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# Outcomes Following Pre-Operative Clopidogrel Administration in Patients With Acute Coronary Syndromes Undergoing Coronary Artery Bypass Surgery

## The ACUITY (Acute Catheterization and Urgent Intervention Triage strategY) Trial

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**Objectives** This study sought to evaluate the impact of upstream clopidogrel in patients with non–ST-segment elevation acute coronary syndromes (NSTE-ACS) requiring coronary artery bypass grafting (CABG) from the ACUITY (Acute Catheterization and Urgent Intervention Triage strategY) trial.

**Background** Despite benefits of clopidogrel in patients with NSTE-ACS undergoing percutaneous coronary intervention, this agent is often not administered upstream (before angiography) as recommended by the American College of Cardiology/American Heart Association guidelines because of potential bleeding in the minority of patients who require CABG.

**Methods** The ACUITY trial enrolled 13,819 patients with NSTE-ACS undergoing early invasive management. The timing of clopidogrel initiation was per investigator discretion. A 5-day washout period before CABG was recommended for patients having received clopidogrel.

**Results** Of 13,819 patients enrolled, 1,539 (11.1%) underwent CABG before discharge. Clopidogrel-exposed patients had a longer median duration of hospitalization (12.0 days vs. 8.9 days, $p < 0.0001$), but fewer adverse composite ischemic events (death, myocardial infarction, or unplanned revascularization) at 30 days; 12.7% vs. 17.3%, $p = 0.01$), with nonsignificantly different rates of non–CABG-related major bleeding (3.4% vs. 3.2%, $p = 0.87$) and post-CABG major bleeding (50.3% vs. 50.9%, $p = 0.83$) compared with those patients not administered clopidogrel. By multivariable analysis, clopidogrel use before CABG was an independent predictor of reduced 30-day composite ischemia (odds ratio: 0.67, 95% confidence interval: 0.48 to 0.92, $p = 0.001$) but not of increased post-CABG major bleeding (odds ratio: 0.98, 95% confidence interval: 0.80 to 1.19, $p = 0.80$).

**Conclusions** Clopidogrel administration before catheterization in patients with NSTE-ACS requiring CABG is associated with significantly fewer 30-day adverse ischemic events without significantly increasing major bleeding, compared to withholding clopidogrel until after angiography. These findings support the American College of Cardiology/American Heart Association guidelines for upstream clopidogrel administration in all NSTE-ACS patients, including those who subsequently undergo CABG. (Comparison of Angiomax Versus Heparin in Acute Coronary Syndromes [ACS]; NCT00093158).
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**Abbreviations and Acronyms**

**ACC** = American College of Cardiology
**ACS** = acute coronary syndromes
**AHA** = American Heart Association
**CABG** = coronary artery bypass grafting
**CI** = confidence interval
**CPK** = creatine phosphokinase
**GP** = glycoprotein
**MI** = myocardial infarction
**NACE** = net adverse clinical events
**NSTE** = non–ST-segment elevation
**NSTEMI** = non–ST-segment elevation myocardial infarction
**OR** = odds ratio
**PCI** = percutaneous coronary intervention
**STS** = Society of Thoracic Surgeons
**UFH** = unfractionated heparin
**ULN** = upper limit of normal

The American College of Cardiology (ACC) and American Heart Association (AHA) guidelines for patients presenting with non–ST-segment elevation (NSTE) acute coronary syndromes (ACS) recommend early/upstream dual antiplatelet therapy with aspirin and either clopidogrel or a glycoprotein (GP) IIb/IIIa inhibitor (1,2). However, for patients in whom an early invasive management strategy is planned, many physicians withhold upstream clopidogrel therapy until after coronary angiography because of potential bleeding complications that might occur in the approximately 10% of patients who require coronary artery bypass grafting (CABG) (3–5). The impact of upstream clopidogrel administration for patients with NSTE-ACS undergoing CABG has not been studied in a contemporary randomized trial. Several, mostly small, retrospective, nonrandomized studies have reported higher transfusion and reexploration rates for patients undergoing CABG after exposure to clopidogrel (6–11). Based on these limited data, the Society of Thoracic Surgeons (STS) and ACC/AHA guidelines recommend cessation of clopidogrel for 5 to 7 days in patients undergoing nonemergent CABG (1,2,12). Moreover, although upstream dual-antiplatelet therapy reduces ischemic end points in patients with NSTE-ACS treated medically or with percutaneous coronary intervention (PCI) (13,14), whether administration of platelet inhibitors before CABG improves clinical outcomes has not been extensively studied.

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In the present analysis, we examined the subgroup of patients enrolled in the ACUITY (Acute Catheterization and Urgent Intervention Triage strategY) trial (a large, prospective, randomized trial of 13,819 patients with moderate- and high-risk NSTE-ACS undergoing early invasive management) who after diagnostic angiography were subsequently managed by CABG (4). We sought to evaluate: 1) the effect of clopidogrel administration before surgery on ischemic and bleeding outcomes and length of stay; and 2) the impact of clopidogrel administration before CABG and the timing of CABG on clinical outcomes in the surgical population.

## Methods

**Study design and analysis.** The study design and principal results from the ACUITY trial have been published (4,15). Briefly, 13,819 patients with NSTE-ACS undergoing an early invasive management strategy were randomly assigned to 1 of 3 antithrombotic regimens: heparin (unfractionated heparin [UFH] or enoxaparin) plus a GP IIb/IIIa inhibitor (the control group), bivalirudin plus a GP IIb/IIIa inhibitor, or bivalirudin monotherapy. The study was approved by the institutional review board or ethics committee at each participating center, and all patients signed written, informed consent.

Coronary angiography was required within 72 h of randomization with subsequent triage to PCI, CABG, or medical management per standard of care. Aspirin (300 to 325 mg orally or 250 to 500 mg intravenously) was administered before angiography. Clopidogrel dosing and timing were left to the discretion of each investigator, but in patients undergoing PCI, the protocol required 300 mg clopidogrel in all cases no later than 2 h after PCI. Clopidogrel 75 mg daily was recommended for 1 year in all patients after PCI, and aspirin 75 to 325 mg daily indefinitely. The exact first dose of clopidogrel and the total duration of that dose were recorded in the case report form only for those patients receiving the initial dose of clopidogrel after randomization; this information was not available for patients maintained on clopidogrel before admission. For patients who received clopidogrel before angiography and in whom CABG was subsequently planned, a 5-day clopidogrel washout period was recommended before surgery.

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All patients undergoing CABG received UFH as the anticoagulant, with dosing per standard institutional practice. For patients randomized to bivalirudin, the drug was to be discontinued for at least 1 h before surgery. Patients randomized to UFH continued on the drug per standard practice. For patients receiving enoxaparin and undergoing elective CABG, the drug was to be stopped for at least 8 h before surgery. For those patients randomized to enoxaparin requiring emergency CABG, the drug was to be stopped for at least 8 h before surgery if possible.

The primary analysis of interest was the determination of 30-day and 1-year outcomes in patients exposed to clopidogrel before CABG versus those in whom CABG was performed without clopidogrel exposure. Patients were defined as exposed to clopidogrel before CABG if they were taking clopidogrel on a regular basis before hospitalization or received clopidogrel in-hospital at any time before CABG. As a secondary analysis, in the subset of patients who received clopidogrel before surgery, we assessed outcomes in patients who underwent CABG within 5 days of the last dose of clopidogrel (the early group) versus those who had CABG more than 5 days after the last dose of clopidogrel (the late group). If clopidogrel was administered after randomization, the exact time of the last dose was used as the stop time. If the last dose of clopidogrel was administered before randomization, the time of randomization was used as the stop time. If clopidogrel exposure was before hospitalization, stop time was counted as the same day as hospitalization.

**End points.** End points assessed in the present analyses included the 3 ACUITY trial 30-day primary end points: 1) composite ischemia (defined as death from any cause, myocardial infarction [MI], or unplanned revascularization for ischemia); 2) non–CABG-related major bleeding (defined as intracranial or intraocular bleeding, access site hemorrhage requiring intervention, ≥5 cm diameter hematoma, reduction in hemoglobin of ≥4 g/dl without or ≥3 g/dl with an overt bleeding source, reoperation for bleeding, or blood product transfusion); and 3) net adverse clinical events (NACE) (composite ischemia or non–CABG-related major bleeding). An MI before angiography in patients without non–ST-segment elevation myocardial infarction (NSTEMI) at admission was defined as any elevation of troponin or creatine phosphokinase (CPK)-MB greater than the upper limit of normal (ULN) (or CPK >ULN in the absence of MB determination). In patients with NSTEMI at presentation, in whom the elevated troponin or CPK-MB (or CPK) levels were documented to be decreasing or had returned to normal, diagnosis of a second infarction required: 1) a new elevation of troponin or CPK-MB >ULN (or CPK >ULN in the absence of MB determination) if the troponin or CPK-MB (or CPK) level had returned to <ULN; or 2) an increase by >50% above the previous nadir level if the troponin or CPK-MB (or CPK) level had not returned to <ULN. In patients with NSTEMI at presentation, in whom the peak troponin or CPK-MB (or CPK) had not yet been reached, diagnosis of a second infarction required: 1) recurrent chest pain ≥30 min; or 2) new electrocardiographic changes consistent with MI; and 3) the next troponin or CPK-MB (or CPK) level measured approximately 8 to 12 h after the event was elevated by at least 50% above the previous level. In patients undergoing CABG, diagnosis of MI required: 1) any CPK-MB ≥10× ULN (or CPK ≥10× ULN in the absence of MB determination) within 24 h of CABG and increased at least 50% over the most recent pre-CABG levels; or 2) any CPK-MB ≥5× ULN (or CPK ≥5× ULN in the absence of MB determination) within 24 h of CABG and increased at least 50% over the most recent pre-CABG levels and new, significant (≥0.04 s) Q waves in ≥2 contiguous electrocardiograph leads.

Composite ischemia and mortality were measured up to 1 year, whereas bleeding end points were assessed up to 30 days. Data on adverse events specific to CABG were also collected and analyzed, including the rates of post-CABG major bleeding (classified similarly to non–CABG-related major bleeding but occurring in the post-CABG period), post-CABG transfusions, reoperation for bleeding, and 24-h chest tube output. Data on length of hospital stay were also collected. All primary end points were adjudicated by a blinded clinical events committee, with the exception of the CABG-related bleeding end points.

**Statistical analysis.** Continuous variables were summarized by means, standard deviation, medians, interquartile ranges, and minimum and maximum values. Categorical variables were summarized by frequencies and percentages. Missing or unknown data values were not imputed unless otherwise specified, and denominators of categorical variables excluded unknown or missing values. Categorical variables were compared using chi-square statistics. A nonparametric Wilcoxon rank sum test was used for comparison of continuous variables. Pairwise comparisons among 3 groups were made without adjustment for multiple comparisons. A value of $p < 0.05$ was considered statistically significant.

Multivariable logistic regression analysis was performed to adjust for potential baseline differences between groups. Covariates were selected using a forward stepwise procedure from a large number of candidate variables using $p < 0.15$ as the criterion for entry into the model and $p < 0.10$ to allow a variable to stay in the model. Candidate variables included actual procedure performed, age ≥65 years, anemia, baseline creatine kinase-MB/troponin elevation, baseline creatinine clearance <60 ml/min, electrocardiographic changes at baseline, diabetes mellitus, sex, hyperlipidemia, hypertension, pre-CABG clopidogrel use, prior MI, prior PCI, prior CABG, randomization to bivalirudin versus heparin plus GP IIb/IIIa inhibitor, and enrollment in the U.S. The adjusted p values, odds ratios (ORs), and corresponding 2-sided 95% confidence intervals (CIs) were computed for these variables. Separate models were run to evaluate predictors of 30-day composite ischemia, non–

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CABG-related major bleeding, and post-CABG major bleeding. Pre-CABG clopidogrel use, the primary interest variable, was forced into each of the models. All statistical analyses were performed using SAS version 8.2 (SAS Institute Inc., Cary, North Carolina).

## Results

**Study population.** Of the 13,819 NSTE-ACS patients enrolled in the ACUITY trial, 1,539 patients (11.1%) underwent CABG. Of these, 1,298 patients (84.3%) had on-pump surgery, 196 (12.7%) had off-pump surgery, and 37 (2.4%) had off-pump surgery that was converted intraoperatively to on-pump surgery. Patients who received ticlopidine (n = 19) were excluded from the analysis. The study cohort thus consists of 1,520 patients with NSTE-ACS undergoing CABG after diagnostic angiography. Follow-up at 1 year was obtained in 91.8% (1,396 of 1,520) of patients.

**Impact of clopidogrel administration before CABG.** Of the 1,520 study patients, 773 (50.9%) received clopidogrel before CABG and 747 (49.1%) did not. Of the 773 patients exposed to clopidogrel, 73 received it before hospitalization only, 157 received it before hospitalization and in hospital, and 543 received clopidogrel in hospital only. Baseline characteristics were similar between the 2 groups (Table 1), although patients who received clopidogrel more often had a history of hypertension ($p = 0.03$). The incidence of clopidogrel use in patients undergoing CABG was significantly higher in patients enrolled outside of the U.S. (non-U.S.) as opposed to U.S. patients (70.3% vs. 36.1%, $p < 0.0001$). The mean (± SD) time from coronary angiography to surgery was 5.0 ± 5.3 days in the clopidogrel-treated group versus 3.0 ± 4.1 days in the non–clopidogrel-treated group ($p < 0.0001$). Patients exposed to clopidogrel before CABG also had a significantly longer total median duration of hospitalization (12.0 days vs. 8.9 days, $p < 0.0001$), because of longer median pre-CABG (4.2 days vs. 2.5 days, $p < 0.0001$) and post-CABG (6.9 days vs. 5.8 days, $p < 0.0001$) lengths of stay.

Unadjusted 30-day results showed significantly lower rates of composite ischemia in patients who received compared with those who did not receive clopidogrel before surgery (12.7% vs. 17.3%, respectively, $p = 0.01$) because of significantly fewer MIs in clopidogrel-treated patients (8.8% vs. 14.5%, $p = 0.0006$), with comparable rates of death and unplanned revascularization (Table 2). The rates of non–CABG-related major bleeding were also similar in patients who did and did not receive clopidogrel before CABG (3.4% vs. 3.2%, respectively, $p = 0.87$). As a result, NACE occurred less frequently in patients exposed to clopidogrel before CABG (15.4% vs. 19.4%, $p = 0.04$). The incidence of post-CABG major bleeding (50.3% vs. 50.9%, $p = 0.83$), blood transfusion (38.4% vs. 38.4%, $p = 1.00$), reoperation for bleeding (1.3% vs. 1.3%, $p = 0.94$), and 24-h chest tube output (590 ml vs. 551 ml, $p = 0.52$) were similar in those patients who did and did not receive clopidogrel before CABG, respectively (Table 2). When the definition of clopidogrel exposure was changed to those who received in-hospital clopidogrel but not before hospitalization (n = 543) or those who received in-hospital clopidogrel regardless of receiving clopidogrel before hospitalization (n = 700), the above analysis showed a similar significant reduction in 30-day ischemic outcomes in those exposed to clopidogrel without a significant increase in non–CABG-

**Table 1** Demographic and Baseline Characteristics of Patients Undergoing CABG According to Clopidogrel Exposure Before Surgery

| | Clopidogrel Before CABG (n = 773) | No Clopidogrel Before CABG (n = 747) | p Value |
|---|---|---|---|
| Age, yrs, median (range) | 65 (33–87) | 64 (35–90) | 0.66 |
| Female | 180/773 (23.3) | 173/747 (23.2) | 0.95 |
| Diabetes | 263/773 (34.0) | 254/747 (34.0) | 1.00 |
| Renal insufficiency* | 132/730 (18.1) | 136/696 (19.5) | 0.48 |
| Hypertension | 537/773 (69.5) | 475/747 (63.6) | 0.03 |
| Current smoker | 213/773 (27.6) | 209/747 (28.0) | 0.19 |
| Prior MI | 197/773 (25.5) | 168/747 (22.5) | 0.13 |
| Prior PCI | 188/773 (24.3) | 150/747 (20.1) | 0.07 |
| Prior CABG | 44/773 (5.7) | 28/747 (3.7) | 0.20 |
| High risk† | 644/751 (85.8) | 610/709 (86.0) | 0.88 |
| Elevated cardiac biomarkers | 533/723 (73.7) | 511/696 (73.4) | 0.90 |
| ECG changes | 399/773 (51.6) | 353/747 (47.3) | 0.09 |
| Aspirin use before CABG | 759/773 (98.2) | 727/747 (97.3) | 0.25 |
| GP IIb/IIIa inhibitor use before CABG | 317/773 (41.0) | 308/747 (41.2) | 0.93 |
| Discharged on aspirin | 706/773 (91.3) | 695/747 (93.0) | 0.22 |
| Discharged on clopidogrel | 507/773 (65.6) | 110/747 (14.7) | <0.0001 |
| Non-U.S. | 461/773 (59.6) | 195/747 (26.1) | <0.0001 |

Values are presented as n/N (%) unless otherwise specified. *Renal insufficiency was defined as calculated creatinine clearance <60 ml/min. †High risk was defined as: creatine kinase-MB or troponin elevation or ST-segment deviation.

CABG = coronary artery bypass grafting; ECG = electrocardiographic; GP = glycoprotein; MI = myocardial infarction; PCI = percutaneous coronary intervention.

**Table 2** Clinical Outcomes at 30 Days and 1 Year in Patients Undergoing CABG According to Clopidogrel Exposure Before Surgery

| | Clopidogrel Before CABG (n = 773) | No Clopidogrel Before CABG (n = 747) | p Value |
|---|---|---|---|
| 30-day clinical outcomes | | | |
| Net adverse clinical events | 119 (15.4) | 145 (19.4) | 0.04 |
| Composite ischemia | 98 (12.7) | 129 (17.3) | 0.01 |
| Death | 30 (3.9) | 29 (3.9) | 1.00 |
| Myocardial infarction | 68 (8.8) | 108 (14.5) | 0.0006 |
| Unplanned revascularization | 16 (2.1) | 7 (0.9) | 0.07 |
| Non–CABG-related major bleeding | 26 (3.4) | 24 (3.2) | 0.87 |
| All major bleeding, post-CABG | 389 (50.3) | 380 (50.9) | 0.83 |
| Transfusion | 297 (38.4) | 287 (38.4) | 1.00 |
| Reoperation for bleeding | 10 (1.3) | 10 (1.3) | 0.94 |
| 24-h chest tube output, ml, median (IQR) | 590 (350–860) | 551 (350–880) | 0.52 |
| Total length of stay, days, median | 12.0 | 8.9 | <0.0001 |
| Pre-CABG length of stay | 4.2 | 2.5 | <0.0001 |
| Post-CABG length of stay | 6.9 | 5.8 | <0.0001 |
| 1-year clinical outcomes | | | |
| Composite ischemia | 142 (18.4) | 160 (21.4) | 0.14 |
| Death | 54 (7.0) | 46 (6.2) | 0.52 |

Values are presented as n (%) unless otherwise specified.
IQR = interquartile range; other abbreviations as in Table 1.

related major bleeding (data not shown). At 1 year, the rates of composite ischemia and death were not significantly different between the 2 groups (Table 2).

By multivariable analysis, clopidogrel administration before CABG was an independent predictor of freedom from composite ischemia at 30 days (OR: 0.67, 95% CI: 0.48 to 0.92, p = 0.001) (Fig. 1), with a nonsignificant trend present for reduced 1-year adverse ischemic events in clopidogrel-exposed CABG patients (OR: 0.77, 95% CI: 0.59 to 1.01, p = 0.06). Other variables identified as independent predictors of higher 30-day composite ischemia included hypertension and prior CABG. The geographic location of patients (U.S. vs. non-U.S.) was not an independent predictor of 30-day composite ischemia. Interaction analysis for rates of clopidogrel exposure in U.S. versus non-U.S. population showed nonsignificant results. Clopidogrel use before CABG was not independently correlated with non–CABG-related major bleeding (OR: 1.04, 95% CI: 0.59 to 1.87, p = 0.87) or with post-CABG major bleeding (OR: 0.98, 95% CI: 0.80 to 1.19, p = 0.80) (Fig. 1).

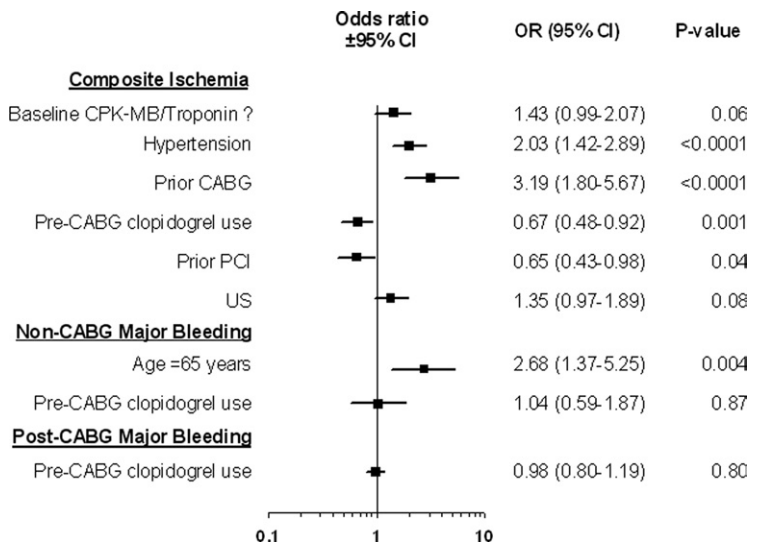


**Figure 1** Predictors of Composite Ischemia

Multivariable predictors of 30-day composite ischemia, major bleeding not related to coronary artery bypass graft (CABG), and post-CABG major bleeding. A separate model, with pre-CABG clopidogrel use forced in, was run for each of the outcomes. CI = confidence interval; OR = odds ratio; PCI = percutaneous coronary intervention.

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**Table 3** Demographic and Baseline Characteristics of Patients by Use and Timing of Clopidogrel in Relation to CABG

| | Clopidogrel Use and Early CABG (<5 days) (n = 524) | Clopidogrel Use and Late CABG (≥5 days) (n = 249) | p Value* | No Clopidogrel (n = 747) | p Value† | p Value‡ |
|---|---|---|---|---|---|---|
| Age, yrs, median (range) | 65 (35–87) | 65 (33–86) | 0.63 | 64 (35–90) | 0.57 | 0.99 |
| Female | 131/524 (25.0) | 49/249 (19.7) | 0.10 | 173/747 (23.2) | 0.45 | 0.25 |
| Diabetes | 179/524 (34.2) | 84/249 (33.7) | 0.94 | 254/747 (34.0) | 0.99 | 0.96 |
| Renal insufficiency§ | 93/491 (18.9) | 39/239 (16.3) | 0.39 | 136/696 (19.5) | 0.80 | 0.27 |
| Hypertension | 370/524 (70.6) | 167/249 (67.1) | 0.32 | 475/747 (63.6) | 0.03 | 0.53 |
| Current smoker | 147/524 (28.1) | 66/249 (26.5) | 0.72 | 209/747 (28.0) | 0.15 | 0.63 |
| Prior MI | 132/524 (25.2) | 65/249 (26.1) | 0.60 | 168/747 (22.5) | 0.13 | 0.47 |
| Prior PCI | 133/524 (25.4) | 55/249 (22.1) | 0.54 | 150/747 (20.1) | 0.03 | 0.70 |
| Prior CABG | 34/524 (6.5) | 10/249 (4.0) | 0.30 | 28/747 (3.7) | 0.08 | 0.83 |
| Discharged on aspirin | 233/249 (93.6) | 473/524 (90.3) | 0.13 | 695/747 (93.0) | 0.07 | 0.77 |
| Discharged on clopidogrel | 166/249 (66.7) | 341/524 (65.1) | 0.66 | 110/747 (14.7) | <0.0001 | <0.0001 |
| High risk‖ | 430/506 (85.0) | 214/245 (87.3) | 0.38 | 610/709 (86.0) | 0.61 | 0.61 |
| Elevated cardiac biomarkers | 354/487 (72.7) | 179/236 (75.8) | 0.37 | 511/696 (73.4) | 0.78 | 0.46 |
| ECG changes | 264/524 (50.4) | 135/249 (54.2) | 0.32 | 353/747 (47.3) | 0.27 | 0.06 |

Values are presented as n/N (%) unless otherwise specified. *p value for the comparison of clopidogrel use and early versus late CABG. †p value for comparison of clopidogrel use and early CABG versus no clopidogrel. ‡p value for comparison of clopidogrel use and late CABG versus no clopidogrel. §Renal insufficiency was defined as calculated creatinine clearance <60 ml/min. ‖High risk was defined as: creatine kinase-MB or troponin elevation or ST-segment deviation.

Abbreviations as in Table 1.

**Impact of CABG timing after clopidogrel exposure.** Of the 773 patients who received clopidogrel before CABG, 524 (67.8%) underwent CABG <5 days after the last clopidogrel dose (the early group) and 249 (32.2%) patients underwent CABG ≥5 days after the last clopidogrel dose (the late group). Baseline characteristics of patients undergoing early versus late CABG were generally comparable with each other and with those who did not receive clopidogrel (Table 3). Hypertension and prior PCI before admission were more common in patients exposed to clopidogrel who underwent early CABG compared with those who were not exposed to clopidogrel.

Compared with patients who did not receive clopidogrel before CABG, those patients who received clopidogrel and underwent CABG within 5 days of the last clopidogrel dose had comparable rates of ischemia at 30 days and 1 year, with no significant differences in any measure of bleeding either before or after CABG (Table 4). In contrast, patients exposed to clopidogrel who underwent CABG ≥5 days after the last clopidogrel dose had significantly lower 30-day rates of composite ischemia (8.8% vs. 17.3%, p = 0.001), NACE (12.9% vs. 19.4%, p = 0.02), and transfusion (31.3% vs. 38.4%, p = 0.04), as well as lower rates of 1-year composite ischemia (14.9% vs. 21.4%, p = 0.02) compared with those who were not exposed to clopidogrel (Table 4), with no increase in any measure of pre- or post-CABG bleeding. However, the pre-CABG and total length of hospital stay were significantly longer in patients undergo-

**Table 4** Clinical Outcomes by Use and Timing of Clopidogrel in Relation to CABG

| | Clopidogrel Use and Early CABG (<5 days) (n = 524) | Clopidogrel Use and Late CABG (≥5 days) (n = 249) | p Value* | No Clopidogrel (n = 747) | p Value† | p Value‡ |
|---|---|---|---|---|---|---|
| 30-day clinical outcomes | | | | | | |
| Net adverse clinical events | 87 (16.6) | 32 (12.9) | 0.18 | 145 (19.4) | 0.20 | 0.02 |
| Composite ischemia | 76 (14.5) | 22 (8.8) | 0.03 | 129 (17.3) | 0.19 | 0.001 |
| Death | 24 (4.6) | 6 (2.4) | 0.14 | 29 (3.9) | 0.54 | 0.27 |
| Non–CABG-related major bleeding | 15 (2.9) | 11 (4.4) | 0.26 | 24 (3.2) | 0.72 | 0.37 |
| Major bleeding, post-CABG | 273 (52.1) | 116 (46.6) | 0.15 | 380 (50.9) | 0.67 | 0.24 |
| Transfusion | 219 (41.8) | 78 (31.3) | 0.005 | 287 (38.4) | 0.23 | 0.04 |
| Reoperation for bleeding | 8 (1.5) | 2 (0.8) | 0.41 | 10 (1.3) | 0.78 | 0.50 |
| 24-h chest tube output, ml, median (IQR) | 600 (360–860) | 550 (320–850) | 0.37 | 551 (350–880) | 0.32 | 0.82 |
| Total length of stay, days, median | 10.4 | 15.6 | <0.0001 | 8.9 | <0.0001 | <0.0001 |
| Pre-CABG length of stay | 2.9 | 8.9 | <0.0001 | 2.5 | 0.58 | <0.0001 |
| Post-CABG length of stay | 6.9 | 6.8 | 0.009 | 5.8 | <0.0001 | 0.15 |
| 1-year clinical outcomes | | | | | | |
| Composite ischemia | 105 (20.0) | 37 (14.9) | 0.08 | 160 (21.4) | 0.55 | 0.02 |
| Death | 42 (8.0) | 12 (4.8) | 0.10 | 46 (6.2) | 0.20 | 0.43 |

Values are presented as n (%) unless otherwise specified. *p value for the comparison of clopidogrel use and early versus late CABG. †p value for comparison of clopidogrel use and early CABG versus no clopidogrel. ‡p value for comparison of clopidogrel use and late CABG versus no clopidogrel.

Abbreviations as in Tables 1 and 2.

ing late CABG compared with those in whom no clopidogrel was administered or in whom CABG was performed within 5 days of clopidogrel administration (Table 4).

## Discussion

The major findings from this analysis of 1,520 patients with moderate- and high-risk NSTE-ACS in whom CABG was performed for revascularization after diagnostic angiography are that: 1) compared with patients who did not receive clopidogrel before CABG, those who received clopidogrel at any time before CABG had significantly reduced rates of composite ischemia and MI at 30 days with comparable rates of pre- and post-CABG major bleeding; 2) multivariable analysis identified clopidogrel administration before CABG as an independent predictor of reduced 30-day composite ischemia (OR: 0.67, $p = 0.001$); 3) compared with patients who did not receive clopidogrel before CABG, the rates of post-CABG major bleeding and transfusion were not significantly increased in patients who received clopidogrel and subsequently underwent CABG; and 4) among clopidogrel-exposed patients who underwent CABG, ischemia and bleeding rates were modestly increased in those patients in whom CABG was performed within 5 days after the cessation of clopidogrel.

The ACC/AHA guidelines for the treatment of patients with NSTE-ACS recommend upstream therapy with aspirin and either clopidogrel or a GP IIb/IIIa inhibitor before angiography to reduce ischemic events (1,2). Frequently, however, clopidogrel is withheld until after angiography because of concerns about bleeding complications for patients subsequently referred for CABG. This deviation from guidelines occurs despite the fact that surgical revascularization in the NSTE-ACS population is required and performed in only approximately 10% of patients, potentially disadvantaging the approximately 60% of patients undergoing PCI in whom the benefits of early dual antiplatelet therapy are well established (13,16). Moreover, data from the CURE (Clopidogrel in Unstable angina to prevent Recurrent ischemic Events) trial suggested that patients with NSTE-ACS undergoing CABG who received clopidogrel before surgery may in fact have a reduction in adverse ischemic outcomes both before and after surgery compared with those undergoing CABG without clopidogrel pretreatment (16,17). Before the present study, however, this observation had not been confirmed.

In the ACUITY trial, 11.1% of patients with moderate- and high-risk NSTE-ACS underwent CABG after diagnostic angiography, approximately one-half of whom had been administered clopidogrel before surgery. To mitigate post-operative bleeding, the ACUITY protocol recommended that patients exposed to clopidogrel in whom CABG was planned wait 5 days if possible before surgical revascularization, per the current STS and ACC/AHA guidelines (1,2,12). In the ACUITY trial, with this strategy applied to NSTE-ACS patients requiring CABG, pre-operative administration of clopidogrel was an independent predictor of freedom from composite ischemia at 30 days, primarily because of a significant reduction in the 30-day rate of MI, consistent with the earlier CURE trial results.

Importantly, patients receiving clopidogrel before CABG had comparable rates of post-CABG major bleeding, transfusion, and 24-h post-operative chest tube output as those who were not exposed to clopidogrel before surgery. This finding is likely caused by effective contemporary surgical strategies for minimizing bleeding, as well as delaying CABG during the index hospitalization in nonurgent cases when possible. This practice did result, however, in a longer median pre-operative length of stay in patients undergoing CABG exposed to clopidogrel than for patients not exposed to clopidogrel (4.2 days vs. 2.5 days, $p < 0.0001$).

Approximately two-thirds of the clopidogrel-exposed patients underwent CABG within 5 days from the last dose of clopidogrel, a rate comparable to that from prior reports (6). The lack of adherence to the recommended 5-day washout period in the majority of patients likely reflects a combination of higher clinical acuity in these patients as well as economic imperatives. Regardless of the reasons, it is reassuring that this practice did not adversely affect net clinical outcomes or adverse ischemic events in the CABG group as a whole, but rather was associated with a reduction in ischemia in the clopidogrel-exposed CABG group compared with those CABG patients who were not exposed to clopidogrel. The finding that pre-operative clopidogrel exposure reduced adverse composite ischemic events in patients with NSTE-ACS who required CABG is thus consistent with the benefits of this agent in PCI and medically managed patients with NSTE-ACS. Further study is required to delineate the mechanisms underlying this effect among CABG patients now seen in 2 large-scale studies.

In our study, the overall rates of bleeding were not significantly increased in all CABG patients exposed to clopidogrel versus those not exposed, or in either the early or the late CABG groups, although the rate of transfusion was modestly increased in the clopidogrel-exposed patients unable to wait 5 days for CABG. These findings are also consistent with data from the CURE trial, in which the overall rates of major bleeding were not significantly increased in the CABG patients exposed to clopidogrel before surgery but were moderately increased (6.3% vs. 9.6%, $p = 0.06$) in patients undergoing surgery within 5 days of clopidogrel exposure (16,17), and support both the ACC/AHA and STS guidelines for a waiting period after termination of clopidogrel unless the procedure is urgent/emergent. Two recent publications also assessed the risk of bleeding in patients exposed to clopidogrel who undergo CABG (18,19). One analysis of 596 patients described significantly increased bleeding in those exposed to clopidogrel within 5 days of CABG (18), whereas another analysis of 4,794 such patients, by far the largest such analysis to date, reported no significant increase in major

bleeding in patients exposed compared with those not exposed to clopidogrel within 5 days of CABG (19).

**Study limitations.** The current study is a retrospective analysis of an unblinded, nonrandomized subgroup from a large, prospective, randomized trial. As such, operators were aware of the clopidogrel status, and this knowledge may have influenced clinical decision making. Specifically, the group of clopidogrel-exposed patients who required CABG within 5 days of clopidogrel exposure represent a clinically high-risk group, making direct comparison with those patients able to wait 5 days for CABG problematic. In this regard, the fact that major bleeding, chest tube output, and reoperation rates were not significantly increased after CABG in the early clopidogrel administration group is reassuring. Intraoperative blood loss was not specifically quantified. CABG-related outcomes such as chest tube output and rates of transfusion were prospectively collected. However, these outcomes were not adjudicated by the clinical events committee. In addition, the ACUITY trial was not powered for the cohort of patients undergoing CABG or any other patient subgroup; all findings should thus be considered hypothesis generating. Finally, although data regarding clopidogrel use were prospectively collected in the case report form, the loading dose and exact timing of the last dose of clopidogrel until the time of CABG in patients receiving clopidogrel before randomization was not always known. Detailed data on clopidogrel use after the initial hospitalization were also not available. These limitations are common to previous trials examining the role of clopidogrel in patients undergoing CABG (6–11,18,19).

## Conclusions

The findings from the present study support the ACC/AHA guidelines for upstream clopidogrel administration in all patients with NSTE-ACS before cardiac catheterization as part of an invasive management strategy. In the approximately 10% of patients who will require CABG after coronary arteriography, clopidogrel administration before surgery is associated with reduced rates of 30-day composite ischemia without significantly increasing post-CABG major bleeding.

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**Key Words:** coronary artery bypass surgery ■ clopidogrel ■ acute coronary syndromes.