

# Impact of Gender and Antithrombin Strategy on Early and Late Clinical Outcomes in Patients With Non-ST-Elevation Acute Coronary Syndromes (from the ACUITY Trial)

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Women with non-ST-elevation acute coronary syndrome are at increased risk for ischemic and bleeding complications compared with men. We examined the impact of gender and antithrombotic therapy for non-ST-elevation acute coronary syndrome on outcomes in patients in the ACUITY trial. Patients were randomized to heparin (unfractionated or enoxaparin) plus a glycoprotein IIb/IIIa inhibitor (GPI), bivalirudin plus a GPI, or bivalirudin alone. We compared major bleeding unconnected to coronary artery bypass grafting, composite ischemia (death, myocardial infarction, or revascularization), and net clinical outcome (composite ischemia or bleeding) in (1) men versus women overall and undergoing percutaneous coronary intervention (PCI) and (2) women overall and undergoing PCI by antithrombotic strategy. Of 13,819 patients enrolled, 4,157 were women (30.1%). Women had similar 30-day composite ischemia (7% vs 8%,  $p = 0.07$ ) but greater 30-day rates of major bleeding (8% vs 3%  $p < 0.0001$ ) and net clinical outcomes (13% vs 10%  $p < 0.0001$ ) than men. One-year composite ischemia and mortality was similar. In women, bivalirudin compared with heparin + GPI resulted in less 30-day major bleeding (5% vs 10%,  $p < 0.0001$ ) but similar composite ischemia (7% vs 6%,  $p = 0.15$ ). No differences were observed in rates of 1-year composite ischemia or mortality in women who received bivalirudin versus heparin + GPI. Results were similar in women undergoing PCI. In conclusion, women had similar 30-day mortality and composite ischemia but higher net clinical adverse events due to more bleeding complications than men; 1-year mortality was similar for men and women. In women, bivalirudin monotherapy compared with a GPI-based strategy resulted in significantly decreased bleeding but similar rates of 1-year composite ischemia and mortality. © 2009 Elsevier Inc. All rights reserved. (Am J Cardiol 2009;103:1196–1203)

Although advances in cardiovascular care have resulted in decreased rates of cardiovascular mortality in men, rates of death attributable to cardiovascular disease have increased in women over the previous 2 decades.<sup>1</sup> Although the results of clinical studies have been inconsistent regarding the influence of gender on mortality after percutaneous coronary intervention (PCI),<sup>2–4</sup> multiple studies consistently have demonstrated that women have significantly higher rates of bleeding and vascular complications compared with men.<sup>5,6</sup> This gender difference has typically been attributed to baseline differences, with women being older and having more co-morbidities such as diabetes and hypertension than men.<sup>3,7,8</sup> In the Acute Cath-

eterization and Urgent Intervention Triage strategy (ACUITY) trial, bivalirudin monotherapy provided similar protection from ischemic events at 30 days and 1 year, with significantly fewer 30-day bleeding complications compared with heparin plus a glycoprotein IIb/IIIa inhibitor (GPI).<sup>9</sup> In this analysis, we evaluate patients overall and in those undergoing PCI in the ACUITY trial to assess 30-day and 1-year outcomes in (1) men versus women, (2) women treated with bivalirudin with and without a GPI versus heparin plus GPI, and (3) women compared with men when treated with bivalirudin alone compared with heparin plus GPI.

## Methods

The design and results of the ACUITY trial have been previously published.<sup>10,11</sup> Briefly, 13,819 patients with moderate or high-risk non-ST-elevation acute coronary syndrome (NSTEMI-ACS) were randomized in an open-label fashion equally to 1 of 3 antithrombotic regimens: heparin (unfractionated or enoxaparin at site discretion) plus a GPI, bivalirudin plus a GPI, or bivalirudin monotherapy, in which GPI administration was allowed only for prespecified indications. The antithrombin dosing regimens have been previously described.

Patients assigned to a GPI arm were further randomized in a 2 × 2 factorial design to upstream GPI initiation

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Table 1  
Baseline characteristics and treatment strategies by gender

Variable	Women (n = 4,157)	Men (n = 9,662)	p Value
Age (yrs), median (range)	66 (25–95)	61 (20–93)	<0.0001
≥75 yrs	1,030/4,157 (25%)	1,411/9,662 (15%)	<0.0001
Weight (kg), median (interquartile range)	74.0 (64.0–86.0)	86.3 (77.2–98.0)	<0.0001
Chronic kidney disease*	1,158/3,854 (30%)	1,311/9,085 (14%)	<0.0001
Diabetes	1,343/4,122 (33%)	2,509/9,587 (26%)	<0.0001
Current smoker	994/4,063 (25%)	2,949/9,494 (31%)	<0.0001
Previous MI	1,066/4,063 (26%)	3,156/9,420 (34%)	<0.0001
Previous PCI	1,501/4,118 (36%)	3,819/9,565 (40%)	0.0001
Previous CABG	545/4,141 (13%)	1,920/9,633 (20%)	<0.0001
Family history of coronary artery disease†	2,023/3,569 (57%)	4,198/8,297 (51%)	<0.0001
Hypertension‡ (on medication)	3,053/4,135 (74%)	6,159/9,612 (64%)	<0.0001
Hyperlipidemia§ (on medication)	2,339/4,075 (57%)	5,408/9,465 (57%)	0.78
High risk	2,803/3,916 (72%)	6,660/9,170 (73%)	0.22
Creatine kinase isoenzyme MB/troponin increase	2,118/3,773 (56%)	5,434/8,939 (61%)	<0.0001
ST-segment deviation	1,509/4,154 (36%)	3,316/9,650 (34%)	0.03
Anemia¶	779/3,895 (20%)	1,421/9,144 (16%)	<0.0001
Treatment strategy			
PCI	2,091/4,157 (50%)	5,698/9,662 (59%)	<0.0001
CABG	355/4,157 (9%)	1,184/9,662 (12%)	<0.0001
Medical management	1,711/4,157 (41%)	2,780/9,662 (29%)	<0.0001
Long-term (1-yr) concomitant medications			
Aspirin	3,318/3,913 (85%)	8,117/9,081 (89%)	<0.0001
Thienopyridine	1,623/3,913 (42%)	4,153/9,081 (46%)	<0.0001
β blockers	2,722/3,913 (70%)	6,641/9,081 (73%)	<0.0001
ACE inhibitors	2,190/3,913 (56%)	5,194/9,081 (57%)	0.19
Statins	2,837/3,913 (73%)	7,166/9,081 (79%)	<0.0001
Received excess dose of GPI#	225/683 (33%)	182/659 (28%)	0.03

ACE = angiotensin-converting enzyme.

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

† Defined as a first-degree relative with coronary artery disease <40 years old for men and <55 years old for women.

‡ Defined as patient on antihypertensive therapy.

§ Defined as patient on lipid-lowering therapy.

|| Defined as increased creatine kinase-MB or troponin or ST deviation.

¶ Anemia was defined using the World Health Organization criteria (hemoglobin ≤13 g/dl for men and ≤12 g/dl for women).

# Defined as an initial eptifibatide bolus >99 μg/kg or an initial infusion >1.1 μg/kg/min in a patient with a creatinine clearance <50 ml/min. Denominators presented reflect only those patients with a creatinine clearance <50 ml/min.

immediately after randomization or to deferred initiation in the catheterization laboratory for those patients triaged to PCI. According to Food and Drug Administration–approved labeling, eptifibatide or tirofiban was permitted for upstream use, and abciximab or eptifibatide was permitted for selective deferred use in the catheterization laboratory. Dosages of all GPIs were done according to the package insert and were adjusted for creatinine clearance.

Coronary angiography was required according to protocol within 72 hours of randomization, with subsequent triage to treatment with PCI, coronary artery bypass grafting (CABG), or medical management according to physician discretion. Aspirin (300 to 325 mg orally or 250 to 500 mg intravenously) was administered before angiography and daily during the index hospitalization. Dosing and timing of clopidogrel were left to the discretion of the investigators, but 300 mg was required according to protocol no later than 2 hours after PCI. Clopidogrel 75 mg/day was recommended for 1 year in all patients after PCI and aspirin 75 to 325 mg/day indefinitely. The study was approved by the institutional review board or ethics committee at each participating center, and all patients signed written informed

consent. Independent quantitative and qualitative angiography (Cardiovascular Research Foundation, New York, New York) was performed in the first 7,000 American patients, and 6,914 angiograms were of suitable quality for analysis.

The ACUTY trial was powered for 3 primary 30-day end points: (1) composite ischemia, defined as death from any cause, nonfatal myocardial infarction (MI), or unplanned revascularization for ischemia; (2) major bleeding (non-CABG related), defined as intracranial, intraocular, or retroperitoneal bleeding, access-site hemorrhage requiring intervention, hematoma ≥5 cm in diameter, decrease in hemoglobin of ≥4 g/dl without or ≥3 g/dl with an overt bleeding source, reoperation for bleeding, or blood product transfusion; and (3) net adverse clinical outcome (composite ischemia or major bleeding). Composite ischemia and death were evaluated at 1 year. All primary and secondary end points were adjudicated by a blinded clinical events committee.

Although gender was a prespecified subgroup for analysis, the ACUTY trial was not powered for formal superiority or noninferiority testing of this or any other subgroup. All analyses are intention to treat. Categorical values were

Table 2  
Baseline angiographic characteristics and percutaneous coronary intervention lesion baseline shape/function by gender

Baseline Angiographic Characteristics	Women (n = 1,790)	Men (n = 3,838)	Relative Risk (95% CI)	p Value*
No. of lesions per patient	2,264	4,650		
Median (Q1, Q3)	3.00 (1.00, 5.00)	4.00 (2.00, 6.00)	N/A	<0.0001
Extent of disease per patient (n)	1,790	3,838		
Median (Q1, Q3)	29.49 (15.30, 47.30)	34.28 (19.34, 56.20)		<0.0001
No. with 0-vessel coronary artery disease	335/2,274 (15%)	308/4,657 (7%)	2.23 (1.92–2.58)	<0.0001
No. with 1-vessel coronary artery disease	533/2,274 (23%)	748/4,657 (16%)	1.46 (1.32–1.61)	<0.0001
No. with 2-vessel coronary artery disease	631/2,274 (28%)	1,315/4,657 (28%)	0.98 (0.91–1.07)	0.69
No. with 3-vessel coronary artery disease	775/2,274 (34%)	2,286/4,657 (49%)	0.69 (0.65–0.74)	<0.0001
Extent of disease per vessel (n)	1,258	2,663		
Median (Q1, Q3) mm	16.00 (10.00, 25.00)	18.14 (10.00, 30.00)	N/A	<0.0001
PCI lesion baseline shape/function	1,109 patients, 1,477 lesions	3,466 patients, 2,552 lesions		
No. of lesion length (mm)	1,416	3,339		
Median (Q1, Q3)	12.00 (9.10, 17.11)	12.88 (10.00, 19.73)	N/A	<0.0001
Reference diameter (mm)	2.61 (2.28, 2.99)	2.77 (2.40, 3.17)	N/A	<0.0001
Baseline diameter stenosis (%)	72.6 (60.7, 85.1)	74.0 (61.5, 86.2)	N/A	0.06
Final diameter stenosis (%)	15.2 (9.7, 21.7)	15.6 (9.9, 22.7)	N/A	0.08
ACC/AHA lesion complexity B2/C	799/1,447 (55%)	2,105/3,466 (61%)	0.91 (0.86–0.96)	0.0004
TIMI grade flow before procedure				
0/1	154/1,439 (11%)	453/3,449 (13%)	0.81 (0.69–0.97)	0.02
2	111/1,439 (8%)	355/3,449 (10%)	0.75 (0.61–0.92)	0.005
3	1,174/1,439 (82%)	2,641/3,449 (77%)	1.07 (1.03–1.10)	0.0001

Extent of disease was defined quantitatively as total length (millimeters) of all lesions with a diameter stenosis >30%.

ACC = American College of Cardiology; AHA = American Heart Association; Q = quartile; TIMI = Thrombolysis In Myocardial Infarction.

\* Compared with chi-square or Fisher's exact test.

compared by chi-square or Fisher's exact test. Continuous variables were tested using Wilcoxon rank-sum test. Medians and interquartile ranges are presented for continuous variables. One-year follow-up analysis was performed using a time-to-event method and compared with log-rank test. The p values were given for information purposes and no multiplicity adjustment was done. Statistical significance was defined by a p value less than an alpha level of 0.05.

Because the ACUITY trial was not designed to compare women with men, Cox proportional hazards regression analysis was performed to adjust for differences in baseline characteristics between men and women overall and in those undergoing PCI, thus demonstrating the true effect of gender on clinical outcomes. Cox proportional hazards regression analysis was also performed to determine predictors of major bleeding in women overall and those undergoing PCI. Potential predictors were selected using stepwise, forward, and backward procedures. Covariates were entered into the model with a p value  $\leq 0.15$  and retained with a p value  $\leq 0.10$ . The final model includes all predictors that were selected by  $\geq 1$  of the 3 selection procedures. The p values, hazard ratios, and corresponding 2-sided 95% confidence intervals (CIs) for predictors are presented. All statistical analyses were performed by SAS 8.2 (SAS Institute, Cary, North Carolina).

## Results

Of the 13,819 randomized patients, 4,157 were women (30.1%) and 9,662 were men (69.9%). Baseline characteristics and treatment strategies are presented in Table 1. Compared with men, women were more likely to be older, have lower body weight, and to have chronic kidney disease, diabetes, hypertension, anemia, and family history of

Table 3  
Clinical outcomes at 30 days by gender

Variable	Women	Men	p Value
Overall population	4,157	9,662	
Net clinical outcome	545 (13%)	1,008 (10%)	<0.0001
Composite ischemia	292 (7%)	766 (8%)	0.07
Death	57 (1%)	152 (2%)	0.37
MI	199 (5%)	506 (5%)	0.27
Unplanned revascularization	89 (2%)	254 (3%)	0.09
Major bleeding (non-CABG)	318 (8%)	327 (3%)	<0.0001
PCI population	2,091	5,698	
Net clinical outcome	363 (17%)	676 (12%)	<0.0001
Composite ischemia	191 (9%)	498 (9%)	0.59
Death	21 (1%)	61 (1%)	0.80
MI	141 (7%)	345 (6%)	0.27
Unplanned revascularization	67 (3%)	200 (4%)	0.51
Major bleeding (non-CABG)	223 (11%)	239 (4%)	<0.0001
CABG population	355	1,184	
Net clinical outcome	74 (21%)	194 (16%)	0.05
Composite ischemia	58 (16%)	172 (15%)	0.40
Death	14 (4%)	47 (4%)	0.98
MI	45 (13%)	132 (11%)	0.43
Unplanned revascularization	7 (2%)	16 (1%)	0.40
Major bleeding (non-CABG)	20 (6%)	32 (3%)	0.007
Medical management population	1,711	2,780	
Net clinical outcome	108 (6%)	138 (5%)	0.05
Composite ischemia	43 (3%)	96 (4%)	0.08
Death	22 (1%)	44 (2%)	0.42
MI	13 (1%)	29 (1%)	0.34
Unplanned revascularization	15 (1%)	38 (1%)	0.14
Major bleeding (non-CABG)	75 (4%)	56 (2%)	<0.0001

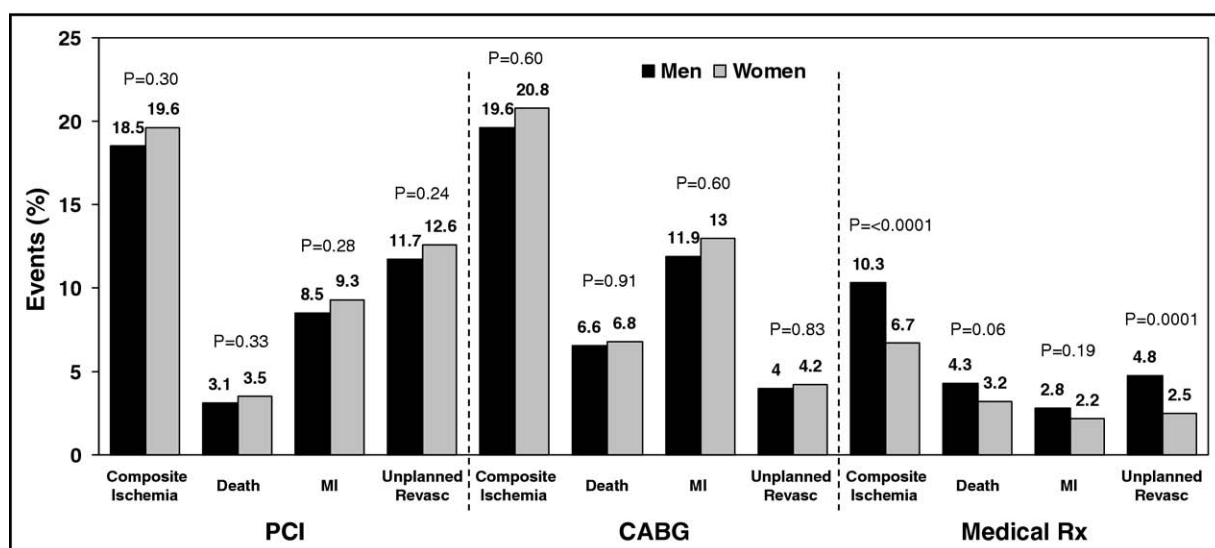


Figure 1. One-year outcomes in men and women by treatment strategy. Medical Rx = medical management.

Table 4

Baseline characteristics and treatment strategies of women by randomized antithrombin group

Variable	Heparin (unfractionated or low-molecular-weight) + GPI (n = 1,354)	Bivalirudin + GPI (n = 1,386)	p <sub>1</sub> Value*	Bivalirudin Monotherapy (n = 1,417)	p <sub>2</sub> Value†
Age (yrs), median (range)	66 (25–91)	66 (28–95)	0.46	66 (25–92)	0.17
≥75 yrs	350 (25.8)	339 (24.5)	0.40	341 (24.1)	0.28
Weight (kg), median (interquartile range)	73.3 (64–85)	73.5 (65–86)	0.57	74.9 (64–87)	0.15
Renal insufficiency‡	77 (6%)	68 (5%)	0.36	64 (5%)	0.16
Diabetes	458 (34%)	437 (32%)	0.21	448 (32%)	0.21
Current smoker	343 (26%)	329 (24%)	0.30	322 (23%)	0.10
Previous MI	329 (25%)	375 (28%)	0.08	362 (26%)	0.40
Previous PCI	461 (34%)	512 (37%)	0.11	528 (38%)	0.07
Previous CABG	162 (12%)	184 (13%)	0.32	199 (14%)	0.10
Family history of coronary artery disease	654 (57%)	655 (56%)	0.62	714 (58%)	0.48
Hypertension (on medication)	987 (73%)	1,041 (75%)	0.23	1,025 (73%)	0.64
Hyperlipidemia (on medication)	745 (56%)	806 (60%)	0.05	788 (57%)	0.66
High risk§	928/1,266 (73%)	916/1,303 (70%)	0.09	959/1,347 (71%)	0.23
Creatine kinase isoenzyme MB/troponin increase	684/1,216 (56%)	710/1,260 (56%)	0.96	724/1,297 (56%)	0.83
ST-segment deviation	496/1,353 (37%)	490/1,385 (35%)	0.49	523/1,416 (37%)	0.88
Anemia	244/1,354 (18%)	259/1,386 (19%)	0.67	276/1,417 (20%)	0.42
Treatment strategy					
PCI	701 (52%)	690 (50%)	0.30	700 (49%)	0.21
CABG	110 (8%)	126 (9%)	0.37	119 (8%)	0.79
Medical management	543 (40%)	570 (41%)	0.59	598 (42%)	0.26
Aspirin¶	1,339 (99%)	1,371 (99%)	0.89	1,402 (99%)	0.91
Previous thienopyridine exposure#	463/701 (66%)	459/688 (67%)	0.79	471/699 (67%)	0.60

\* Comparison between bivalirudin plus GPI and heparin (unfractionated or enoxaparin) plus GPI.

† Comparison between bivalirudin alone and heparin (unfractionated or enoxaparin) plus GPI.

‡ Calculated creatinine clearance &lt;60 ml/min using the Cockcroft-Gault equation.

§ Defined as increased creatine kinase-MB or troponin or ST deviation.

|| Defined using the World Health Organization criteria (hemoglobin ≤13 g/dl for men and ≤12 g/dl for women).

¶ Aspirin use before randomization or administration before angiography.

# Defined as longer-term use, any administration before randomization, any dose before angiography (in patients with CABG and medically managed patients), or before PCI for patients treated with PCI.

coronary artery disease. Women were also more likely to have baseline electrocardiographic changes and higher ejection fraction than men. Conversely, men were more likely to be smokers, to have increased cardiac markers at baseline,

and to have previous MI, PCI, and CABG. Men were more often triaged to PCI and CABG, whereas women were more likely to be managed medically. A total of 407 patients received an excess dose of eptifibatid, defined as patients

Table 5  
Clinical outcomes at 30 days in women and women undergoing percutaneous coronary intervention by randomized antithrombin group

Variable	Heparin (unfractionated or low-molecular-weight) + GPI	Bivalirudin + GPI	p <sub>1</sub> Value*	Bivalirudin Monotherapy	p <sub>2</sub> Value <sup>†</sup>
Overall population	1,354	1,386		1,417	
Net clinical outcome	183 (14%)	197 (14%)	0.60	165 (12%)	0.14
Composite ischemia	80 (6%)	109 (8%)	0.04	103 (7%)	0.15
Death	13 (1%)	28 (2%)	0.02	16 (1%)	0.66
MI	54 (4%)	72 (5%)	0.13	73 (5%)	0.14
Unplanned revascularization	25 (2%)	31 (2%)	0.47	33 (2%)	0.38
Major bleeding (non-CABG)	131 (10%)	115 (8%)	0.21	72 (5%)	<0.0001
Intracranial	2 (0.1%)	2 (0.1%)	0.98	2 (0.1%)	0.96
Intraocular	0 (0.0%)	1 (0.1%)	0.32	0 (0.0%)	—
Retroperitoneal	18 (1%)	15 (1%)	0.55	3 (0.2%)	<0.001
Access site <sup>‡</sup>	58 (4%)	51 (4%)	0.42	21 (2%)	<0.0001
Hemoglobin decrease $\geq 3$ g/dl with overt bleeding	60 (4%)	39 (3%)	0.02	20 (1%)	<0.0001
Hemoglobin decrease $\geq 4$ g/dl without overt bleeding	17 (1%)	17 (1%)	0.95	16 (1%)	0.76
Reoperation for bleeding	0 (0.0%)	1 (0.1%)	0.32	2 (0.1%)	0.17
Transfusion	71 (5%)	62 (5%)	0.35	46 (3%)	0.009
Minor bleeding	337 (25%)	336 (24%)	0.69	203 (14%)	<0.0001
TIMI bleeding	130 (10%)	111 (8%)	0.14	75 (5%)	<0.0001
Major	44 (3%)	35 (3%)	0.26	22 (2%)	0.003
Minor	127 (9%)	104 (8%)	0.08	70 (5%)	<0.0001
Thrombocytopenia	111 (8%)	124 (9%)	0.48	113 (8%)	0.83
PCI population	701	690		700	
Net clinical outcome	117 (17%)	142 (21%)	0.06	104 (15%)	0.35
Composite ischemia	55 (8%)	71 (10%)	0.11	65 (9%)	0.34
Death	5 (1%)	11 (2%)	0.12	5 (1%)	0.99
MI	38 (5%)	54 (8%)	0.07	49 (7%)	0.22
Unplanned revascularization	19 (3%)	24 (4%)	0.41	24 (3%)	0.44
Major bleeding (non-CABG)	83 (12%)	96 (14%)	0.25	44 (6%)	<0.001
Intracranial	0 (0.0%)	1 (0.1%)	0.31	0 (0.0%)	—
Retroperitoneal	13 (2%)	13 (2%)	0.97	2 (0.3%)	0.004
Access site <sup>‡</sup>	40 (6%)	41 (6%)	0.85	13 (2%)	<0.001
Hemoglobin decrease $\geq 3$ g/dl with overt bleeding	39 (6%)	37 (5%)	0.87	12 (2%)	0.0001
Hemoglobin decrease $\geq 4$ g/dl without overt bleeding	10 (1%)	17 (3%)	0.16	12 (2%)	0.66
Reoperation for bleeding	0 (0.0%)	1 (0.1%)	0.31	1 (0.1%)	0.32
Transfusion	43 (6%)	56 (8%)	0.15	26 (4%)	0.04
Minor bleeding	228 (33%)	236 (34%)	0.51	120 (17%)	<0.0001
TIMI bleeding	84 (12%)	88 (13%)	0.66	47 (7%)	<0.001
Major	28 (4%)	29 (4%)	0.84	9 (1%)	0.002
Minor	83 (12%)	85 (12%)	0.78	44 (6%)	<0.001
Thrombocytopenia	45 (6%)	53 (8%)	0.36	32 (5%)	0.13

Abbreviation as in Table 2.

\* Comparison between bivalirudin plus GPI and heparin (unfractionated or enoxaparin) plus GPI.

<sup>†</sup> Comparison between bivalirudin monotherapy and heparin (unfractionated or enoxaparin) plus GPI.

<sup>‡</sup> Defined as access-site hemorrhage requiring intervention or a hematoma  $\geq 5$  cm at puncture site.

with a creatinine clearance  $<50$  ml/min ( $n = 1,342$ ) who received an initial bolus  $>99$   $\mu\text{g}/\text{kg}$  or an initial infusion of  $>1.1$   $\mu\text{g}/\text{kg}/\text{min}$ . Women were significantly more likely to receive an excess dose of eptifibatide than men.

Table 2 presents baseline angiographic characteristics and PCI lesion characteristics for men and women. Men had significantly more lesions, a greater extent of disease, and lower baseline ejection fraction and were more likely to have 3-vessel coronary artery disease than women. Conversely, women were significantly more likely to have only single-vessel coronary artery disease and to have better Thrombolysis In Myocardial Infarction flow and blush scores. PCI lesions were more focal, in smaller vessels, with more Thrombolysis In Myocardial Infarction grade 3 flow in women and more complex in men.

Clinical outcomes at 30 days for men versus women overall and by treatment strategy are presented in Table 3. Overall, no significant differences were observed in the rate of composite ischemia or its components in men versus women at 30 days. Women had significantly higher rates of non-CABG major bleeding compared with men, resulting in a higher rate of 30-day net clinical outcomes. At 1 year, there were no significant differences in rates of mortality (3.7% vs 3.9%,  $p = 0.58$ ), MI (7.3% vs 6.7%,  $p = 0.19$ ), or urgent revascularization (8.7% vs 7.7%,  $p = 0.05$ ), although rates of composite ischemia were significantly higher in men than in women (16.3% vs 14.4%,  $p = 0.005$ ) in the overall population.

Regardless of the treatment modality used (PCI, CABG, or medical management) women had significantly higher

rates of 30-day non-CABG major bleeding, with a resultant increase in net clinical outcomes (Table 3). There were no significant differences in rates of composite ischemia or its components including mortality at 30 days in women versus men. At 1 year, there were no significant differences in rates of composite ischemia for women versus men undergoing PCI or CABG (Figure 1). However, in medically managed patients, rates of 1-year composite ischemia were significantly lower in women, ( $p < 0.0001$ ) with a trend ( $p = 0.06$ ) toward decreased mortality.

Cox models were used to adjust for differences in baseline characteristics between men and women. Adjusted results were consistent with those of unadjusted analyses and demonstrated that female gender was associated with increased risk of 30-day non-CABG major bleeding (adjusted hazard ratio 1.96, 95% CI 1.66 to 2.32,  $p < 0.0001$ ) and net clinical outcomes (adjusted hazard ratio 1.30, 95% CI 1.16 to 1.45,  $p < 0.0001$ ). Similar to the unadjusted analysis findings, female gender was not associated with an increase in 30-day composite ischemia (adjusted hazard ratio 0.93, 95% CI 0.80 to 1.08,  $p = 0.33$ ). Results were similar in the subgroup of patients undergoing PCI.

Baseline characteristics and treatment strategies in women by randomized antithrombin group were similar (Table 4). Overall, aspirin was administered to approximately 99% of women and a thienopyridine to approximately 67%. Women treated with bivalirudin plus a GPI had higher rates of 30-day mortality and composite ischemia compared with those treated with heparin plus a GPI (Table 5). This difference between bivalirudin plus GPI and heparin plus GPI was not sustained at 1 year (4.4% vs 3.8%,  $p = 0.44$  for mortality) and (15.7% vs 13.4%,  $p = 0.07$  for composite ischemia).

Bivalirudin monotherapy resulted in similar rates of composite ischemia and net clinical outcomes at 30 days compared with heparin plus GPI, with significantly lower rates of major bleeding. Among the components of major bleeding, rates of retroperitoneal and access-site bleeding, hemoglobin decrease  $\geq 3$  g/dl, and transfusion were significantly lower with bivalirudin monotherapy. Protocol-defined minor bleeding and Thrombolysis In Myocardial Infarction major and minor bleeding also occurred significantly less often with bivalirudin monotherapy compared with heparin plus GPI (Table 5). The relative risk decrease in non-CABG major bleeding with bivalirudin monotherapy compared with heparin plus GPI was similar in women (47%) and men (48%). At 1 year, bivalirudin monotherapy resulted in similar rates of mortality (2.8% vs 3.8%,  $p = 0.11$ ) and composite ischemia (14.0% vs 13.4%,  $p = 0.60$ ) compared with heparin plus GPI.

In women undergoing PCI there were no significant differences in outcomes between the 2 GPI arms (Table 5). Although composite ischemia and net clinical outcome at 30 days were similar for the bivalirudin monotherapy arm compared with the heparin plus GPI arm, major bleeding was significantly lower with bivalirudin monotherapy. Rates of retroperitoneal and access-site bleeding, hemoglobin decrease  $\geq 3$  g/dl, transfusion, protocol-defined minor bleeding, and Thrombolysis In Myocardial Infarction–defined major and minor bleeding were significantly lower with bivalirudin monotherapy.

No significant differences were observed in rates of 1-year composite ischemia and mortality for patients treated with bivalirudin monotherapy versus heparin plus GPI

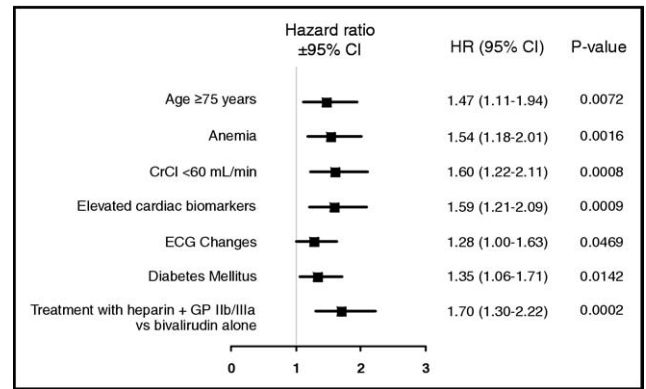


Figure 2. Multivariate analysis of the predictors of 30-day major bleeding in women, displayed as hazard ratio (HR) (black boxes) with 95% CIs (horizontal limit lines). CrCl = creatinine clearance; ECG = electrocardiographic.

(19.4% vs 17.7%,  $p = 0.40$ , and 2.6% vs 3.7%,  $p = 0.23$ , respectively). Similarly, there were no significant differences in 1-year composite ischemia and mortality rates with bivalirudin plus GPI versus heparin plus GPI (21.6% vs 17.7%,  $p = 0.06$ , and 4.2% vs 3.7%,  $p = 0.64$ , respectively).

A Cox proportional hazards regression analysis was performed to evaluate the impact of baseline characteristics on 30-day major bleeding (non-CABG related) in women overall and in women undergoing PCI. Treatment with heparin (unfractionated or enoxaparin) plus routine use of GPIs rather than bivalirudin monotherapy was an independent predictor of major bleeding in women in the overall population (hazard ratio 1.70, 1.30 to 2.22,  $p = 0.0002$ ; Figure 2) and the PCI-treated women. Other predictors of major bleeding included age  $\geq 75$  years, anemia, creatinine clearance  $< 60$  ml/min, increased cardiac biomarkers, electrocardiographic changes, and diabetes mellitus in the overall population and the PCI population with the exception of increased biomarkers (Table 5).

## Discussion

This analysis demonstrates that, despite differences in risk factors, women with NSTEMI-ACS did not appear to be at increased risk of 1- and 12-month ischemic complications or mortality compared with men. Women are more likely to develop major bleeding complications. In women, treatment with bivalirudin monotherapy resulted in similar short- and long-term protection from ischemic events with significantly less bleeding compared with treatment with heparin plus GPI irrespective of the treatment strategy selected, namely PCI, CABG, or medical therapy.

Coronary heart disease is the leading cause of death in the United States and recent advances have not led to a decrease in mortality in women.<sup>12</sup> There are gender differences in many aspects of ACS, including presentation and delay to diagnosis and treatment, accuracy of diagnostic tests, drug side effects, and differences in biomarkers.<sup>13</sup> In addition, women have unique physiologic conditions including smaller arteries and less endothelial dysfunction possibly mediated by sex hormones that may contribute to

the pathogenesis of coronary artery disease,<sup>13,14</sup> and our findings reinforce the observation that women with ACS are older and present with more co-morbid conditions.<sup>15</sup> Specifically, our study demonstrated that women presenting with ACS had more chronic kidney disease, diabetes, and hypertension, but had significantly less extensive and complex coronary artery disease, smaller vessels, better coronary flow, and myocardial perfusion than men. These factors likely account for the lower baseline cardiac markers and enzyme release observed in women and similar rates of mortality and ischemic events compared with men observed with all treatment strategies in this study.

In the treatment of ACS, early use of antithrombin and antiplatelet therapy plays a key role in improving patient outcomes.<sup>9,16–18</sup> However, female gender has been linked to an increased bleeding risk with a variety of antithrombotic agents including thrombolytics, unfractionated heparin, and low-molecular-weight heparin.<sup>19–21</sup> And although GPIs have been demonstrated to be beneficial in patients with high-risk NSTEMI-ACS, several clinical trials and meta-analyses have raised concerns about their relative risks and benefits in women.<sup>9,16,22,23</sup>

In the contemporary era of coronary stenting, multiple studies of ACS and PCI have demonstrated more short-term adverse outcomes, such as in-hospital mortality, intraprocedural coronary artery injury, and bleeding complications in women than in men.<sup>4,24,25</sup> Recent data have suggested that achieving efficacy at the expense of safety, namely bleeding, actually leads to increased mortality.<sup>5,26–28</sup> The optimal strategy, therefore, is prevention of bleeding complications with an antithrombin that provides effective anticoagulant activity and decreases bleeding.

Bivalirudin, a direct thrombin inhibitor that has consistently demonstrated similar protection from ischemic events as seen with heparin plus GPIs, but with significantly lower bleeding complications, may be an attractive treatment option for women. A subgroup analysis of women in the Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events (REPLACE)-2 PCI trial<sup>29</sup> found that female gender was a univariate predictor of bleeding complications and death. There was no significant difference in the composite ischemic end point (death, MI, or revascularization) at 30 days and 6 months in those treated with bivalirudin versus heparin plus GPIs. However, treatment with bivalirudin resulted in statistically lower rates of protocol-defined major and minor bleeding compared with heparin plus GPIs. Multivariate modeling found no significant interactions between gender and the composite ischemic end point, major bleeding, or 1-year mortality.<sup>29</sup>

In the present analysis, multivariate modeling found that randomization to heparin plus GPI was a significant predictor of major bleeding for women. An analysis of the ACUITY trial data confirms these findings.<sup>30</sup> Not only was major bleeding significantly higher in patients treated with heparin plus GPI compared with bivalirudin, but its occurrence was also found to be a powerful independent predictor of 30-day mortality in patients with ACS managed invasively (odds ratio [OR] 7.55, 95% CI 4.68 to 12.18,  $p < 0.0001$ ). Several factors were found to independently predict major bleeding, including treatment with heparin plus GPI compared with bivalirudin monotherapy (OR 1.95, 95% CI 1.56 to 2.44,  $p < 0.0001$ ) and female gender

(OR 1.92, 95% CI 1.61 to 2.29,  $p < 0.0001$ ).<sup>30</sup> Furthermore, women with NSTEMI-ACS who received a GPI, regardless of whether it was used in conjunction with heparin or bivalirudin, had higher rates of 30-day net clinical adverse outcomes compared with bivalirudin monotherapy, driven primarily by major bleeding.

Because bivalirudin monotherapy confers similar protection from ischemic events as heparin plus GPI, the addition of a GPI is not essential for improved outcomes and represents a potential safety concern, thereby making bivalirudin an effective and safe alternative for use in women with NSTEMI-ACS.

There are several limitations to the present analysis. First, the ACUITY trial was not powered for subgroup analyses and therefore these results should be considered exploratory. Despite being underpowered, this is the largest cohort of women in a prospective NSTEMI-ACS trial. Second, results may have been affected by treatment bias because the ACUITY trial was an open-label study; however, every end point was adjudicated by an independent, blinded clinical events committee using source documents and all core laboratories were also blinded. Third, selection biases may have exerted differential effects between men and women when the decision to enroll them was made. Fourth, the results of this study apply only to patients with NSTEMI-ACS in whom coronary angiography in the first 72 hours is planned.

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