Journal of the American College of Cardiology
© 2007 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 49, No. 12, 2007
ISSN 0735-1097/07/$32.00
doi:10.1016/j.jacc.2007.02.027

Impact of Major Bleeding on 30-Day Mortality and Clinical Outcomes in Patients With Acute Coronary Syndromes

An Analysis From the ACUITY Trial

Steven V. Manoukian, MD, FACC,* Frederick Feit, MD, FACC,† Roxana Mehran, MD, FACC,‡ Michele D. Voeltz, MD,* Ramin Ebrahimi, MD, FACC,§ Martial Hamon, MD,‖ George D. Dangas, MD, PHD, FACC,‡ A. Michael Lincoff, MD, FACC,¶ Harvey D. White, DSC, FACC# Jeffrey W. Moses, MD, FACC,‡ Spencer B. King III, MD, MACC** E. Magnus Ohman, MD, FACC,†† Gregg W. Stone, MD, FACC‡

Atlanta, Georgia; Los Angeles, California; New York, New York; Caen, France; Cleveland, Ohio; Auckland, New Zealand; and Durham, North Carolina

Objectives The purpose of this study was to determine the predictors of major bleeding and the impact of major bleeding on outcomes, including mortality, in acute coronary syndromes (ACS).

Background Whether major bleeding independently predicts mortality in patients with ACS undergoing an early invasive strategy is undefined.

Methods Patients (n = 13,819) with moderate- and high-risk ACS were randomized to heparin (unfractionated or enoxaparin) plus glycoprotein IIb/IIIa inhibition (GPI), bivalirudin plus GPI, or bivalirudin monotherapy (plus provisional GPI). Logistic regression was used to determine predictors of 30-day major bleeding and mortality.

Results Major bleeding rates in patients treated with heparin plus GPI were higher versus bivalirudin monotherapy (5.7% vs. 3.0%, $p < 0.001$) and similar versus bivalirudin plus GPI (5.7% vs. 5.3%, $p = 0.38$). Independent predictors of major bleeding were advanced age, female gender, diabetes, hypertension, renal insufficiency, anemia, no prior percutaneous coronary intervention, cardiac biomarker elevation, ST-segment deviation ≥1 mm, and treatment with heparin plus GPI versus bivalirudin monotherapy. Patients with major bleeding had higher 30-day rates of mortality (7.3% vs. 1.2%, $p < 0.0001$), composite ischemia (23.1% vs. 6.8%, $p < 0.0001$), and stent thrombosis (3.4% vs. 0.6%, $p < 0.0001$) versus those without major bleeding. Major bleeding was an independent predictor of 30-day mortality (odds ratio 7.55, 95% confidence interval 4.68 to 12.18, $p < 0.0001$).

Conclusions Major bleeding is a powerful independent predictor of 30-day mortality in patients with ACS managed invasively. Several factors independently predict major bleeding, including treatment with heparin plus GPI compared with bivalirudin monotherapy. Knowledge of these findings might be useful to reduce bleeding risk and improve outcomes in ACS. (J Am Coll Cardiol 2007;49:1362–8) © 2007 by the American College of Cardiology Foundation

*From the Department of Medicine, Emory University School of Medicine, Atlanta, Georgia; **Fuqua Heart Center, Atlanta, Georgia; †Department of Medicine, New York University School of Medicine, New York, New York; ‡Department of Medicine, Columbia University Medical Center and the Cardiovascular Research Foundation, New York, New York; §Department of Medicine, University of California Los Angeles, Los Angeles, California; ‖Service des Maladies du Cœur et des Vaisseaux, Centre Hospitalier Universitaire de Caen, Caen, France; ¶Department of Cardiovascular Medicine, Cleveland Clinic Foundation, Cleveland, Ohio; #Green Lane Cardiovascular Service, Auckland City Hospital, Auckland, New Zealand; and the ††Department of Medicine, Duke University School of Medicine, Durham, North Carolina. The trial was funded by The Medicines Company, Parsippany, New Jersey, and Nycomed, Roskilde, Denmark. Drs. Manoukian, Mehran, Dangas, White, and Stone have received lecture fees from The Medicines Company. Drs. Manoukian and Stone have received lecture fees from Nycomed. Dr. Feit holds equity interests in The Medicines Company, Johnson & Johnson, and Millennium Pharmaceuticals. Drs. Feit, Ohman, White, and Stone have received consulting fees from The Medicines Company. Dr. Lincoff has received research support from The Medicines Company. Dr. White has received consulting fees and lecture fees from Sanofi-Aventis and grant support from The Medicines Company, Sanofi-Aventis, Proctor and Gamble, Schering Plough, and Eli Lilly. Dr. Moses has received consulting fees from Johnson & Johnson and is on the speaker's bureau for Astra Zeneca. Dr. Ohman has received consulting fees from Sanofi-Aventis, Liposcience, Inovise Medical, Response Biomedical, and Savacor; holds equity interests in Medtronic and Savacor; received lecture fees from Schering Plough, Bristol Myers Squibb, and Datascope; and has received grant support from Schering Plough, Bristol Myers Squibb, and Berlex.

Manuscript received February 10, 2007; revised manuscript received February 26, 2007, accepted February 26, 2007.

Antithrombotic therapy is an important component of the management of patients with acute coronary syndromes (ACS) (unstable angina or non–ST-segment elevation myocardial infarction) (1). Although advances in antithrombotic therapy have reduced rates of ischemic events, they typically have increased the risk of bleeding complications (2,3), and data suggest an adverse relationship between bleeding and outcomes (4,5).

Bivalirudin has demonstrated anti-ischemic efficacy and favorable bleeding complication rates in percutaneous coronary intervention (PCI) and ACS (6,7). In the REPLACE (Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events)-2 trial, bivalirudin (plus provisional glycoprotein IIb/IIIa inhibition [GPI]) was noninferior to unfractionated heparin plus planned GPI in suppressing ischemic events, while markedly reducing bleeding (6). In the ACUITY (Acute Catheterization and Urgent Intervention Triage strategY) trial, bivalirudin (plus provisional GPI) resulted in similar 30-day composite ischemic event rates, less bleeding, and superior net clinical outcomes, compared with heparin (unfractionated or enoxaparin) plus GPI in ACS (7).

This analysis examines the predictors of major bleeding and its impact on 30-day outcomes, including mortality, in the ACUITY trial.

Abbreviations and Acronyms

ACS = acute coronary syndromes
CABG = coronary artery bypass graft surgery
GRACE = Global Registry of Acute Coronary Events
GPI = glycoprotein IIb/IIIa inhibitor/inhibition
MI = myocardial infarction
PCI = percutaneous coronary intervention

Methods

Study design. In the ACUITY trial (7), 13,819 patients with moderate- and high-risk ACS were randomly assigned in open-label fashion to heparin (unfractionated or enoxaparin) plus GPI, bivalirudin plus GPI, or bivalirudin monotherapy (plus provisional GPI). Unfractionated heparin was administered intravenously as a 60 IU/kg bolus plus 12 IU/kg/h infusion, to achieve an activated partial thromboplastin time of 50 to 75 s before angiography and an activated clotting time of 200 to 250 s during PCI. The median maximum activated clotting time among patients undergoing PCI with unfractionated heparin was 239 s (interquartile range 211 to 291 s) (7). Enoxaparin was administered 1 mg/kg subcutaneously twice a day, with a 0.3 mg/kg intravenous bolus immediately before PCI, if the last subcutaneous dose was >8 h earlier or 0.75 mg/kg if >16 h earlier. Bivalirudin was administered intravenously as a 0.1 mg/kg bolus plus 0.25 mg/kg/h infusion, with a bolus of 0.5 mg/kg and an increase in the infusion to 1.75 mg/kg/h before PCI. Antithrombotic monitoring was not performed for enoxaparin or bivalirudin. Antithrombins were routinely discontinued after angiography or after PCI. The GPI group patients were randomized again (2×2 factorial design) to either initiation upstream or deferred (before PCI). Provisional GPI was permitted in deferred GPI or bivalirudin monotherapy patients for severe breakthrough ischemia and during PCI in bivalirudin monotherapy patients for prespecified criteria. The GPI was administered per labeling and continued 12 to 18 h after PCI. Coronary angiography was required within ≤72 h, with triage to PCI, coronary artery bypass graft surgery (CABG), or medical management. Aspirin (300 to 325 mg orally or 250 to 500 mg intravenously) was administered daily during hospital stays. Thienopyridine dosing and timing were left to investigator discretion; however, the protocol required a clopidogrel loading dose of ≥300 mg ≤2 h after PCI, and 75 mg daily was recommended for 1 year in coronary artery disease patients. The institutional review or ethics board at each center approved the study, and patients signed written, informed consent.

End points and statistical methods. The ACUITY study was powered for 3 primary 30-day end points: composite ischemia, major bleeding (not CABG-related), and net clinical outcomes. A blinded clinical events committee adjudicated all primary and secondary end points. Major bleeding (not CABG-related) was defined as: intracranial or intraocular; access site bleeding requiring intervention; ≥5-cm diameter hematoma; hemoglobin reduction of ≥4 g/dl without or ≥3 g/dl with an overt source; reoperation for bleeding; or blood product transfusion. All analyses are intention to treat. Chi-square test was used for categorical variables, unless the observation in any cell was <5, in which the Fisher exact test was used. Continuous variables were tested with the Wilcoxon rank sum test. Medians and interquartile ranges are presented for continuous variables. Time-to-event distributions are displayed according to the Kaplan-Meier method and compared with log-rank test. The p values are given for informational purposes and no multiplicity adjustment was done. Predictors of major bleeding and 30-day mortality were identified with logistic regression analyses. Potential predictors were selected with stepwise, forward, and backward procedures. For each procedure, a prediction factor entered into the model with $p \leq 0.20$ and retained with $p \leq 0.10$. The final model includes all predictors selected by at least 1 of the procedures. The p values, odds ratios (ORs), and corresponding 2-sided 95% confidence interval (CI) for predictors are presented. Statistical analyses were performed by SAS version 8.2 (SAS Institute Inc., Cary, North Carolina).

Results

Patient characteristics. Of 13,819 patients, 644 (4.7%) experienced major bleeding. Patients with major bleeding were older, more likely female, and of lower body weight. They were more likely to have diabetes, hypertension, anemia, and renal insufficiency and less likely to have hyperlipidemia, smoke, or have prior PCI. Patients with major bleeding more often