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Impact of Clopidogrel in Patients With Acute Coronary Syndromes Requiring Coronary Artery Bypass Surgery

A Multicenter Analysis

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Objectives The purpose of our multicenter study was to examine the impact of pre-operative administration of clopidogrel on reoperation rates, incidence of life-threatening bleeding, inpatient length of stay, and other bleeding-related outcomes in acute coronary syndrome (ACS) patients requiring cardiopulmonary bypass (coronary artery bypass graft surgery [CABG]) in a broad cross section of U.S. hospitals.

Background There is relative uncertainty about the relationship between clopidogrel and CABG-associated outcomes in the setting of ACS.

Methods A retrospective cohort analysis was performed of randomly selected ACS patients requiring CABG in 14 hospitals across the U.S. Patients exposed to clopidogrel were compared with those not exposed to clopidogrel within 5 days prior to surgery.

Results Of the 596 patients enrolled in the study, 298 had been exposed to clopidogrel within 5 days (Group A). Patients in Group A were more than 3-fold more likely to require reoperation for assessment of bleeding than patients not exposed to clopidogrel (6.4% vs. 1.7% Group B, $p = 0.004$). Major bleeding occurred in 35% of Group A patients versus 26% of Group B patients ($p = 0.049$). Length of stay was greater in Group A compared with Group B (9.7 ± 6.0 days vs. 8.6 ± 4.7 days, unadjusted $p = 0.016$). After logistic regression analysis, clopidogrel exposure within 5 days of CABG was the strongest predictor of reoperation (odds ratio [OR]: 4.60, 95% confidence interval [CI]: 1.45 to 14.55) and major bleeding (OR: 1.824, 95% CI: 1.106 to 3.008).

Conclusions After ACS, patients who undergo CABG within 5 days of receiving clopidogrel are at increased risk for reoperation, major bleeding, and increased length of stay. These risks must be balanced by the clinical benefits of clopidogrel use demonstrated in randomized clinical trials. (J Am Coll Cardiol 2008;52:1693–701) © 2008 by the American College of Cardiology Foundation

Randomized clinical trials have demonstrated the superiority of clopidogrel versus placebo on a background of aspirin therapy in the setting of acute coronary syndrome (ACS) (1–3). Although clopidogrel causes an increase in major bleeding, its main effect is in reducing cardiovascular morbidity and mortality in this high-risk group of patients (4). Accordingly, the most recent ACS guidelines make early clopidogrel treatment a class I recommendation with grade A evidence (5,6). However, one must exercise caution administering clopidogrel to patients undergoing surgical revascularization. Current guidelines support the discontinuation of clopidogrel 5 to 7 days before elective coronary artery bypass graft surgery (CABG), whereas more urgent surgery, if necessary, may be performed by experienced surgeons if the incremental bleeding risk is considered acceptable (5).

Accumulating data suggest that between 10% and 16% of patients admitted with ACS undergo surgical revasculariza-

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Abbreviations and Acronyms

ACC/AHA = American College of Cardiology/American Heart Association
ACS = acute coronary syndrome
CABG = coronary artery bypass graft surgery
CI = confidence interval
LOS = length of stay
OR = odds ratio

tion during the initial hospitalization (7–9). Although not all (10), several retrospective studies have reported a relationship between use of clopidogrel and the risk of perioperative bleeding and blood product transfusion (9,11–14). The existing data have several important limitations; many studies were undertaken at single centers (10–12,14), used a cut-off of 5 days (9), (thus not permitting an evaluation of time from drug cessation and bleeding), or did not report a full range of potential confounders (laboratory values, coagulation markers, and operative findings) or clinically relevant adverse events such as surgical re-exploration (9). Furthermore, many published studies were not performed in the ACS setting (10,12–14) or included patients several weeks, on average, after their presenting ACS event (13), a time when the bleeding risk is substantially lower. As a result, the American College of Cardiology/American Heart Association (ACC/AHA) Guideline Committee for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction believes that more data on the overall relative benefits versus risks of clopidogrel and bypass surgery are required to further direct patient care (5).

To better characterize the relationship between clopidogrel administration and bypass surgery in the setting of ACS, we prospectively developed a multicenter protocol to collect patient-level hospitalization data. Study cohorts at individual sites were randomly selected to reduce potential confounders of variability in surgical practice and standards of care in each hospital setting. Using this study design, we were able to investigate the association between the proximity of clopidogrel exposure and CABG-related adverse events, including reoperation and bleeding-related outcomes.

Methods

This study was a protocol-driven, retrospective cohort analysis of randomly selected patients with an admitting diagnosis of ACS undergoing CABG during their index hospitalization at 14 hospitals across the U.S. Stand-alone cardiac specialty hospitals were not included. A coinvestigator and study coordinator were recruited at each participating hospital site. Each site's coinvestigator was responsible for submitting the protocol to the institution's Investigational Review Board for evaluation and approval.

Setting. The study population included patients from hospitals that performed at least 350 CABG procedures annually. Hospitals were selected from a broad geographic distribution, with no more than 4 hospitals from any of 4 geographic regions of the U.S. (Northeast, Midwest, South, and West including Alaska and Hawaii). The study institutions included both teaching and nonteaching hospitals and those performing both on-pump and off-pump procedures. To qualify for study participation, sites were required to demonstrate that their standard of care for patients with an admitting diagnosis of ACS permitted those requiring CABG, upon the discretion of the treating cardiologist and cardiothoracic surgeon, to proceed to surgery whether or not clopidogrel had been administered. Site recruitment began in November 2006 and concluded in August 2007. Case records of patients treated between January 2004 and December 2006 were included in the study. (The participating hospitals and health care systems and coinvestigators are listed in the Online Appendix.)

Each study coordinator was trained in the study procedures and case report form by 1 of the investigators and provided with a randomization table for selection of cases. Sites randomly selected up to 50 cases (25 in each of the 2 comparison groups using a randomization table) meeting inclusion/exclusion to achieve a pre-specified 1:1 ratio of patients either exposed (Group A) or not exposed (Group B) to clopidogrel within 5 days of surgery. Group B included patients who were clopidogrel naïve or those who had received a dose >5 days before the time of CABG. Inclusion in either group was determined by subtracting the date and time of the last dose of clopidogrel from the date and time of the initial sternotomy incision.

Data from 14 participating sites on a total of 677 patients were collected for the study. In sites that had fewer than 25 cases in either cohort for the study period, cases and controls were randomly selected to provide an equal number in each cohort to reduce confounding site-specific characteristics that could bias or skew the results in the overall group. Case records from 596 patients were used in this analysis (Fig. 1).

Enrollment criteria. Patients were included if they met each of the following criteria: ≥30 years of age, presented with ACS, underwent CABG during the index hospitalization, and remained at 1 hospital for management (unless complete records were available from a referring hospital). Patients were excluded if they met any of the following criteria: end-stage renal disease, other open-heart procedures (e.g., valvular replacement or repair, ventricular septal defect repair) with CABG, bleeding disorder identified pre-operatively (e.g., Von Willebrand disease, hemophilia), lost to follow-up within 30 days after CABG surgery, death unrelated to cardiac condition or surgery, surgery not performed within 7 days of the index hospitalization or angiography for ACS, presumed cardiac rupture (post-infarction), and chronic use of corticosteroids.

End points. There were 3 coprimary end points in this analysis: reoperation, major bleeding, and length of hospital stay. Major bleeding was defined as a >5 g/dl drop in hemoglobin, intracranial bleed, fatal bleed, or cardiac tamponade. In addition to this definition, we also evaluated the CURE (Clopidogrel in Unstable Angina to Prevent Recur-

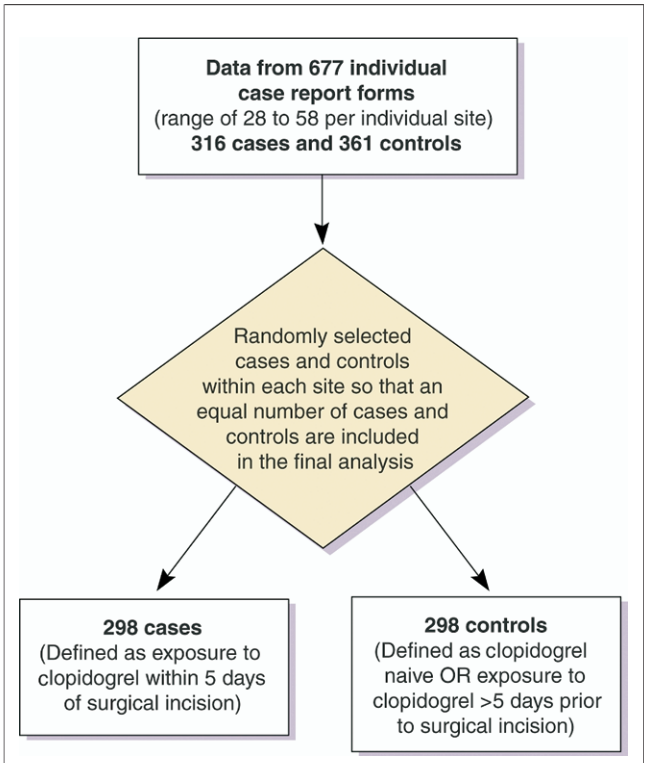

Figure 1 Study Population

rent Events) study (3) definition of major bleeding (substantially disabling bleeding, intraocular bleeding leading to the loss of vision, or bleeding necessitating the transfusion of at least 4 units of blood), and the TIMI (Thrombolysis In Myocardial Infarction) study (15) definition of life-threatening major bleeding (intracranial bleeding, hemorrhagic death, cardiac tamponade, or any clinically apparent bleeding associated with a decrease in hemoglobin of >5 g/dl or a >15% reduction in hematocrit-adjusted for red blood cell transfusions).

Sample size. A sample size calculation performed before study initiation indicated that inclusion of 310 patients in each group would allow 80% power to detect a probability of 0.565 that length of stay (LOS) was shorter in Group B than Group A using a Wilcoxon (Mann-Whitney) rank sum test, with a 0.050 2-sided significance level. The estimate of probability of differences was calculated assuming a median LOS of 9 days in Group A and a median LOS of 7 days in Group B.

Statistical analysis. The chi-square test was used for categorical variables. For continuous variables, we used either the Student *t* test or the Mann-Whitney *U* test depending on whether the data were normally distributed. The relationships between different treatment variables were assessed before and during regression analysis for multicolinearity. The correlation was assessed by using the Pearson correlation coefficient. If the correlation coefficient between 2 variables was >0.7 and statistically significant, then only 1 of the variables was used in regression model. The primary outcomes of the study were assessed by univariate analysis, followed by logistic regression analysis, to identify independent predictive variables from the categorical and continuous variables. Potential confounders were entered into models if they were clinically relevant or showed statistical significance at $p \leq 0.10$ during the univariate analysis between the 2 groups. We also used the propensity scores risk adjustment method to adjust baseline characteristics and/or clinical factors that could impact the decision to give patients clopidogrel.

A p value of ≤0.05 was considered to declare statistical significance. All analyses were performed using SPSS version 15.0 (SPSS, Inc., Chicago, Illinois), and STATA (STATA Corp., College Station, Texas).

Results

Fourteen sites across the U.S. were included in this study (Online Appendix). All patients underwent CABG within 7 days of their index hospitalization or angiography for ACS. Of the 596 patients enrolled in the study, 298 were in Group A and 298 in Group B. In Group A, the mean time between last clopidogrel exposure and CABG surgery was 56 ± 48.11 h, 95 had received a loading dose (most commonly 300 mg), and 230 received a maintenance dose (most commonly 75 mg).

Overall, mean age was 64 years, 68% were male, and 89% were white. Table 1 provides a summary of baseline characteristics. Patients in Group A had a greater prevalence of prior cerebrovascular accident, myocardial infarction, and percutaneous coronary intervention. The classification of ACS on admission was similar between groups (Table 2). The number of vessels grafted and use of the left internal mammary artery as a bypass conduit were less in the clopidogrel-exposed group. Surgery was postponed for 46 patients in Group A compared with 32 patients in Group B ($p < 0.001$). As expected, antifibrinolytic drugs were used more frequently in the operating room for Group A patients than for Group B patients (66% vs. 56%, respectively, $p = 0.0009$).

The overall incidence of reoperation, excessive or major bleeding, and LOS was influenced significantly by preoperative clopidogrel exposure in the univariate analysis (Table 3). Length of stay was on average 1 day longer in Group A than in Group B. There were 24 (4.0%) reoperations in the combined cohort. Patients in Group A were more likely to require reoperation than were patients in Group B (6.4% vs. 1.7%, $p = 0.004$). As expected, the majority of reoperations were performed for the management of bleeding complications. After multivariable adjustment, clopidogrel exposure within 5 days was the strongest predictor of reoperation (odds ratio [OR]: 4.60, 95% confidence interval [CI]: 1.45 to 14.55, $p < 0.01$) (Table 4). Major bleeding occurred in 124 (20.8%) patients: 35% in Group A versus 26% in Group B ($p = 0.049$). This finding was numerically consistent across each of the major bleeding definitions evaluated (3,15). After logistic regression analy-

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Table 1 Baseline Characteristics

	Group A (n = 298)	Group B (n = 298)	p Value
Baseline demographics			
Age, yrs (±SD)	64.5 (±11.24)	64.0 (±10.88)	0.625
BMI, kg/m^2 (±SD)	29.1 (±6.13)	30.2 (±5.86)	0.026
Male, n (%)	207 (69.5)	200 (67.1)	0.538
Caucasian, n (%)	264 (89.5)	259 (88.1)	0.591
Clinical history			
Diabetes mellitus, n (%)	103 (34.6)	112 (37.6)	0.443
Admission creatinine clearance, n (%)			
<30 ml/min	57 (19.7)	50 (17.1)	0.408
30–60 ml/min	104 (36.0)	128 (43.7)	0.058
>60 ml/min	128 (44.3)	115 (39.2)	0.218
Hypertension, n (%)	230 (77.2)	234 (78.5)	0.693
Congestive heart failure, n (%)	28 (9.4)	26 (8.7)	0.775
Previous CABG, n (%)	17 (5.7)	13 (4.4)	0.454
Previous MI, n (%)	85 (28.5)	57 (19.1)	0.007
Previous PCI, n (%)	98 (32.9)	46 (15.4)	<0.001
COPD, n (%)	38 (12.8)	35 (11.7)	0.708
CVA, n (%)	35 (11.7)	20 (6.7)	0.034
Current tobacco smoker, n (%)	77 (25.8)	84 (28.2)	0.518
Alcohol abuse, n (%)	22 (7.4)	8 (2.7)	0.009

BMI = body mass index; BSA = body surface area; CABG = coronary artery bypass graft surgery; COPD = chronic obstructive pulmonary disease; CVA = cerebrovascular accident; MI = myocardial infarction; PCI = percutaneous coronary intervention.

sis for the combined end point of major bleeding or reoperation, clopidogrel exposure within 5 days was associated with a significantly increased risk (OR: 1.55, 95% CI: 1.00 to 2.41, p = 0.048, data not shown). We also ran these analyses using the propensity score method to control for confounding and demonstrated an increased risk for reoperation (OR: 9.80, 95% CI: 2.18 to 43.95, p < 0.01), major bleeding (OR: 1.82, 95% CI: 1.11 to 3.01, p = 0.02), and increased LOS (OR: 1.47, 95% CI: 1.00 to 2.165, p = 0.05) with clopidogrel exposure within 5 days. Figure 2 illustrates the incidence of reoperation or major bleeding according to the proximity of clopidogrel exposure, and its subsequent cessation, before surgery.

There was no difference in mean hematocrit on admission, or during pre-operative or intraoperative testing between the groups. However, in the immediate post-operative period, and on post-operative days 1 and 2, mean hematocrit was lower in Group A than in Group B (p < 0.05, for all). No difference was detected between groups in routine coagulation measurements of international normalized ratio, prothrombin time, or partial thromboplastin time at any time point. There was a >2-fold increase in blood product transfusions among patients in Group A compared with Group B. Table 5 describes the relationship between clopidogrel exposure, timing of transfusions, and chest tube output. Patients exposed to clopidogrel were more likely to receive transfusions both in the intraoperative and post-operative periods. In addition, they were also more likely to have received a platelet transfusion intraoperatively. In the post-operative period, transfusion of platelets, packed red blood cells, fresh frozen plasma, and cryoprecipitate were all used more frequently in Group A. The increase in chest tube output for Group A compared with Group B was greatest in the first 6 h (Table 5). Multivariate analysis confirmed that group A patients received more blood transfusions and had more chest tube output when controlling all other factors (data not shown).

There were 5 deaths in the study population, 4 in Group A and 1 in the Group B. No significant difference was detected for the composite of death, reinfarction, or stroke. Group A patients were more likely to require inotropes and to have cardiac tamponade than were Group B patients. No significant difference was observed between groups for hospital readmission within 30 days of discharge.

Discussion

In this large, prospectively designed, retrospective cohort study to evaluate the relationship between clopidogrel exposure and CABG-related outcomes among patients with ACS, we found a significantly increased risk of reoperation, major bleeding, and LOS among those who received clopidogrel within 5 days of their surgery. Our data showed a clear dependency between time of clopidogrel cessation and CABG-related bleeding.

In addition to "hard" clinical end points such as major bleeding and reoperation, we also evaluated the reason for reoperation, as well as laboratory parameters before, during, and after surgery. A major strength of our study is its representation of practice in multiple centers across the U.S. and inclusion of patients treated in rural and urban, teaching and nonteaching, and not-for-profit and for-profit hospitals. As a result, the data are likely to be more generalizable and not dominated by individual surgeons, processes of care,

Table 2 Clinical Presentation and Hospital Course

	Group A (n = 298)	Group B (n = 298)	p Value*
ACS admission diagnosis, n (%)†			
Unstable angina	203 (68.1)	187 (62.8)	0.168
NSTE ACS	93 (31.2)	85 (28.5)	0.474
STE ACS	56 (18.8)	45 (15.1)	0.230
PCI, n (%)	(n = 33)	(n = 11)	
PCI initially successful then failed	12 (36.4)	4 (36.4)	1.000
PCI initially failed	21 (63.6)	7 (63.6)	1.000
Angiogram vessel anatomy suggests CABG	(n = 294)	(n = 283)	
Acute, n (%)	261 (88.8)	268 (94.7)	0.007
Pre-operative statin use, n (%)	217 (72.8)	203 (68.1)	0.209
ASA scores, n (%)	(n = 296)	(n = 296)	
2–3	47 (15.9)	40 (13.5)	0.416
4–5	249 (84.1)	256 (86.5)	0.416
Repeat CABG, n (%)	17 (5.7)	13 (4.4)	0.454
Emergent cases, n (%)	36 (12.1)	21 (7.0)	0.037
Urgent cases, n (%)	205 (68.8)	194 (65.1)	0.338
Elective cases, n (%)	57 (19.1)	83 (27.9)	0.012
Number of vessel grafts (±SD)	3.38 (±1.13)	3.73 (±1.20)	<0.001
Graft site, n (%)	(n = 298)	(n = 298)	
Distal vein	244 (81.8)	249 (83.6)	0.588
LIMA	251 (84.2)	275 (92.3)	0.002
RIMA	6 (2)	3 (0.1)	0.313
Both LIMA and RIMA	5 (1.6)	4 (1.3)	0.737
Right radial artery	1 (<1)	2 (<11)	0.563
Left radial artery	20 (6.7)	25 (8.4)	0.438
Both radial arteries	0	1 (<1)	0.317
Not available	3 (1.0)	1 (<1)	0.317
Postponed surgery	(n = 46)	(n = 32)	
Due to antiplatelet therapy, n (%)	35 (76.1)	10 (31.3)	<0.001
Due to recent MI, n (%)	4 (8.7)	10 (31.3)	0.011
Due to recent CVA, n (%)	2 (4.3)	0	0.510
Sent home, n (%)	3 (6.5)	4 (12.5)	0.436
Remained in hospital, n (%)	43 (93.5)	28 (87.5)	0.436
Postponed with sudden change to emergent status, n (%)	3 (6.5)	0	0.265
Days surgery postponed, median (range)	5 (2–7)	6 (1–9)	0.050
Other surgical data			
On-pump, n (%)	215 (72.1)	216 (72.5)	0.927
Duration of pump (min), mean (±SD)	95.6 (±41.20)	94.2 (±36.12)	0.929
Duration of surgery (min), mean (±SD)	225.5 (±73.30)	226.9 (±64.1)	0.538
Time from admission to CABG (days), mean (±SD)	2.5 (±2.57)	2.8 (±2.48)	0.950
Time from PCI to CABG (h), mean (±SD)	43.7 (±44.19)	47.2 (±49.26)	0.809
Perioperative medications, n (%)			
Antifibrinolytic drugs	197 (66.1)	166 (55.7)	0.009
Trasylol (aprotinin)	103 (34.6)	95 (31.9)	0.487
Amicar (aminocaproic acid)	93 (31.2)	69 (23.2)	0.027
Cyklokapron (tranexamic acid)	2 (0.7)	5 (1.7)	0.450
Factor VIIa (NovoSeven)	45 (15.1)	34 (11.4)	0.184
Glycoprotein IIIa/IIb inhibitor	48 (16.1)	33 (11.1)	0.073
Aspirin	280 (94.0)	268 (89.9)	0.071
Heparin			
UFH	283 (95.0)	280 (94.0)	0.591
LMWH	44 (14.8)	56 (18.8)	0.188
Both UFH and LMWH	11 (3.7)	11 (3.7)	1.000
Statins	217 (72.8)	203 (68.1)	0.209
Beta-blockers	245 (82.2)	217 (72.8)	0.006

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Table 2 Continued

	Group A (n = 298)	Group B (n = 298)	p Value*
Calcium-channel blockers	56 (18.8)	48 (16.1)	0.388
Thrombolytic agents	10 (3.4)	2 (0.7)	0.020

*Binary variables compared by chi-square or Fisher exact tests and continuous variables compared by Student *t* test or Mann-Whitney *U* test for skewed data. †Some patients were diagnosed with both unstable angina and NSTE ACS.

ACS = acute coronary syndrome; ASA = American Society of Anesthesiologists; LIMA = left internal mammary artery; LMWH = low molecular weight heparin; NSTE = non–ST-segment elevation; RIMA = right internal mammary artery; STE = ST-segment elevation; UFH = unfractionated heparin; other abbreviations as in Table 1.

or clinical outcomes reflecting 1 hospital with or without expertise in the management of patients with ACS. Finally, the patients reflect those encountered regularly in clinical practice, rather than an inherently lower-risk group of patients participating in clinical trials (16).

Table 3 Primary and Secondary Outcomes, Unadjusted

	Group A (n = 298)	Group B (n = 298)	p Value*
Primary outcomes			
Patients requiring reoperation, n (%)	19 (6.4)	5 (1.7)	0.004
Patients with excessive or major bleeding,† n (%)	71 (34.5)	53 (25.6)	0.049
In-patient LOS, days (±SD)	9.7 ± 6.0	8.6 ± 4.7	0.016
Secondary outcomes			
Reoperation for bleeding complication, n (%)	14 (4.7)	4 (1.3)	0.017
CURE major bleeding, n (%)	113 (53.8)	73 (34.9)	<0.001
TIMI major bleeding, n (%)	114 (54.3)	98 (46.9)	0.130
Nonlife-threatening bleeding,‡ n (%)	56 (18.8)	55 (18.5)	0.916
In-hospital death, n (%)	4 (1.3)	1 (0.3)	0.373
Death/reinfarction/stroke, n (%)	8 (2.7)	5 (1.7)	0.400
Transfusion received, mean units§ (±SD)	4.90 (±7.90)	2.03 (±3.75)	<0.001
Hospital readmission within 30 days	27 (9.1)	24 (8.1)	0.670
Post-surgical LOS, days (±SD)	7.2 (±5.53)	6.3 (±3.87)	0.054
ICU LOS, days (±SD)	2.7 (±3.17)	2.4 (±2.52)	0.059
Post-operative complications, n (%)			
Atrial fibrillation	70 (23.5)	56 (18.8)	0.160
Infection	22 (7.4)	17 (5.7)	0.408
Ischemic CVA	5 (1.7)	3 (1.0)	0.725
Hemorrhagic CVA	0	0	—
Post-operative mortality	3 (1.0)	0	0.249
Hemodynamic instability	37 (12.4)	25 (8.4)	0.107
Inotropes needed	102 (34.2)	73 (24.5)	0.009
Mediastinitis	2 (0.7)	0 (0.0)	0.157
Bleeding/tamponade	20 (6.7)	7 (2.3)	0.010
Cardiac arrest	4 (1.3)	2 (0.7)	0.686

*Binary variables compared by chi-square or Fisher exact tests and continuous variables compared by Student *t* test or Mann-Whitney *U* test for skewed data. †Some cases were missing the necessary Hg values for this definition, thus, n = 206 and n = 207, respectively, comprise the group analyzed for this parameter. Major bleeding includes patients with fatality due to bleeding, a post-operative decrease in hemoglobin concentration of >5 g/dl, hypotension requiring the use of inotropes post-operatively or surgical intervention, or intracranial bleeding. ‡Nonlife-threatening bleeding was defined as bleeding that required transfusion of ≥2 but <4 units of blood products in the intraoperative and post-operative period combined. §Includes intraoperative and post-operative transfusions of all types of blood products (platelets, packed red blood cells, fresh frozen plasma, cryoprecipitate), all patients included; if no blood products were transfused, the individual patient's total was 0.

CURE = Clopidogrel in Unstable Angina to Prevent Recurrent Events study; CVA = cerebrovascular accident; ICU = intensive care unit; LOS = length of stay; TIMI = Thrombolysis In Myocardial Infarction study.

The highly significant relationship between clopidogrel exposure and reoperation or major bleeding after CABG was independent of other factors known to play an important role in hemostasis. Among patients in Group A, the odds of requiring reoperation were increased nearly 5-fold. In addition, patients were at risk for major bleeding, and had an increased LOS. Importantly, risk decreased with each subsequent day between clopidogrel exposure and CABG, reaching the background level of risk at 6 days between the cessation of clopidogrel and surgery. To our knowledge, this important relationship has not been clarified previously.

Clopidogrel is an irreversible platelet P2Y12 receptor antagonist (17). From the time of drug discontinuation, restoration of normal hemostasis is dependent upon the introduction of platelets into the circulation from bone marrow and extramedullary sources. Studies on the antiplatelet effect of clopidogrel have shown a time-dependent

Table 4 Logistic Regression Model of Predicting Reoperation

Variable	OR	95% Confidence Interval		p Value
		Lower	Upper	
Clopidogrel exposure <5 days	4.601	1.454	14.554	0.009
Age	0.998	0.952	1.046	0.941
Female gender	2.091	0.766	5.708	0.150
Body mass index	1.042	0.970	1.119	0.258
History of alcohol abuse	4.383	0.946	20.315	0.059
History of renal insufficiency	2.179	0.555	8.554	0.264
Admission creatinine clearance <60 ml/min	0.807	0.278	2.341	0.693
Perioperative exposure to antifibrinolytic agents	2.314	0.629	8.512	0.207
Pre-operative exposure to thrombolytic agents	0.942	0.071	12.479	0.964
Pre-operative exposure to glycoprotein IIb/IIIa inhibitors	1.825	0.504	6.613	0.360
Pre-operative exposure to aspirin	0.616	0.109	3.483	0.584
History of both MI and PCI	0.675	0.027	16.772	0.811
Pre-operative ejection fraction	1.004	0.968	1.042	0.817
History of previous CABG	5.299	1.050	26.734	0.043
ASA score 4–5	0.312	0.101	0.964	0.043
Urgent surgical classification	1.645	0.420	6.451	0.475
Emergent surgical classification	1.155	0.134	9.963	0.896
On-pump CABG	0.353	0.099	1.264	0.110

OR = odds ratio; other abbreviations as in Tables 1 and 2.

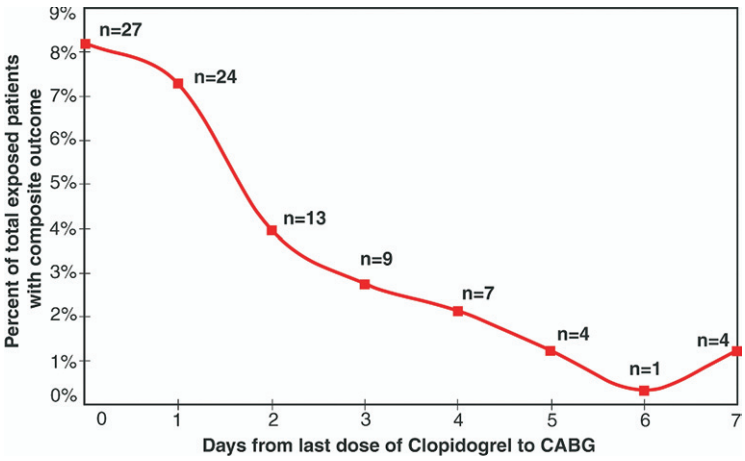

Figure 2 **Incidence of Composite Outcome by Day Clopidogrel Stopped Before Surgery**

The composite outcome (reoperation or major bleeding) incidence is shown by day clopidogrel was stopped before surgery. The denominator for the points on this curve is the total number of patients who were exposed to clopidogrel ≤7 days (n = 329); 89 patients experienced the composite outcome. **Red line** = clopidogrel exposure.

response with complete recovery of platelet function 7 days after the last dose (18). Because cardiothoracic surgery represents a major hemostatic challenge (19) and is required in upward of 15% of patients admitted to the hospital with ACS (7–9), clinicians are confronted regularly with complex decisions concerning clopidogrel cessation and surgical revascularization. In fact, data from the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines) initiative noted that 30% of patients undergoing CABG received clopidogrel on admission for ACS, and 87% of these patients went to surgery ≤5 days from their last clopidogrel dose (9). Although the ACC/AHA guidelines recommend waiting 5 to 7 days between clopidogrel exposure and CABG, the committee members ask for more data to help dictate patient care (5). To add further complexity to the decision-making process, the recently published TRITON–TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombosis In Myocardial Infarction 38) study (20), showed that prasugrel reduced myocardial infarction compared with clopidogrel, but at a cost of increased major and life-threatening hemorrhage. Among patients undergoing CABG, there was a 10% absolute increase in major bleeding among those receiving at least 1 dose of prasugrel (20). Thus, as for clopidogrel and other platelet antagonists, the role and timing of prasugrel use in the setting of cardiac surgery will need to be investigated thoroughly.

Several studies have evaluated the relationship between clopidogrel exposure and cardiovascular morbidity after CABG. Many of these studies included differing patient populations; 2 studies included patients with non–ST-elevation ACS (9,13), 2 included urgent or emergent CABG (11,12), and 2 included low-risk CABG (10,14). Although not all did (10), most identified a significant association between clopidogrel exposure and major hemorrhage (9,11–14). Nevertheless, only 2 studies reported adjusted rates of major bleeding, with ORs that ranged from 1.4 to 4.2 (9,12). However, no previously published study evaluated the adjusted risk for reoperation. Our study was designed to assess whether exposure to clopidogrel had a significant effect on the risk of major bleeding and reoperation. In the CURE trial (3), patients undergoing CABG who were exposed to clopidogrel within 5 days before surgery experienced a 3.3% absolute increase of major hemorrhagic complications. Moreover, they demonstrated an increased risk for reoperation (relative risk: 1.79, 95% CI: 0.85 to 3.74) (3). The wide confidence interval precluded a firm conclusion from being drawn. An important distinguishing feature between the CURE study and the present study is the time interval between ACS and surgical revascularization. In the CURE study, the mean time

Table 5 **Relationship Between Clopidogrel and Transfusion and Chest Tube Output, Unadjusted**

	Group A (n = 298)	Group B (n = 298)	p Value*
Transfusions, n (%)			
Pre-operative	5 (1.7)	4 (1.3)	0.751
Intraoperative	128 (43.0)	96 (32.2)	0.007
Post-operative	149 (50.0)	106 (35.6)	<0.001
Chest tube output, ml (±SD)			
0–3 h	219.6 (±177.07)	174.01 (±120.3)	0.005
3–6 h	139.9 (±137.77)	114.6 (±94.9)	0.083
6–12 h	181.2 (±260.68)	151.5 (±141.94)	0.979
12–18 h	127.5 (±108.70)	117.0 (±96.68)	0.375
Total	668.3 (±515.50)	557.2 (±339.01)	0.026

*Binary variables compared by chi-square or Fisher exact tests, and continuous variables compared by Student *t* test or Mann-Whitney *U* test for skewed data.

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between ACS and CABG was 25.5 days, whereas in the present analysis, CABG was performed within 7 days of hospitalization or angiography for ACS.

We also assessed the impact of other clinical features on the risk of major bleeding or reoperation. Similar to previous models for bleeding (21,22), we found a significant relationship between older age and female gender on the risk of reoperation and major bleeding. We also found evidence of increased morbidity among patients with a history of alcohol abuse. This finding is consistent with the excess risk of hemorrhagic stroke among patients who are moderate or heavy drinkers (23–26).

Study limitations. Retrospective studies must address concerns about bias (27). We minimized potential bias by accruing the study population from multiple sites, by representing each geographic region in the U.S., and by randomly selecting patients in each cohort and at each site according to prospectively designed inclusion and exclusion criteria to reduce confounders of variability in surgical practice, standards of care, or hospital setting. It is also unlikely that a greater proportion of Group A patients were inherently at greater risk for reoperation given the absence of differences between groups for known risk factors and perioperative characteristics. Although patients in Group A had a greater prevalence of prior myocardial infarction and percutaneous coronary intervention than did patients in Group B, it is unlikely that this small difference accounted for the 5-fold relative odds of reoperation. Our results are not based on patient self-report of clopidogrel cessation before CABG. All patients underwent surgery during their index hospitalization for ACS, providing carefully collected information for abstraction from medical records at each participating institution.

The association we observed between clopidogrel administration and reoperation has several important features of a causal relationship (27). It is strong, time dependent, and biologically plausible. It follows an appropriate temporal sequence, and is supported by previous reports. In addition, the relationship persisted after controlling for a variety of potential confounders.

Conclusions

After ACS, patients who undergo CABG within 5 days of receiving clopidogrel are at increased risk for reoperation, major bleeding, and a prolonged LOS. In multivariate analysis, clopidogrel exposure within 5 days was the strongest predictor of reoperation. For the first time, we clearly demonstrate a relationship between the proximity of clopidogrel exposure to the time of surgery and the risk of reoperation or major bleeding. Nevertheless, these risks must be balanced by the benefits of clopidogrel use demonstrated in randomized clinical trials. Future studies are required to investigate safe and effective strategies to reduce clopidogrel-related perioperative hemorrhagic bleeding complications.

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Key Words: clopidogrel ■ coronary artery bypass graft surgery ■ acute coronary syndrome.

APPENDIX

For a list of hospitals, health care centers, and coinvestigators involved in this study, please see the online version of this article.