Acute Clopidogrel Use and Outcomes in Patients With Non–ST-Segment Elevation Acute Coronary Syndromes Undergoing Coronary Artery Bypass Surgery

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METHODS
We sought to characterize patterns of clopidogrel use before coronary artery bypass grafting (CABG) and examine the drug’s impact on risks for postoperative transfusions among patients with non–ST-segment elevation acute coronary syndromes (NSTE ACS).

BACKGROUND
Adherence in community practice to American College of Cardiology/American Heart Association guidelines for clopidogrel use among NSTE ACS patients has not been previously characterized.

OBJECTIVES
We evaluated 2,858 NSTE ACS patients undergoing CABG at 264 hospitals participating in the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines) Initiative. We examined the patterns of acute clopidogrel therapy and its association with bleeding risks among those having "early" CABG ≤ 5 days and again among those having "late" surgery >5 days after catheterization.

RESULTS
Within 24 h of admission, 852 patients (30%) received clopidogrel. In contrast to national guidelines, 87% of clopidogrel-treated patients underwent CABG ≤ 5 days after treatment. Among those receiving CABG within ≤ 5 days of last treatment, the use of clopidogrel was associated with a significant increase in blood transfusions (65.0% vs. 56.9%, adjusted odds ratio [OR] 1.36, 95% confidence interval [CI] 1.10 to 1.68) as well as the need for transfusion of ≥ 4 U of blood (27.7% vs. 18.4%, OR 1.70, 95% CI 1.32 to 2.19). In contrast, acute clopidogrel therapy was not associated with higher bleeding risks if CABG was delayed >5 days (adjusted OR 1.18, 95% CI 0.54 to 2.58).

CONCLUSIONS
Despite guideline recommendations, the overwhelming majority of NSTE ACS patients treated with acute clopidogrel needing CABG have their surgery within ≤ 5 days of treatment. A failure to delay surgery is associated with increased blood transfusion requirements that must be weighed against the potential clinical and economic impacts of such delays. (J Am Coll Cardiol 2006;48:281–6) © 2006 by the American College of Cardiology Foundation
Abbreviations and Acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>ACC/AHA</td>
<td>American College of Cardiology/American Heart Association</td>
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<tr>
<td>CABG</td>
<td>coronary artery bypass graft</td>
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<tr>
<td>CI</td>
<td>confidence interval</td>
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<tr>
<td>CRUSADE</td>
<td>Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines Initiative</td>
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<tr>
<td>CURE</td>
<td>Clopidogrel in Unstable Angina to Prevent Recurrent Events trial</td>
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<tr>
<td>GP</td>
<td>glycoprotein</td>
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<tr>
<td>NSTE ACS</td>
<td>non–ST-segment elevation acute coronary syndromes</td>
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<tr>
<td>OR</td>
<td>odds ratio</td>
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<tr>
<td>RBC</td>
<td>red blood cell</td>
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<tr>
<td>RR</td>
<td>relative risk</td>
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purposes of this study were to characterize patterns of clopidogrel use before CABG and to examine the time-dependent risks for postoperative transfusion among NSTE ACS patients treated at 264 hospitals participating in the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines) National Quality Improvement Initiative (8,9).

METHODS

Patient population. We reviewed the CRUSADE data from patients with NSTE ACS who underwent CABG surgery during their initial hospital stay. Patients with NSTE ACS were defined as having ischemic symptoms within 24 h of presentation and either ST-segment depression, transient ST-segment elevation, or positive cardiac markers (elevated troponin I or T and/or creatine kinase-MB greater than the upper limit of normal for participating institutions) (8,9). We excluded patients from hospitals without CABG capabilities; patients who were transferred in from other institutions or who were transferred out from the initial institution (because data on presentation characteristics, acute treatments, clinical outcomes, and use and timing of invasive procedures were not available for those patients); patients in whom information on clopidogrel treatment was not available; and those who received transfusion before CABG.

Of a total of 42,156 patients with NSTE ACS admitted to CABG-capable hospitals, 3,977 (9.4%) underwent CABG between January 2003 and September 2004 in 264 hospitals participating in the CRUSADE Initiative. After allowing for the aforementioned exclusions, 2,858 patients undergoing CABG constituted the study population for this analysis.

Data collection. The institutional review board of each institution approved participation in the CRUSADE Initiative. Data were collected in an anonymous fashion during the initial hospitalization and included baseline clinical characteristics, use of acute medications (<24 h of hospital arrival), contraindications to specific therapies, use and timing of invasive cardiac procedures, laboratory results, in-hospital clinical outcomes, and discharge therapies and interventions.

Statistical analysis. Patients were divided into four groups for analysis: Specifically, we looked at patients receiving clopidogrel therapy or not among those going to CABG “early,” i.e., within 5 days of cardiac catheterization. We also examined the effects of clopidogrel therapy on outcomes among those going to “late CABG” defined as more than 5 days after catheterization. In these analyses, we conservatively assumed that the use of clopidogrel initiated acutely was continued until the time of cardiac catheterization but stopped afterwards (when coronary anatomy became known and treatment plans for CABG were formulated).

Continuous variables were described using mean or median values, and categorical variables were described as percentages. The Wilcoxon test was used to test for differences in continuous variables, and the chi-square test was used to detect global differences in categorical variables. We used generalized estimating equations to determine the effect of the use and timing of clopidogrel on the need for red blood cell (RBC) transfusions and the number of units transfused (10). Both models were adjusted for age, baseline hematocrit, gender, and signs of congestive heart failure on presentation. Also, for the need for transfusion outcome, we adjusted for body mass index, previous percutaneous coronary intervention, previous congestive heart failure, renal insufficiency, heart rate, and positive cardiac markers. For the RBC units’ transfused outcome, we adjusted for blood pressure and hospital region. Race, insurance status, family history of coronary artery disease, ST-segment deviation, diabetes, current/recent smoking, hypercholesterolemia, previous myocardial infarction, previous stroke, hypertension, previous CABG, specialty of the caring physician, availability of cardiac catheterization laboratories and revascularization procedures, and academic status of the hospital were nonsignificant in both models and, thus, no adjustments were made for these variables. Two sets of pair-wise adjusted comparisons were made to examine the effects of clopidogrel therapy versus not among the “early CABG” group (within 5 days) and the “late CABG group” (>5 days). A p value of <0.05 was established as the level of statistical significance for all tests. All statistical analyses were performed using SAS software (version 8.2, SAS Institute, Cary, North Carolina).

RESULTS

Of the 2,858 patients in our study, 852 (30%) received clopidogrel within 24 h of their admission. Of those patients treated with clopidogrel, 739 (87%) underwent CABG within 5 days of their last dose of clopidogrel, whereas the remaining 113 (13%) underwent CABG surgery >5 days after discontinuing clopidogrel. Similarly, the
majority of patients not treated with clopidogrel underwent CABG >5 days of their cardiac catheterization (91%).

The baseline clinical characteristics of the 4 patient groups are shown in Table 1. Patients who underwent CABG >5 days with or without clopidogrel had more high-risk features, including older age, a history of previous revascularization, previous stroke, renal insufficiency, and a higher prevalence of diabetes compared with the respective group of patients undergoing early CABG with or without clopidogrel. Patients with delayed surgery also were more likely to present with clinical characteristics associated with a greater risk of adverse outcomes, such as signs of congestive heart failure, higher heart rate, positive cardiac enzymes, or severe left ventricular systolic dysfunction. In contrast, there were no significant differences between the clinical characteristics and presenting features of patients who did not receive clopidogrel and underwent early CABG and those who received CABG within 5 days of clopidogrel. Similarly, there were no significant differences in the baseline and presenting clinical features between patients undergoing late CABG with and without clopidogrel. Although the use of acute medications was similar in the four groups of patients, those who received clopidogrel within 5 days of CABG surgery were more likely to receive intravenous glycoprotein (GP) IIb/IIIa inhibitors (Table 2).

The proportion of patients requiring RBC transfusion in the four groups is as shown in Table 3. Among the early CABG group, clopidogrel therapy was associated with a significant increased need for RBC transfusion compared with those not receiving clopidogrel. This difference persisted after adjusting for differences in baseline clinical factors between the two groups (adjusted odds ratio [OR] 1.36, 95% confidence interval [CI] 1.10 to 1.68). If a higher cutpoint is used, 28% of patients receiving clopidogrel within 5 days of CABG required four or more units of RBCs compared with only 18% of patients not treated with clopidogrel and undergoing early surgery (adjusted OR 1.70, 95% CI 1.32 to 2.19). More patients who had CABG within 5 days of clopidogrel received any platelet transfusion (33.7%) compared with those not treated with clopidogrel and undergoing early CABG (22.3%; mean platelet units transfused 1.33 vs. 0.76, median 0 in both groups).

In contrast to these results, among those in whom CABG was delayed >5 days after catheterization, acute clopidogrel therapy was not associated with increased need for transfusion (adjusted OR 0.81, 95% CI 0.44 to 1.48) or at risk for large transfusions of four or more units of RBCs (adjusted OR 1.18, 95% CI 0.54 to 2.58). No difference was observed in the need for platelet transfusions in the two late CABG groups (Table 3).
Death rates generally were low in this population (Table 3). After adjusting for baseline clinical factors, there was no difference in in-hospital mortality in patients treated with clopidogrel versus not among those having early CABG surgery within 5 days of catheterization (adjusted OR 1.31, 95% CI 0.79 to 2.19). Among those undergoing CABG within 5 days after catheterization, the in-hospital death rates were 5.3% versus 3.9% in the clopidogrel versus no-clopidogrel-treated patients. The small number of patients in these two late CABG groups precluded any multivariable adjustments. Other adjusted outcome measures such as death or nonfatal myocardial infarction, and cardiogenic shock were also similar in the two clopidogrel groups compared with the respective two no-clopidogrel groups. The median post-CABG length of stay was also similar in the four groups.

Because those patients receiving clopidogrel and early CABG also were more likely to be treated acutely with a GP IIb/IIIa inhibitor, a factor that may increase the risk for perioperative bleeding after early CABG (11), we performed a sensitivity analysis by excluding all patients treated within 18 h of surgery with a GP IIb/IIIa receptor antagonist. This interval was chosen to be consistent with the pharmacological impact of these agents on bleeding risks with surgery. This exclusion had a limited effect on the results, as patients receiving clopidogrel and early CABG continued to show an increased risk of requiring RBC transfusions compared with the early CABG-no clopidogrel group (adjusted OR 1.37, 95% CI 1.08 to 1.75). Similarly, if we extended our analysis to exclude all patients receiving GP receptor antagonists any time before their CABG, those receiving clopidogrel 5 days before CABG continued to have a greater need for transfusions compared with the early CABG-no clopidogrel group (adjusted OR 1.74, 95% CI 1.32 to 2.29).

**DISCUSSION**

Our analysis is the first to provide insight into patterns of clopidogrel use and outcomes in the setting of CABG performed on patients with NSTE ACS. We found that as many as 30% of patients currently receive clopidogrel before CABG surgery within 5 days of catheterization (adjusted OR 1.31, 95% CI 0.79 to 2.19). Among those undergoing CABG within 5 days of catheterization, the in-hospital death rates were 5.3% versus 3.9% in the clopidogrel versus no-clopidogrel-treated patients. The small number of patients in these two late CABG groups precluded any multivariable adjustments. Other adjusted outcome measures such as death or nonfatal myocardial infarction, and cardiogenic shock were also similar in the two clopidogrel groups compared with the respective two no-clopidogrel groups. The median post-CABG length of stay was also similar in the four groups.

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### Table 2. Acute Care (<24 h) Patterns and In-Hospital Procedures by Clopidogrel Use in Patients Undergoing CABG Surgery*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No Clopidogrel (n = 1,826)</th>
<th>Clopidogrel (n = 739)</th>
<th>No Clopidogrel (n = 180)</th>
<th>Clopidogrel (n = 113)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>94.9</td>
<td>96.6</td>
<td>90.5</td>
<td>95.5</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>88.2</td>
<td>89.0</td>
<td>87.4</td>
<td>95.2</td>
</tr>
<tr>
<td>Heparin—any</td>
<td>92.2</td>
<td>93.1</td>
<td>92.5</td>
<td>92.0</td>
</tr>
<tr>
<td>Unfractionated heparin</td>
<td>54.2</td>
<td>53.4</td>
<td>59.8</td>
<td>44.6</td>
</tr>
<tr>
<td>LMWH</td>
<td>46.0</td>
<td>49.3</td>
<td>45.4</td>
<td>53.6</td>
</tr>
<tr>
<td>GP IIb/IIIa inhibitor</td>
<td>39.2</td>
<td>45.0</td>
<td>36.1</td>
<td>40.8</td>
</tr>
<tr>
<td>Arrival to CABG‡</td>
<td>69 (40, 104)</td>
<td>73 (44, 104)</td>
<td>193 (162, 236)</td>
<td>203 (164, 251)</td>
</tr>
<tr>
<td>Number of diseased vessels</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>22.8</td>
<td>27.9</td>
<td>21.5</td>
<td>28.2</td>
</tr>
<tr>
<td>3</td>
<td>72.1</td>
<td>65.7</td>
<td>72.9</td>
<td>59.1</td>
</tr>
<tr>
<td>Moderate (25%–40%)</td>
<td>17.2</td>
<td>16.7</td>
<td>27.7</td>
<td>27.9</td>
</tr>
<tr>
<td>Severe (&lt;25%)</td>
<td>3.7</td>
<td>3.1</td>
<td>12.7</td>
<td>9.0</td>
</tr>
</tbody>
</table>

Data presented as percentages except where indicated. *Among patients without listed contraindications. †From the time of cardiac catheterization. ‡Presented as median (interquartile range).

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### Table 3. In-Hospital Outcomes by Clopidogrel Use in Patients Undergoing CABG Surgery

<table>
<thead>
<tr>
<th>Hospital Outcomes</th>
<th>Early CABG ≤5 Days*</th>
<th>Late CABG &gt;5 Days*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any RBC transfusion</td>
<td>56.9</td>
<td>65.0</td>
</tr>
<tr>
<td>RBC transfusion &gt;4 U</td>
<td>18.4</td>
<td>27.7</td>
</tr>
<tr>
<td>RBC units transfused†</td>
<td>1.0 (0, 3)</td>
<td>2.0 (0, 4)</td>
</tr>
<tr>
<td>Any platelet transfusion</td>
<td>20.3</td>
<td>33.7</td>
</tr>
<tr>
<td>Death</td>
<td>2.9</td>
<td>3.5</td>
</tr>
<tr>
<td>Death or reinfarction</td>
<td>5.7</td>
<td>5.0</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
<td>4.2</td>
<td>3.8</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.4</td>
<td>1.6</td>
</tr>
<tr>
<td>Length of stay (days)†</td>
<td>9.0 (7, 13)</td>
<td>9.0 (7, 12)</td>
</tr>
<tr>
<td>Length of stay post-CABG (days)†</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>

Data presented as percentages except where indicated. *From the time of cardiac catheterization. †Presented as median (interquartile range).
CABG surgery, and, of these, nearly 90% have surgery within 5 days of treatment, contrary to the ACC/AHA guidelines recommendations. Our data also showed that the performance of CABG within 5 days of clopidogrel treatment is associated with an increase in the proportion of patients requiring blood transfusion and a greater number of packed RBC units transfused. We confirmed that rate of transfusion requirement returned to normal (vs. rate of patients not treated with clopidogrel) if surgery was delayed >5 days after clopidogrel was stopped, results similar to those observed in the CURE study (1,7). Thus, our data support the ACC/AHA guidelines recommendations that encourage the discontinuation of clopidogrel >5 days before CABG to minimize the perioperative bleeding risk and the need for blood transfusion.

It could be hypothesized that the rush to early CABG is related to the high-risk features or unstable presenting features of the patients. However, contrary to these expectations, patients undergoing CABG within 5 days of clopidogrel treatment did not differ significantly from those who did not receive clopidogrel and underwent early CABG in the presence of high-risk features, such as diabetes, previous revascularization, prior stroke, and renal insufficiency, and with unstable presenting features, such as signs of congestive heart failure, higher heart rate, and elevated cardiac enzymes. This finding suggests that surgery was electively performed sooner than is recommended after the discontinuation of clopidogrel in the vast majority of patients. We did not collect information on the reasons for early or late surgery in patients receiving clopidogrel and thus can only speculate as to why this occurs. Higher-risk patients on clopidogrel wait longer for CABG because physicians may need more time to discuss the risks with them and their families, they may want the patients to be more stable before surgery, or they may hope to provide the best milieu to the patient while awaiting surgery. Data from the CURE trial suggest that the use of clopidogrel in patients with NSTE ACS is associated with very early effects on various outcome measures. Thus, the use of clopidogrel was associated with a lower incidence of in-hospital events, including myocardial infarction (relative risk [RR], 0.60; 95% CI 0.48 to 0.76), severe ischemia (RR, 0.74; 95% CI 0.61 to 0.90; p = 0.003) or recurrent angina (RR, 0.91; 95% CI 0.85 to 0.98; p = 0.01) (1,7). Our observational study, however, was not able to confirm these benefits because we did not have systematic postprocedural enzyme measurements or a rigorous clinical trials event committee. Additionally, the benefits of delaying CABG surgery for >5 days after the administration of clopidogrel must be weighed against the potential risks of events while waiting as well as the economic consequences of extended hospital length of stay.

**Study limitations.** First, we considered the time between cardiac catheterization and CABG surgery as a proxy for the time between the discontinuation of clopidogrel and CABG because the exact time of discontinuation of clopidogrel before CABG was not available. Second, we did not collect data on the incidence of re-exploration after CABG, although this has been done in previous studies (2–6). However, consistent with previous studies, when we looked at RBC transfusions requiring four or more units as a surrogate for reoperation, the risk was higher among patients on clopidogrel undergoing early CABG compared with those undergoing early CABG but not receiving clopidogrel. Third, serial hemoglobin values were not collected in our dataset at the time of the initiation of the CRUSADE Initiative, and therefore we are unable to provide the actual values of hemoglobin/hematocrit that led to transfusions. However, the similar levels of nadir hematocrit post-CABG in the four groups suggest that perhaps the threshold for transfusion was not significantly different.
between the four groups (median nadir hematocrit post-
CABG among patients who received any RBC transfusion-
clopidogrel/early CABG group 25.1 %, clopidogrel/late
CABG group 25.6%, no-clopidogrel/early CABG group
25.8%, and no-clopidogrel/late CABG group 25.9%). Per-
haps other factors besides nadir hematocrit may be impor-
tant in determining RBC transfusions, such as rate of
bleeding or hemodynamic instability. Fourth, our compar-
sions of clinical outcomes by treatment strategy were obser-
vational. Although we adjusted all comparisons for baseline
clinical factors, we cannot exclude any persistent unmea-
sured confounding. Nonetheless, because a randomized
clinical trial evaluating the benefits and risks of patients
undergoing early versus late CABG is unlikely to be
undertaken as most physicians would consider this to be
unethical in view of data from the CURE trial (1,7), this
study is the first to provide insight into the scope of this
issue at a national level.

Conclusions. When CABG is required, the majority
(87%) of patients treated with acute clopidogrel did not have
their surgery delayed for the recommended 5-day interval,
contrary to current ACC/AHA guidelines. These patients
demonstrated an increase in bleeding complications com-
pared with patients who did not receive clopidogrel and
underwent early CABG. However, these bleeding risks
must be weighed against the benefits of clopidogrel use
demonstrated in randomized clinical trials, as well as against
the economic impact of delaying CABG surgery.

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