusion of red blood cells were 93% (95% CI, 81–107%) and 87% (95% CI, 56–117%) of the amount observed in clopidogrel-naive patients, respectively. These findings were well within or even below the predefined equivalence range of ±25%. However, due to the common practice of in-hospital clopidogrel withdrawal, the length of hospital stay in clopidogrel-treated patients was longer than in clopidogrel-naive patients and is consistent with the previous reports.[6,16]

Despite the clinical efficacy associated with dual antiplatelet therapy (DAPT), irreversible $P2Y_{12}$ blockade carries substantial risks of bleeding in patients undergoing CABG.[5–7,16,17,19,27–29] Bleeding complications and transfusion of red blood cells have been associated with short- and long-term mortality by increasing the risk of infection and myocardial infarction.[8–11] Available studies show conflicting results with both similar and increased bleeding in patients undergoing CABG <5 days and ≥5 days after clopidogrel withdrawal.[6,16,17,19,27] This heterogeneity is further substantiated by a recent meta-analysis of 34 studies involving 22 584 patients.[5] Potential explanations for these conflicting results are various bleeding definitions and transfusion triggers; retrospective and registry analyses; not controlling for cardiopulmonary bypass or use of aspirin, GP IIb/IIIa inhibitor, and antifibrinolytics; and small sample sizes including redo operations, combined procedures, and varying surgical experiences.[5,6,16,19,27,30] Nevertheless, the current evidence indirectly suggests an association between the level of platelet reactivity and the risk of bleeding both by demonstrating a 0.6% increase in major non–CABG-related bleeding and a 10.2% increase in CABG-related bleeding in patients on prasugrel as compared with clopidogrel.[29] Furthermore, there is a clustering of CABG-related hemorrhagic complications in those patients undergoing surgery during the first 24–48 hours after clopidogrel withdrawal.[16,17] Using the Multiplate analyzer, Sibbing et al[31] recently demonstrated an increased risk of post-PCI Thrombolysis In Myocardial Infarction major bleeding in patients treated with clopidogrel who had platelet reactivity below a cutoff. However, cutoffs for major bleeding after PCI may not apply for CABG-related bleeding, particularly with respect to the specifics of cardiopulmonary bypass.[32]

Chen et al[33] first demonstrated that ADP-induced aggregation <40% predicted 92% of severe CABG-related bleeding in clopidogrel-treated patients undergoing first time on-pump CABG. Likewise, Rannucci et al[34] demonstrated that in clopidogrel-treated patients undergoing different on-pump cardiac procedures, ADP-induced platelet aggregation as measured by Multiplate analyzer was independently associated with excessive bleeding with a cutoff of 31 U, yielding an area under the curve of 0.71 and a negative predictive value of 92%. However, the latter data may be biased by the retrospective study design, the inherent different bleeding risks of isolated CABG and combined procedures, and a therapeutic algorithm treating microvascular bleeding based on preoperative aggregation values.

TEG-based algorithms have been demonstrated to reduce transfusion requirements, and the addition of platelet fibrin-clot strength measurement to an existing risk prediction model significantly improved the risk stratification for excessive blood loss in patients undergoing on-pump cardiac surgery.[35–37] Furthermore, we have earlier demonstrated an association between both platelet-fibrin clot strength and MA_{ADP} with short- and long-term post-PCI ischemic event occurrences.[22,38]

In patients presenting for elective off-pump CABG during DAPT, Kwak et al[39] demonstrated that irrespective of the time between drug withdrawal and surgery, patients in the highest tertile of platelet inhibitory response (>76.5% inhibition) had higher chest tube output and higher transfusion rates as compared with patients in the other tertiles. Importantly, the highest tertile of platelet inhibitory response remained the only independent risk factor associated with an adjusted 11-fold relative increased risk of transfusion in off-pump CABG patients.[39]

Because there is wide variability in clopidogrel response and also variability in platelet function recovery after clopidogrel withdrawal, a uniform waiting period may not benefit all patients needing CABG. In contrast to previous studies searching for a bleeding threshold in patients undergoing CABG,[33,34,39] the current prospective study was designed with a targeted approach for patients on DAPT undergoing first-time isolated on-pump CABG. In the absence of a validated cutoff predicting on-pump CABG-related bleeding, we chose these above expert opinion, based TEG cutoffs for targeted waiting. The rationale for scheduling surgery with no delay in patients with an MA_{ADP} >50 mm was based on the evidence that MA_{ADP} >47 mm was associated with short- and long-term ischemic events after PCI, suggesting sufficient platelet function to overcome increased bleeding risk.[22]

Our results corroborate and extend those of Kwak et al[39] by demonstrating that a targeted approach combining platelet function monitoring and a tailored waiting period in clopidogrel-treated patients undergoing on-pump CABG is safe in terms of equivalent bleeding as compared with clopidogrel-naive patients. Furthermore, our results support the recommendations of the *2011 Update to the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists' Blood Conservation Clinical Practice Guidelines* to consider that the interval between discontinuation of irreversible $P2Y_{12}$ blockers and elective surgery may be as short as 3 days.[21] The current study provides the first prospective evidence to support the recommendation to consider platelet function monitoring to determine the timing of surgery in clopidogrel-treated patients as compared with the current practice of unselected timing.[21]

Study Limitations

Several limitations to this study should be noted. TARGET-CABG was a single-center, nonrandomized study, which could compromise generalizability of the results. Although we used ANCOVA to adjust for univariate significant variables and other confounders that are known to affect bleeding, we cannot exclude a bias induced by unknown covariates. To minimize potential bias, patients underwent CABG by 1 of 3 surgeons who were blinded to immediate preoperative platelet function, and patients were treated by a standardized protocol including perioperative aspirin administration, strict transfusion triggers, and routine use of antifibrinolytics as well as standardized anesthesia administration. We believe that the parallel postoperative trend of hemoglobin and platelets in both patient groups substantiates adherence to these standards. Furthermore, our protocol prohibited the use of hetastarch because of its known adverse effect on fibrin polymerization and bleeding.[40] In the absence of a validated cutoff for on-pump CABG related bleeding, we used an expert opinion–based cutoff for targeted waiting. Our study design does not allow validation of this cutoff. However, equivalence in chest output and noninferiority of transfusion requirements suggest its potential suitability, albeit a general recommendation needs prior validation by further studies. The study was not designed to assess the association of clopidogrel withdrawal and occurrence of major adverse ischemic events. However, apart from the different length of hospital stay, there were no differences in outcomes between clopidogrel-treated and clopidogrel-naive patients. Finally, although the median preoperative waiting period corresponded with the predefined waiting time, protocol deviations occurred in 18–35% due to scheduling problems and occurrence of ischemic symptoms while waiting for surgery. However, as the majority of these protocol deviations reduced the time between clopidogrel withdrawal and surgery, a negative impact on bleeding would be expected, which was not substantiated by the data.

Conclusions

A strategy based on preoperative platelet function testing to determine the timing of CABG in clopidogrel-treated patients was associated with the same amount of bleeding observed in clopidogrel-naive patients and ≈50% shorter waiting time than recommended in the current guidelines. Clearly, before implementing in routine practice, our results demonstrating the utility of a MA_{ADP} >50 cutoff must be validated in a large-scale, prospective study.

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Platelet Function Measurement–Based Strategy to Reduce Bleeding and Waiting Time in Clopidogrel-Treated Patients Undergoing Coronary Artery Bypass Graft Surgery: The Timing Based on Platelet Function Strategy to Reduce Clopidogrel-Associated Bleeding Related to CABG (TARGET-CABG) Study

Elisabeth Mahla, Thomas A. Suarez, Kevin P. Bliden, Peter Rehak, Helfried Metzler, Alejandro J. Sequeira, Peter Cho, Jeffery Sell, John Fan, Mark J. Antonino, Udaya S. Tantry and Paul A. Gurbel

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