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Safety and Efficacy of Bivalirudin With and Without Glycoprotein IIb/IIIa Inhibitors in Patients With Acute Coronary Syndromes Undergoing Percutaneous Coronary Intervention

1-Year Results From the ACUITY (Acute Catheterization and Urgent Intervention Triage strategY) Trial

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Objectives This study was designed to determine the impact of bivalirudin on 1-year outcomes in acute coronary syndrome (ACS) patients undergoing percutaneous coronary intervention (PCI).

Background The ACUITY (Acute Catheterization and Urgent Intervention Triage strategY) trial demonstrated that in moderate- and high-risk ACS patients undergoing PCI, bivalirudin alone compared to unfractionated heparin (UFH) or enoxaparin plus a glycoprotein (GP) IIb/IIIa inhibitor resulted in less major bleeding and similar ischemic outcomes at 30 days. The impact of bivalirudin on 1-year outcomes in ACS patients undergoing PCI is unknown.

Methods In the ACUITY trial, 13,819 patients were enrolled, and 7,789 (56.4%) patients had PCI. Composite ischemia (death, myocardial infarction, or unplanned revascularization) and mortality at 1 year were assessed.

Results Among patients undergoing PCI, 2,561, 2,609, and 2,619 were randomized to UFH or enoxaparin plus a GP IIb/IIIa inhibitor, bivalirudin plus a GP IIb/IIIa inhibitor, and bivalirudin monotherapy, respectively. At 1 year, there were no differences in composite ischemia (17.8% vs. 19.4% vs. 19.2%, p = NS) or mortality (3.2% vs. 3.3% vs. 3.1%, p = NS) among the 3 groups, respectively.

Conclusions Bivalirudin compared with UFH or enoxaparin plus a GP IIb/IIIa inhibitor results in similar rates of composite ischemia and mortality at 1 year in moderate- and high-risk ACS patients undergoing PCI. (J Am Coll Cardiol 2008;52:807–14) © 2008 by the American College of Cardiology Foundation

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Abbreviations and Acronyms

ACS = acute coronary syndrome
CABG = coronary artery bypass graft
CI = confidence interval
GP = glycoprotein
HR = hazard ratio
IV = intravenous
LMWH = low-molecular-weight heparin
MI = myocardial infarction
NSTE-ACS = non–ST-segment elevation acute coronary syndromes
PCI = percutaneous coronary intervention
TIMI = Thrombolysis In Myocardial Infarction
UFH = unfractionated heparin

In patients with moderate- and high-risk non–ST-segment elevation acute coronary syndromes (NSTE-ACS), an early invasive strategy of angiography and subsequent coronary revascularization coupled with an antithrombotic regimen has been shown to improve long-term outcomes (1–4). The American College of Cardiology/American Heart Association and the European Society of Cardiology guidelines recommend initiation of antiplatelet therapy (aspirin and clopidogrel), unfractionated heparin (UFH), or low-molecular-weight heparin and glycoprotein (GP) IIb/IIIa inhibitors for NSTE-ACS patients undergoing percutaneous coronary intervention (PCI) (5,6). Although this intensive antiplatelet and antithrombin regimen reduces ischemic events, such treatment regimens are often associated with an increased risk of bleeding, a complication that is strongly associated with early and late mortality (7–11).

Bivalirudin is a direct thrombin inhibitor that has several advantages over heparin. Bivalirudin inhibits both circulating and clot-bound thrombin, does not activate platelets, and has a short, 25-min half-life that allows for a rapid return to hemostasis (12). In the REPLACE-2 (Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events) trial, treatment with bivalirudin and provisional GP IIb/IIIa inhibitor use (in 7% of patients) in patients undergoing PCI provided similar protection from ischemic events as heparin plus routine use of GP IIb/IIIa inhibitors, but with a significant 41% relative reduction in major bleeding (13). At 1 year, there was a trend toward reduced mortality in the bivalirudin group, a benefit that was greatest in high-risk patient subgroups (5,14). The 2007 American College of Cardiology/American Heart Association guidelines provide a class I recommendation for use of bivalirudin monotherapy in patients with acute coronary syndromes (ACS) undergoing PCI (5).

The ACUITY (Acute Catheterization and Urgent Intervention Triage StrategY) trial randomized 13,819 patients with moderate- and high-risk NSTE-ACS to UFH or enoxaparin plus a GP IIb/IIIa inhibitor, bivalirudin plus a GP IIb/IIIa inhibitor, or bivalirudin alone. Treatment with bivalirudin monotherapy was associated with similar rates of composite ischemia but significantly reduced bleeding complications compared with UFH or enoxaparin plus a GP IIb/IIIa inhibitor (15). Thirty-day outcomes in the patients undergoing PCI were consistent with the overall findings, with comparable ischemic outcomes and 48% less major bleeding with bivalirudin monotherapy (16).

The impact of a bivalirudin-alone strategy as compared with UFH/enoxaparin plus a GP IIb/IIIa inhibitor on long-term ischemia outcomes and mortality in moderate- and high-risk ACS patients undergoing PCI has not been reported. Therefore, we assessed the incidence of ischemic outcomes at 1 year in patients in the ACUITY trial undergoing PCI. In addition, we examined 1-year mortality across multiple prespecified subgroups.

Methods

The design of the ACUITY trial has been described previously (17). In brief, patients age 18 years or older with symptoms of unstable angina lasting ≥10 min within 24 h were eligible if they met 1 or more of the following criteria: new ST-segment depression or transient elevation ≥1 mm; elevated troponin I, troponin T, or creatine kinase-myocardial band; known coronary artery disease, or all 4 other Thrombolysis In Myocardial Infarction (TIMI) risk criteria (18). Exclusion criteria included acute ST-segment elevation myocardial infarction (MI) or shock; bleeding diathesis or major bleeding within 2 weeks; thrombocytopenia; creatinine clearance ≤30 ml/min; or recent administration of abciximab, warfarin, fondaparinux, fibrinolytic agents, bivalirudin, or >1 dose of low-molecular-weight heparin. The study was approved by institutional review boards or ethics committees at each center, and all patients gave written informed consent.

Randomization and study procedures. The ACUITY trial randomized 13,819 patients to receive UFH or enoxaparin with a GP IIb/IIIa inhibitor, bivalirudin plus a GP IIb/IIIa inhibitor, or bivalirudin alone. The UFH was administered as a 60 IU/kg intravenous (IV) bolus followed by an infusion of 12 IU/kg/h to target an activated partial thromboplastin time of 50 to 75 s before angiography and an activated clotting time of 200 to 250 s during PCI. Enoxaparin 1 mg/kg subcutaneous twice daily was initiated before angiography, with an additional 0.3 mg/kg or 0.75 mg/kg IV bolus given before PCI if the most recent subcutaneous dose had been given more than 8 or 16 h earlier, respectively. Bivalirudin was administered as a 0.1 mg/kg IV bolus and an infusion of 0.25 mg/kg/h. An additional IV bolus of 0.5 mg/kg was administered before PCI, and the infusion was increased to 1.75 mg/kg/h.

Patients assigned to one of the GP IIb/IIIa inhibitor arms were further randomized in a 2 × 2 factorial design to either upstream GP IIb/IIIa inhibitor initiation immediately after

received consulting fees from The Medicines Company, Bristol-Myers Squibb, Schering-Plough, and Sanofi-Aventis, and lecture fees from The Medicines Company and Nycomed. Dr. Mehran has received lecture fees from The Medicines Company, Cordis, and Boston Scientific. Dr. Moses has received consulting fees from Johnson & Johnson and is on the Speakers' Bureau for AstraZeneca.

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randomization or to deferred initiation for selected use in the catheterization laboratory starting immediately before PCI. In accordance with current guidelines (5,6), either eptifibatide or tirofiban, per the investigator's choice, was permitted for upstream use and continued through PCI. Either abciximab or eptifibatide was permitted for deferred use initiated in the catheterization laboratory. In patients randomized to deferred use of GP IIb/IIIa inhibitors or to bivalirudin monotherapy, provisional use was permitted before angiography for severe breakthrough ischemia and during PCI in bivalirudin monotherapy patients for pre-specified procedural complications (16,17).

Per protocol, angiography was intended in all patients within 72 h of randomization with subsequent triage to PCI, coronary artery bypass graft (CABG) surgery, or medical management. Aspirin was administered daily during hospitalization (300 to 325 mg orally or 250 to 500 mg IV). Although timing and initial dosing of clopidogrel were left to the investigator's discretion, a loading dose of 300 mg or more was required within 2 h after PCI in all cases. Clopidogrel (75 mg daily) was recommended for 1 year in all patients undergoing PCI, and aspirin (75 to 25 mg daily) was recommended indefinitely.

End points and statistical analyses. End points were assessed at 30 days and 1 year. Pre-specified 30-day primary end points in the trial were composite ischemia, defined as death, MI, or unplanned revascularization for ischemia; non-CABG ACUITY-scale major bleeding; and net clinical outcome (composite ischemia or non-CABG ACUITY-scale major bleeding). Non-CABG ACUITY-scale major bleeding was defined as intracranial or intraocular bleeding, access site hemorrhage requiring intervention, hematoma ≥5 cm in diameter, reduction in hemoglobin of ≥3 g/dl with an overt bleeding source or ≥4 g/dl with no source identified, reoperation for bleeding, or blood product transfusion. Only composite ischemia was evaluated after 30 days. All 30-day and 1-year primary end points were adjudicated by a blinded Clinical Events Committee.

Analyses of 1-year composite ischemia and mortality in patients undergoing PCI were pre-specified. Analysis was performed using time-to-event data (with patients censored at the time of withdrawal from the study or last follow-up), displayed using Kaplan-Meier methodology, and compared with the log-rank test. Hazard ratios (HRs) with 95% confidence intervals (CIs) are presented for treatment comparisons.

The effect of treatment assignment on 1-year mortality and composite ischemia was tested in multiple subgroups using formal interaction testing. A 2-sided $\alpha = 0.05$ was used for all superiority testing. The impact of the timing of clopidogrel administered on 1-year mortality was also evaluated.

Results

Study population and clinical outcomes. Patient disposition is presented in Figure 1. Baseline characteristics (Table 1) were similar among the 3 treatment groups. Details of study medication administration and procedural details have been published previously (16).

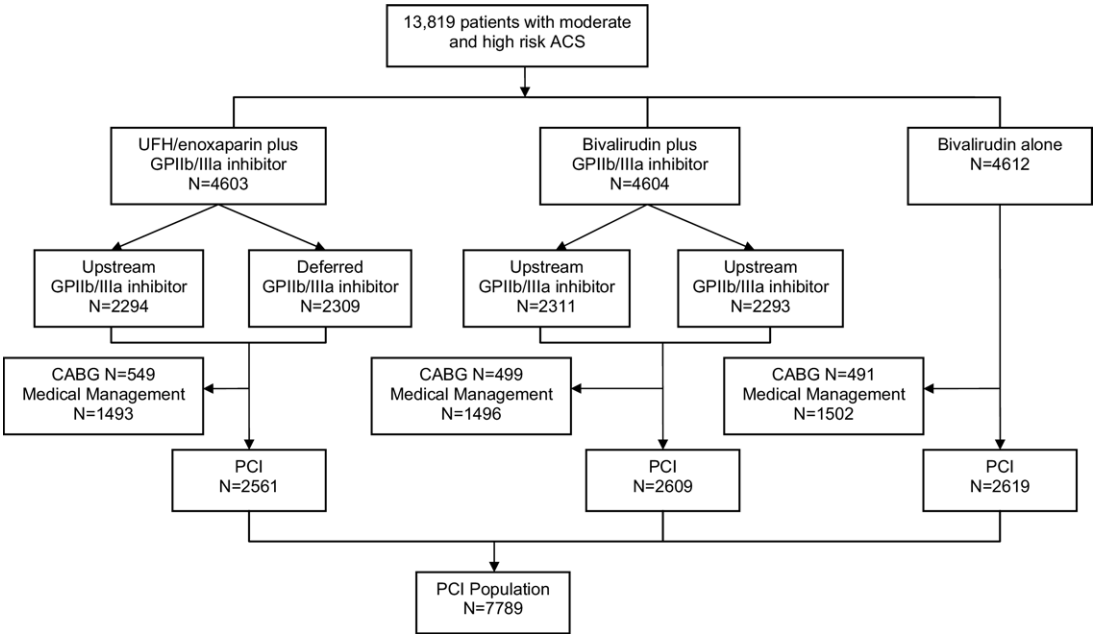

Figure 1 Enrollment and Randomization of the ACUITY Trial

ACS = acute coronary syndromes; CABG = coronary artery bypass graft surgery; GP = glycoprotein; PCI = percutaneous coronary intervention; UFH = unfractionated heparin.

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Table 1 Baseline Characteristics of Patients Undergoing PCI

	Heparin (UFH or Enoxaparin) + GP IIb/IIIa Inhibitor (n = 2,561) (%)	Bivalirudin + GP IIb/IIIa Inhibitor (n = 2,609) (%)	Bivalirudin Alone (n = 2,619) (%)
Age, median [range], yrs	63 [25–91]	62 [21–95]	63 [30–92]
Gender (male)	1,850 (72.6)	1,919 (73.6)	1,919 (73.3)
Weight, median [IQR], kg	84 [73, 96]	84 [74, 96]	84 [75, 95]
Diabetes	703/2,543 (27.6)	713/2,595 (27.5)	721/2,603 (27.7)
Insulin-requiring	205/703 (29.2)	208/713 (29.2)	224/721 (31.1)
Hypertension	1,673/2,546 (65.7)	1,690/2,594 (65.2)	1,714/2,611 (65.6)
Hyperlipidemia	1,409/2,519 (55.9)	1,440/2,555 (56.4)	1436/2566 (56.0)
Current smoker	770/2,507 (30.7)	797/2,563 (31.1)	795/2,571 (30.9)
Prior MI	761/2,506 (30.4)	760/2,549 (29.8)	798/2,565 (31.1)
Prior PCI	979/2,545 (38.5)	978/2,585 (37.8)	1030/2,596 (39.7)
Prior CABG	442/2,555 (17.3)	450/2,605 (17.3)	468/2,613 (17.9)
Renal insufficiency*	136/2,534 (5.4)	156/2,579 (6.0)	158/2,599 (6.1)
Baseline high-risk features			
Elevated cardiac biomarker or ST-segment deviation ≥1 mm	1,874/2,441 (76.8)	1,886/2,506 (75.3)	1,931/2,508 (77.0)
Elevated cardiac biomarker (CK-MB or troponin)	1,547/2,376 (65.1)	1,555/2,439 (63.8)	1,626/2,450 (66.4)
Elevated troponin	1,436/2,215 (64.8)	1,447/2,308 (62.7)	1,513/2,285 (66.2)
Baseline ST-segment deviation ≥1 mm	907/2,559 (35.4)	958/2,608 (36.7)	923/2,618 (35.3)
TIMI risk score			
0–2	377/2,262 (16.7)	357/2,328 (15.3)	376/2,346 (16.0)
3–4	1,179/2,262 (52.1)	1,272/2,328 (54.6)	1,248/2,346 (53.2)
5–7	706/2,262 (31.2)	699/2,328 (30.0)	722/2,346 (30.8)

*Calculated creatinine clearance using the Cockcroft-Gault equation <60 ml/min.

CABG = coronary artery bypass graft; CK-MB = creatine kinase-myocardial band; GP = glycoprotein; IQR = interquartile ratio; MI = myocardial infarction; PCI = percutaneous coronary intervention; TIMI = Thrombolysis In Myocardial Infarction; UFH = unfractionated heparin.

The median time from randomization to PCI was 4.9 h in the heparin plus GP IIb/IIIa group, 4.9 h in the bivalirudin plus GP IIb/IIIa inhibitor group, and 5.1 h in the bivalirudin monotherapy group. Major bleeding occurred in 7% of the UFH/enoxaparin plus GP IIb/IIIa inhibitor group and 4% in the bivalirudin group, $p < 0.0001$. Patients experiencing a major bleed had a significantly longer hospital stay than those without a major bleed (5.0 days vs. 3.0 days, respectively, $p < 0.0001$). No differences were observed in rates of composite ischemia or mortality at 1 year in those who received bivalirudin with or without a GP IIb/IIIa inhibitor compared with those who received UFH or enoxaparin plus a GP IIb/IIIa inhibitor (Table 2). At 1 year, 82, 85, and 80 patients had died in the UFH or enoxaparin plus GP IIb/IIIa inhibitor, bivalirudin plus GP IIb/IIIa inhibitor, and bivalirudin monotherapy arms, respectively. Between 30 days and 1 year, 58, 55, and 52 patients died in the 3 groups, respectively.

The interaction p value for patients treated with PCI versus patients in the overall ACUITY trial is $p = 0.592$ for the 3 groups and $p = 0.701$ for bivalirudin versus UFH/enoxaparin plus GP IIb/IIIa antagonist. The incidence of composite ischemia for upfront use of GP IIb/IIIa antagonists versus in-lab use was 17.2% versus 18.4%, $p = 0.439$ for UFH/enoxaparin and 17.4% versus 21.5%, $p = 0.009$ for bivalirudin; and for death 3.1% versus 3.3%, $p = 0.0870$ for UFH/enoxaparin and 2.8% versus 3.7%, $p = 0.209$ for bivalirudin.

Results were similar in patients previously treated with UFH or enoxaparin and switched to bivalirudin monotherapy at randomization. There were no significant differences in rates of 1-year mortality (2.7% vs. 2.9% [HR: 0.93,

Table 2 Clinical Outcomes at 1 Year in Patients Undergoing PCI

	Heparin (UFH or Enoxaparin) + GP IIb/IIIa Inhibitor (n = 2,561) (%)	Bivalirudin + GP IIb/IIIa Inhibitor (n = 2,609) (%)	Hazard Ratio (95% CI)	p Value*	Bivalirudin Alone (n = 2,619) (%)	Hazard Ratio (95% CI)	p Value†
Composite ischemia	456 (17.8)	507 (19.4)	1.11 (0.98–1.26)	0.11	502 (19.2)	1.09 (0.96–1.23)	0.19
Death from any cause	82 (3.2)	85 (3.3)	1.02 (0.75–1.38)	0.91	80 (3.1)	0.95 (0.70–1.30)	0.76
Myocardial infarction	201 (7.8)	237 (9.1)	1.17 (0.97–1.41)	0.10	244 (9.3)	1.19 (0.99–1.44)	0.06
Unplanned revascularization for ischemia	292 (11.4)	326 (12.5)	1.11 (0.94–1.29)	0.21	310 (11.8)	1.04 (0.89–1.22)	0.63

*Comparison between bivalirudin plus a GP IIb/IIIa inhibitor and heparin (UFH or enoxaparin) plus a GP IIb/IIIa inhibitor. †Comparison between bivalirudin alone and heparin (UFH or enoxaparin) plus a GP IIb/IIIa inhibitor.

CI = confidence interval; other abbreviations as in Table 1.

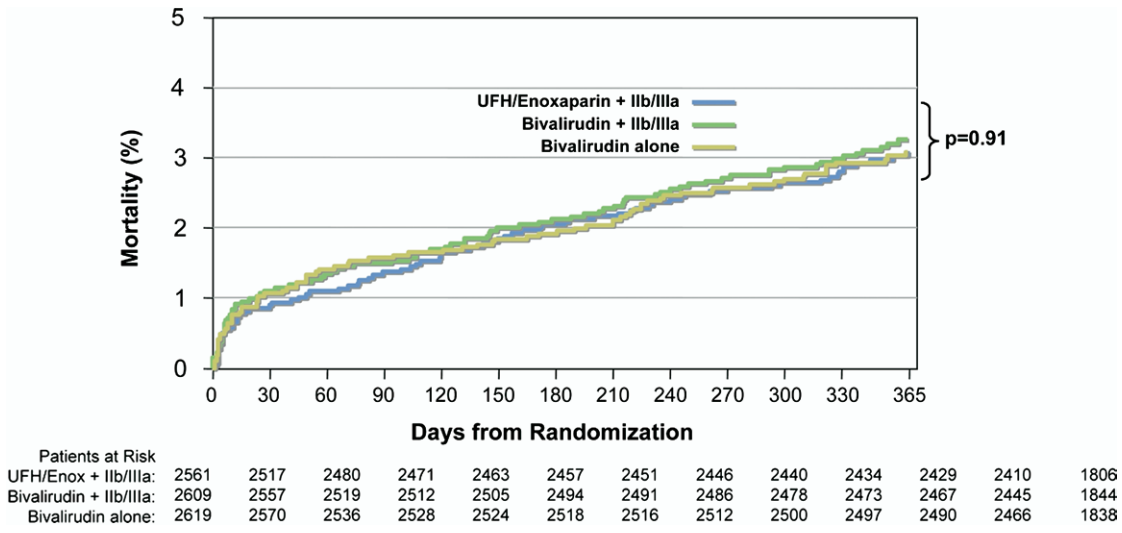

Figure 2 **Time to Death**

Time-to-event curve comparing patients randomized to heparin (unfractionated or enoxaparin) plus GP IIb/IIIa inhibitors, bivalirudin plus GP IIb/IIIa inhibitors, and bivalirudin monotherapy for mortality with a log-rank p value. Enox = enoxaparin; other abbreviations as in Figure 1.

95% CI: 0.58 to 1.48], p = 0.75) or composite ischemia (18.0% vs. 18.4% [HR: 0.99, 95% CI: 0.82 to 1.19], p = 0.89) compared with rates in patients who received consistent therapy with UFH or enoxaparin.

Treatment effects with respect to composite ischemia were consistent across multiple subgroups examined, with the exception of the impact of clopidogrel administration. However, no interaction was observed with respect to mortality (Figs. 3A and 3B). No significant interactions for composite ischemia or mortality were noted with regard to age, gender, diabetic status, renal function, baseline risk (elevated creatine kinase-myocardial band/troponin, ST-segment deviations, and TIMI risk scores), and time to intervention.

Discussion

This analysis of patients undergoing PCI from the ACUITY trial demonstrates that, in addition to significantly less bleeding at 30 days, treatment with bivalirudin monotherapy yields comparable 1-year composite ischemia and mortality compared with UFH or enoxaparin plus a GP IIb/IIIa inhibitor. These findings were observed regardless of the timing of thienopyridine pretreatment, baseline high-risk characteristics, and prior antithrombin treatment.

These results are consistent with the overall ACUITY trial, in which bivalirudin monotherapy (with provisional use of GP IIb/IIIa inhibitors in <10% of patients) resulted in similar rates of composite ischemia and mortality at 1 year (20). In the current study, mortality was similar in the bivalirudin and heparin plus GP IIb/IIIa arms despite the 41% reduction in bleeding with bivalirudin and the significant association of major bleeding with 1-year mortality. This is not surprising given that the ACUITY trial was statistically powered for 30-day composite ischemia and bleeding end points, not for mortality at 12 months. A substantially larger study would have been required to show an effect of bleeding. Further, the numerical difference in MI would not be expected to differentially affect mortality among treatment arms.

The reduced rates of major bleeding after PCI with bivalirudin is an important finding, as multiple studies (7–10) have reported a strong association between bleeding complications in ACS and in PCI with mortality. In the REPLACE-2 trial in elective and lower-risk ACS patients undergoing PCI (21), which showed that there were significantly higher mortality rates at 30 days, 6 months, and 1 year in patients who had major bleeding compared with those who did not, major bleeding was an independent predictor of 1-year mortality (odds ratio: 2.66, 95% CI: 1.44 to 4.92, p = 0.002). In the overall ACUITY trial, major bleeding was an independent predictor of 30-day mortality (odds ratio: 7.55, 95% CI 4.68 to 12.18, p < 0.0001) (11).

The findings of the present analysis were consistent across multiple subgroups, including patients with high-risk baseline characteristics, diabetes, and renal insufficiency. These data also suggest that long-term survival after bivalirudin in patients with ACS undergoing PCI is not dependent on the timing of clopidogrel administration. No interaction existed for mortality and clopidogrel use, and the interaction observed for composite ischemia

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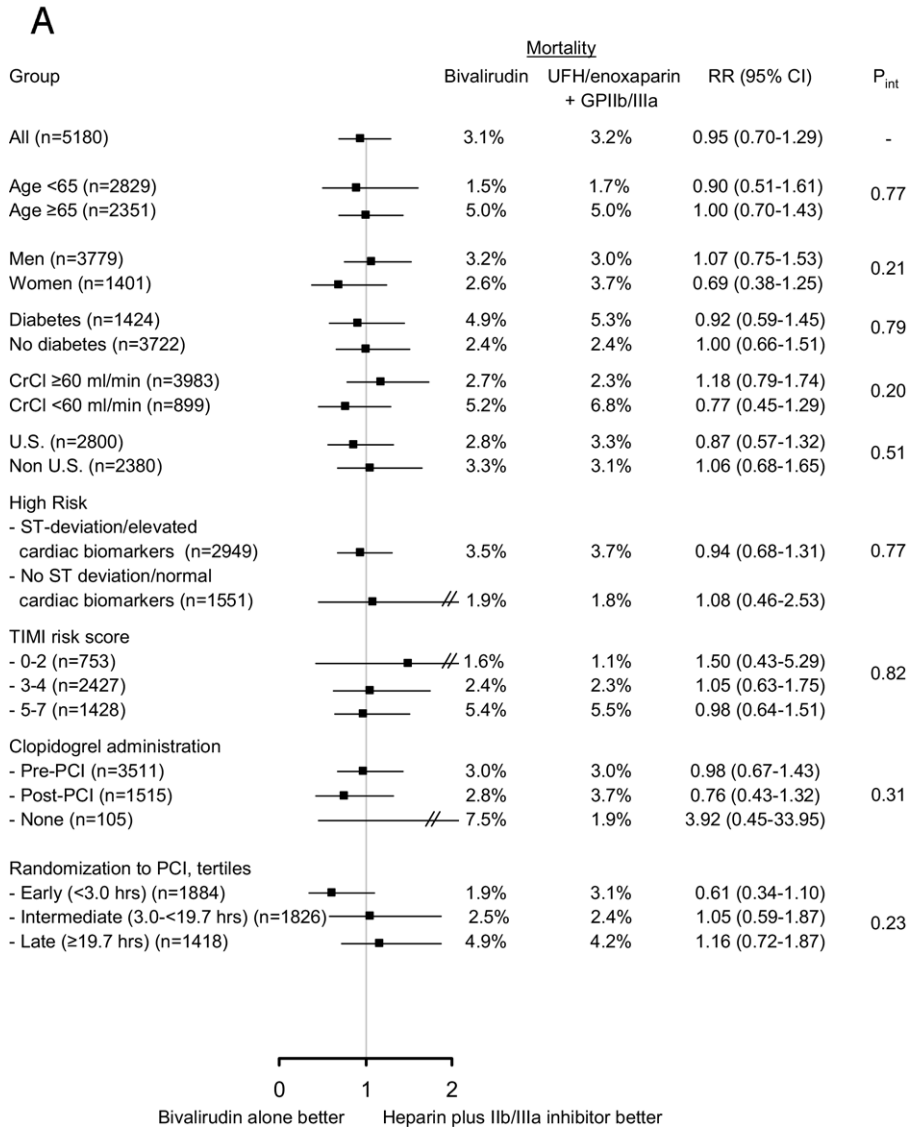

Figure 3 **Mortality and Composite Ischemia in Subgroups**

Comparison of mortality **(A)** and composite ischemia **(B)** in patients randomly assigned to UFH or enoxaparin plus a GP IIb/IIIa inhibitor versus bivalirudin monotherapy, displayed as risk ratio (RR) **(black boxes)** with 95% CI **(horizontal lines)**. CI = confidence interval; CrCl = creatinine clearance; p_{int} = value for the interaction between the variable and the relative treatment effect; TIMI = Thrombolysis In Myocardial Infarction; other abbreviations as in Figure 1. *Continued on next page.*

seemed to be largely driven by patients who did not receive clopidogrel.

Many patients with NSTE-ACS are initiated on an antithrombin agent either in a transferring hospital or in the emergency department before angiography (22). In the SYNERGY (Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors) trial (22), there was no difference in ischemic outcomes between enoxaparin and UFH, but significantly more bleeding in the enoxaparin arm. In the SYNERGY trial, crossover from UFH to enoxaparin or vice versa was associated with increased bleeding rates. However in the REPLACE-2 trial, patients who switched at the time of randomization from UFH or enoxaparin to bivalirudin had no increase in bleeding (23). Conversely, in patients randomized to receive UFH plus GP IIb/IIIa inhibitors, pre-treatment with either UFH or enoxaparin was associated with increased major and minor bleeding as well as transfusions. In the present analysis, a protocol-mandated switch at randomization to bivalirudin monotherapy from prior UFH or enoxaparin resulted in similar 1-year mortality rates of 2.9% versus 2.7% in patients treated with bivalirudin monotherapy compared with UFH or enoxaparin plus GP IIb/IIIa inhibition. These findings demonstrate that patients undergoing PCI can be safely switched to bivalirudin monotherapy from UFH

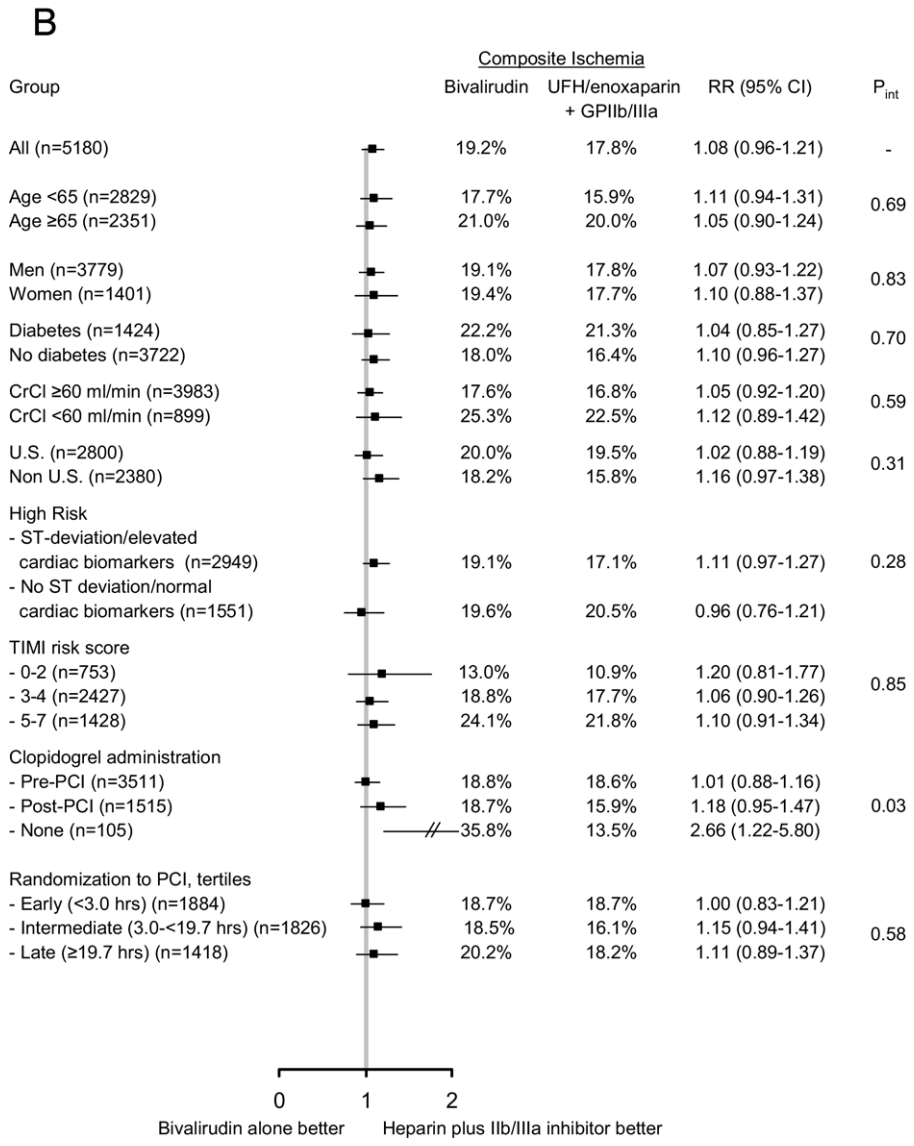

Figure 3 Continued

or enoxaparin, gaining the advantage of an approximate 43% reduction in bleeding with bivalirudin in patients undergoing PCI without increasing 30-day ischemic events or long-term mortality (16).

Prevention of major bleeds may also translate into a reduction in hospital costs. In the present analysis, PCI patients experiencing a major bleed had a significantly longer hospital stay compared with those who did not bleed. An analysis of the REPLACE-2 trial (23) found that treatment with bivalirudin with provisional use of GP IIb/IIIa inhibitors resulted in a $405 and $374 reduction in in-hospital and 30-day costs, respectively, compared with heparin plus a GP IIb/IIIa inhibitor. Hospital savings were due primarily to reductions in major bleeding ($107 per patient). Given the large number of PCI procedures performed in the U.S. (>1 million/year) (24), even modest cost savings on a per patient basis have the potential to result in substantial savings to the health care system.

Study limitations. The decision to perform PCI occurred following randomization; however, the baseline characteristics of the 3 groups were well matched, and an invasive strategy was part of the design of the trial. The PCI cohort was underpowered for noninferiority testing and subgroups, and all analyses should be considered hypothesis-generating. Also, the study design was open-label, and bias may have occurred in assessment of end points. This is mitigated to some extent by all end points being adjudicated by a blinded events committee with original source documents.

Conclusions

In patients with moderate- and high-risk ACS undergoing PCI, bivalirudin alone results in significantly less bleeding at 30 days and comparable composite ischemia and mortality at 1 year compared with heparin (either unfractionated or enoxaparin) plus a GP IIb/IIIa inhibitor. These results were consistent across all subgroups examined regardless of patient risk, exposure to prior antithrombin therapy, or timing of clopidogrel administration. These findings, together with the significant reduction in bleeding at 30 days, make bivalirudin rather than UFH or enoxaparin plus a GP IIb/IIIa inhibitor an attractive antithrombotic choice for moderate- and high-risk ACS patients undergoing PCI.

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