Antithrombotic Strategies in Patients With Acute Coronary Syndromes Undergoing Early Invasive Management

One-Year Results From the ACUITY Trial

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Context At 30-day follow-up, patients with moderate- and high-risk acute coronary syndromes (ACS) undergoing early invasive treatment in the ACUITY trial with bivalirudin monotherapy vs heparin plus glycoprotein (GP) IIb/IIIa inhibitors had noninferior rates of adverse ischemic events with reduced rates of major bleeding. Deferred upstream use of GP IIb/IIIa inhibitors for selective administration to patients undergoing percutaneous coronary intervention (PCI) resulted in a significant reduction in major bleeding, although a small increase in composite ischemia could not be excluded.

Objective To determine 1-year ischemic outcomes for patients in the ACUITY trial.

Design, Setting, and Patients A prospective, randomized, open-label trial with 1-year clinical follow-up at 450 academic and community-based institutions in 17 countries. A total of 13 819 patients with moderate- and high-risk ACS undergoing invasive treatment were enrolled between August 23, 2003, and December 5, 2005.

Interventions Patients were assigned to heparin plus GP IIb/IIIa inhibitors (n=4603), bivalirudin plus GP IIb/IIIa inhibitors (n=4604), or bivalirudin monotherapy (n=4612). Of these patients, 4605 were assigned to routine upstream GP IIb/IIIa administration and 4602 were deferred to selective GP IIb/IIIa inhibitor administration.

Main Outcome Measure Composite ischemia (death, myocardial infarction, or unplanned revascularization for ischemia) at 1 year.

Results Composite ischemia at 1 year occurred in 15.4% of patients assigned to heparin plus GP IIb/IIIa inhibitors and 16.0% assigned to bivalirudin plus GP IIb/IIIa inhibitors (compared with heparin plus GP IIb/IIIa inhibitors, HR, 1.05; 95% CI, 0.95-1.16; *P*=.35), and 16.2% assigned to bivalirudin monotherapy (HR, 1.06; 95% CI, 0.95-1.17; *P*=.29). Mortality at 1 year occurred in an estimated 3.9% of patients assigned to heparin plus GP IIb/IIIa inhibitors, 3.9% assigned to bivalirudin plus GP IIb/IIIa inhibitors (HR, 0.99; 95% CI, 0.80-1.22; *P*=.92), and 3.8% assigned to bivalirudin monotherapy (HR, 0.96; 95% CI, 0.77-1.18; *P*=.67). Composite ischemia occurred in 16.3% of patients assigned to deferred use compared with 15.2% of patients assigned to upstream administration (HR, 1.08; 95% CI, 0.97-1.20; *P*=.15).

Conclusions At 1 year, no statistically significant difference in rates of composite ischemia or mortality among patients with moderate- and high-risk ACS undergoing invasive treatment with the 3 therapies was found. There was no statistically significant difference in the rates of composite ischemia between patients receiving routine upstream administration of GP IIb/IIIa inhibitors vs deferring their use for patients undergoing PCI.

Trial Registration clinicaltrials.gov Identifier: NCT00093158

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EARLY ANGIOGRAPHY FOLLOWED by interventional or surgical revascularization when appropriate has been shown to result in reduced rates of death, myocardial infarction (MI), refractory ischemia, and rehospitalization in patients with acute coronary syndromes (ACS; unstable angina or non–ST-segment elevation MI).[1,2] Because both MI and hemorrhagic complications have been associated with early and late mortality in patients with ACS and in those undergoing percutaneous coronary intervention (PCI),[3-12] the optimal adjunctive pharmacological regimen to support the invasive approach in ACS would ideally suppress adverse ischemic and thrombotic events while minimizing iatrogenic bleeding.

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In the large-scale, prospective Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial, randomization of moderate-risk and high-risk patients with ACS undergoing early invasive management to monotherapy with the direct thrombin inhibitor bivalirudin compared with a heparin-based regimen plus glycoprotein (GP) IIb/IIIa inhibitors resulted in noninferior 30-day rates of composite ischemia (7.8% vs 7.3%, respectively; $P=.32$; relative risk [RR], 1.08; 95% confidence interval [CI], 0.93-1.24) and significantly reduced major bleeding (3.0% vs 5.7%, respectively; $P<.001$; RR, 0.53; 95% CI, 0.43-0.65).[13] In addition, in a separate randomization of the patients assigned to GP IIb/IIIa inhibitors, deferring the routine upstream use of GP IIb/IIIa inhibitors for selective administration in the catheterization laboratory only to patients undergoing PCI was found in this trial to result in a significant reduction in major bleeding at 30 days (4.9% vs 6.1%, respectively; $P=.009$; RR, 0.80; 95% CI, 0.67-0.95), although a small increase in composite ischemia could not be excluded (7.9% vs 7.1%, respectively; $P=.13$; RR, 1.12; 95% CI, 0.97-1.29).[14]

The long-term effect of bivalirudin monotherapy and a deferred selective GP IIb/IIIa inhibitor utilization strategy on composite ischemia and mortality are unknown. This issue is particularly relevant given the slightly higher point estimates for composite ischemia at 30 days with these 2 therapies compared with the control therapy. Our study therefore describes the 1-year clinical outcomes of patients enrolled in the ACUITY trial.

METHODS

Patient Population

The ACUITY trial protocol has been previously described in detail.[15] In summary, patients older than 18 years with symptoms of unstable angina lasting for at least 10 minutes within the preceding 24 hours were eligible for enrollment if 1 or more of the following criteria were met: (1) new ST-segment depression or transient elevation of at least 1 mm, (2) troponin I or T or creatine kinase–MB elevation, (3) known coronary artery disease, or (4) all 4 other Thrombolysis in Myocardial Infarction (TIMI) unstable angina risk criteria[16] positive. Major exclusion criteria included acute ST-segment elevation MI or shock; bleeding diathesis or major bleed within 2 weeks; thrombocytopenia; calculated creatinine clearance level of less than 30 mL/min (to convert to mL/s, multiply by 0.0167); current warfarin use; administration of abciximab or fibrinolytic therapy within 24 hours of randomization, bivalirudin within 6 hours, 2 or more doses of low-molecular-weight heparin, or any fondaparinux use for the present admission; or allergy to study drugs or iodinated contrast that could not be premedicated. The study was approved by the institutional review board or ethics committee at each participating center, and all patients signed written informed consent.

Randomization and Study Protocol

Telephone randomization was performed using an interactive voice response system in blocks of 6 stratified by site and by the use or intent to administer a thienopyridine before angiography. Patients were equally assigned to the open-label use of 1 of 3 antithrombin regimens begun before angiography: heparin (either unfractionated or enoxaparin at site discretion) plus GP IIb/IIIa inhibitors, bivalirudin plus GP IIb/IIIa inhibitors, or bivalirudin alone (FIGURE 1). The antithrombin dosing regimens have been previously described.[15]

Patients assigned to heparin plus GP IIb/IIIa inhibitors or bivalirudin plus GP IIb/IIIa inhibitors were randomized again in a 2×2 factorial design to routine upstream GP IIb/IIIa inhibitor initiation in all patients immediately after randomization vs deferred selective GP IIb/IIIa inhibitor initiation in the catheterization laboratory only after diagnostic angiography identified which patients would undergo immediate PCI (Figure 1). Per the American College of Cardiology/American Heart Association and European Society of Cardiology guidelines, either eptifibatide or tirofiban were permitted for upstream use in ACS, and either double-bolus eptifibatide or abciximab were allowed for initiation in the catheterization laboratory before PCI.[16,17] Provisional GP IIb/IIIa inhibitor use was permitted before angiography in patients randomized to deferred GP IIb/IIIa inhibitor use for severe breakthrough ischemia, and in patients receiving bivalirudin monotherapy for protocol-specified thrombotic complications occurring during PCI. Details of the antithrombin and GP IIb/IIIa inhibitor dosing regimens have been previously described.[15]

Angiography was performed in all patients within 72 hours after randomization, after which treatment was by PCI, coronary artery bypass graft (CABG) surgery, or medication per physician discretion. Aspirin was administered either orally at 300 to 325 mg/d or intravenously at 250 to 500 mg/d during the index hospitalization, and 75 to 325 mg/d was prescribed indefinitely after discharge. The initial dosing and timing of clopidogrel were left to investigator discretion per local standards, although a 300 mg or more loading dose was required in all cases within 2 hours after PCI. Clopidogrel (75 mg/d) was recommended for 1 year in all patients with coronary artery disease.

Clinical End Points and Statistical Methods

Clinical end points were assessed at 30 days (permitted follow-up range, 25-35 days) and at 1 year (permitted follow-up range, 335-395 days). As previously described,[13,14] the primary 30-day end points of the trial included composite ischemia (death from any cause, MI, or unplanned revascularization for ischemia), major bleeding not related to CABG surgery, and net clinical outcomes (composite ischemia or

major bleeding). Only composite ischemic end points were systematically evaluated after 30 days and comprise the basis of our study. A clinical events committee blinded to treatment assignment adjudicated all 30-day and 1-year primary end point events using original source documents.

Follow-up analysis was performed by using time-to-event data (for which patients were censored at the time of withdrawal from the study or at last follow-up), are displayed using Kaplan-Meier methodology, and were compared with the log-rank test. The 1-year end point was prespecified to be determined at 365 days. Although follow-up between 365 days and 395 days was obtained in some patients, the Kaplan-Meier curves are truncated at exactly 365 days because of rapid decline in the number patients at risk after 1 year. All follow-up data and any known events to 395 days were used in the calculation of hazard ratios (HRs) and CIs so as to not exclude the contribution of any known adverse events. Because the baseline features between randomized treatment groups were well-matched, multivariate adjustment was not required.

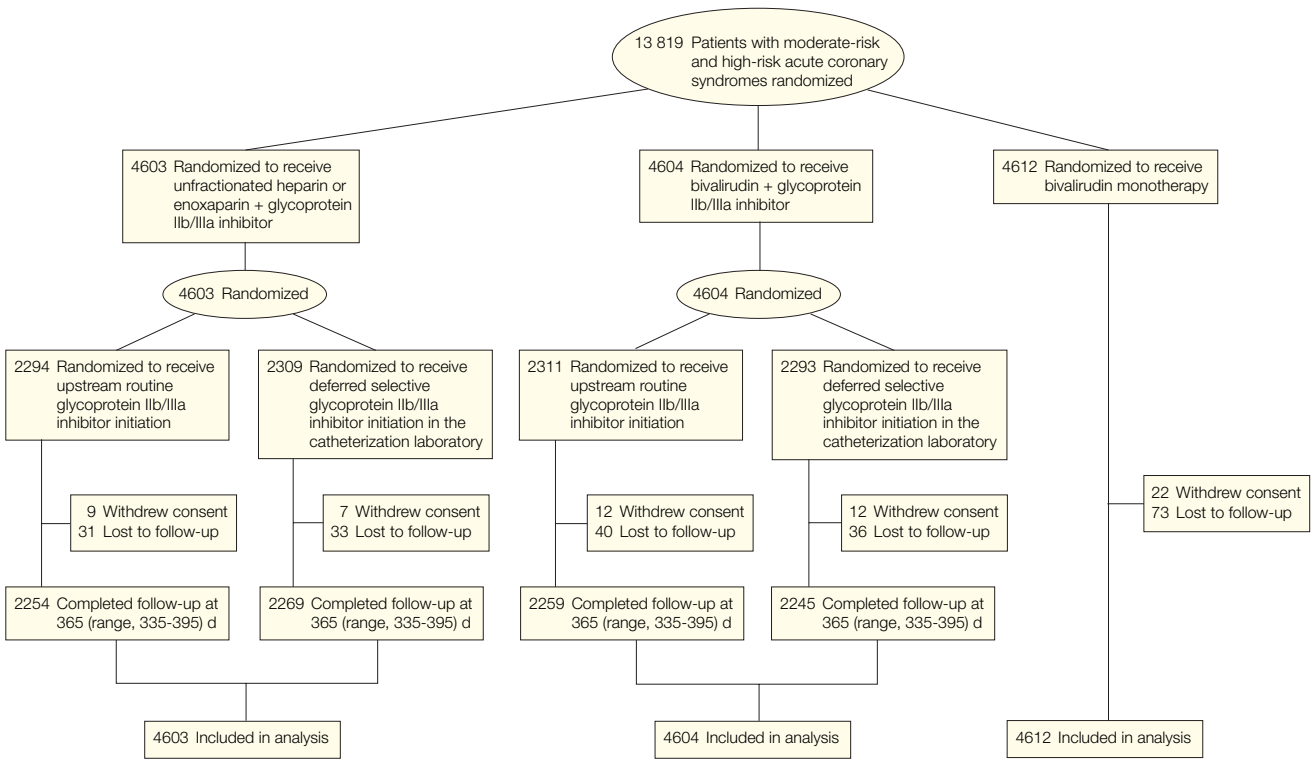
The ACUITY trial was designed as a sequential noninferiority and superiority trial for the primary end points at 30 days, with noninferiority powered using a 25% relative margin.[13,14] This study represents a prespecified analysis of 1-year events from the ACUITY trial. However, no formal noninferiority margin was prespecified at 1 year. The effects of treatment assignment on the occurrence of composite ischemia and mortality were tested in multiple subgroups (all of which were prespecified except for United States vs non-US enrollment site), with formal interaction testing to determine whether differential effects of treatment assignment were present across the subgroup strata. All statistical analyses were performed by using SAS version 8.2 (SAS Institute Inc, Cary, North Carolina) and Stata version 9.2 (StataCorp, College Station, Texas).

RESULTS

Patients

Between August 23, 2003, and December 5, 2005, 13 819 patients with ACS were enrolled at 450 academic and community-based centers in 17 countries and randomized to heparin (unfractionated or enoxaparin) plus GP IIb/IIIa inhibitors (n=4603), bivalirudin plus GP IIb/IIIa inhibitors (n=4604), or bivalirudin monotherapy (n=4612) (Figure 1). Of 9207 patients randomized to receive GP IIb/IIIa inhibitors, 4605 and 4602 patients were assigned to either routine upstream or deferred selective GP IIb/IIIa inhibitor admin-

Figure 1. Randomization Flow and Follow-up of the ACUITY Trial



ACUITY indicates Acute Catheterization and Urgent Intervention Triage Strategy. Clinical end points were assessed at 365 days (permitted follow-up range, 335-395 days). Patients who withdrew consent are censored at the time of last follow-up.

Table 1. Selected Baseline Characteristics, Medication Use, and Treatments of the Study Population[a]

Characteristics	Heparin + GP IIb/IIIa Inhibitors (n = 4603)	Bivalirudin + GP IIb/IIIa Inhibitors (n = 4604)	Bivalirudin Monotherapy (n = 4612)
Baseline features			
Age, mean (SD), y	62.7 (11.5)	62.5 (11.9)	62.5 (11.6)
Male sex	3249/4603 (70.6)	3218/4604 (69.9)	3195/4612 (69.3)
Diabetes	1298/4564 (28.4)	1267/4568 (27.7)	1287/4577 (28.1)
Hypertension	3058/4577 (66.8)	3074/4577 (67.2)	3080/4593 (67.1)
Hyperlipidemia	2580/4511 (57.2)	2588/4508 (57.4)	2579/4521 (57.0)
Current smoker	1308/4508 (29.0)	1323/4522 (29.3)	1312/4527 (29.0)
Prior myocardial infarction	1419/4493 (31.6)	1372/4491 (30.5)	1431/4499 (31.8)
Renal insufficiency[b]	826/4298 (19.2)	824/4302 (19.2)	819/4339 (18.9)
Baseline troponin or creatine kinase MB elevation	2503/4213 (59.4)	2479/4236 (58.5)	2570/4263 (60.3)
Baseline troponin elevation	2290/3931 (58.3)	2276/3980 (57.2)	2349/3971 (59.2)
Baseline ST-segment deviation ≥1 mm	1618/4598 (35.2)	1628/4599 (35.4)	1579/4607 (34.3)
Treatment strategy			
PCI	2561/4603 (55.6)	2609/4604 (56.7)	2619/4612 (56.8)
CABG surgery	549/4603 (11.9)	499/4604 (10.8)	491/4612 (10.6)
Medical therapy	1493/4603 (32.4)	1496/4604 (32.5)	1502/4612 (32.6)
Antiplatelet medication use			
Aspirin			
Before angiography or intervention	4446/4535 (98.0)	4427/4528 (97.8)	4442/4536 (97.9)
At hospital discharge	3787/4419 (85.7)	3779/4391 (86.1)	3764/4392 (85.7)
30-d follow-up[c]	4141/4470 (92.6)	4124/4442 (92.8)	4142/4451 (93.1)
1-y follow-up[c]	3789/4324 (87.6)	3816/4321 (88.3)	3830/4349 (88.1)
In patients with PCI only[c]	2235/2428 (92.1)	2259/2472 (91.4)	2312/2503 (92.4)
Thienopyridine			
Before angiography or intervention	2842/4526 (62.8)	2924/4520 (64.7)	2911/4532 (64.2)
At hospital discharge	2872/4419 (65.0)	2891/4391 (65.8)	2905/4392 (66.1)
30-d follow-up[c]	2979/4470 (66.6)	3050/4442 (68.7)	3055/4451 (68.6)
1-y follow-up[c]	1936/4324 (44.8)	1918/4321 (44.4)	1922/4349 (44.2)
In patients with PCI only[c]	1400/2428 (57.7)	1392/2472 (56.3)	1377/2503 (55.0)

Abbreviations: CABG, coronary artery bypass graft; GP, glycoprotein; PCI, percutaneous coronary intervention.
[a] Heparin indicates unfractionated heparin or enoxaparin at site discretion. Data are expressed as No./total No. (%) unless otherwise indicated. The total denominators for each treatment are represented at the top of each group column; for each cell, the specific denominator with available data is provided. Because of rounding, percentages may not total 100.
[b] Creatinine clearance calculated as less than 60 mL/min using the Cockcroft-Gault equation (to convert to mL/s, multiply by 0.0167).
[c] Taken on more than 50% of days since last visit.

istration, respectively. One-year follow-up was completed in 13 544 patients (98.0%). Selected baseline characteristics and medication use are shown in TABLE 1 and were well balanced between the 3 primary groups. Angiography was performed at a median time of 19.6 hours after admission (mean, 23.9 hours), following treatment by PCI in 7789 patients (56.4%), CABG surgery in 1539 patients (11.1%), and medical therapy in 4491 patients (32.5%). Compliance with aspirin was high throughout the 1-year period, whereas thienopyridine usage was less frequent between the 30-day and 1-year follow-up periods.

One-Year Clinical Outcomes

Compared with the control group of heparin plus GP IIb/IIIa inhibitors in which the 1-year estimated rate of composite ischemia was 15.4%, composite ischemia occurred in 16.0% of patients assigned to bivalirudin plus GP IIb/IIIa inhibitors (HR, 1.05; 95% CI, 0.95-1.16; $P = .35$) and in 16.2% of patients assigned to bivalirudin monotherapy (HR, 1.06; 95% CI, 0.95-1.17; $P = .29$) (TABLE 2 and FIGURE 2). There were no significant differences in the rates of the individual components of death, MI, or unplanned revascularization for ischemia between the 3 groups (Table 2). A total of 524 patients died within 1 year (range, 335-395 days) of randomization, including 178, 176, and 170 patients in the heparin plus GP IIb/

Table 2. Clinical Outcomes at 1 Year According to Antithrombin Randomization[a]

	Heparin + GP IIb/IIIa Inhibitors (n = 4603)[b]	Bivalirudin + GP IIb/IIIa Inhibitors (n = 4604)[b]	Hazard Ratio (95% CI)[c]	*P* Value[c]	Bivalirudin Monotherapy (n = 4612)[b]	Hazard Ratio (95% CI)[d]	*P* Value[d]
Composite ischemia	15.4 (693)	16.0 (723)	1.05 (0.95-1.16)	.35	16.2 (731)	1.06 (0.95-1.17)	.29
Death from any cause	3.9 (172)	3.9 (173)	0.99 (0.80-1.22)	.92	3.8 (169)	0.96 (0.77-1.18)	.67
Myocardial infarction	6.9 (310)	7.1 (320)	1.03 (0.88-1.21)	.68	7.8 (349)	1.13 (0.97-1.32)	.11
Q-wave	1.5 (69)	1.3 (60)	0.85 (0.60-1.19)	.34	1.5 (67)	0.96 (0.69-1.34)	.80
Non–Q-wave	5.4 (244)	5.9 (264)	1.09 (0.92-1.30)	.32	6.4 (286)	1.18 (0.99-1.40)	.054
Unplanned revascularization for ischemia	8.4 (368)	9.1 (400)	1.10 (0.96-1.27)	.16	8.7 (385)	1.05 (0.91-1.21)	.49

Abbreviations: CI, confidence interval; GP, glycoprotein.
[a] Heparin indicates unfractionated heparin or enoxaparin at site discretion.
[b] Percentages are expressed as Kaplan-Meier estimates (No. of events) at exactly 365 days.
[c] For comparison of bivalirudin plus GP IIb/IIIa inhibitors vs heparin plus GP IIb/IIIa inhibitors.
[d] For comparison of bivalirudin monotherapy vs heparin plus GP IIb/IIIa inhibitors.

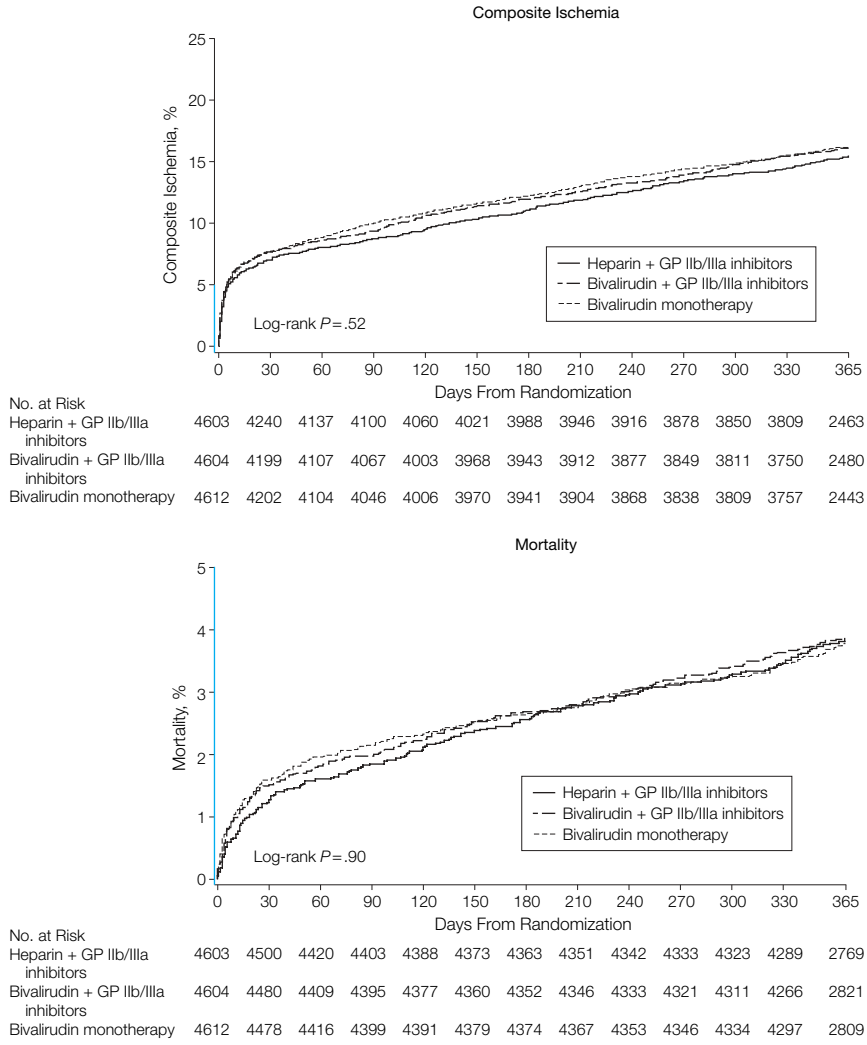
IIIa inhibitor, bivalirudin plus GP IIb/IIIa inhibitor, and bivalirudin monotherapy groups, respectively. Within the first 30 days after randomization, 64, 71, and 74 patients died in the 3 groups, respectively. Between the end of the 30-day and 1-year follow-up periods, 114, 105, and 96 patients died in the 3 groups, respectively. The 95% CI of the HR comparing bivalirudin monotherapy to heparin plus GP IIb/IIIa inhibitors during the 1-year follow-up period was 0.77 to 1.18 (Table 2). The results comparing the 3 treatment groups for 1-year composite ischemia and mortality did not materially change in a sensitivity analysis in which all patients lost to follow-up were assumed to have died the day after last patient contact.

Formal interaction testing demonstrated that the treatment comparison of bivalirudin monotherapy vs heparin plus GP IIb/IIIa inhibitors for 1-year composite ischemia was consistent across multiple prespecified subgroups, including patients biomarker-positive, those with high-risk TIMI criteria, and those treated with PCI. Although the point estimate for composite ischemia at 1 year in patients first receiving a thienopyridine either after angiography or PCI, or not at all favored heparin plus GP IIb/IIIa inhibitors, this interaction did not reach statistical significance (P=.18) (FIGURE 3). Moreover, no significant interaction between randomized treatment and any subgroup, including the timing of thienopyridine administration, was present with regard to 1-year mortality, and the point estimate and HR for 1-year mortality favored bivalirudin monotherapy in patients in whom a thienopyridine was administered either before or after angiography (FIGURE 4).

Deferred selective GP IIb/IIIa inhibitor administration compared with routine upstream use (pooled across antithrombin randomization) did not result in statistically significant differences in the 1-year rates of composite ischemia (16.3% vs 15.2%; HR, 1.08; 95% CI, 0.97-1.20; P=.15) or mortality (4.0% vs 3.8%; HR, 1.05; 95% CI, 0.85-1.29; P=.66) (FIGURE 5).

Serious adverse events within 1 year of randomization were reported by the sites (but not adjudicated by central committee) in 1439 of the 13 819 enrolled patients (10.4%). The most common adverse events included cardiac disorders (552 [4.0%]), general disorders including administration site (280 [2.0%]), infections (182 [1.3%]), respiratory disorders (164 [1.2%]), vascular disorders (126 [0.9%]), nervous system disorders (121 [0.9%]), and gastrointestinal disorders (81 [0.6%]). Any serious adverse event was reported in 491 patients assigned to heparin plus GP IIb/IIIa inhibitors (10.7%), in 455 patients assigned to bivalirudin plus GP IIb/IIIa inhibitors (9.9%), and in 493 patients assigned

Figure 2. Kaplan-Meier Estimates Comparing Patients Randomized to Heparin (Unfractionated or Enoxaparin) Plus Glycoprotein (GP) IIb/IIIa Inhibitors, Bivalirudin Plus GP IIb/IIIa Inhibitors, and Bivalirudin Monotherapy for Composite Ischemia and Mortality



Y-axis shown in blue indicates range of 0% to 5%. Compared with the control group of heparin (unfractionated or enoxaparin) plus GP IIb/IIIa inhibitors, no statistically significant difference was found in the rates of composite ischemia from bivalirudin plus GP IIb/IIIa inhibitors (log-rank P=.35) or bivalirudin monotherapy (log-rank P=.29), or in the rates of mortality from bivalirudin plus GP IIb/IIIa inhibitors (log-rank P=.92) or bivalirudin monotherapy (log-rank P=.67).

to bivalirudin monotherapy (10.7%). There were no significant differences among treatment groups in the occurrence of overall or system-specific serious adverse events.

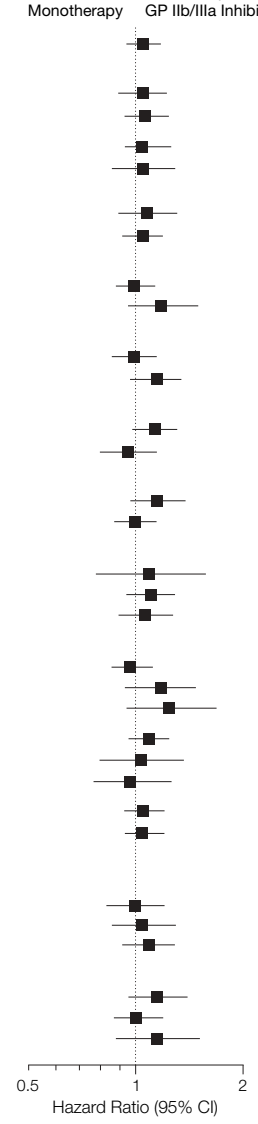
COMMENT

Antithrombotic Strategies in ACS

Therapeutic imperatives in the early treatment phase of patients with moderate-risk and high-risk ACS include coronary angiography followed by revascularization when appropriate to stabilize the ruptured atherosclerotic plaque. Evidence has accumulated demonstrating the deleterious effect of ma-

Figure 3. Subgroup Analyses Comparing Patients Randomized to Heparin Plus Glycoprotein (GP) IIb/IIIa Inhibitors and Bivalirudin Monotherapy for the 1-year Kaplan-Meier Estimated Rates of Composite Ischemia

Group	No.	Composite Ischemia, Kaplan-Meier Percentage: Bivalirudin Monotherapy	Composite Ischemia, Kaplan-Meier Percentage: Heparin + GP IIb/IIIa Inhibitor	Hazard Ratio (95% CI)	*P* Value for Interaction
All	9215	16.2	15.4	1.06 (0.95-1.17)	
Age, y					
<65	5051	14.2	13.6	1.05 (0.90-1.22)	.83
≥65	4164	18.7	17.6	1.07 (0.93-1.23)	
Men	6444	17.1	16.2	1.06 (0.94-1.20)	.96
Women	2771	14.3	13.7	1.05 (0.86-1.29)	
Diabetes					
Yes	2585	19.5	17.9	1.08 (0.90-1.30)	.91
No	6556	14.9	14.3	1.05 (0.92-1.19)	
Creatinine clearance, mL/min					
≥60	6992	14.7	14.7	1.00 (0.89-1.13)	.16
<60	1645	22.2	18.8	1.19 (0.96-1.48)	
US study site					
Yes	5224	16.5	16.6	1.00 (0.87-1.14)	.20
No	3991	15.9	13.9	1.15 (0.98-1.34)	
Creatine kinase MB/troponin I or T					
Elevated	5073	17.7	15.6	1.14 (0.99-1.30)	.12
Normal	3403	14.2	14.8	0.96 (0.80-1.14)	
ST-segment deviation					
Yes	3197	19.0	16.6	1.16 (0.98-1.37)	.16
No	6008	14.8	14.8	1.00 (0.88-1.14)	
TIMI risk score					
0-2	1291	10.4	9.5	1.10 (0.78-1.56)	.97
3-4	4407	15.5	14.2	1.11 (0.95-1.29)	
5-7	2449	21.7	20.2	1.07 (0.90-1.27)	
Thienopyridine administration					
Preangiography or PCI	5753	16.0	16.3	0.98 (0.86-1.11)	.18
Postangiography or PCI	1770	18.4	16.0	1.18 (0.94-1.47)	
None	1564	13.7	10.9	1.26 (0.95-1.68)	
PCI	5180	19.4	17.9	1.09 (0.96-1.23)	.70
CABG surgery	1040	21.1	20.7	1.04 (0.80-1.36)	
Medical therapy	2995	9.1	9.2	0.98 (0.77-1.25)	
Upstream GP IIb/IIIa inhibitor	6906	16.2	15.5	1.05 (0.93-1.20)	NA
Deferred GP IIb/IIIa inhibitor	6921	16.2	15.4	1.06 (0.93-1.20)	
Randomization to angiography or intervention (tertiles)					
Early (<3.0 h)	2918	14.6	14.7	1.00 (0.83-1.21)	.76
Intermediate (3.0-19.7 h)	2925	14.8	13.9	1.06 (0.87-1.28)	
Late (≥19.7 h)	2982	18.5	17.1	1.09 (0.92-1.29)	
Antithrombin crossovers					
No prior antithrombin	3100	16.2	13.8	1.16 (0.96-1.39)	NA
Consistent therapy	5419	16.2	15.6	1.02 (0.88-1.19)	
Crossover	3255	16.0	14.0	1.16 (0.89-1.50)	

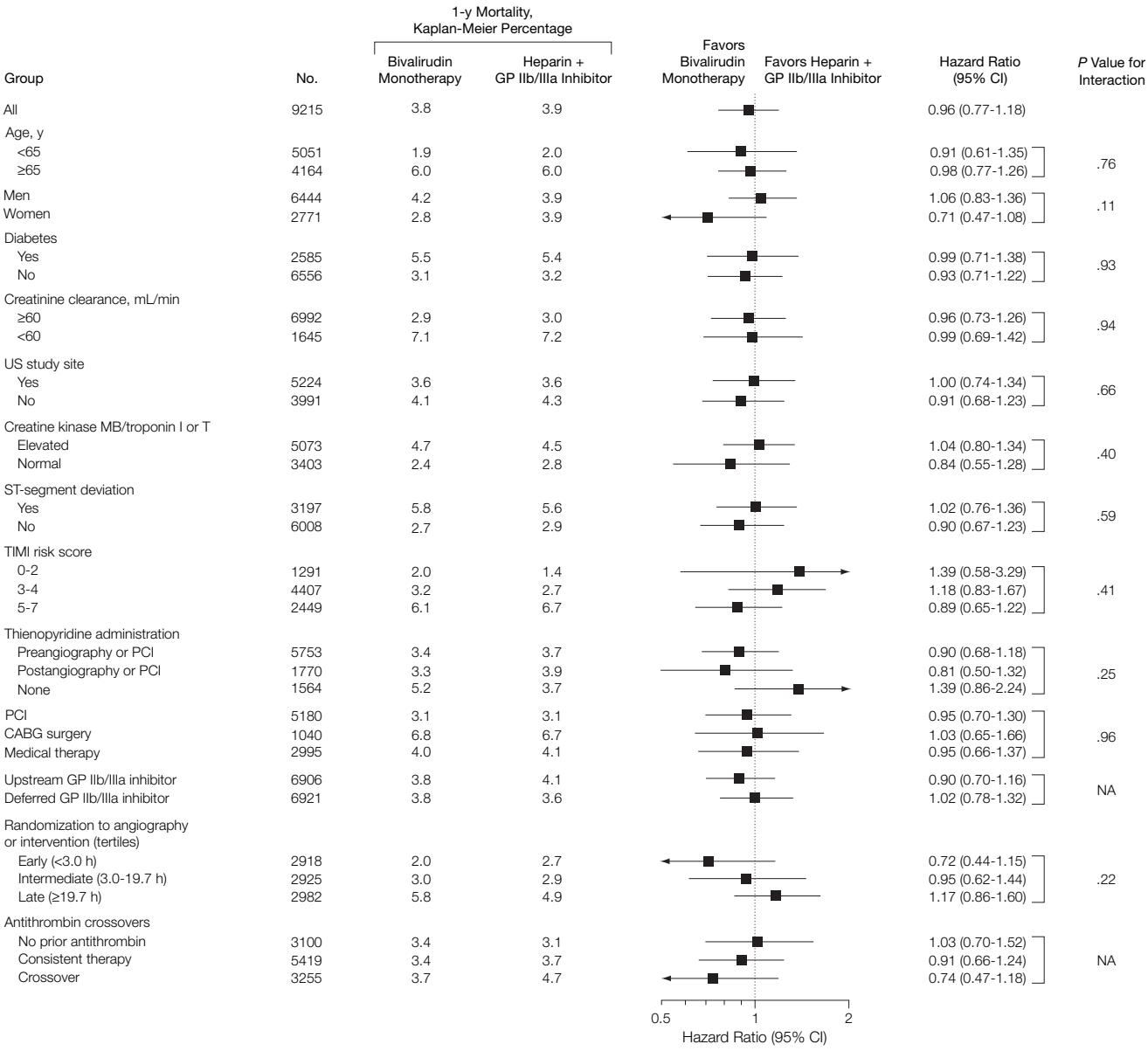


CI indicates confidence interval; TIMI, Thrombolysis in Myocardial Infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; NA, determination of interaction *P* value not applicable as the groups are not mutually exclusive. Heparin indicates unfractionated heparin or enoxaparin at site discretion. Black squares indicate hazard ratios with horizontal lines indicating 95% CIs. *P* value for interaction is the interaction between the variable and the relative treatment effect. Note that the hazard ratio reflects the relative risk over the entire 1-year period and as such does not simply reflect the rates at the end of the follow-up period. Randomization to PCI refers to the time from primary study drug randomization to the start of PCI, analyzed in 3 approximately equal-sized groups (tertiles) from shortest to longest duration of delay. The prior antithrombin subgroup analysis refers to antithrombin use before the time of randomization only.

jor bleeding as well as MI in patients with ACS and in those undergoing PCI. As such, the optimal pharmacological regimen to support an early invasive strategy in ACS would ideally suppress adverse ischemic and thrombotic events before and during intervention while minimizing iatrogenic hemorrhagic complications.

We previously reported 30-day results from the ACUITY trial. In patients with moderate-risk and high-risk ACS undergoing an early invasive strategy compared with treatment with heparin plus GP IIb/IIIa inhibitors, bivalirudin both with and without GP IIb/IIIa inhibitors was noninferior with respect to composite ischemia, and

Figure 4. Subgroup Analyses Comparing Patients Randomized to Heparin Plus Glycoprotein (GP) IIb/IIIa Inhibitors and Bivalirudin Monotherapy for the 1-year Kaplan-Meier Estimated Rates of Mortality



CI indicates confidence interval; TIMI, Thrombolysis in Myocardial Infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; NA, determination of interaction *P* value not applicable as the groups are not mutually exclusive. Heparin indicates unfractionated heparin or enoxaparin at site discretion. Black squares indicate hazard ratios with horizontal lines indicating 95% CIs. *P* value for interaction is the interaction between the variable and the relative treatment effect. Note that the hazard ratio reflects the relative risk over the entire 1-year period and as such does not simply reflect the rates at the end of the follow-up period. Randomization to PCI refers to the time from primary study drug randomization to the start of PCI, analyzed in 3 approximately equal-sized groups (tertiles) from shortest to longest duration of delay. The prior antithrombin subgroup analysis refers to antithrombin use before the time of randomization only.

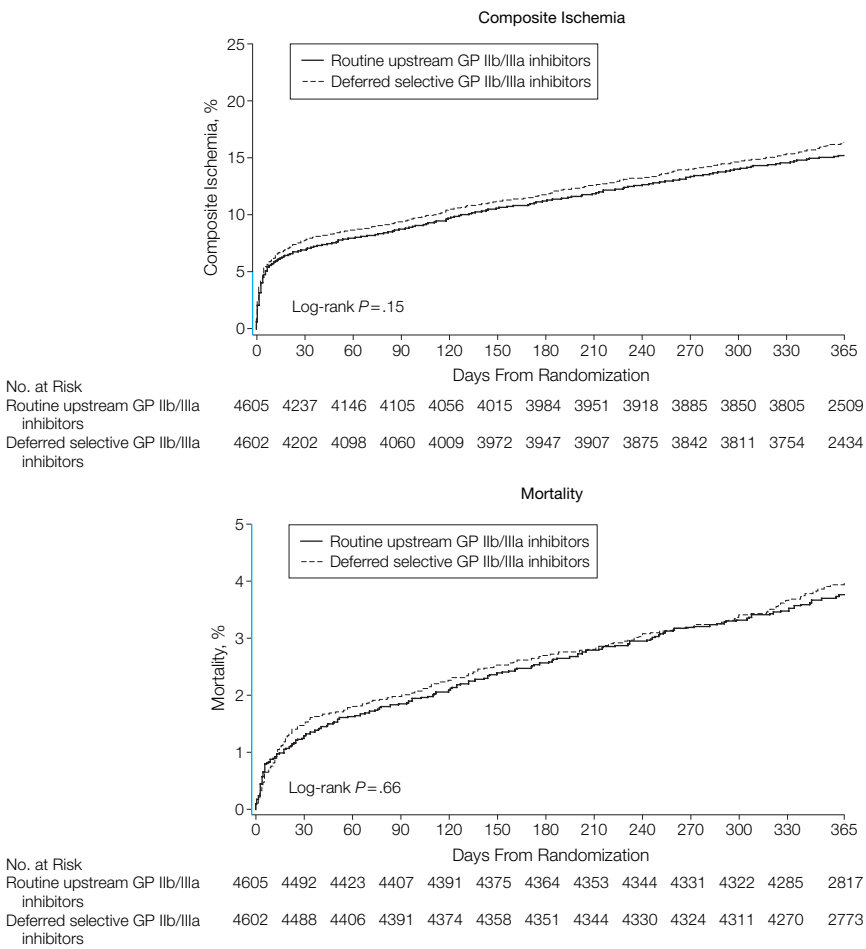
bivalirudin monotherapy was associated with decreased rates of bleeding.[13] We also reported that deferring the routine upstream use of GP IIb/IIIa inhibitors for selective administration in the catheterization laboratory only to patients undergoing PCI resulted in a significant reduction in major bleeding at 30 days, although a small increase in composite ischemia could not be excluded.

After hospital discharge, therapeutic success in patients with ACS is measured in terms of long-term survival and freedom from recurrent ischemia. Our 1-year results provide information that helps to address this issue. At 30 days, treatment with heparin plus GP IIb/IIIa inhibitors, bivalirudin with GP IIb/IIIa inhibitors, and bivalirudin monotherapy resulted in composite ischemia rates of 7.4%, 7.9%, and 8.0%, respectively.[13] Between the 30-day and 1-year follow-up periods, the absolute differences in composite ischemia between the 3 groups remained roughly parallel such that the event rates at the end of the follow-up period were not significantly different (15.4%, 16.0%, and 16.2%, respectively). The 1-year upper bound of the 95% CIs of the HRs for bivalirudin with or without GP IIb/IIIa inhibitors compared with heparin plus GP IIb/IIIa inhibitors was 1.16 and 1.17, respectively. These observed rates are consistent with what has been suggested as acceptable for clinical therapeutic interchangeability (relative difference <20%).[18]

Despite high compliance with all protocol mandated class I guideline therapies, including early revascularization,[16,17] mortality by the end of the 1-year follow-up period occurred in 524 patients, with approximately 60% of the deaths occurring after 30 days, reflecting the high-risk nature of the study cohort. Mortality between the end of the 30-day and 1-year follow-up periods occurred in 114, 105, and 96 patients assigned to heparin plus GP IIb/IIIa inhibitors, bivalirudin plus GP IIb/IIIa inhibitors, and bivalirudin monotherapy, respectively, with the curves crossing at approximately 6 months. As a result, mortality at 365 days occurred in an estimated 3.9%, 3.9%, and 3.8% of patients, respectively. The HR for 1-year mortality comparing bivalirudin monotherapy to heparin plus GP IIb/IIIa inhibitors was 0.96 (95% CI, 0.77-1.18), with an upper bound of 18% higher mortality, also consistent with clinical therapeutic interchangeability.

The observation that the rate of 1-year mortality for bivalirudin monotherapy was not statistically significantly different from heparin plus GP IIb/IIIa inhibitors may reflect the opposing effects of the risk of MI[11,12,19] (point estimate slightly but nonsignificantly greater in the bivalirudin monotherapy group) and the risk of major bleeding within 30 days[3-10] (significantly reduced in the bivalirudin monotherapy group) on subsequent mortality.[20] Further studies are required to determine whether the prevention of major bleeding directly prolongs survival and, if this were found, to elucidate the mechanisms underlying such a beneficial effect.

Figure 5. Kaplan-Meier Estimates Comparing Routine Upstream Glycoprotein (GP) IIb/IIIa Inhibitor Administration and Deferred Selective GP IIb/IIIa Inhibitor Administration for Composite Ischemia and Mortality



Y-axis shown in blue indicates range of 0% to 5%.

Subgroup Analysis

Formal interaction testing among patients randomized to bivalirudin monotherapy vs heparin plus GP IIb/IIIa inhibitors revealed no treatment differences related to multiple baseline demographic and procedural vari-

ables for the occurrence of composite ischemia at 1 year. Although composite ischemia by 1 year tended to occur more frequently in patients randomized to bivalirudin monotherapy if a thienopyridine was not administered before angiography or PCI, this interaction was not statistically significant ($P=.18$). Moreover, the point estimate for mortality at 1 year favored bivalirudin monotherapy in patients in whom a thienopyridine was administered either before or after angiography. Mortality rates at 1 year were also comparable in other subgroups of patients treated with bivalirudin monotherapy compared with heparin plus GP IIb/IIIa inhibitors, including those with increased baseline troponin or creatine kinase MB levels, ST-segment deviation, high TIMI unstable angina risk score, advanced age, and renal insufficiency.

GP IIb/IIIa Inhibitor Administration Strategies

Deferred selective GP IIb/IIIa inhibitor use compared with routine upstream GP IIb/IIIa inhibitor administration resulted in a nonsignificant slightly greater point estimate for 1-year composite ischemia, with the upper bound of the 95% CI of the HR being 1.20. The observed rates of mortality at 1 year were nearly identical with these 2 strategies (4.0% and 3.8%, respectively), despite nonsignificant but numerical increases in the occurrence of MI and unplanned revascularization for ischemia with the selective approach. This observation might be due to the reduction in 30-day bleeding with the deferred selective use of GP IIb/IIIa inhibitors compared with their routine upstream administration.[14]

Study Strengths and Limitations

The ACUITY trial was designed and powered to evaluate sequential noninferiority and superiority between the 3 antithrombin regimens and the 2 glycoprotein utilization strategies for the 30-day composite end points of composite ischemia, major bleeding, and net clinical outcomes. Formal noninferiority or superiority hypotheses were not prespecified for 1 year and the power for the 1-year analysis was not prospectively determined. As such, the results of our study should be considered exploratory and hypothesis generating. Nonetheless, with relatively high mortality in this large prospective study and with 1-year follow-up achieved in 98% of patients, large differences in the 1-year rates of composite ischemia and mortality between bivalirudin monotherapy and heparin plus GP IIb/IIIa inhibitors, and in composite ischemia between the different GP IIb/IIIa inhibitor utilization strategies, are unlikely.

Our study did not have optimal power for robust superiority or noninferiority testing among the subgroups, the results of which should also be considered hypothesis generating, especially given noncorrection for multiple comparisons.[21] In addition, interaction testing is inherently underpowered and we cannot exclude that significant differences may exist in some of the subgroups, especially those in which the HRs vary moderately between groups. Further study is also required to determine the optimal antithrombotic and antiplatelet regimens in patients with ACS excluded from randomization, such as those with severe renal insufficiency or in patients treated conservatively without early invasive treatment.

Other limitations of the ACUITY trial have been previously discussed and apply to this study.[13,14] In brief, the logistic complexities of the trial necessitated an open-label design, mitigated by adjudication of all primary clinical end point events through 1 year by an independent committee blinded to treatment assignment and requiring original source documents for confirmation. To reflect current practice, the selection of unfractionated heparin vs enoxaparin and the choice of eptifibatide vs tirofiban for upstream use or eptifibatide vs abciximab for catheterization laboratory initiation were left to physician discretion, given the lack of randomized studies demonstrating clinically important differences in outcomes between these agents for their indicated uses.[22] Further study, including propensity adjustment for the selection of one agent vs another, is required to exclude any possible effect of this pooling on the study conclusions. Analysis regarding the impact of dosing errors and protocol nonadherence in the treatment and control groups also has not yet been completed.

Crossover from prerandomization heparin to bivalirudin was common and may have adversely affected the results among patients treated with bivalirudin. Given the heterogeneous nature of the patients enrolled and therapies received, including the decision whether to administer clopidogrel before angiography, varying choice of antithrombin and antiplatelet agents, and treatment of patients following angiography with either PCI, CABG, or medical therapy (the thresholds for which vary between physicians), definitive conclusions cannot be made regarding the relative safety and efficacy of the assigned treatments in all scenarios.

CONCLUSIONS

At 1-year follow-up of the ACUITY trial, there was no statistically significant difference in rates of composite ischemia or mortality among patients with moderate-risk and high-risk ACS undergoing invasive treatment with heparin plus GP IIb/IIIa inhibitors, bivalirudin plus GP IIb/IIIa inhibitors, or bivalirudin monotherapy. There was no statistically significant difference in rates of composite ischemia between patients receiving routine upstream administration of GP IIb/IIIa inhibitors vs deferring their use for patients undergoing PCI.

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Manoukian); and London School of Hygiene and Tropical Medicine, London, England (Dr Pocock and Mr Clayton).

Author Contributions: Dr Stone had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition of data: Moses, White, Feit, Colombo, McLaurin, Cox, Manoukian, Mehran.

Analysis and interpretation of data: Stone, Ware, Bertrand, Lincoff, Moses, Ohman, White, Colombo, Cox, Manoukian, Fahy, Clayton, Mehran, Pocock.

Drafting of the manuscript: Stone.

Critical revision of the manuscript for important intellectual content: Ware, Bertrand, Lincoff, Moses, Ohman, White, Feit, Colombo, McLaurin, Cox, Manoukian, Fahy, Clayton, Mehran, Pocock.

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Independent Statistical Analysis: The accuracy of the data analysis was independently verified by Martin Fahy, MSc (The Cardiovascular Research Foundation, an affiliate of Columbia University), and Tim Clayton, MSc (The London School of Hygiene and Tropical Medicine), both of whom received the entire raw database as well as the analysis plan, and collectively replicated the analyses that were reported in the accepted manuscript. No discrepancies were discovered. Neither Mr Fahy nor Mr Clayton or their parent institutions received any funding for this independent analysis.

A complete list of the ACUITY Investigators was published previously as an online appendix to *N Engl J Med*. 2006;355:2203-2216.

REFERENCES

1. Mehta SR, Cannon CP, Fox KA, et al. Routine vs selective invasive strategies in patients with acute coronary syndromes: a collaborative meta-analysis of randomized trials. *JAMA*. 2005;293(23):2908-2917.

2. Bavry AA, Kumbhani DJ, Rassi AN, Bhatt DL, Askari AT. Benefit of early invasive therapy in acute coronary syndromes: a meta-analysis of contemporary randomized clinical trials. *J Am Coll Cardiol*. 2006;48(7):1319-1325.

3. Moscucci M, Fox KA, Cannon CP, et al. Predictors of major bleeding in acute coronary syndromes: the Global Registry of Acute Coronary Events (GRACE). *Eur Heart J*. 2003;24(20):1815-1823.

4. Segev A, Strauss BH, Tan M, et al. Predictors and 1-year outcome of major bleeding in patients with non-ST-elevation acute coronary syndromes: insights from the Canadian Acute Coronary Syndrome Registries. *Am Heart J*. 2005;150(4):690-694.

5. Rao SV, O'Grady K, Pieper KS, et al. Impact of bleeding severity on clinical outcomes among patients with acute coronary syndromes. *Am J Cardiol*. 2005;96(9):1200-1206.

6. Eikelboom JW, Mehta SR, Anand SS, et al. Adverse impact of bleeding on prognosis in patients with acute coronary syndromes. *Circulation*. 2006;114(8):774-782.

7. Rothman MT. Drug insight: bleeding after percutaneous coronary intervention-risks, measures and impact of anticoagulant treatment options. *Nat Clin Pract Cardiovasc Med*. 2005;2(9):465-474.

8. Kinnaird TD, Stabile E, Mintz GS, et al. Incidence, predictors, and prognostic implications of bleeding and blood transfusion following percutaneous coronary interventions. *Am J Cardiol*. 2003;92(8):930-935.

9. Rao SV, Jollis JG, Harrington RA, et al. Relationship of blood transfusion and clinical outcomes in patients with acute coronary syndromes. *JAMA*. 2004;292(13):1555-1562.

10. Stone GW. Advantages of direct thrombin inhibition in high- and low-risk patients *J Invasive Cardiol*. 2004;16(suppl G):12-17.

11. Ellis SG, Chew D, Chan A, et al. Death following creatine kinase-MB elevation after coronary intervention. *Circulation*. 2002;106(10):1205-1210.

12. Stone GW, Mehran R, Dangas G, et al. Differential impact on survival of electrocardiographic Q-wave versus enzymatic myocardial infarction after percutaneous intervention: a device-specific analysis of 7147 patients. *Circulation*. 2001;104(6):642-647.

13. Stone GW, McLaurin BT, Cox DA, et al; ACUITY Investigators. Bivalirudin for patients with acute coronary syndromes. *N Engl J Med*. 2006;355(21):2203-2216.

14. Stone GW, Bertrand ME, Moses JW, et al. Routine upstream initiation vs deferred selective use of glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: the ACUITY timing trial. *JAMA*. 2007;297(6):591-602.

15. Stone GW, Bertrand M, Colombo A, et al. Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial: study design and rationale. *Am Heart J*. 2004;148(5):764-775.

16. Braunwald E, Antman EM, Beasley JW, et al. ACC/AHA guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction, 2002: summary article. *Circulation*. 2002;106(14):1893-1900.

17. Bertrand ME, Simoons ML, Fox KA, et al; Task Force on the Management of Acute Coronary Syndromes of the European Society of Cardiology. Management of acute coronary syndromes in patients presenting without persistent ST-segment elevation [published corrections appear in *Eur Heart J*. 2003;24:485 and *Eur Heart J*. 2003;24:1174-1175]. *Eur Heart J*. 2002;23(23):1809-1840.

18. Ware JH, Antman EM. Equivalence trials. *N Engl J Med*. 1997;337(16):1159-1161.

19. Antman EM, Braunwald E. Acute myocardial infarction. In: Braunwald E, ed. *Heart Disease: A Textbook of Cardiovascular Medicine*. Philadelphia, PA: WB Saunders Co; 1997:1184-1288.

20. Lincoff AM, Kleiman NS, Kereiakes DJ, et al. Long-term efficacy of bivalirudin and provisional glycoprotein IIb/IIIa blockade vs heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary revascularization: REPLACE-2 randomized trial. *JAMA*. 2004;292(6):696-703.

21. Hernández AV, Boersma E, Murray GD, Habbema JD, Steyerberg EW. Subgroup analyses in therapeutic cardiovascular clinical trials: are most of them misleading? *Am Heart J*. 2006;151(2):257-264.

22. Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non ST-Elevation Myocardial Infarction): developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons: endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine [published ahead of print August 6, 2007]. *Circulation*. 2007;116(7):e148-e304.

