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Bleeding Events Before Coronary Angiography in Patients With Non-ST-Segment Elevation Acute Coronary Syndrome

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ABSTRACT

BACKGROUND Upstream administration of antithrombotic drugs to patients with non–ST-segment elevation acute coronary syndromes before coronary angiography is a common practice despite an incomplete understanding of the risks and benefits.

OBJECTIVES The authors analyzed the incidence of bleeding and ischemic events occurring before angiography and assessed their association with antithrombotic drugs and mortality risk.

METHODS All patients from the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial with planned angiography after enrollment were included. Bleeding events were classified according to the ACUITY scale as major or nonmajor bleeding. Kaplan-Meier and Cox proportional hazards analyses were performed.

RESULTS Of 13,726 patients, 275 (2.0%) bled before angiography, including 52 (0.4%) with major bleeding. Forty-four (0.3%) experienced myocardial infarction. The median time from randomization to coronary angiography was 4.5 h (interquartile ratio [IQR]: 1.7 to 19.7 h) for patients who did not bleed while waiting for angiography and 27.9 h (IQR: 21.9 to 65.6 h) for patients who bled while waiting for angiography ($p < 0.001$). Bleeding events accrued linearly over time, reaching 10.4% at 96 h post-randomization. Independent predictors of bleeding before angiography included age (adjusted hazard ratio [HR]: 1.03 per year of age; 95% confidence interval [CI]: 1.01 to 1.04; $p < 0.001$), renal insufficiency (adjusted HR: 1.48; 95% CI: 1.07 to 2.04; $p = 0.02$), and use of multiple antithrombotic drugs (adjusted HR: 1.33; 95% CI: 1.14 to 1.56; $p < 0.001$). Bleeding before coronary angiography was associated with longer hospitalization (4.8 days [IQR: 3.0 to 8.9 days] vs. 3.0 days [IQR: 1.9 to 5.9 days]; $p < 0.001$). Patients who bled before angiography were more likely to die within 1 year than patients who did not bleed (8.5% vs. 4.1%; $p < 0.001$; adjusted HR: 1.89 (95% CI: 1.23 to 2.90; $p = 0.004$).

CONCLUSIONS Upstream antithrombotic treatment of patients with non–ST-segment elevation acute coronary syndromes awaiting coronary angiography is associated with excess bleeding with mortality implications. Bleeding avoidance strategies before angiogram, including early angiography, may negate the need to prolong upstream antithrombotic treatment and improve the overall risk-benefit balance for these patients. (Acute Catheterization and Urgent Intervention Triage Strategy [ACUITY]; NCT00093158) (J Am Coll Cardiol 2016;68:2608–18) © 2016 by the American College of Cardiology Foundation.

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Upstream (before coronary angiography) administration of antithrombotic drugs to patients with non-ST-segment elevation acute coronary syndrome (NSTEACS) may reduce the risk of ischemic events, but increases the bleeding risk (1–5). Bleeding events occurring during or after percutaneous coronary intervention (PCI) are associated with increased mortality (6–10); however, the incidence, predictors, and impact of bleeding events occurring before angiography on clinical prognosis have not been well-detailed. We report and compare the incidence of bleeding and ischemic events occurring before coronary angiography in the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial, with emphasis on their association with antithrombotic drugs and mortality risk.

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METHODS

The ACUITY trial design has been reported in detail (11). Briefly, it was a multicenter, prospective, randomized trial of patients with moderate- and high-risk NSTEACS who were managed with an early invasive strategy. Patients were randomly assigned before coronary angiography to heparin (unfractionated or low molecular weight) plus a glycoprotein IIb/IIIa inhibitor (GPI), bivalirudin plus a GPI, or bivalirudin monotherapy with provisional GPI use. Patients assigned to 1 of the GPI arms were further randomized in a 2 × 2 factorial design to upstream GPI initiation or a deferred selective strategy in which GPI was given only in patients with PCI. Angiography was planned for all patients within 72 h of randomization. Depending on coronary anatomy, patients were then treated with PCI, coronary artery bypass grafting, or medical therapy. Dual antiplatelet therapy with aspirin and clopidogrel was strongly recommended for at least 1 year. All patients were anticoagulated during coronary artery bypass grafting with unfractionated heparin, with dosing per standard institutional practice. Detailed information regarding date and time of day was available for: 1) time of randomization; 2) time of coronary angiography; 3) time of initiation of in-hospital treatment with antiplatelet and anticoagulant drugs; and 4) in-hospital bleeding or ischemic events. The study was approved by the institutional review board or ethics committee at each center, and all patients provided written informed consent. All major adverse events were adjudicated by an independent clinical events committee blinded to treatment assignment.

STUDY POPULATION, OBJECTIVES, AND ANGIOGRAPHIC ANALYSIS. Of the 13,819 patients enrolled in ACUITY, 93 were enrolled at the time of or after coronary angiography and were excluded from the present study. The remaining 13,726 constituted the study population (Figure 1A). Our primary objectives were: 1) describe the incidence of bleeding events occurring before coronary angiography; 2) study the unadjusted and adjusted association between the number of antithrombotic drugs administered to the patients and these bleeding events; and 3) study the unadjusted and adjusted association between having a bleeding event before angiography and long-term mortality risk. We performed a sensitivity analysis restricted to patients who had coronary angiography (n = 13,614) (Figure 1B). The same statistical models (i.e., the same covariates) were used in the sensitivity analyses.

DEFINITIONS. Bleeding events were classified as major or nonmajor according to the ACUITY scale. Major bleeding was defined as any intracranial or intraocular bleeding, any overt bleeding associated with a hemoglobin drop ≥3 g/dl, any hemoglobin drop ≥4 g/dl, or any bleeding associated with a blood transfusion. Nonmajor bleeding was defined as any clinically significant overt bleeding that did not meet the criteria for major bleeding. Bleeding was classified as procedure-related or not procedure-related, and the date and time of the bleeding episode was recorded as the time when bleeding started. Recurrent myocardial infarction (MI) was defined as previously described (11). For patients with unstable angina (no biomarker elevation at baseline), MI was defined as any elevation of troponin or creatine kinase-myocardial band isoenzyme (CK-MB) greater than the upper limit of normal. For patients with MI (elevated biomarkers at baseline), MI (i.e., reinfarction) was defined as follows: 1) if the peak troponin or CK-MB had not yet been reached: recurrent chest pain lasting ≥30 min or new electrocardiographic changes consistent with MI and the next troponin or CK-MB measured approximately 8 to 12 h after the event elevated by at least 50% above the previous level; 2) if the troponin or CK-MB was falling or had returned to normal: a new elevation of troponin or CK-MB above the upper limit of normal or a rise by 50% above the previous nadir level if the troponin or CK-MB had not returned to less than the upper limit of normal.

STATISTICAL ANALYSIS. Continuous data are presented as mean ± SD and were compared using the Student *t* test or the Wilcoxon rank sum test, as

ABBREVIATIONS AND ACRONYMS

CI = confidence interval

CK-MB = creatine kinase-myocardial band isoenzyme

GPI = glycoprotein IIb/IIIa inhibitor

GRACE = Global Registry of Acute Coronary Events

HR = hazard ratio

MI = myocardial infarction

NSTEACS = non-ST-segment elevation acute coronary syndrome

PCI = percutaneous coronary intervention

TIMI = Thrombolysis In Myocardial Infarction