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Bleeding Outcomes Associated with Coronary Artery Bypass Graft Surgery and Recent Clopidogrel Exposure

Danielle M. Blais, PharmD,[1] Sarah M. Zukkoor, PharmD,[2] Charles Hayes III, PharmD,[3] Kerry K. Pickworth, PharmD,[1] Kyle Porter,[4] Michael S. Firstenberg, MD[5]

Departments of [1]Pharmacy, and [4]Biostatistics, The Ohio State University Wexner Medical Center, Columbus, Ohio; [2]Department of Pharmacy, St. Luke's Medical Center – Aurora Health Care, Milwaukee, Wisconsin; [3]Department of Pharmacy, St. Luke's Hospital, Kansas City, Missouri, USA [5] Department of Surgery (Cardiothoracic), Akron City Hospital, Northeast Ohio Medical University, Akron Ohio, USA

ABSTRACT

Background: Guidelines recommend discontinuing clopidogrel for at least 5 days before elective coronary artery bypass graft surgery (CABG) to limit blood transfusions and for at least 24 hours before urgent CABG to reduce major bleeding complications. Studies have produced conflicting results regarding whether recent exposure to clopidogrel increases bleeding, the need for intraoperative and postoperative blood products, postoperative complications, and hospital length of stay. We evaluated the effect of clopidogrel exposure on major bleeding at our institution within 5 days of CABG.

Methods: We conducted a retrospective review of patients who underwent CABG at a tertiary academic medical center. The primary outcome was major bleeding, defined as transfusion of 4 units of packed red blood cells (PRBCs) and/or a need for reexploration. Secondary outcomes included non–life-threatening bleeding, defined as transfusion of 2 units but <4 units of PRBCs; postoperative complications; hospital length of stay; readmission within 30 days of the procedure; and hospital mortality. Major bleeding events were analyzed with a logistic regression model that adjusted for covariates of bleeding risk factors.

Results: Of the 715 patients we reviewed, 169 patients received clopidogrel within 5 days before CABG, and 546 patients did not. A significantly higher incidence of major bleeding was observed in the clopidogrel group compared with the group not exposed to clopidogrel (32% versus 17%, $P = .002$). After adjusting for covariates, patients exposed to clopidogrel had significantly higher odds of major bleeding (odds ratio, 2.1; 95% confidence interval, 1.3-3.4; $P = .003$). The groups were similar with respect to postoperative complications, except for infection. The clopidogrel-exposed group had a significantly higher rate of leg site infections (3% versus 0.2%, $P = .003$).

Conclusions: Clopidogrel exposure within 5 days of CABG is associated with an increased risk of major bleeding.

Michael Firstenberg, MD, is a principal investigator for The Medicines Company.

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Correspondence: Danielle M. Blais, PharmD, BCPS, Clinical Assistant Professor – Cardiology, Department of Pharmacy, The Ohio State University Medical Center, 368 Doan Hall, 410 W 10th Ave, Columbus, Ohio 43210, USA; 1-614-366-4053; fax: 1-614-293-3165 (e-mail: Danielle.blais@osumc.edu).

INTRODUCTION

Antiplatelet therapy with clopidogrel, an adenosine diphosphate (ADP) receptor antagonist, has been established as a mainstay in the treatment of acute coronary syndrome (ACS) patients for reducing the incidences of ischemic events and cardiovascular death [CAPRIE 1996; Chen 2005; Lewis 2005; Sabatine 2005]. Clopidogrel, a selective antagonist of the ADP P2Y12 receptor, irreversibly inhibits platelet aggregation and thereby reduces thromboembolic events. Antiplatelet activity can persist for at least 5 days, potentially increasing the risk of acute hemorrhagic events in patients who undergo coronary artery bypass graft surgery (CABG) and have recent exposure to clopidogrel.

Current American College of Cardiology (ACC) and American Heart Association (AHA) guidelines recommend discontinuing clopidogrel for at least 5 days before elective CABG to limit blood transfusions and for at least 24 hours before urgent CABG to limit major bleeding complications [Wright 2011]. This recommendation is largely based on results from the Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events (CURE) Trial [Lewis 2005]. The CURE Trial randomized non–ST-elevation ACS patients to clopidogrel or placebo, and results revealed significant reductions in cardiovascular death, myocardial infarction (MI), or stroke in the treatment group; however, major and minor bleeding was increased in clopidogrel-treated patients who underwent CABG within 5 days of discontinuing clopidogrel. Several smaller randomized studies that have examined the relationship of clopidogrel to postoperative bleeding in CABG produced conflicting results regarding whether recent exposure to clopidogrel (within 5 days before surgery) increases bleeding, a need for intraoperative and postoperative blood products, postoperative complications, and hospital length of stay [Hongo 2002; Karabulut 2004; Mehta 2006; Maltais 2008; Ebrahimi 2009; Firanescu 2009; Herman 2010; Dasarathan 2011].

According to the Society of Thoracic Surgery (STS) and the Society of Cardiovascular Anesthesiologists (SCA), cardiac operations consume as much as 10% to 15% of the

nation's blood supply, and the demand may increase with the complexity of cardiac surgical procedures [Ferraris 2011]. Clinicians must attempt to minimize the risk of bleeding by avoiding excessive use of antithrombotic drugs. Major bleeding is strongly associated with higher rates of morbidity, MI, and stroke [Mehran 2009]. Significant bleeding can require reoperation and may subsequently increase the risk of complications that accompany a surgical procedure. A major contributor to infectious complications is transfusion of packed red blood cells (PRBCs) or fresh frozen plasma (FFP) [Banbury 2006]. Patients who experience a major bleeding episode will likely require excessive blood transfusions (ie, PRBCs and FFP), which carry additional risks, including infection, ischemia, transfusion-related acute lung injury, and mortality [Biancari 2011]. In CABG patients, blood transfusion is associated with a unit-dependent, risk-adjusted increase in postoperative morbidity, including mortality, renal failure, prolonged ventilatory support, cardiac complications, and neurologic events [Biancari 2011]. In patients requiring CABG, discontinuation of clopidogrel for at least 5 days before surgery is ideal to ensure sufficient platelet function and to decrease the risk of perioperative bleeding and the requirement for blood transfusions. Owing to the conflicting literature and the lack of strong evidence supporting this recommendation, there is substantial uncertainty regarding optimal management of clopidogrel in the perioperative period. Additionally, the decision to defer surgery for 5 days in patients with recent clopidogrel exposure is economically unfavorable because of the prolonged preoperative hospital stay and increased healthcare costs. Delaying surgery for patients who require urgent intervention may not be a viable option and can place the patient at risk for additional ischemic events. Current American College of Cardiology Foundation and AHA guidelines state that if urgent surgery is necessary in patients with recent clopidogrel exposure, CABG may be performed by experienced surgeons if the incremental bleeding risk is considered acceptable [Wright 2011]. The absence of a standardized method to assess surgeon experience and to adequately define bleeding risk renders this recommendation difficult to apply in clinical situations.

To assess the importance of clopidogrel and major bleeding risk in patients undergoing CABG at our institution, we conducted a retrospective analysis to compare outcomes in patients who had recent exposure to clopidogrel and those who did not receive clopidogrel within 5 days before surgery.

METHODS

Adult patients who received only a CABG surgery at the Ohio State University Medical Center were retrospectively identified through our institutional STS database. Pregnant women, patients under 18 years of age, and patients who received thrombolytics before CABG were excluded. Data collected included demographics, patient risk factors/comorbidities, operation details, intraoperative and postoperative medications and blood products, and perioperative laboratory values of hemoglobin and the international normalized ratio (INR). The day of discontinuation was documented for patients who

Table 1. Baseline Characteristics and Comorbidities among Those Exposed to Clopidogrel versus Not Exposed to Clopidogrel within 5 Days before Coronary Artery Bypass Grafting*

	Clopidogrel Exposed (n = 169)	Not Exposed (n = 546)
Demographics		
Age, y	60.7 ± 12.3	62.9 ± 10.5
Male sex, n (%)	125 (74.0)	410 (75.1)
BMI, kg/m^2	29.4 ± 5.6	30.5 ± 6.5
Comorbidities, n (%)		
Previous MI	135 (79.9)	262 (48.0)
Diabetes mellitus	59 (34.9)	260 (47.6)
Cerebrovascular disease	24 (14.2)	109 (20.0)
Hyperlipidemia	160 (94.7)	511 (93.6)
Hypertension	146 (86.4)	497 (91.0)
Heart failure	43 (25.4)	142 (26.0)
NYHA class, n (%)		
I	3 (7.0)	5 (3.5)
II	9 (20.9)	48 (33.8)
III	21 (48.8)	55 (38.7)
IV	10 (23.3)	34 (23.9)
Clinical features		
Hb, g/dL	12.5 ± 2.1	12.8 ± 2.0
INR	1.10 ± 0.17	1.09 ± 0.12
SCr, mg/dL	1.18 ± 0.97	1.18 ± 1.02
Aspirin use, n (%)	159 (94.1)	474 (86.8)
GP IIb/IIIa inhibitor use, n (%)	21 (12.4)	13 (2.4)
Eptifibatide, n (%)	19 (11.2)	13 (2.4)
D/C time to OR, h	14.9 ± 13.1	15.5 ± 9.1
Abciximab, n (%)	2 (1.2)	0 (0)
D/C time to OR, h	31.5 ± 41.4	NA
Surgical features, n (%)		
Status		
Elective	34 (20.1)	235 (43.0)
Emergent	18 (10.7)	24 (4.4)
Urgent	117 (69.2)	287 (52.6)
CPB use		
Full	109 (64.5)	349 (63.9)
Combination	8 (4.7)	17 (3.1)
None	52 (30.8)	180 (33.0)

*Data are presented as the mean ± SD where indicated. BMI indicates body mass index; MI, myocardial infarction; NYHA, New York Heart Association; Hb, hemoglobin; INR, international normalized ratio; SCr, serum creatinine; GP, glycoprotein; D/C, discontinue; OR, operating room; NA, not applicable; CPB, cardiopulmonary bypass.

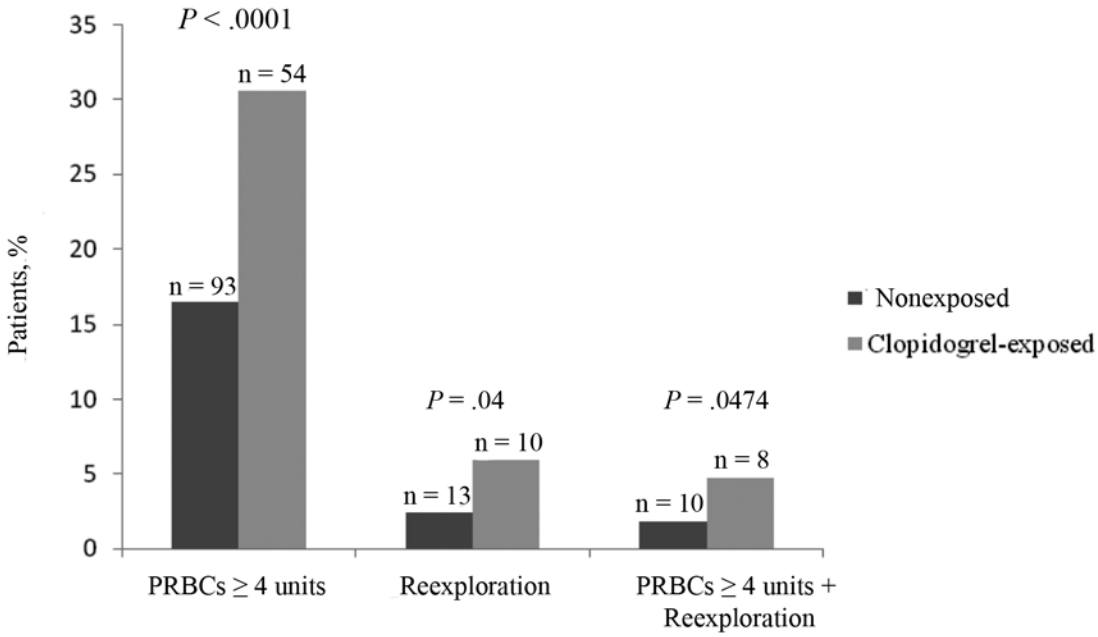

Figure 1. Breakdown of major bleeding components in nonexposed versus clopidogrel-exposed patients. PRBCs indicates packed red blood cells.

received clopidogrel within 5 days before CABG. We recorded postoperative complications, as defined by standard STS criteria, for pneumonia, sepsis, site infection, renal failure, tamponade, paralysis, coma >24 hours, transient ischemic attack, stroke, and prolonged ventilation (>24 hours). Data were retrieved from our institutional STS database as well as from centralized electronic hospital records. This study was approved by the institutional review committee.

The primary outcome was the incidence of major bleeding, defined as transfusion of 4 units of PRBCs intraoperatively and postoperatively and/or the need for reexploration. Secondary outcomes included non–life-threatening bleeding, defined as the transfusion of 2 units but <4 units of PRBCs, postoperative complications, hospital and intensive care unit lengths of stay, readmission within 30 days of the procedure, and hospital mortality.

Statistical Analysis

A sample size of 120 patients in the clopidogrel group and 500 patients in the nonclopidogrel group was calculated to have an 80% power to detect an odds ratio of 2.0 (α = .05), on the assumption that 15% to 20% of patients in the nonclopidogrel group would have a major bleeding event. Major bleeding events (4 units PRBCs and/or surgical reoperation for bleeding) were analyzed with a logistic regression model. Exposure to clopidogrel within 5 days of surgery was the independent variable of interest. The model adjusted for the following covariates: age, sex, body mass index (BMI), surgery status (elective, emergent, urgent), cardiopulmonary bypass (CPB) use (full, combination, none), heart failure, previous MI, diabetes mellitus, hyperlipidemia, hypertension, cardiovascular disease, last serum creatinine value, glycoprotein (GP) IIb/IIIa inhibitor and aspirin use, and baseline INR. Secondary end points were compared with chi-square tests for categorical outcomes and with Student t tests or Wilcoxon rank sum tests for continuous outcomes. All analyses were performed with SAS/STAT software (version 9.2; SAS Institute, Cary, NC, USA).

RESULTS

Major Bleeding

A total of 715 patients who underwent isolated CABG were included: 169 patients received clopidogrel within 5 days before surgery, and 546 patients did not. Patients were predominantly male (74.8%), with a mean (±SD) age of 62.4 ± 11 years and a mean BMI of 30.3 ± 6.3 kg/m2 (Table 1). The 2 groups had similar baseline characteristics, except that patients exposed to clopidogrel had a higher prevalence of previous MI (79.9% versus 48.0%) and a lower percentage of elective surgery (20.1% versus 43.0%).

Major bleeding occurred in 32% (54 patients) of the clopidogrel-exposed group and in 17% (93 patients) of the nonexposed group. Examination of the specific nature of the major bleeding events revealed that patients who had been exposed to clopidogrel had an increased incidence of transfusion of 4 units of PRBCs (30.6% versus 16.5%, P < .0001), surgical reexploration for bleeding (5.9% versus 2.4%, P = .04), and both criteria of transfusion of 4 units of PRBCs and surgical reexploration for bleeding (4.7% versus 1.8%, P = .047) (Figure 1). After adjusting for covariates, we found that patients exposed to clopidogrel within 5 days of surgery still had significantly higher odds of major bleeding than patients who were not exposed (odds ratio [OR], 2.1; 95% confidence interval [CI], 1.3-3.4); P = .003] (Table 2).

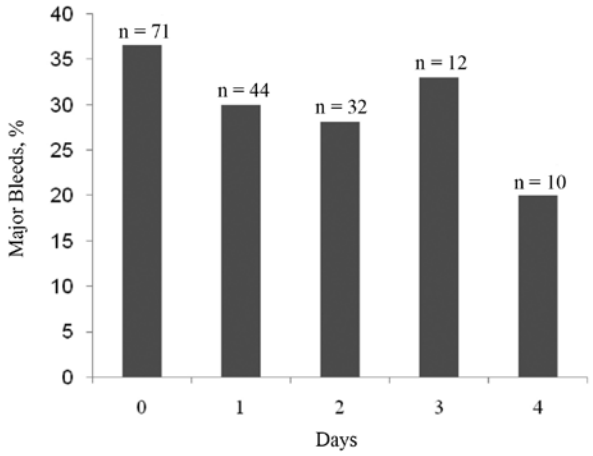

Figure 2. Day of discontinuation of clopidogrel prior to coronary artery bypass grafting (CABG) and the incidence of major bleeding. Day 0 indicates zero days of discontinuation of clopidogrel prior to CABG.

Of the 169 patients in the clopidogrel-exposed group, 71 patients were given clopidogrel on the day of CABG, and clopidogrel was withheld before surgery for 1 day in 44 patients, for 2 days in 32 patients, for 3 days in 12 patients, and for 4 days in 10 patients (Figure 2). The rates of bleeding were similar in patients who were exposed to clopidogrel within 5 days before CABG (range, 26.4%-16.7%).

Secondary End Points

The groups did not differ significantly with respect to non–life-threatening bleeding, hospital mortality, and readmission within 30 days (Table 3). The median postoperative hospital stay was 6 days (interquartile range, 5-8 days), and the 2 groups did not differ significantly in this respect. Patients in the 2 groups had similar postoperative increases in INR (median, 0.3), as well as a median decrease in hemoglobin of 1.8 mg/dL. Patients exposed to clopidogrel experienced a higher frequency of transfusion for all perioperative blood products than did nonexposed patients (40% versus 20%, $P < .002$). The numbers of units transfused for PRBCs, FFP, and platelets were significantly higher in the clopidogrel-exposed group than in the nonexposed group (Table 4).

The 2 groups had similar rates of postoperative complications, with the exception of infection of the surgical site,

Table 2. Logistic Regression Results for the Odds of a Major Bleeding Event*

Variable	Odds Ratio	95% CI	*P*
Exposure to clopidogrel within 5 days of surgery	2.11	1.30-3.45	.003
Age†	1.21	1.09-1.34	<.001
Sex, female versus male	2.56	1.60-4.08	<.001
BMI‡	0.72	0.59-0.87	<.001
Previous MI	1.49	0.93-2.39	.10
Heart Failure	1.56	0.97-2.52	.07
Diabetes mellitus	1.18	0.74-1.88	.48
Hyperlipidemia	1.75	0.66-4.62	.26
Hypertension	1.43	0.66-3.12	.37
Cardiovascular disease	.91	0.53-1.58	.74
Last serum creatinine	1.21	1.01-1.44	.04
INR before surgery §	1.63	1.14-2.32	.007
GP IIb/IIIa inhibitor use	1.03	0.40-2.63	.96
Aspirin use	1.38	0.65-2.93	.40
Status, emergent versus elective	2.89	1.60-7.08	.02
Status, urgent versus elective	1.08	0.66-1.77	.76
CPB use, combination versus none	6.82	2.37-19.65	<.001
CPB use, full versus none	3.66	2.12-6.33	<.001

*CI indicates confidence interval; BMI, body mass index; MI, myocardial infarction; INR, international normalized ratio; GP, glycoprotein; CPB, cardiopulmonary bypass.

†Odds ratio for a 5-year increase.

‡Odds ratio for a 5-unit increase.

§Odds ratio for a 0.2-unit increase.

Table 3. Outcomes*

	Clopidogrel Exposed (n = 169)	Not Exposed (n = 546)	*P*
Major bleeding, n (%)	54 (32.0)	93 (17.0)	.002†
Secondary Outcomes			
Bleeding (not life-threatening), n (%)	42 (24.9)	146 (26.7)	.63
Hospital mortality, n (%)	2 (1.2)	7 (1.3)	.92
Mortality by 30 days	No additional deaths reported		
Readmission by 30 days, n (%)	21 (12.4)	58 (10.6)	.51
MI, n (%)	4 (2.4)	5 (0.9)	.23
Transient ischemic attack, n (%)	1 (0.6)	0 (0)	.24
Trans-RIND stroke, n (%)	0 (0)	0 (0)	1.00
Coma >24 h, n (%)	0 (0)	1 (0.2)	.58
Paralysis, n (%)	1 (0.6)	1 (0.2)	.42
Ventilator time >24 h, n (%)	36 (21.3)	92 (16.9)	.19
Pneumonia, n (%)	9 (5.3)	30 (5.5)	.93
Renal failure, n (%)	6 (3.6)	19 (3.5)	.97
Postoperative dialysis, n (%)	4 (2.4)	7 (1.3)	.32
Tamponade, n (%)	0 (0)	1 (0.2)	.58
Infection, n (%)	7 (4.1)	4 (0.7)	.005
Sternal	1 (0.6)	3 (0.6)	.95
Thoracic	1 (0.6)	0 (0)	.24
Leg	5 (3.0)	1 (0.2)	.003
Arm	0 (0)	0 (0)	1.00
Sepsis, n (%)	2 (1.2)	7 (1.3)	.92
Postoperative hospital LOS, d	7.6 ± 5.2	7.4 ± 5.4	.40
INR increase	0.30 ± 0.25	0.30 ± 0.21	.93
Hemoglobin decrease, g/dL	1.84 ± 2.19	1.76 ± 1.98	.66

*Data are presented as the mean ± SD where indicated. MI indicates myocardial infarction; RIND, reversible ischemic neurologic deficit; LOS, length of stay; INR, international normalized ratio

†Covariate-adjusted *P* value from logistic regression model.

Table 4. Perioperative Transfusions*

	Clopidogrel Exposed (n = 169)	Not Exposed (n = 546)	*P*†
Any, n (%)	68 (40)	147 (27)	.002
Patients receiving units‡			
PRBCs	58 (34); 2 (2-4)	129 (24); 2 (2-3)	.003
FFP	21 (12); 4 (2-4)	26 (5); 4 (2-4)	<.001
Cryoprecipitate	2 (1); 1 (1-2)	3 (1); 1 (1-1)	.39
Platelets	36 (21); 2 (2-2)	42 (8); 2 (2-2)	<.001

*PRBCs indicates packed red blood cells; FFP, fresh frozen plasma.

†Unadjusted chi-square test for any versus none; unadjusted Wilcoxon-Mann-Whitney rank sum test for all others.

‡Data are presented as: n (%); median (interquartile range).

which was higher in the clopidogrel-exposed group (4.1% versus 0.7%, $P = .005$). A higher rate of leg infection was found in the clopidogrel-exposed group than in the nonexposed group (3% versus 0.2%, $P = .003$), but the 2 groups had similar rates of infections at sternal and thoracic sites. Our standard practice for obtaining the saphenous vein graft is endoscopic vein harvesting, and we use a small interrupted incision to assist with endoscopic harvesting when we require large side branches or small single segments of vein. Of the 5 patients in the clopidogrel-exposed group who had leg infection, 4 patients experienced the primary end point of major bleeding. Rates of MI, stroke, and hospital mortality were similar for the 2 groups (Table 3).

DISCUSSION

The results of this study suggest that patients exposed to clopidogrel within 5 days of CABG experience 2-fold higher odds of major bleeding. Clopidogrel's effect on major bleeding was significant, even after adjusting for other bleeding risk factors, including female sex, renal dysfunction, previous MI, nonelective surgery, on-pump procedure, and GP IIb/IIIa inhibitor and aspirin use, as determined with our logistic regression model.

Transfusion frequency was significantly increased in the clopidogrel-exposed group, compared with the nonexposed group, with the number of units transfused being higher for each blood product (PRBCs, FFP, and platelets). This finding indicates that patients exposed to clopidogrel experience a higher rate of transfusions overall, which places them at increased risk for short- and long-term adverse events.

Hemorrhagic complications correlate with higher risks of infection, ischemia, and mortality. In this study, major bleeding was associated with a higher rate of infection, which was driven by an increased incidence of leg infections in the clopidogrel-exposed group. Of the 5 patients who experienced leg infection in the clopidogrel-exposed group, 4 had major bleeding and leg hematomas. The single patient who experienced leg infection in the nonexposed group did not have a major bleeding event. This finding suggests clopidogrel-exposed patients may be at higher risk for leg infections due to development of a hematoma and thus may benefit from a temporary drain placed at the vein-harvest site—regardless of the technique used to harvest the vein. Although a secondary outcome, this finding is unique in that it has been not reported in similar studies. Further investigation is warranted.

Our results indicate that a higher bleeding risk is evident among CABG patients exposed to clopidogrel within 5 days of CABG; however, considerable disparity exists in the literature regarding the risk of hemorrhagic complications in patients treated with clopidogrel before cardiac surgery. A recent meta-analysis of 34 studies (22,584 patients) conducted by Nijjer et al has demonstrated the limitations of examining the effect of clopidogrel on major bleeding [Nijjer 2011]. The review aimed to determine the risk of continued clopidogrel use for various times up to the time of CABG. Significant increases were found in transfusions of PRBCs (by 1.1 units; 95% CI, 0.58-1.64 units; $P < .0001$), platelets (by 0.18 units; 95% CI, 0.14-0.21 units; $P = .006$), and FFP (by 0.49 units; 95% CI, 0.14-0.84 units; $P = .006$) in patients with recent exposure to clopidogrel. The rate of reoperation in the clopidogrel-exposed group was also increased, compared with patients without recent exposure to clopidogrel (OR, 2.32; 95% CI, 1.76-3.06; $P < .00001$); mortality was also increased (OR, 1.6; 95% CI, 1.30-1.96; $P < .00001$). The authors stated that the data were heterogeneous, with potential for sampling bias, which may not translate into hard outcomes. Nonetheless, they concluded that several ACS patients had undergone CABG safely with recent clopidogrel exposure and therefore promoted this practice in patients requiring urgent CABG until the completion of more trials that evaluate the balance between ischemia and bleeding. Another recent meta-analysis suggests the data are suboptimal for evaluating discontinuation times before CABG and thus are insufficient for safely recommending the continuation of clopidogrel in the setting of CABG, because of the increased risks of postoperative death, reoperations for bleeding, blood loss, and need for blood transfusions [Biancari 2011].

Differences in outcomes may be influenced by several factors, including inconsistencies among the various trials in the definitions for bleeding. Bleeding definitions vary with respect to clinical indicators, including reexploration for bleeding, chest tube output, access site hemorrhage, and intracranial or intraocular bleeding. Units of transfusion and decreases in hemoglobin and/or the hematocrit are also used as surrogate markers of major bleeding. In our study, we used 4 units of PRBCs and/or reoperation to signify a major bleeding event, with the realization that up to 50% of patients who undergo cardiac surgery procedures receive blood transfusions. We believe 4 units or a need for reoperation is clinically significant. The development of a nationally accepted standardized definition for bleeding is crucial to truly translate bleeding markers into clinical outcomes. Recognizing this need, the Bleeding Academic Research Consortium recently published a consensus report with standardized definitions for bleeding for use in cardiovascular clinical trials [Mehran 2011]. These definitions still need to be used and validated so that trials examining the association of various antiplatelet agents with bleeding risk can be accurately compared.

Individual variation in responses to clopidogrel may also contribute to the conflicting results among studies regarding the impact of clopidogrel on major bleeding in CABG patients. The antiplatelet effect of clopidogrel has been shown to be heterogeneous in the overall patient population, and this variation can affect clinical outcomes [Angiolillo 2007]. Enhanced platelet reactivity to clopidogrel could possibly place patients at a higher risk of bleeding. Likewise, patients who have a reduced responsiveness to clopidogrel may be at lower risk for bleeding. In this study, similar rates of bleeding were seen in patients exposed to clopidogrel within 5 days before CABG, regardless of the day of discontinuation. This finding correlates with the variability in clopidogrel-induced antiplatelet effects. Platelet function assays may be a valuable clinical tool to determine individual platelet responses to clopidogrel, thereby allowing physicians to make more-informed decisions on the timing of cardiac surgery

in clopidogrel-exposed patients. The ACC/AHA and STS/SCA suggest the use of platelet function testing to ascertain which patients may require longer wait times before surgery after exposure to clopidogrel; however, the level of evidence is weak [Biancari 2011; Wright 2011]. Therefore, we have yet to implement the use of platelet function testing before cardiac surgery at our institution. Additional studies are needed to determine the significance of platelet function testing as a tool for assessing individualized risk of surgical bleeding and the timing of cardiac surgery [Burcham 2011]. It is hoped that the development of protocols that use newer intravenous, short-acting, and reversible antiplatelet agents may also assist in the management of these patients [Angiolillo 2012].

Limitations

This study has several limitations, including being a single-site, retrospective study. Variation in surgical practices is a possible confounder, particularly with the transfusion of blood products. The operating surgeon's knowledge of clopidogrel exposure may lead to a lower threshold for transfusion in exposed patients. Long-term adverse events due to major bleeding may not have been captured, because data were collected only for the duration of the hospital stay and patients may have experienced complications after their discharge. Although no additional deaths by 30 days were reported, mortality status was not known for the entire study population. The rationale to use 4 units of PRBCs and reexploration as indicators of major bleeding was largely based on the clinical experience at our institution, which has shown that transfusion of 4 units of PRBCs truly represents a major bleed, as well as a threshold for complications. We chose not to use the commonly used criterion of chest tube output, which can include constituents other than blood, such as serous fluid and residual intraoperative fluids (ie, warm saline) used to irrigate the mediastinum and pleural spaces before chest closure.

Our study indicates that in ACS patients undergoing CABG, clopidogrel is associated with a higher incidence of major bleeding and possibly infection at the vein harvest site. To determine the optimal use of perioperative antiplatelet therapies in cardiac surgery requires the implementation of consistent definitions of bleeding among trials, as well as a better assessment of the role of tests to analyze an individual's platelet function. Additional studies are needed to determine if platelet function testing will help in decreasing bleeding events in patients exposed to clopidogrel before CABG.

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