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Safety and Efficacy of Bivalirudin Monotherapy in Patients With Diabetes Mellitus and Acute Coronary Syndromes

A Report From the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) Trial

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Objectives We sought to evaluate clinical outcomes of patients with diabetes mellitus in the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial, overall and by treatment arm.

Background In the ACUITY trial, 13,819 patients with moderate- or high-risk acute coronary syndromes (ACS) were randomized to heparin (unfractionated or enoxaparin) plus glycoprotein IIb/IIIa inhibition (GPI), bivalirudin plus GPI, or bivalirudin monotherapy. Compared with heparin plus GPI, bivalirudin monotherapy resulted in similar protection from ischemic events with less major bleeding. Whether these results apply to patients with diabetes is unknown.

Methods We evaluated the impact of diabetes on 30-day net adverse clinical outcomes (composite ischemia [death, myocardial infarction, or unplanned ischemic revascularization] or major bleeding), overall and by antithrombotic strategy.

Results Diabetes was present in 3,852 randomized patients (27.9%). Compared with nondiabetic patients, diabetic patients had higher 30-day rates of net adverse clinical outcomes (12.9% vs. 10.6%; $p < 0.001$), composite ischemia (8.7% vs. 7.2%; $p = 0.003$), and major bleeding (5.7% vs. 4.2%; $p < 0.001$). Among diabetic patients, compared with heparin plus GPI, bivalirudin plus GPI resulted in similar rates of net adverse clinical outcomes (14.0% vs. 13.8%; $p = 0.89$), while bivalirudin monotherapy resulted in a similar rate of composite ischemia (7.9% vs. 8.9%; $p = 0.39$) and less major bleeding (3.7% vs. 7.1%; $p < 0.001$), yielding fewer net adverse clinical outcomes (10.9% vs. 13.8%; $p = 0.02$).

Conclusions Diabetic patients with ACS managed invasively have higher rates of composite ischemia and major bleeding. Compared with treatment with heparin plus GPI, bivalirudin monotherapy provides similar protection from ischemic events with less major bleeding, resulting in a significant reduction in net adverse clinical outcomes.
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Although mortality from coronary artery disease is decreasing for the general population in the U.S., this is not true for those with diabetes mellitus, who account for approximately 30% of patients presenting with acute coronary syndromes (ACS) (1,2). Despite technological and pharmacologic advances in the treatment of heart disease, diabetic patients

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Abbreviations and Acronyms

ACS = acute coronary syndromes

CABG = coronary artery bypass graft surgery

GPI = glycoprotein IIb/IIIa inhibitor

MI = myocardial infarction

PCI = percutaneous coronary intervention

TIMI = Thrombolysis In Myocardial Infarction

continue to have worse outcomes than nondiabetic patients (2,3). A recent meta-analysis supports the clinical recommendation that administration of a glycoprotein IIb/IIIa inhibitor (GPI) should be considered to be the standard of care for diabetic patients with ACS, given a significant reduction in periprocedural ischemic events and mortality at 30 days and 6 months (4). However, GPIs result in an increased incidence of hemorrhagic complications and thrombocytopenia, both of which have been associated with early and late mortality in the ACS population (5–9).

Bivalirudin, a direct thrombin inhibitor, is theoretically an attractive alternative to unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH), given its ability to inhibit both circulating and clot-bound thrombin as well as thrombin-mediated platelet activation, its linear pharmacokinetics, and short half-life (~25 min) (10,11). An analysis of diabetic patients undergoing elective or urgent percutaneous coronary intervention (PCI) in the REPLACE (Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events)-2 trial showed similar protection from ischemic events and significantly decreased minor bleeding with bivalirudin monotherapy compared with UFH plus a GPI (12).

Limited data exist in diabetic patients comparing bivalirudin, either alone or in combination with a GPI, to an indirect thrombin inhibitor (either UFH or enoxaparin) plus a GPI in the ACS population. The ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial was the first large-scale investigation to examine whether clinical outcomes of patients with moderate- or high-risk ACS treated with all class I agents recommended in the American College of Cardiology/American Heart Association guidelines could be further improved by a new pharmacologic regimen using bivalirudin (13). That trial demonstrated that bivalirudin monotherapy was associated with a significant reduction in 30-day net adverse clinical outcomes (composite ischemia or major bleeding) and significantly reduced major bleeding compared to heparin plus a GPI (13).

We sought in the present report to evaluate the pre-specified subgroup of diabetic patients in the ACUITY trial to assess 30-day clinical outcomes: 1) in patients with versus without diabetes mellitus; and 2) in diabetic patients treated with bivalirudin with and without routine GPI, compared with those treated with a heparin-based regimen plus routine GPI.

Methods

Patient population, randomization, and study protocol. The design and primary results of the ACUITY trial have been previously published (13,14). Briefly, 13,819 patients with ACS undergoing an invasive management strategy were randomly assigned in an open-label fashion equally to 1 of 3 antithrombotic regimens starting immediately after randomization: a heparin (UFH or enoxaparin) plus a GPI (the control group), bivalirudin plus a GPI, or bivalirudin monotherapy, in which GPI administration was permitted only for limited pre-specified indications. The UFH was administered as an intravenous (IV) bolus of 60 IU/kg body weight plus an infusion of 12 IU/kg/h 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. One milligram of enoxaparin per kg was administered subcutaneously (SC) twice daily before angiography. An IV bolus of an additional 0.3 mg/kg was administered before PCI if the most recent SC dose had been given >8 h earlier, or an IV bolus of an additional 0.75 mg/kg was administered before PCI if the most recent SC dose had been given >16 h earlier. Bivalirudin was begun before angiography, with an IV bolus of 0.1 mg/kg and an infusion of 0.25 mg/kg/h. Before PCI, an additional IV bolus of 0.5 mg/kg was administered, and the infusion was increased to 1.75 mg/kg/h.

Patients assigned to the heparin plus GPI or bivalirudin plus GPI arms were randomized again in a 2 × 2 factorial design to either upstream GPI initiation in all patients immediately after randomization or to deferred GPI initiation for selective use in PCI patients only starting in the catheterization laboratory. Crossover to upfront GPI administration was permitted for patients assigned to deferred GPI initiation for refractory ischemia before angiography. According to the Food and Drug Administration–approved labeling, either eptifibatide or tirofiban was permitted for upstream use and either eptifibatide or abciximab was permitted for deferred selective use. Dosages of all GPIs followed the package insert and were adjusted for renal impairment.

Coronary angiography was performed within 72 h of randomization with subsequent triage to PCI, coronary artery bypass graft surgery (CABG), or medical management according to the standard of care. Aspirin was administered before angiography. Clopidogrel dosing and timing were left to the discretion of the investigators, but the protocol required 300 mg clopidogrel in all cases no later than 2 h after PCI. The study was approved by the institutional review board or ethics committee at each participating center, and all patients signed written informed consent. The authors had full access to the data and take responsibility for its integrity. All of the authors have read and agree to the manuscript as written.

End points and statistical methods. The ACUITY trial was powered for 3 primary 30-day end points: 1) net adverse clinical outcome (composite ischemia or major bleeding); 2) composite ischemia, defined as death from any cause, nonfatal myocardial infarction (MI), or unplanned revascu-