Journal of the American College of Cardiology Vol. 52, No. 22, 2008

Published by Elsevier Inc.
ISSN 0735-1097/08/$34.00
doi:10.1016/j.jacc.2008.08.021

Economic Evaluation of Bivalirudin With or Without Glycoprotein IIb/IIIa Inhibition Versus Heparin With Routine Glycoprotein IIb/IIIa Inhibition for Early Invasive Management of Acute Coronary Syndromes

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Objectives The aim of this study was to determine the economic impact of several anticoagulation strategies for moderate- and high-risk non–ST-segment elevation acute coronary syndrome (NSTE-ACS) patients managed invasively.

Background The ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial demonstrated that bivalirudin monotherapy yields similar rates of ischemic complications and less bleeding than regimens incorporating glycoprotein IIb/IIIa receptor inhibitors (GPI) for moderate- and high-risk NSTE-ACS.

Methods In ACUITY, 7,851 U.S. patients were randomized to: 1) heparin (unfractionated or enoxaparin) + GPI; 2) bivalirudin + GPI; or 3) bivalirudin monotherapy. Patients assigned to GPI were also randomized to upstream GPI before catheterization or selective GPI only with percutaneous coronary intervention. Resource use data were collected prospectively through 30-day follow-up. Costs were estimated with standard methods including resource-based accounting, hospital billing data, and the Medicare fee schedule.

Results At 30 days, ischemic events were similar for all groups. Major bleeding was reduced with bivalirudin monotherapy compared with heparin + GPI or bivalirudin + GPI ($p < 0.001$). Length of stay was lowest with bivalirudin monotherapy or bivalirudin + catheterization laboratory GPI ($p = 0.02$). Despite higher drug costs, aggregate hospital stay costs were lowest with bivalirudin monotherapy (mean difference range: $184 to $1,081, $p < 0.001$ for overall comparison) and at 30 days (mean difference range: $123 to $938, $p = 0.005$). Regression modeling demonstrated that hospital savings were primarily due to less major and minor bleeding with bivalirudin ($8,658/event and $2,282/event, respectively).

Conclusions Among U.S. patients in the ACUITY trial, bivalirudin monotherapy compared with heparin + GPI resulted in similar protection from ischemic events, reduced bleeding, and shorter length of stay. Despite higher drug costs, aggregate hospital and 30-day costs were lowest with bivalirudin monotherapy. Thus bivalirudin monotherapy seems to be an economically attractive alternative to heparin + GPI for patients with moderate- and high-risk NSTE-ACS. (Comparison of Angiomax Versus Heparin in Acute Coronary Syndromes [ACS]; NCT00093158) (J Am Coll Cardiol 2008;52:1758–68) © 2008 by the American College of Cardiology Foundation

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Manuscript received January 14, 2008; revised manuscript received July 7, 2008, accepted August 11, 2008.

The ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial investigated whether antithrombotic therapy with bivalirudin—either alone (monotherapy) or in conjunction with a parenteral glycoprotein IIb/IIIa receptor antagonist (GPI)—could yield improved outcomes for a broad population of patients with moderate- and high-risk acute coronary syndrome (ACS) undergoing an early invasive strategy (1). The overall results of the ACUITY trial demonstrated that bivalirudin monotherapy was statistically noninferior to heparin + GPI and bivalirudin + GPI in terms of ischemic complications but was associated with substantially lower rates of bleeding complications. However, the economic impact of using bivalirudin in this setting remains unknown. In particular, there has been concern that prolonged periods of pre-treatment before performance of cardiac catheterization and revascularization could lead to substantially higher costs with this novel therapy.

We therefore performed a prospective economic evaluation, from the perspective of the U.S. health care system, in conjunction with the ACUITY trial. The objectives of the study were: 1) to compare the in-hospital and 30-day costs of using bivalirudin monotherapy with those of heparin + GPI or bivalirudin + GPI among patients with ACS undergoing an early invasive strategy; and 2) to explore the impact of both ischemic and bleeding complications on the cost of care for this common condition.

Abbreviations and Acronyms

CABG = coronary artery bypass graft surgery
GPI = glycoprotein IIb/IIIa receptor antagonist
LMWH = low-molecular weight heparin
LOS = length of stay
MI = myocardial infarction
NSTE-ACS = non–ST-segment elevation acute coronary syndrome
PCI = percutaneous coronary intervention
UFH = unfractionated heparin

Methods

Patient population and treatment protocol. Between August 2003 and December 2005, 13,819 patients were enrolled in the ACUITY trial. As specified in the study protocol, the economic analysis was confined to those patients enrolled at U.S. treatment sites (n = 7,851). The ACUITY study design has been described previously (2). Briefly, ACUITY was a prospective, open-label, randomized, multicenter trial comparing 3 antithrombotic regimens: heparin (unfractionated heparin [UFH] or low-molecular weight heparin [LMWH]) + GPI (standard care group), bivalirudin + GPI, or bivalirudin monotherapy. Patients assigned to heparin + GPI or bivalirudin + GPI were also randomly assigned again in a factorial design to routinely receive GPI immediately after randomization (the "upstream" group) or to selective deferred treatment with GPI starting in the catheterization laboratory, for use only in patients undergoing percutaneous coronary intervention (PCI). The study protocol was approved by the institutional review board at each site, and each patient provided informed consent before enrollment.

The UFH and LMWH were administered as standard, weight-adjusted doses as per current guidelines (3). Bivalirudin was begun before angiography, with an intravenous bolus of 0.1 mg/kg and an infusion of 0.25 mg/kg/h. Before PCI, an additional intravenous bolus of 0.5 mg/kg was administered, and the infusion was increased to 1.75 mg/kg/h (2). Patients assigned to receive GPI could receive either eptifibatide or tirofiban before catheterization or eptifibatide or abciximab at the time of PCI (in their approved doses). Among patients assigned to bivalirudin monotherapy, provisional GPI could be administered at the operator's discretion to treat potential thrombotic complications. All patients received aspirin before PCI, and pre-treatment with clopidogrel (300 mg) was encouraged. After PCI, all patients received aspirin indefinitely + clopidogrel (75 mg/day) for at least 30 days (1 year recommended).

Assessment of in-hospital outcomes and clinical follow-up. Baseline characteristics, procedural details, and clinical outcomes during the initial hospital stay and 30-day follow-up period were recorded on standardized case report forms. All primary end point events, including death, myocardial infarction (MI), unplanned revascularization, and major bleeding, were adjudicated according to predefined criteria by a blinded independent committee with original source documentation (2). Composite ischemia was defined as death, MI, or unplanned revascularization.

Major bleeding (ACUITY scale) was defined as intracranial bleeding, intraocular bleeding, access site hemorrhage requiring intervention, ≥5 cm diameter hematoma, reduction in hemoglobin concentration of ≥4 g/dl without an overt source of bleeding, reduction in hemoglobin concentration of ≥3 g/dl with an overt source of bleeding, reoperation for bleeding, or use of any blood product transfusion. Bleeding events attributable to coronary artery bypass graft surgery (CABG) were excluded (2).

Determination of medical care costs. Medical care costs for the initial hospital stay and for the 30-day follow-up period were assessed for all patients from the perspective of the U.S. health care system with a combination of resource-based costs and hospital billing data, as previously described (4). Costs were expressed in 2005 U.S. dollars, and discounting was not performed, given the brief time horizon of the analysis.

Cardiac catheterization laboratory costs. Detailed resource use was recorded for each procedure, and the cost of each item was estimated on the basis of the mean hospital acquisition cost for the item in 2005. Costs for antithrombotic agents (bivalirudin, tirofiban, eptifibatide, abciximab, LMWH, and UFH) were based on the actual measured bolus and infusion volumes and current average wholesale prices, assuming that partially unused vials would be discarded. Costs of bivalirudin were $412/vial, abciximab $504/vial, eptifibatide $68/bolus vial and $214/infusion vial, and tirofiban $425/vial. Costs of additional disposable equipment, overhead, and depreciation for the cardiac catheterization laboratory were esti-

mated on the basis of the average cost/procedure at Beth Israel Deaconess Medical Center in 2005 and then adjusted for actual procedure duration.

Other costs. All other hospital costs were determined with "top-down" accounting methods based on each hospital's Medicare cost report (4). For approximately 3,000 randomly selected patients, itemized bills were obtained for the initial hospital stay and any subsequent cardiovascular hospital stays during the follow-up period. In addition, we obtained billing data for all patients who experienced a major in-hospital complication. Hospital costs were then determined by multiplying itemized hospital charges by the cost-center specific cost-to-charge ratio obtained from the hospital's Medicare cost report as previously described (5,6). For those admissions for which billing data were not collected (n = 4,808), non-procedural hospital costs were imputed on the basis of a linear regression model developed with the hospital admissions for which complete billing information was available (n = 3,615). Independent variables for this model included length of stay (LOS), intensive care unit LOS, in-hospital complications, and revascularization procedures (model $R^2 = 0.75$).

Physician costs for inpatient services, procedures, and diagnostic tests were estimated on the basis of the 2005 Medicare Fee Schedule. Costs for outpatient medical services and medications were not assessed due to the short duration of follow-up for the economic analysis.

Statistical analysis. Although the primary clinical analysis compared outcomes across 3 treatment groups (heparin + GPI, bivalirudin + GPI, and bivalirudin monotherapy) and pooled data for routine upstream and deferred selective catheterization laboratory-based GPI regimens, we hypothesized that use of upstream GPI would add significantly to treatment costs. Therefore, we analyzed costs separately for each of the 5 arms: 1) heparin + upstream GPI; 2) heparin + catheterization laboratory GPI; 3) bivalirudin + upstream GPI; 4) bivalirudin + catheterization laboratory GPI; and 5) bivalirudin monotherapy. The pre-specified primary end point of the economic study was total 30-day costs. In addition, a secondary end point of index hospital costs was examined to consider the perspective of a typical hospital that is reimbursed for each episode of care.

To reduce the impact of high-cost outliers on group means, it was pre-specified in the study protocol that in-hospital and 30-day costs greater than the 99th percentile for each treatment group would be assigned costs equal to the 99th percentile for the group. Discrete data are reported as frequencies; continuous data are reported as mean ± SD. Cost data are reported as both mean and median values. Discrete variables were compared by the Fisher exact test. Normally distributed continuous variables were compared by analysis of variance. Non-normally distributed data including cost and LOS were compared by the Kruskall-Wallis test. Confidence intervals for cost differences were estimated with bootstrap resampling with bias correction (1,000 replicates) (7). All statistical analyses were performed according to the intention-to-treat principle.

Multiple linear regression was performed to identify independent predictors of initial hospital costs. Candidate variables for this analysis included patient characteristics, ischemic complications, repeat procedures, and bleeding complications as defined in the protocol. Because the goal of this analysis was explanatory rather than predictive, intermediate variables (including LOS) were not considered for these models. Untransformed cost was used as the dependent variable for these analyses for ease of interpretation and because model fit did not improve appreciably with log-transformed costs. Attributable costs were calculated by multiplying the independent cost of each event (derived from the regression model coefficients) by its frequency in the treatment group. The absolute cost savings associated with prevention of specific clinical events were estimated by multiplying the independent cost of each event by the difference in event frequency between the experimental (i.e., bivalirudin) and standard care (i.e., heparin + GPI) groups.

Results

Patient population. Baseline characteristics of the population for the economic substudy (i.e., the U.S. cohort) are summarized in Table 1. Among the 5 treatment groups, patient characteristics were generally comparable in terms of demographic characteristics, disease history, and presenting clinical features. Overall, approximately 50% of patients were biomarker positive at the time of enrollment and 87% had Thrombolysis In Myocardial Infarction risk score ≥3. Coronary angiography was performed in 99% of patients, with a median time from randomization to angiography of 4.2 h (mean 10.2 h). Approximately one-third of patients had a time from randomization to angiography of >9 h. The intended revascularization strategy was also similar across the 5 treatment groups, including planned PCI in 53% to 57% and planned CABG in 11% to 13%.

Resource use, outcomes, and costs. In-hospital resource use for the study cohort is summarized in Table 2. In general, most patients received only the assigned antithrombotic regimen, although approximately 2% of patients in the heparin + GPI groups also received open-label bivalirudin. The use of provisional GPI therapy either before coronary angiography (because of refractory ischemia) or during PCI (because of thrombotic complications) occurred in 7.6% of patients in the bivalirudin monotherapy group. The cost of anticoagulants differed significantly across the 5 treatment groups ($p < 0.001$) and was lowest for patients assigned to heparin + catheterization laboratory GPI (mean cost = $515/patient; median = $399) and highest for patients assigned to bivalirudin + upstream GPI (mean = $1,537; median = $1,192). For patients treated with initial PCI, there were no other significant differences in procedural resource use, including procedure duration, contrast volume, and number and type of stents implanted. Reanalysis of costs including those patients with costs above the 99th percentile and below the 1st percentile did not alter the cost

Table 1 Baseline Clinical Characteristics and Intended Management Strategy

	Heparin		Bivalirudin		Bivalirudin Monotherapy
	Upstream GPI (n = 1,301)	Catheterization Laboratory GPI (n = 1,308)	Upstream GPI (n = 1,325)	Catheterization Laboratory GPI (n = 1,302)	No GPI (n = 2,615)
Age (yrs), mean ± SD	62 ± 12	62 ± 12	62 ± 12	62 ± 12	61 ± 12
Male, %	68.9	68.5	67.9	66.9	66.9
Diabetes, %	31.5	32.3	30.5	31.1	32.3
Current cigarette smoker, %	28.4	30.7	29.5	30.4	29.2
Previous MI, %	34.5	37.5	32.0	35.1	35.8
Previous PCI, %	48.1	48.3	46.2	46.5	48.2
Previous CABG, %	23.3	22.0	21.6	21.2	22.4
Biomarker positive, %	51.7	50.5	49.5	52.5	52.8
TIMI risk score, %					
0–2	12.9	13.6	12.5	11.3	12.5
3–4	55.4	56.5	58.5	58.6	57.2
5–7	31.6	29.9	29.0	30.1	30.3
Time, randomization to catheterization (h)*	4.2 (1.8–16.6)	4.3 (1.8–17.0)	4.0 (1.8–16.5)	4.3 (1.8–17.6)	4.3 (1.7–17.2)
Initial management strategy, %					
PCI	53.0	53.7	56.8	54.4	54.5
CABG	13.2	12.3	11.6	10.8	11.1
Medical therapy	33.8	34.0	31.6	34.8	34.4

p = NS for all comparisons. *Median value and interquartile range.

CABG = coronary artery bypass graft surgery; GPI = glycoprotein IIb/IIIa receptor antagonist; MI = myocardial infarction; PCI = percutaneous coronary intervention; TIMI = Thrombolysis In Myocardial Infarction.

rankings across treatment groups or the statistical significance of the comparisons.

Consistent with the results of the overall clinical trial, there were no significant differences in in-hospital ischemic complications, including death, MI, unplanned revascularization procedures, or their composite, during the initial hospital stay across the 5 treatment groups (Table 3). There were significant differences in the incidence of both protocol-defined major and minor bleeding across the 5 groups, with the lowest values consistently in the bivalirudin monotherapy group ($p < 0.001$ for both comparisons). Similar findings were noted for 30-day ischemic and bleeding end points (data not shown).

Although anticoagulation costs were lowest with heparin + catheterization laboratory GPI compared with the other regimens (cost savings ranging from $381 to $1,022/patient), costs for hospital room and ancillary services as well as physician costs were lowest for patients assigned to bivalirudin monotherapy. Overall costs of the index hospital stay differed significantly across the treatment groups ($p < 0.001$ for the 5-way comparison), and both mean and median costs were lowest with bivalirudin monotherapy (mean $13,844, median $11,372) compared with heparin + catheterization laboratory GPI (mean $14,028, median $11,832) and heparin + upstream GPI (mean $14,416, median $12,018) as well as both bivalirudin + GPI groups. On the basis of bootstrap simulation, the probability that bivalirudin monotherapy was cost-saving compared with heparin + upstream GPI was 94.6%, whereas the probability of cost savings versus heparin + catheterization laboratory GPI was 68.3% (Fig. 1).

Between hospital discharge and 30 days, there were no significant differences in follow-up medical care costs among the 5 antithrombotic regimens (Table 3). Cumulative 30-day costs thus remained lowest with bivalirudin monotherapy compared with regimens including GPI (cost savings ranging from $123/patient vs. heparin + catheterization laboratory GPI to $938/patient vs. bivalirudin + upstream GPI, $p = 0.005$ for the overall comparison). On the basis of bootstrap simulation, the probability of 30-day cost savings with bivalirudin monotherapy versus heparin + upstream GPI was 85.3%, whereas the probability of 30-day cost savings versus heparin + catheterization laboratory GPI was 57.4% (Fig. 2).

Determinants of hospital cost. Independent predictors of initial hospital cost (exclusive of study drug costs) according to multiple linear regression are displayed in Table 4. In-hospital events, including death, unplanned revascularization procedures, and bleeding complications, were the strongest correlates of hospital cost. In particular, the incremental cost associated with protocol-defined major bleeding was $8,658/event, whereas the incremental costs associated with minor bleeding or a protocol-defined MI were $2,282 and $3,388, respectively. Several baseline patient characteristics, including age, diabetes, and male gender, were also associated with higher initial hospital costs, whereas prior PCI was associated with a lower cost. Finally, the initial revascularization strategy selected was also a strong correlate of in-hospital cost, with incremental costs

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Table 2 Procedural Resource Use and Cost

	Heparin		Bivalirudin		Bivalirudin Monotherapy	
	Upstream GPI (n = 1,301)	Catheterization Laboratory GPI (n = 1,308)	Upstream GPI (n = 1,325)	Catheterization Laboratory GPI (n = 1,302)	No GPI (n = 2,615)	p Value
Anticoagulant use, %						
Bivalirudin	2.5	2.0	97.7	97.6	98.8	<0.001
GPI	98.2	53.7	97.7	54.2	7.6	<0.001
LMWH*	42.3	42.5	1.9	2.4	2.7	<0.001
UFH*	62.7	61.5	13.0	11.2	12.8	<0.001
Anticoagulant vials†						
Bivalirudin	1.3 ± 0.6	1.7 ± 1.4	2.0 ± 2.8	2.2 ± 3.9	2.2 ± 2.6	<0.001
Eptifibatide	4.5 ± 2.6	4.6 ± 1.6	4.3 ± 2.4	4.5 ± 1.5	4.7 ± 2.5	<0.001
Tirofiban	1.7 ± 1.7	1.4 ± 0.6	1.6 ± 1.4	1.5 ± 0.6	1.6 ± 1.3	0.90
Abciximab	5.3 ± 1.5	3.8 ± 1.2	3.0 ± 1.4	3.7 ± 0.9	4.1 ± 1.8	0.12
Anticoagulant costs	$896 ± $2,854 [$725]	$515 ± $584 [$399]	$1,537 ± $1,407 [$1,192]	$1,315 ± $1,727 [$1,000]	$976 ± $1,139 [$824]	<0.001
Index PCI resources‡						
Contrast	246 ± 119	248 ± 162	241 ± 120	240.48 ± 120	245 ± 124	0.71
Balloons	1.4 ± 1.3	1.4 ± 1.5	1.4 ± 1.1	1.4 ± 1.2	1.4 ± 1.2	0.86
Number of stents, bare-metal	0.2 ± 0.6	0.2 ± 0.7	0.3 ± 0.7	0.2 ± 0.6	0.3 ± 0.6	0.07
Number of stents, drug-eluting	1.4 ± 1.1	1.3 ± 1.1	1.3 ± 1.1	1.3 ± 1.0	1.4 ± 1.1	0.82
Drug-eluting stent used (%)	83.6	81.0	81.2	81.9	80.7	0.60
PCI costs (excluding anticoagulants)	$5,979 ± $3,058 [$4,888]	$6,009 ± $3,075 [$4,931]	$5,962 ± $2,919 [$4,942]	$5,985 ± $4,323 [$4,823]	$6,058 ± $3,131 [$4,883]	0.98

p values represent overall comparison across the 5 groups. Values in brackets are medians. *A small proportion of patients received both unfractionated heparin (UFH) and low-molecular weight heparin (LMWH); †among patients receiving the specified anticoagulant; ‡among patients undergoing PCI as planned initial revascularization.
Abbreviations as in Table 1.

of $29,461 and $8,279 for CABG and PCI, respectively, compared with medical therapy alone.

Attributable cost calculations demonstrated that both major and minor bleeding were important drivers of overall hospital cost for the heparin + GPI groups (Table 4). For the heparin + upstream GPI group, the attributable cost of major bleeding was $446/patient (i.e., $8,658 × 0.515), whereas the attributable cost of minor bleeding was $656/patient (i.e., $2,282 × 0.288). For the heparin + catheterization laboratory GPI group, these values were $371/patient and $518/patient, respectively. By contrast the attributable cost of myocardial (re)-infarction for both heparin + GPI groups was approximately $160/patient.

Similar calculations for the comparison of bivalirudin monotherapy with heparin + upstream GPI demonstrated that reductions in major bleeding accounted for $211/patient in overall cost offsets (i.e., $8,658 × 0.0243), whereas reductions in minor bleeding accounted for an additional $266/patient. For the comparison of bivalirudin versus heparin + catheterization laboratory GPI, reduced major and minor bleeding accounted for cost offsets of $136/patient and $128/patient, respectively. The remainder of the observed cost savings was largely explained by minor imbalances in other in-hospital events and revascularization procedures.

Subgroup analyses. The results of pre-specified subgroup analyses according to age, gender, biomarker status, creatinine clearance, and Thrombolysis In Myocardial Infarction risk score failed to reveal any significant interaction between the magnitude of 30-day cost savings with bivalirudin monotherapy compared with heparin + either upstream GPI (Fig. 3) or catheterization laboratory GPI (Fig. 4) (p = NS for all interaction tests). Moreover, there was no evidence that the extent of cost savings with bivalirudin varied according to the time interval between randomization and cardiac catheterization. In fact, for the highest tertile of time from randomization to angiography (>9.1 h), the mean cost savings with bivalirudin compared with heparin + upstream GPI was $1,860/patient (95% confidence interval: $104 to $3,617) and the mean cost savings with bivalirudin compared with heparin + catheterization laboratory GPI was $1,104/patient (95% confidence interval: $2,730 less to $522 more). Although costs differed substantially according to whether CABG, PCI, or medical therapy was selected as the initial revascularization strategy, there was also no evidence of a significant treatment × revascularization interaction. Similar findings were observed for subgroup analyses of bivalirudin monotherapy compared with either bivalirudin + GPI regimen (data not shown).

Discussion

For patients with non–ST-segment elevation acute coronary syndrome (NSTE-ACS) undergoing an early invasive management strategy, current guidelines recommend use of combined anticoagulation and antiplatelet therapy (3). In

Table 3 Hospital Outcomes, Resource Use, and Costs

	Heparin + GPI		Bivalirudin + GPI		Bivalirudin Monotherapy	
	Upstream GPI	Catheterization Laboratory GPI	Upstream GPI	Catheterization Laboratory GPI	No GPI	p Value
Death, %	0.8	0.3	0.7	0.8	0.9	0.35
MI, %	4.7	4.9	5.1	4.8	5.0	0.99
Unplanned revascularization, %	0.9	0.8	1.1	1.6	0.9	0.22
PCI	0.6	0.5	0.6	1.3	0.7	0.09
CABG	0.3	0.3	0.5	0.3	0.2	0.84
Death or MI, %	5.4	5.0	5.5	5.5	5.6	0.96
Death, MI, or unplanned revascularization, %	5.9	5.6	6.0	6.6	6.0	0.87
Major bleeding, %	5.1	4.3	6.1	3.7	2.7	<0.001
Minor bleeding, %	28.2	20.9	27.5	22.8	14.1	<0.001
Transfusion, %	8.4	7.0	9.1	5.8	6.9	0.007
Length of stay, days	3.7 ± 3.5 [2.0]	3.6 ± 3.4 [2.0]	3.5 ± 3.5 [2.0]	3.3 ± 3.2 [2.0]	3.4 ± 3.3 [2.0]	0.02
ICU length of stay, days	1.3 ± 2.7 [0]	1.2 ± 2.3 [0]	1.2 ± 2.0 [0]	1.2 ± 2.6 [0]	1.2 ± 2.5 [0]	0.10
Costs						
Anticoagulant medications	$896 ± $2,854 [$725]	$515 ± $583 [$399]	$1,537 ± $1,407 [$1,192]	$1,315 ± $1,727 [$1,000]	$976 ± $1,139 [$824]	<0.001
Catheterization laboratory procedures	$3,207 ± $3,775 [$2,672]	$3,243 ± $3,793 [$2,672]	$3,399 ± $3,714 [$3,528]	$3,335 ± $4,435 [$2,887]	$3,336 ± $3,846 [$2,824]	0.58
Hospital room and ancillary services	$8,705 ± $12,301 [$4,757]	$8,610 ± $12,149 [$4,757]	$8,244 ± $11,284 [$4,329]	$7,933 ± $10,139 [$4,329]	$7,887 ± $10,610 [$4,329]	0.04
Physician fees	$2,071 ± $2,620 [$1,486]	$1,957 ± $2,278 [$1,486]	$1,958 ± $2,224 [$1,486]	$1,798 ± $2,115 [$1,430]	$1,867 ± $2,218 [$1,431]	0.02
Total cost for initial hospital stay	$14,416 ± $11,944 [$11,443]	$14,028 ± $12,069 [$11,377]	$14,925 ± $11,652 [$12,058]	$14,153 ± $11,321 [$11,765]	$13,844 ± $11,621 [$10,927]	<0.001
Discharge to 30 days cost	$767 ± $3,254 [$0]	$856 ± $3,370 [$0]	$774 ± $3,230 [$0]	$945 ± $3,691 [$0]	$917 ± $3,610 [$0]	0.658
Total 30-day cost	$15,183 ± $12,646 [$12,018]	$14,884 ± $12,576 [$11,832]	$15,699 ± $12,094 [$12,649]	$15,099 ± $11,991 [$12,304]	$14,761 ± $12,347 [$11,372]	0.005

Values in brackets are medians.

ICU = intensive care unit, other abbreviations as in Table 1.

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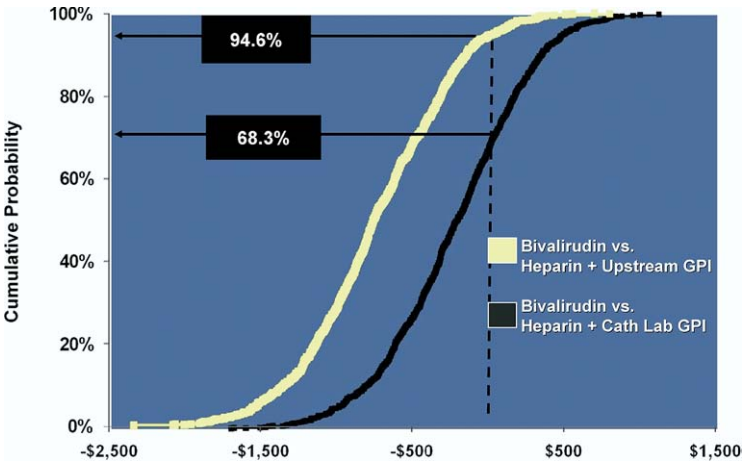

Figure 1 **Bootstrap Analysis of Index Hospital Stay Costs**

Performance of 1,000 bootstrap replicates indicates a 94.6% probability of cost savings with bivalirudin monotherapy compared with heparin (unfractionated or low-molecular weight heparin) with upstream glycoprotein IIb/IIIa receptor inhibition (GPI) **(yellow line)** and a 68.3% probability of lower cost with bivalirudin monotherapy compared with heparin (unfractionated or low molecular weight heparin) and catheterization laboratory (cath lab)-initiated GPI **(black line).**

the ACUITY trial, the use of bivalirudin monotherapy—started before cardiac catheterization—was found to be statistically noninferior to either heparin + GPI or bivalirudin + GPI for the prevention of ischemic complications and superior to both GPI-containing regimens for prevention of bleeding complications (1). More recently, the ACUITY Investigators reported similar rates of 1-year mortality across the alternative antithrombotic regimens as well (8). Given these comparable rates of major ischemic events, other considerations including cost might provide further important insight into the optimal antithrombotic regimen.

This prospective economic analysis shows that, during the initial hospital stay, use of bivalirudin monotherapy was associated with net cost savings of approximately $600/patient compared with heparin + routine upstream GPI and approximately $200/patient compared with heparin + catheterization laboratory GPI for patients undergoing PCI. These cost savings were obtained despite similar or higher costs for antithrombotic therapy and were explained mainly by reductions in bleeding complications and LOS. In contrast, costs for regimens involving both bivalirudin + GPI (which provided no significant clinical benefits) were

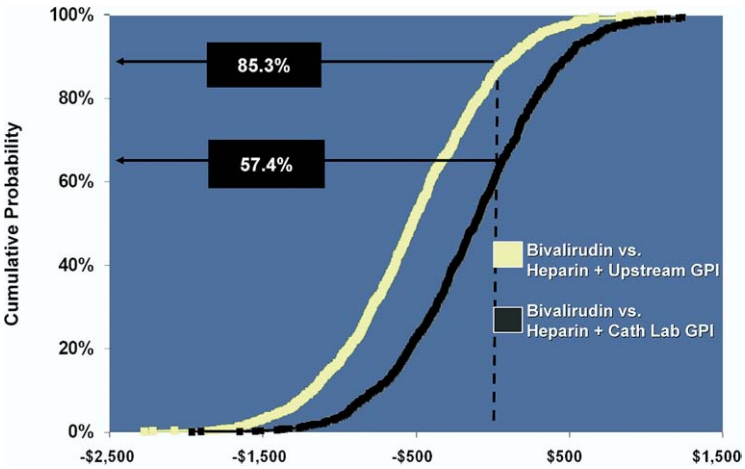

Figure 2 **Bootstrap Analysis of 30-Day Costs**

Performance of 1,000 bootstrap replicates indicates an 85.3% probability of cost savings with bivalirudin monotherapy compared with heparin (unfractionated or low molecular weight heparin) with upstream GPI **(yellow line)** and a 57.4% probability of lower cost with bivalirudin monotherapy compared with heparin (unfractionated or low molecular weight heparin) and catheterization laboratory-initiated GPI **(black line).** Abbreviations as in Figure 1.

Table 4 Independent Predictors of Initial Hospital Cost and Attributable Costs

Event or Patient Characteristic	Estimated Cost*	95% Confidence Interval	Heparin + Upstream GPI Group	Heparin + Catheterization Laboratory GPI Group	Attributable Cost in Heparin + Upstream GPI Group	Attributable Cost in Heparin + Catheterization Laboratory GPI Group
In-hospital events						
Death	$9,061	($4,451 to $13,670)	0.77%	0.31%	$70	$28
MI	$3,388	($1,746 to $5,030)	4.69%	4.89%	$159	$166
Major bleed (protocol defined)	$8,658	($6,789 to $10,527)	5.15%	4.28%	$446	$371
Minor bleed	$2,282	($1,325 to $3,238)	28.75%	22.71%	$656	$518
Unplanned PCI or CABG	$12,293	($9,225 to $15,362)	1.15%	0.99%	$142	$122
Patient characteristics						
Age (yrs)	$56	($24 to $88)	62.1	61.6	$3,477	$3,448
Gender (male)	$705	(−$106 to $1,516)	68.87%	68.50%	$486	$483
Diabetes	$896	($86 to $1,706)	31.45%	32.31%	$282	$289
Previous PCI	(−$1,106)	(−$1,863 to −$350)	48.07%	48.31%	(−$532)	(−$534)
Initial management strategy						
PCI	$8,279	($7,439 to $9,118)	52.99%	53.75%	$4,387	$4,450
CABG	$29,461	($28,130 to $30,792)	13.21%	12.28%	$3,892	$3,617
Total cost of complications					$1473	$1205

Values in the "estimated cost" column represent the individual regression coefficients from a linear regression model relating total in-hospital costs with patient characteristics as well as outcomes/complications. "Attributable cost" values represent the product of the estimated cost/event and either the proportion of patients with the specific attribute (for binary covariates) or the mean value for the group (for continuous variables, like age). *Estimated cost of each complication on the basis of a linear regression model of initial costs among patients with billing data (model $R^2 = 0.51$).
Abbreviations as in Table 1.

consistently higher than those for either bivalirudin monotherapy or heparin + catheterization laboratory GPI. The results were generally similar (although slightly attenuated) at 30 days and were consistent across a broad range of pre-specified patient subsets. There were no statistically significant differences in costs in the interval between discharge and 30 days, indicating that minor differences in follow-up costs were likely due to chance alone.

These findings represent the first prospective economic evaluation of alternative antithrombotic strategies for NSTE-ACS in patients undergoing early invasive management and suggest that bivalirudin monotherapy might provide both a clinical advantage (in terms of reduced major and minor bleeding complications, thrombocytopenia, and fewer blood product transfusions) as well as a modest economic advantage over current standard approaches.

In addition to quantifying the extent of cost savings associated with the use of bivalirudin, this study provides important insight into those factors that determine the cost of hospital stay for patients with NSTE-ACS. As demonstrated by our regression analysis (Table 4), on a "per event" basis, the most important factors increasing costs among patients undergoing early invasive management for ACS are complications, including unplanned revascularization, death, and major bleeding. In contrast, when the frequency of complications was also considered, the attributable costs of death or unplanned revascularization were both <$200/patient due to their rare occurrence, whereas major and minor bleeding were the most costly complications on a "per-patient" basis, because these were far more frequent. For example, for patients receiving heparin + upstream GPI, the attributable costs of major and minor bleeding were $446/patient and $656/patient and accounted for approximately 8% of the total cost of the hospital stay. The findings were similar for the heparin + catheterization laboratory GPI group. By reducing the frequency of both major and minor bleeding complications by 33% to 50%, bivalirudin monotherapy thus led to substantial hospital cost savings compared with either heparin + GPI-based treatment strategy. These savings reflect not only the shorter length of stay observed with bivalirudin monotherapy but also likely relate to reduced intensity of ancillary testing and physician services associated with avoidance of these resource-intensive complications. Nevertheless, it is important to note that reduced bleeding did not fully account for the entirety of cost savings observed in the ACUITY trial. To some extent, it is likely that additional factors, including minor imbalances in baseline patient characteristics and management strategies as well as other advantages of bivalirudin monotherapy (e.g., fixed dosing without need for monitoring or dose adjustment, fewer intravenous lines, and shorter infusion durations), might have also contributed to cost savings in this open-label trial.

Comparison with previous studies. Few previous studies have directly compared the costs of care for patients receiving alternative antithrombotic regimens in the setting of NSTE-ACS—particularly for patients undergoing an early invasive management strategy. Mark et al. (9) performed a prospective economic analysis alongside the PURSUIT (Platelet IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrelin Therapy) trial comparing heparin + eptifibatide versus heparin alone for patients with NSTE-ACS undergoing both conservative and early invasive management. They found that, despite the additional cost of

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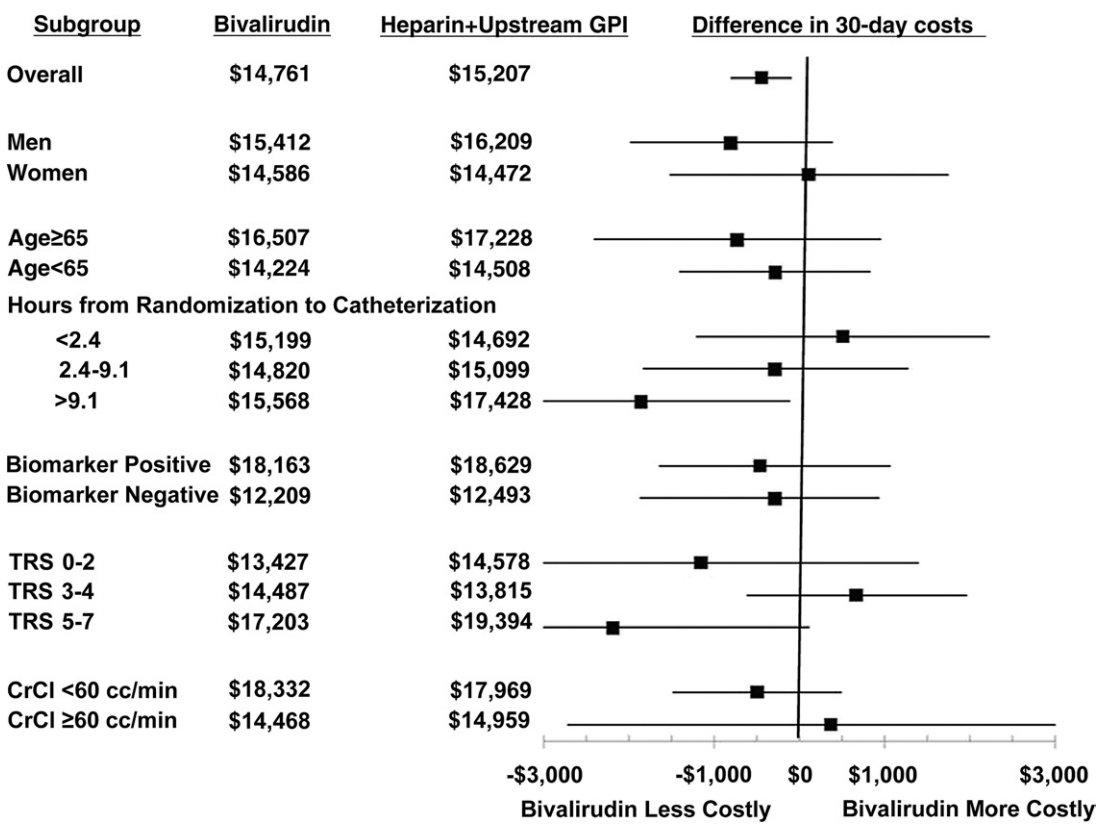

Figure 3 **Stratified Analyses of Aggregate 30-Day Costs by Treatment Group According to Pre-Specified Patient Characteristics**

The graph indicates the mean difference in costs between the bivalirudin and heparin (unfractionated or low molecular weight heparin) + upstream glycoprotein IIb/IIIa receptor inhibitor (GPI) **(black squares)** along with the associated 95% confidence interval **(bars)**. No interaction p values were significant, indicating that the overall treatment effect represents the most meaningful treatment effect for these subgroups (all p values for interaction >0.05).

$1,217/patient, use of eptifibatide was associated with an improvement in life expectancy of 0.11 years and a favorable incremental cost-effectiveness ratio of $16,491/year of life gained. Glaser et al. (10) used a decision-analytic model to compare the cost-effectiveness of heparin + upstream use of a small molecule GPI with heparin + catheterization laboratory use of the monoclonal antibody abciximab. They found that the upstream GPI strategy was clinically superior and was associated with a favorable cost-effectiveness ratio of $18,000/year of life gained. Although these studies do not relate directly to our study, both provide indirect support for the consideration of heparin + upstream GPI as the primary reference strategy for our empirical comparison.

The only previous study to directly compare the costs of bivalirudin monotherapy with heparin + GPI was the REPLACE-2 (Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events) trial (11). In the REPLACE-2 trial, use of bivalirudin with provisional GPI versus heparin + routine GPI for patients undergoing nonemergent PCI was associated with a cost savings of approximately $400/patient during both the index hospital stay and at 30 days. Although our overall findings of cost savings with bivalirudin are similar to the results of the REPLACE-2 trial, there are several important differences between the 2 studies. First, the population of the REPLACE-2 trial consisted entirely of stable or low-risk ACS patients undergoing PCI. In contrast, the ACUITY trial was conducted among patients with moderate- and high-risk ACS who were undergoing a combination of medical therapy, PCI, and bypass surgery. Moreover in the REPLACE-2 trial, the cost savings achieved with bivalirudin compared with heparin + GPI, both initiated in the catheterization laboratory, were due to a combination of lower study drug costs as well as reduced bleeding complications. In contrast, when compared with heparin + either upstream or catheterization laboratory-initiated GPI in the ACUITY trial, bivalirudin initiated before cardiac catheterization was actually associated with higher drug acquisition costs, which were still more than offset by in-hospital cost savings. These findings reflect the fact that the incremental costs of major and minor bleeding were actually higher in the ACUITY than in the REPLACE-2 trial. Although the precise explanation for these differences is unknown, one possibility is that the higher cost/bleeding event in the ACUITY trial reflects the greater complexity and underly-

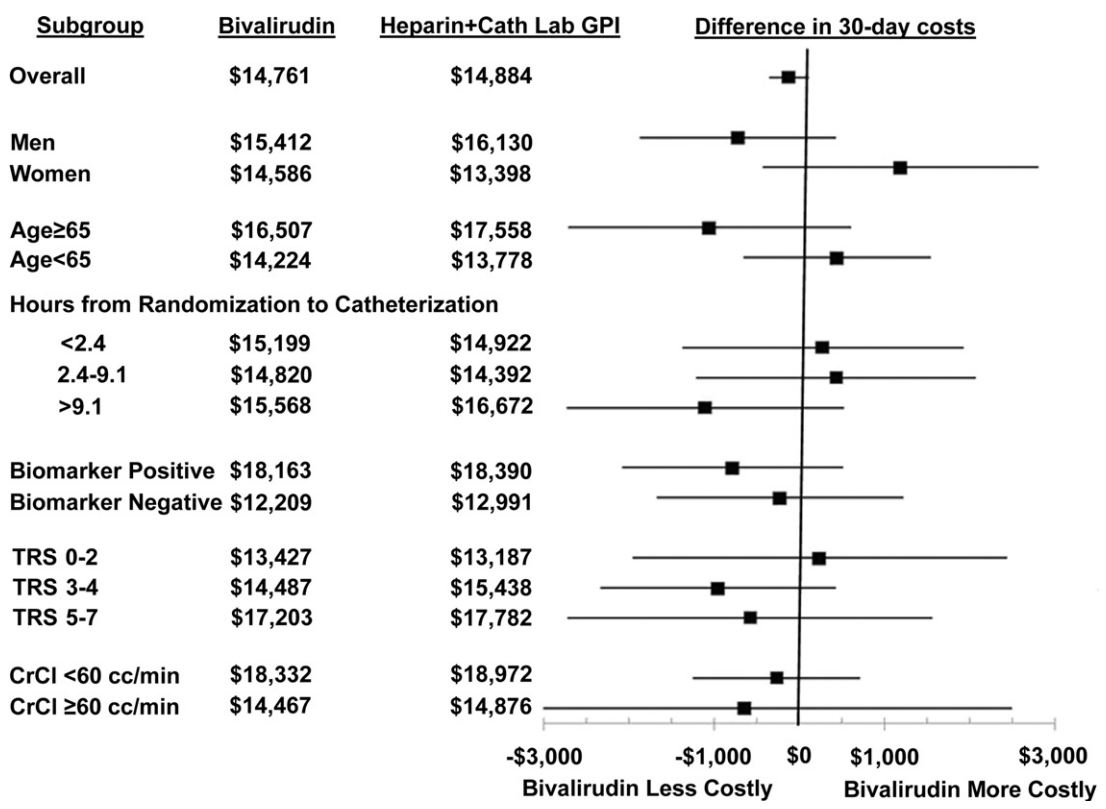

Figure 4 **Stratified Analyses of Aggregate 30-Day Costs by Treatment Group According to Pre-Specified Patient Characteristics**

The graph indicates the mean difference in costs between the bivalirudin and heparin (unfractionated or low molecular weight heparin) + catheterization laboratory-initiated GPI **(black squares)** along with the associated 95% confidence interval **(bars)**. There was no evidence of heterogeneity of treatment effect across any of the subgroups (all p values for interaction >0.05). CrCl = creatinine clearance; TRS = Thrombolysis In Myocardial Infarction risk score; other abbreviations as in Figure 1.

ing disease severity of the ACS patient population, particularly when identified before coronary angiography.

Clinical implications. The results of our economic study, in concert with the findings of reduced bleeding and similar rates of early and late ischemia and mortality, support the use of bivalirudin monotherapy before cardiac catheterization as a valid if not the preferred antithrombotic strategy for patients with ACS undergoing an early invasive strategy. It is important to note that the economic benefits of bivalirudin monotherapy did depend to some extent on the comparator strategy. When compared with the "gold standard" strategy of heparin + upstream GPI, bivalirudin monotherapy was associated with a cost savings of approximately $600/patient during the initial hospital stay and approximately $400/patient at 30 days, and bootstrap simulation demonstrated that the probability of net cost savings with bivalirudin was >95% in hospital and >85% at 30 days. Given the substantial interindividual variability in costs, however, the comparison versus heparin + catheterization laboratory GPI was less definitive. Although, on average, bivalirudin monotherapy was associated with the lowest costs at both hospital discharge and 30 days, bootstrap simulation demonstrated that, compared with heparin + catheterization laboratory GPI, the confidence limits on these cost differences were wide, and the probabilities of net cost savings in hospital and at 30 days were only 68% and 57%, respectively. Nonetheless, these findings should be considered in the context of both the ACUITY Timing trial results, where formal criteria for noninferiority were not met for the comparison of catheterization laboratory-initiated GPI versus upstream GPI (in terms of ischemic events) (12), as well recent follow-up data that demonstrated virtually identical mortality rates at 1 year across all 5 treatment groups (8).

Study limitations. We did not collect primary cost data on all study participants. Given the size and scope of the trial, we felt that such an effort would have been relatively inefficient. Instead, we elected to collect primary cost data on a large subset of patients (>2,500) selected at random, including all patients who experienced a major complication. As a result, our imputation model was both highly predictive (model $R^2 = 0.75$) and stable over a broad range of alternative sampling scenarios. Second, the results of this analysis apply only to the U.S. health care system. Given different drug acquisition costs, treatment patterns, and cost structures, separate analyses will be required to

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understand the economic implications for other health care systems.

It is important to note that this study did not include a sixth arm of heparin alone; as a result, potential comparisons of our economic results versus such a strategy (which would certainly have a very low cost of antithrombotic therapy) are speculative at best. Although it is possible that much of the bleeding advantage of bivalirudin monotherapy relates to avoidance of GPI, the economic and long-term clinical consequences of any increase in ischemic complications would need to be considered in such an analysis as well. As noted previously, the economic analysis of the PURSUIT trial suggested that the addition of a GPI to heparin alone was reasonably cost-effective despite an increase in bleeding (cost-effectiveness ratio approximately $19,000/life-year gained) (9)—a finding that supports the use of heparin + GPI as the reference strategy for our economic analysis. Whether these findings still apply in the current era of aggressive use of upstream clopidogrel for ACS patients is unknown, however. It is intuitively obvious, however, that if heparin alone could yield comparable rates of both ischemic and bleeding complications to the regimens examined in this study, it would be an economically dominant strategy.

Finally, it is important to note that the duration of "upstream" therapy provided in ACUITY was relatively brief (median of 4.2 h). Nonetheless, it is reassuring that there was no significant interaction between the duration of upstream therapy and the economic benefits of bivalirudin; in fact, the absolute cost savings with bivalirudin were greatest among the tertile of patients who underwent coronary angiography >9.1 h after randomization (median 20.7 h in this tertile), reflecting current U.S. practice.

Conclusions

Among U.S. patients undergoing an early invasive strategy for management of NSTE-ACS, treatment with bivalirudin monotherapy compared with heparin + either upstream or catheterization laboratory-initiated GPI resulted in similar rates of ischemic events, reduced bleeding, and shorter LOS. Despite higher drug treatment costs, aggregate hospital and 30-day costs were lowest with bivalirudin monotherapy due to a shorter LOS and the prevention of bleeding complications. These findings suggest that bivalirudin monotherapy is an economically attractive alternative to heparin and GPI in patients with moderate- and high-risk NSTE-ACS.

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Key Words: direct thrombin inhibition ■ economic analysis ■ non–ST-segment myocardial infarction.