Platelet activity measured by a rapid turnaround assay identifies coronary artery bypass grafting patients at increased risk for bleeding and transfusion complications after clopidogrel administration

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Background: We sought to establish a metric for easily estimating bleeding and transfusion risks for cardiac surgery patients after antiplatelet agent use.

Methods: Deidentified records of patients who underwent coronary artery bypass grafting (CABG) at our institution (January 2010-June 2011) were searched for patients without identified risk factors for excessive bleeding who underwent documented $P2Y_{12}$ testing after clopidogrel administration (n = 276). Clinical outcomes were analyzed according to whether preoperative platelet function was higher (platelet reactivity units [PRUs], ≥237) or lower (PRU, <237) and according to preoperative PRU cutoffs: high (>290, or no clopidogrel), intermediate (200-290), or low (<200).

Results: Eighty-five patients (57%) received allogeneic blood products at 24 hours or less postoperatively: 33 (22%) received fresh frozen plasma, and 57 (38%) received platelets. The median 12-hour chest tube output (CTO) was 350 mL (interquartile range, 260-490 mL); CTO was "high" (>437 mL) in 62 (42%) of the clopidogrel-treated patients. Lower-PRU patients were more likely to receive coagulation factors (odds ratio [OR], 2.82; $P = .0004$) and to have high CTO or coagulation factor transfusion (OR, 2.35; $P = .02$) than higher-PRU patients. Likewise, intermediate- and low-PRU patients had incrementally greater incidences of high CTO (OR, 1.72; $P = .002$) and coagulation factor transfusion (OR, 2.08; $P < .0001$) than high-PRU/no clopidogrel patients. High CTO or coagulation factor transfusion was more frequent in intermediate-PRU (OR, 2.67; $P = .02$) and low-PRU (OR, 5.08; $P = .0002$) patients than in high-PRU/no clopidogrel patients.

Conclusions: Among clopidogrel-treated CABG patients, preoperative platelet function testing can identify those at increased risk for postoperative bleeding and transfusion. (J Thorac Cardiovasc Surg 2013;146:1259-66)

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Many patients who undergo open heart surgery are receiving long-term antiplatelet treatment at the time of the procedure because of recent percutaneous coronary intervention (PCI), for acute coronary syndromes, or for other reasons.[1] More specifically, nearly 21% of patients who have undergone PCI subsequently undergo coronary artery bypass grafting (CABG) surgery, and nearly 13% of CABG patients present for surgery while receiving clopidogrel or another adenosine diphosphate inhibitor.[2,3] Patients who undergo CABG while receiving such antiplatelet therapy have been reported to be at an increased risk of bleeding, transfusion complications, reoperation for bleeding, and mortality.[4-8] However, discontinuing antiplatelet therapy may increase patients' risk of ischemic events, including stent thrombosis.[9,10] It is important to balance these risks when deciding whether clopidogrel should be discontinued for a given patient.[1,11-14]

The "2012 ACCF/AHA focused update of the guideline for the management of patients with unstable angina/non-ST-elevation myocardial infarction" recommends withdrawing clopidogrel at least 5 days before CABG.[15] However, there is marked variability in patients' responses to clopidogrel therapy because of variations in patient genotype, as well as other factors.[16-18] This considerable heterogeneity potentially makes it difficult to safely use such an arbitrary interval for discontinuing clopidogrel treatment before CABG without incurring excessive thrombotic or bleeding risks with premature versus excessively delayed discontinuation, respectively.

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Abbreviations and Acronyms

ACCF = American College of Cardiology Foundation
AHA = American Heart Association
BSA = body surface area
CABG = coronary artery bypass grafting
CI = confidence interval
CTO = chest tube output
IQR = interquartile range
OR = odds ratio
PCI = percutaneous coronary intervention
PRU = platelet reactivity units
QA = quality assurance
SBU = Stony Brook University
SQDUG = Surgical Quality Data Users Group
SQIP = Surgical Quality Improvement Program
STS = Society of Thoracic Surgeons

To implement these American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) guidelines optimally, cardiac surgeons need to understand how their patients previously prescribed clopidogrel have responded to it. As part of the preoperative assessment of these patients, platelet functioning tests may be useful in identifying patients whose individual response to clopidogrel treatment puts them at highest risk of bleeding or thrombotic complications. Therefore, the purpose of this study was to identify preoperative "high-risk" cardiac surgery patients from preoperative platelet function testing.

METHODS

Design

As part of the Surgical Quality Improvement Program (SQIP) of the Stony Brook University (SBU) School of Medicine's Division of Cardiothoracic Surgery in the Department of Surgery, an expanded patient registry was designed and authorized by the SBU School of Medicine's Division of Medical and Regulatory Affairs. Under this program, SQIP routinely reported safety and outcomes data for all cardiac surgical patients to the Division of Cardiothoracic Surgery, Department of Surgery, and institutional quality assurance (QA) committees. The SQIP database comprised data from other QA program databases, including the New York State Cardiac Surgery Reporting System and the Society of Thoracic Surgeons (STS) National Adult Cardiac Surgery Database, as well as our cardiac surgery patient records. Moreover, for specific SBU QA projects, supplemental data were extracted from the medical records of surgical patients.

A Surgical Quality Data Users Group (SQDUG) secondarily reviewed and provided approval, as appropriate, of analyses of data extracts from patient records deidentified by the SQIP group, under the SQDUG protocol approved by the SBU School Institutional Review Board (Committee on Research in Human Subjects 170753-5). Under these protocols, this study was approved as a retrospective cohort study using deidentified records that had previously been gathered for QA reporting purposes.

Study Population

Deidentified records were extracted for all patients who underwent a "CABG-only" procedure at our institution from January 2010 to June 2011 (n = 366). These patients underwent coronary bypass procedures either off-pump or with cardiopulmonary bypass and mild to moderate hypothermia according to our clinical standards, including the use of cell salvage. For this SQDUG-approved analysis, records were excluded for patients with an excessive risk of bleeding or transfusion, as established by STS guidelines,[14] including evidence of liver failure, dialysis, or renal dysfunction (creatinine $\geq$ 1.5 mg/dL) (n = 38). Patients were also excluded for nonaspirin, nonclopidogrel glycoprotein IIb/IIIa inhibitor use (n = 8) or clopidogrel use without $P2Y_{12}$ testing (n = 18), or if their record was incomplete (n = 26).

Platelet Functional Monitoring

Preoperative platelet function was assayed using fresh blood samples drawn within 24 hours of surgery by measuring $P2Y_{12}$ receptor blockade with the VerifyNow system (Accumetrics, San Diego, Calif). Technical details have been described elsewhere.[19] For this study, historically reported platelet inhibition levels were converted into the inversely correlated platelet reactivity unit (PRU) scale more recently proposed by the vendor (Appendix 1, available online). A platelet inhibition level of 20% or less, which was previously considered a negligible or "safe" level of platelet inhibition for patients undergoing coronary bypass surgery,[20] was accordingly translated into a PRU threshold of 237 or more (with a receiver-operator characteristic area under the curve of 0.93).

CABG-Related Bleeding Outcomes

Chest tube output (within the first 12 hours postoperatively), intraoperative and postoperative transfusions (within the first 24 hours), bleeding-related complications (eg, reoperation for bleeding), 30-day operative mortality, 30-day readmission, and prolonged postoperative length of stay (greater than the upper 95% confidence limit for the "no clopidogrel" control group) served as the main outcomes for this study. Because patients with no preoperative use of clopidogrel may be regarded as having a "normal" 12-hour chest tube output, this subset's upper limit threshold (95% confidence interval [CI]) was used as the cutoff value to dichotomize a chest tube output that was normal versus significantly higher than normal. In addition to the total units of allogeneic blood product transfused, transfusions were also coded dichotomously with regard to whether any amount of a given product—allogeneic red blood cells, platelets, or fresh frozen plasma—had been transfused intraoperatively or within 24 hours postoperatively. Finally, a composite outcome indicative of surgery-related bleeding events was defined as "high" chest tube output or coagulation product (platelet or fresh frozen plasma) transfusion.

Statistical Analysis: Primary Hypothesis Testing

To test our primary study hypothesis, we divided the patients into 2 groups according to their preoperative platelet function: higher PRU ($\geq$237; ie, the literature-based threshold for bleeding due to platelet dysfunction, equivalent to 0%-20% platelet inhibition) and lower PRU (<237; ie, the literature-based equivalent to platelet inhibition >20%).[20] Outcomes between these groups were compared by using χ^2 and Fisher exact tests. Differences in demographics and preoperative medication use were adjusted for by multivariate logistic regression to determine whether the higher- and lower-PRU groups differed with regard to CABG bleeding-related outcomes. A 95% CI was used. All calculations were performed with SAS, version 9.2, software (SAS Institute, Inc, Cary, NC).

Exploratory Analyses

For supplemental analyses, the PRU predictor variable was recategorized through histogram plotting (Figure 1). A threshold analysis was performed to identify PRU cutoffs to optimize differences between subgroup outcomes using the estimation approach described by Tobin.[21] This analysis separated patients into 3 groups on the basis of platelet function: high-PRU (>290), intermediate-PRU (200-290), and low-PRU (<200). These 3 groups' outcomes were compared by using χ^2, Fisher exact, and

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