JACC: CARDIOVASCULAR INTERVENTIONS VOL. 3, NO. 6, 2010

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER INC. DOI: 10.1016/j.jcin.2010.03.015

Antithrombotic Strategy in Non–ST-Segment Elevation Myocardial Infarction Patients Undergoing Percutaneous Coronary Intervention

Insights From the ACTION (Acute Coronary Treatment and Intervention Outcomes Network) Registry

Renato D. Lopes, MD, PhD, MHS,* Eric D. Peterson, MD, MPH,* Anita Y. Chen, MS,* Matthew T. Roe, MD, MHS,* Tracy Y. Wang, MD, MHS,* E. Magnus Ohman, MD,* David J. Magid, MD, MPH,† P. Michael Ho, MD, PhD,‡ Stephen D. Wiviott, MD,§ Benjamin M. Scirica, MD,§ Karen P. Alexander, MD*

Durham, North Carolina; Denver, Colorado; and Boston, Massachusetts

Objectives The aim of this study was to examine the use of and outcomes associated with antithrombotic strategies in patients with non–ST-segment elevation myocardial infarction (NSTEMI) who undergo percutaneous coronary intervention (PCI).

Background A variety of antithrombotic strategies have been tested in clinical trials for NSTEMI patients treated with PCI.

Methods Antithrombotic strategies for NSTEMI patients undergoing PCI at 217 ACTION (Acute Coronary Treatment and Intervention Outcomes Network) hospitals from January 1, 2007, to December 31, 2007, (n = 11,085) were classified into commonly observed antithrombotic groups: heparin alone (Hep alone; low-molecular-weight heparin or unfractionated heparin), bivalirudin alone (Bival alone), heparin with glycoprotein IIb/IIIa inhibitors (Hep/GPI), and bivalirudin with GPI (Bival/GPI). Baseline characteristics are shown across treatment groups. In addition, unadjusted and adjusted rates of in-hospital major bleeding and death are shown.

Results The standard strategy used was Hep/GPI (64%), followed by Hep or Bival alone (28%), and Bival/GPI (8%). Patients who received Hep or Bival alone were older with more comorbidities, higher baseline bleeding and mortality risk, and lower peak troponin. Compared with patients who received Hep/GPI , those who received Hep alone and Bival alone had lower rates of major bleeding (adjusted odds ratio [OR]: 0.52; 95% confidence interval [CI]: 0.42 to 0.65; adjusted OR: 0.48; 95% CI: 0.39 to 0.60; respectively), yet only patients who received Bival alone had lower mortality (adjusted OR: 0.39; 95% CI: 0.21 to 0.71).

Conclusions NSTEMI patients undergoing PCI are more likely to receive Bival or Hep alone when at higher baseline bleeding risk than when at lower baseline bleeding risk. Despite higher baseline risk, those receiving Bival or Hep alone had less bleeding. (J Am Coll Cardiol Intv 2010;3:669–77)

From the *Duke Clinical Research Institute, Duke University Medical Center, Durham, North Carolina; †Institute for Health Research, Kaiser Permanente Colorado, and the Departments of Emergency Medicine and Preventive Medicine and Biometrics, University of Colorado Health Science Center, Denver, Colorado; ‡Section of Cardiology, Denver VA Medical Center, and University of Colorado Health Sciences Center, Denver, Colorado; and the §Brigham and Women's Hospital, Boston, Massachusetts. The National Cardiovascular Data Registry ACTION Registry is administered by the American College of Cardiology Foundation (ACCF) and sponsored by Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership, Genentech, and Schering-Plough Corporation, who provide material support for the operation of the data collection and infrastructure. The sponsors had no additional role in this project, including the selection of topic, analysis of data, decision to publish, or approval of the manuscript before publication. Data analysis was performed independently by a statistician (Dr. Chen) from the Duke Clinical Research Institute.

Manuscript received February 19, 2010, accepted March 4, 2010.

Antithrombotic therapy is central in the treatment of the activated thrombotic process in non–ST-segment elevation myocardial infarction (NSTEMI), particularly among moderate- or high-risk patients who undergo an initial invasive strategy (1–3). Yet, invasive care also increases risk for bleeding due to arterial puncture and the use of antithrombotics in the catheterization laboratory. Guidelines emphasize the importance of risk stratification for ischemic and bleeding complications when selecting treatments to optimize short- and long-term clinical outcomes (2).

See page 678

Although outcomes associated with antithrombotic strategies used in NSTEMI patients undergoing percutaneous coronary intervention (PCI) have been well-studied in clinical trials, the patterns of use and outcomes in clinical practice are less well-described (4–6). Therefore, our objectives were to describe: 1) the selection of antithrombotic strategies among NSTEMI patients undergoing PCI in the ACTION (Acute Coronary Treatment and Intervention Outcomes Network) registry as a function of patient profiles; 2) the selection of antithrombotic strategies according to baseline risk of in-hospital mortality and major bleeding; and 3) the timing of antithrombotic therapy in relation to PCI. Additionally, we assessed the association between antithrombotic strategy and in-hospital major bleeding and mortality before and after adjustment for clinical factors.

Abbreviations and Acronyms

Bival = bivalirudin
CABG = coronary artery bypass grafting
CI = confidence interval
GPI = glycoprotein IIb/IIIa inhibitor
HCT = hematocrit
Hep = heparin
MI = myocardial infarction
NSTEMI = non–ST-segment elevation myocardial infarction
OR = odds ratio
PCI = percutaneous coronary intervention
RBC = red blood cell

Methods

National Cardiovascular Data Registry's ACTION registry. The National Cardiovascular Data Registry's ACTION registry is a national quality improvement registry of ST-segment elevation myocardial infarction (MI) and NSTEMI patients that began enrolling on January 1, 2007 (7). Patients are eligible for inclusion in ACTION if they present within 24 h from onset of ischemic symptoms and receive a primary diagnosis of NSTEMI or ST-segment elevation MI. De-identified data are extracted from existing medical records on a web-based case form by trained data collectors at each center. Study participation at each center was approved by local institutional review boards. The National Cardiovascular Data Registry has a data quality program in place to ensure consistent and reliable data. Quality assurance measures, such as data quality reports and random site audits by trained nurse abstractors, are used to maximize the completeness and accuracy of all records submitted.

Study population. The study population was limited to the 11,085 NSTEMI patients treated with PCI from January 1, 2007 to December 31, 2007, at 217 ACTION hospitals. The original NSTEMI population included 31,036 patients enrolled at 275 ACTION hospitals. The following patients were excluded sequentially: those who did not have PCI performed or were missing PCI status (n = 18,172); those with contraindications to antithrombin therapy (n = 118) or glycoprotein IIb/IIIa inhibitors (GPI) (n = 506); those who did not receive any heparin, bivalirudin, or GPI (n = 205); those who received other less commonly used antithrombotic agents (n = 908); and those who received bivalirudin before hospital stay (n = 42). The remaining 11,085 PCI patients receiving antithrombotic therapy were divided into 4 groups of antithrombotic treatment by use of GPI and antithrombins, either alone or in combination. Patients who received any bivalirudin were classified in 1 of the 2 bivalirudin groups—Bival alone or Bival/GPI—even if they previously received heparin. Some patients received low-molecular-weight heparin or unfractionated heparin and were classified as Hep alone as long as use of bivalirudin or GPI was not recorded. Patients who received GPI with or without heparin were classified as Hep/GPI, because only 3.8% received GPI alone. Therefore, the 4 antithrombotic treatment groups were denoted as: Hep alone, Bival alone, Hep/GPI, and Bival/GPI.

Definitions. Major bleeding was defined as intracranial hemorrhage, documented retroperitoneal bleed, hematocrit (HCT) drop ≥12% (baseline to nadir ≥12%), any red blood cell (RBC) transfusion when baseline HCT ≥28%, or any RBC transfusion when baseline HCT <28% with witnessed bleed. The HCT cut-point of 28% was chosen to ensure that transfusions given for baseline anemia were not considered to be bleeding events. Coronary artery bypass grafting (CABG) patients were included in the analysis, but bleeding events were censored at the time of surgery. Baseline and nadir (lowest-recorded) HCT were abstracted on the data collection form. Blood transfusion was defined as any nonautologous transfusion of whole or packed RBCs. Witnessed bleeding was a variable on the case report form requiring evidence of a bleeding location. Prior-PCI timing was defined as any time from hospital presentation up to 1 h before the procedure. Peri-procedure timing was defined as 1 h before the procedure to any time after the procedure. We excluded patients for whom the time was unknown from the timing analyses. Key outcomes included in-hospital major bleeding and death, and secondary outcomes included post-admission MI, heart failure, stroke, RBC

transfusion, and cardiogenic shock. Other study definitions are available at the National Cardiovascular Data Registry website.

Statistical analyses. Among patients who underwent PCI, baseline patient demographic data, medical history, presentation features, treatment patterns, and in-hospital outcomes were presented across the 4 most common antithrombotic treatment strategies. Continuous variables were presented as medians (25th, 75th percentiles), whereas categorical variables were presented as percentages. Continuous variables were compared with the nonparametric Kruskal-Wallis test, whereas nominal categorical variables were compared with chi-square tests.

Selection of patients on each antithrombotic treatment was explored by the baseline bleeding and mortality risk with the Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the American College of Cardiology/American Heart Association guidelines (CRUSADE) bleeding score (c-index = 0.72) and the CRUSADE mortality model (c-index = 0.80), respectively (8–10). The CRUSADE bleeding score takes into account 8 baseline clinical presentation and laboratory characteristics: sex, diabetes, peripheral vascular disease, heart rate, systolic blood pressure, signs of congestive heart failure, baseline HCT <36%, and creatinine clearance. Patients may be classified with a low (score ≤40) or high (score >40) bleeding risk. The CRUSADE mortality model includes systolic blood pressure, age, signs of heart failure on admission, renal insufficiency, heart rate, dyslipidemia, prior stroke, troponin ratio, prior heart failure, body mass index, diabetes, electrocardiogram changes (ST-segment depression and transient ST-segment elevation), and prior PCI. Patients may then be classified by tertiles of mortality risk as low (<1.77%), moderate (1.77% to 4.53%), and high (≥4.53%). In addition, the timing of medications (i.e., acute clopidogrel, low-molecular-weight heparin, unfractionated heparin, bivalirudin, and GPI) and PCI was explored across antithrombotic therapies.

To investigate the relationship between in-hospital major bleeding and mortality and antithrombotic therapies, logistic generalized estimating equations with exchangeable working correlation matrix were used to adjust for baseline factors and to account for within-hospital clustering, because patients at the same hospital are more likely to have similar responses relative to patients at other hospitals (i.e., within-center correlation for response). This method produces estimates similar to those from ordinary logistic regression, but their variances are adjusted for the correlation of outcomes within a hospital (11). Variables included in the model were determined through clinical input from the investigators and included age, sex, body mass index, race, hypertension, diabetes, current/recent smoker, hypercholesterolemia, prior peripheral arterial disease, prior MI, prior PCI, prior CABG, prior heart failure, prior stroke, dialysis, signs of heart failure on presentation, systolic blood pressure, and heart rate at presentation. Adjusted associations for in-hospital major bleeding and mortality were displayed as odds ratios (ORs) with 95% confidence intervals (CIs), and each antithrombotic therapy was compared with Hep/GPI. Furthermore, a sensitivity analysis of in-hospital major bleeding and mortality was performed by excluding patients who received excess doses of low-molecular-weight heparin, unfractionated heparin, or GPI. Lastly, the unadjusted rates of major bleeding for antithrombotic therapy groups were displayed across CRUSADE bleeding risk score.

A p value <0.05 was considered significant for all tests. All analyses were performed with SAS software (version 9.1, SAS Institute, Cary, North Carolina).

Results

We found that Hep/GPI was the most common strategy, used in almost two-thirds of the PCI patients (7,086 of 11,085 = 64%), followed by Bival alone (1,771 of 11,085 = 16%), Hep alone (1,365 of 11,085 = 12%), and Bival/GPI (863 of 11,085 = 8%). Among patients who received Hep alone, 31% received low-molecular-weight heparin only, 58% received unfractionated heparin only, and 11% received both.

Demographic and baseline characteristics. The demographic data, medical histories, and baseline characteristics of the population according to antithrombotic strategy are shown in Table 1. Patients who received Hep alone or Bival alone were older; more often female; more often had signs of heart failure and higher heart rate at presentation; and had more cardiovascular risk factors such as hypertension, diabetes, dyslipidemia, prior MI, congestive heart failure, and stroke when compared with those patients who received Hep/GPI or Bival/GPI.

Bleeding and mortality risks. Patients who received Hep alone or Bival alone had a higher risk of bleeding with the CRUSADE bleeding score at baseline than those who received either drug with a GPI (Table 1). In addition, patients who received Hep alone or Bival alone were also more often at high risk for in-hospital mortality according to the CRUSADE mortality risk model (Table 1).

However, when patients were stratified into 4 groups on the basis of high and low risk of bleeding or mortality, therapy selection differed more on the basis of the risk of bleeding than on risk of mortality (Fig. 1). In other words, within the groups at low or high risk of bleeding, the use of different strategies did not vary by low or high risk of mortality. Specifically, within the groups at low or high risk of mortality, the use of different strategies varied primarily by risk of bleeding. Patients at high risk of bleeding more

Table 1. Baseline Characteristics According to Antithrombotic Treatment Among Patients who Underwent PCI

	Hep Alone (n = 1,365)	Bival Alone (n = 1,771)	Hep/GPI (n = 7,086)	Bival/GPI (n = 863)	p Value
Age (yrs)*	66 (55, 77)	66 (56, 77)	61 (52, 71)	61 (52, 71)	<0.0001
Female sex (%)	39	37	30	29	<0.0001
Race (%)					0.009
White	85	86	86	85	
Black	8	7	7	6	
Hispanic	3	4	3	5	
Asian	1	1	1	2	
Other	3	3	2	3	
BMI (kg/m^2)*	29 (25, 33)	29 (25, 33)	29 (26, 33)	29 (26, 33)	NS
Signs of heart failure (%)	15	14	10	12	<0.0001
Heart rate (beats/min)*	80 (68, 95)	80 (70, 94)	78 (67, 90)	77 (67, 90)	<0.0001
Systolic blood pressure (mm Hg)*	145 (126, 165)	148 (129, 167)	145 (126, 165)	147 (126, 165)	0.003
Creatinine clearance (ml/min)*†	75 (48, 104)	75 (51, 107)	88 (63, 115)	87 (61, 114)	<0.0001
HCT baseline (%)*	41 (38, 44)	41 (38, 44)	43 (39, 45)	43 (39, 45)	<0.0001
Peak troponin within 24 h (>5× ULN) (%)	78	77	85	87	<0.0001
BNP (ng/ml)*	219 (77, 720)	256 (87, 636)	163 (50, 478)	168 (55, 518)	<0.0001
ST-segment depression (%)	24	23	29	23	<0.0001
Transient ST-segment elevation (%)	5	4	7	5	<0.0001
History (%)					
Hypertension	73	74	66	67	<0.0001
Diabetes	35	33	26	29	<0.0001
Hyperlipidemia	61	61	58	59	0.03
Congestive heart failure	11	10	6	6	<0.0001
Peripheral artery disease	10	11	7	7	<0.0001
CABG	22	21	14	16	<0.0001
PCI	31	31	23	24	<0.0001
MI	28	26	22	22	<0.0001
Stroke	7	7	5	6	0.0001
Current/recent smoker	31	32	39	37	<0.0001
Renal insufficiency/dialysis	3	2	1	1	<0.0001
CRUSADE bleeding score*‡	29 (17, 44)	27 (17, 42)	21 (12, 34)	22 (12, 35)	<0.0001
CRUSADE mortality risk (%)					<0.0001
Low risk	42	44	52	53	
Moderate risk	35	36	33	33	
High risk	22	19	13	13	

*Continuous variables are presented as median (25th, 75th percentile). †Creatinine clearance estimated by the Cockroft-Gault formula. ‡Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the American College of Cardiology/American Heart Association guidelines (CRUSADE) bleeding score calculated on population without death in 48 h, home warfarin, transferred-out patients, and missing age, sex, and race (n = 10,451).

Bival alone = bivalirudin only; Bival/GPI = bivalirudin and glycoprotein IIb/IIIa inhibitor; BMI = body mass index; BNP = brain natriuretic peptide; CABG = coronary artery bypass grafting; HCT = hematocrit; Hep alone = heparin only; Hep/GPI = heparin/glycoprotein IIb/IIIa inhibitor; MI = myocardial infarction; PCI = percutaneous coronary intervention; ULN = upper limit of normal.

often received Hep alone or Bival alone regardless of their mortality risk strata.

Concomitant medications and in-hospital procedures. Medications given and in-hospital procedures performed within the first 24 h (early) according to the antithrombotic strategy are shown in Table 2. Patients who received Hep or Bival alone less often received beta-blockers, angiotensin-converting enzyme inhibitors, and statins within the first 24 h when compared with those patients who received Hep/GPI or Bival/GPI. Most notable, however, was the relatively lower use of clopidogrel overall among those patients who received Hep or Bival alone. Early cardiac catheterization and PCI were less often performed in patients who received Hep or Bival alone when compared with those who received Hep/GPI or Bival/GPI. The median time from symptom onset to cardiac catheterization and PCI was longer in patients who received Hep or Bival alone than in those who received either with GPI.

Antithrombotic therapy and timing of PCI. The timing of antithrombotic agents in relation to the start time of PCI among patients who received these treatments is shown in Table 3. Despite receiving less clopidogrel overall, patients

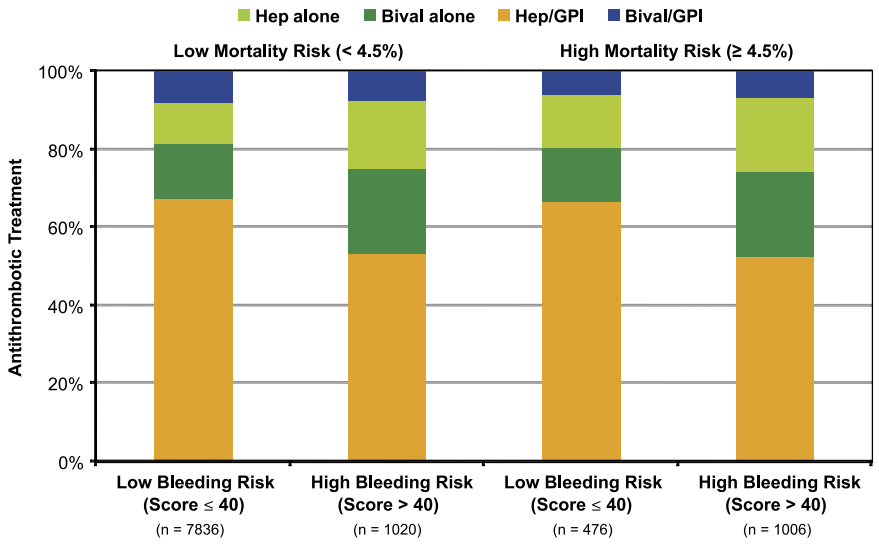

Figure 1. Unadjusted Rates of Antithrombotic Treatment in Low and High Baseline Bleeding and Mortality Risk Groups

Bival alone = bivalirudin only; Bival/GPI = bivalirudin and glycoprotein IIb/IIIa inhibitor; Hep alone = heparin only; Hep/GPI = heparin/glycoprotein IIb/IIIa inhibitor.

treated with Hep or Bival alone more often received clopidogrel before PCI than those who were initially treated with a GPI. Still just approximately one-half of the Hep or Bival alone patients received clopidogrel in advance of 1 h before PCI start, as recommended by the guidelines. In addition, bivalirudin was often started at the time of PCI and not as an initial strategy. Unfractionated heparin was commonly used before PCI, regardless of the subsequent antithrombotic strategy. Similar results were seen for low-weight-molecular heparin. This suggests that unfractionated heparin and low-weight-molecular heparin are part of an initial antithrombotic strategy that gets altered when PCI is planned.

Clinical outcomes. Unadjusted in-hospital outcome rates according to antithrombotic strategy are shown in Table 4. The OR for major bleeding after adjustment was also lower for Hep alone (OR: 0.52; 95% CI: 0.42 to 0.65) and for Bival alone (OR: 0.48; 95% CI: 0.39 to 0.60) but not for Bival/GPI (OR: 1.23; 95% CI: 0.98 to 1.56) when compared with standard therapy with Hep/GPI (reference group) (Fig. 2A). The rates of major bleeding increased as a function of CRUSADE bleeding score, yet within every CRUSADE bleeding score group, the observed rates of major bleeding were lower among those treated with Hep or Bival alone compared with those treated with either Hep/GPI or Bival/GPI (Fig. 3). Lastly, only the use of Bival alone was associated with lower in-hospital mortality after adjustment (OR: 0.39; 95% CI: 0.21 to 0.71) when compared with standard therapy with Hep/GPI (reference group) (Fig. 2B).

In a sensitivity analysis where any patient who received an excess dose of an antithrombin agent was excluded (n = 2,661), adjusted rates of major bleeding remained significantly lower with Bival alone (OR: 0.46; 95% CI: 0.36 to 0.60) and Hep alone (OR: 0.44; 95% CI: 0.33 to 0.59) when compared with standard therapy with Hep/GPI (reference group). However, in-hospital mortality rates were similar among the antithrombotic groups—Hep alone (0.97%), Bival alone (0.67%), Hep/GPI (0.85%), and Bival/GPI (1.06%) (p = NS)—and adjusted ORs for mortality when compared with Hep/GPI were no longer significant for Bival alone (OR: 0.47; 95% CI: 0.22 to 1.01) and Hep alone (adjusted OR: 0.64; 95% CI: 0.26 to 1.56).

Discussion

Among an NSTEMI population undergoing PCI, the most common antithrombotic strategy continues to be heparin with a GPI. Contemporary trials confirm the safety of bivalirudin or heparin alone in patients undergoing PCI (4,5,12–14); however, this strategy was used only 30% of the time. The strategy of heparin or bivalirudin alone without a GPI was more common among patients at higher risk of bleeding than at lower risk, and despite this higher-risk, patients treated with heparin or bivalirudin without a GPI had less major bleeding. In addition, patients treated with bivalirudin alone had lower mortality. A sensitivity analysis eliminating patients who received excess doses of antithrombins did not alter these findings. The addition of clopidogrel occurred in 80% overall and was more often

Table 2. Acute Medications and In-Hospital Procedures According to Antithrombotic Treatment Among PCI Patients

	Hep Alone (n = 1,365)	Bival Alone (n = 1,771)	Hep/GPI (n = 7,086)	Bival/GPI (n = 863)	p Value
Medications within 24 h (%)					
Aspirin	97	97	99	98	0.0006
Clopidogrel	73	78	81	82	<0.0001
Beta-blocker	93	93	95	94	0.001
ACE inhibitor	44	44	50	50	<0.0001
Statin	60	61	66	67	<0.0001
Any heparin	100	77	94	81	<0.0001
Number of diseased vessels (%)					0.004
0 or 1	42	39	42	38	
2	31	33	33	36	
3	27	29	25	25	
Cath within 24 h of arrival (%)	55	62	75	71	<0.0001
Overall type of PCI stent (%)					0.0003
Drug-eluting	63	64	61	69	
Bare-metal	36	35	38	30	
PCI within 24 h of arrival (%)	52	59	73	67	<0.0001
Assessment of LVEF (%)	91	92	94	95	<0.0001
LVEF (%)					0.0021
≥50, normal	60	64	61	60	
40–49, mild dysfunction	21	18	23	23	
25–39, moderate dysfunction	15	14	13	12	
<25, severe dysfunction	4	3	3	4	
CABG (%)	2	0.3	2	0.8	0.0002
Time from hospital presentation to					
Cath (h)*	24 (12, 47)	21 (10, 40)	16 (4, 27)	17 (6, 33)	<0.0001
PCI (h)*	26 (13, 50)	22 (10, 43)	17 (4, 28)	19 (7, 39)	<0.0001
CABG (h)*	69 (46, 143)	166 (36, 201)	79 (47, 115)	56 (40, 105)	NS
First ECG (min)*	11 (5, 21)	10 (5, 22)	9 (5, 19)	9 (5, 18)	0.001

Medication groups are determined by antithrombotic strategy at time of PCI. *Continuous variables are presented as median (25th, 75th percentile).
ACE = angiotensin-converting enzyme; Cath = cardiac catheterization; ECG = electrocardiogram; LVEF = left ventricular ejection fraction; other abbreviations as in Table 1.

given before PCI in those treated with heparin or bivalirudin alone, suggesting that it was part of the strategy in these patients. We also observed that even among those at low risk of bleeding there was a paradoxical greater use of GPI in those at lower risk for mortality (75.7% vs. 72.7%). These observations underscore that safety profiles demonstrated in clinical trials are important in the translation of evidence into practice. Clinicians select strategies with lower treatment associated bleedings and preferentially apply them to patients at higher risk of bleeding in practice.

Several clinical trials have demonstrated the superior bleeding profile of bivalirudin with provisional GPI over antithrombins with planned GPI in similar acute coronary syndromes populations. First, among 4,098 patients with unstable or post-infarction angina undergoing angioplasty, those treated with bivalirudin demonstrated similar ischemic events (11.4% vs. 12.2%) but less bleeding (3.8% vs. 9.8%) compared with heparin (15). The REPLACE (Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events)-2 trial of 6,010 patients undergoing urgent or elective PCI demonstrated that the 30-day composite end point of death, MI, repeat revascularization, and in-hospital major bleeding was similar between patients treated with bivalirudin alone with provisional GPI or heparin/GPI (9.2% vs. 10%); however, bleeding rates were lower with bivalirudin alone (13). Similarly, in the ISAR-REACT (Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment)-3 trial, bivalirudin demonstrated similar ischemic benefits with significantly less bleeding when compared with unfractionated heparin (14). In the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial, bivalirudin alone was compared with enoxaparin or unfractionated heparin plus GPI and bivalirudin plus GPI (4,5). No differences in the composite end point of 30-day death, MI, or unplanned revascularization were observed across the 3 arms, but bivalirudin alone was associated with significantly lower rates of bleeding when compared with combined therapy. In this population, longer times to catheterization and PCI were observed among the anticoagulant-only treatment

Table 3. Use of Antithrombotic Agents According to Start Time of PCI

	Hep Alone	Bival Alone	Hep/GPI	Bival/GPI	p Value
Clopidogrel (%)					<0.001
Peri PCI	45	48	61	51	
Before PCI	55	52	39	49	
UFH (%)					<0.001
Peri PCI	22	9	27	12	
Before PCI	78	91	73	88	
Low-molecular-weight heparin (%)					0.02
Peri PCI	6	10	9	7	
Before PCI	94	90	91	93	
Bivalirudin (%)					
Peri PCI	n/a	97	n/a	96	0.7
Before PCI	n/a	3	n/a	4	
GPI (%)					0.19
Peri PCI	n/a	n/a	54	55	
Before PCI	n/a	n/a	46	45	

Before PCI was from presentation to 1 h before the PCI procedure. Peri PCI was from 1 h before the procedure to any time after the procedure.
n/a = not applicable due to antithrombotic treatment definition; other abbreviations as in Table 1.

groups, but time to catheterization and PCI for the anticoagulant with GPI groups still averaged approximately 18 h. The safety of bivalirudin was found to be relatively greater (approximately 50%) in the elderly population (age ≥75 years) undergoing PCI due to their higher baseline risk of bleeding (16). Excess dosing has also been suggested as an explanation for the increased bleeding among patients treated with GPI (17). In the present study, we observed that major bleeding across treatment strategies persisted after eliminating patients with excess dosing. Higher-risk profiles in the community (compared with a trial population) might accentuate observed treatment differences. The application of these strategies across groups that differ in comorbidity extends the observed safety advantage of bivalirudin or heparin alone in clinical practice.

Timing of therapy might also play a role in treatment-associated bleeding. For example, the optimal timing of GPI was recently evaluated in the EARLY ACS (Early Glycoprotein IIb/IIIa Inhibition in Non–ST-segment Elevation Acute Coronary Syndrome) trial. The study com-

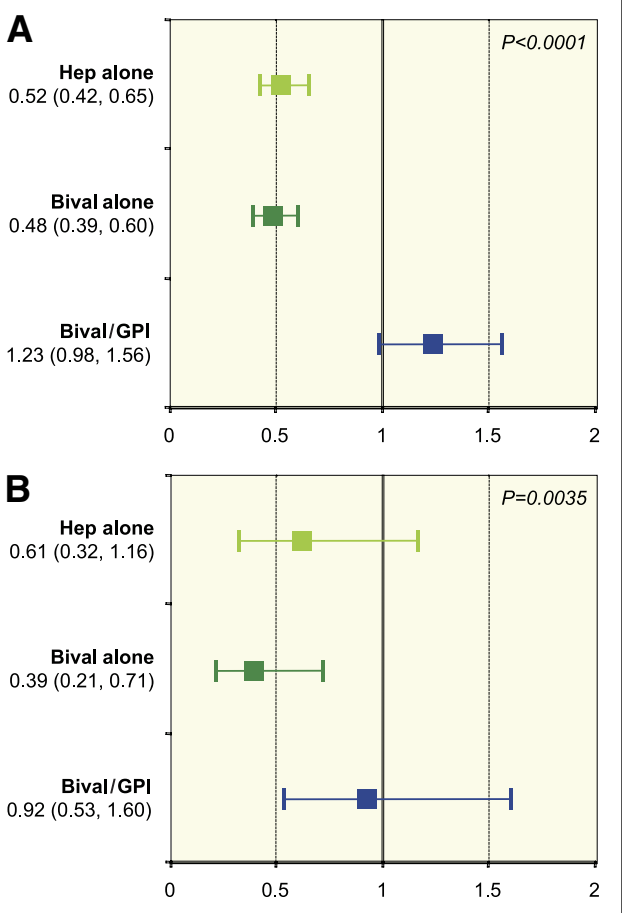

Figure 2. Adjusted Odds Ratio for Major Bleeding and In-Hospital Mortality by Antithrombotic Strategy

Adjusted odds ratio (95% confidence interval) for **(A)** major bleeding and **(B)** in-hospital mortality by antithrombotic strategy. The reference group is Hep/GPI. Abbreviations as in Figure 1.

Table 4. Crude Rates for In-Hospital Outcomes by Antithrombotic Strategy

	Hep Alone (n = 1,365)	Bival Alone (n = 1,771)	Hep/GPI (n = 7,086)	Bival/GPI (n = 863)	p Value
Death	1.3	0.7	1.3	1.3	NS
Re-MI	1.3	0.9	1.1	2.3	0.006
Death or re-MI	2.4	1.5	2.3	3.2	0.04
Cardiogenic shock	2.3	1.1	2.2	2.2	0.025
Heart failure	4.5	4.1	3.5	3.6	NS
Stroke	0.0	0.2	0.3	0.1	NS
Major bleeding	6.5	5.7	8.8	10.7	<0.0001
Non-CABG transfusions	5.1	4.9	5.0	6.4	NS

Data presented as %.
Re-MI = recurrent myocardial infarction; other abbreviations as in Table 1.

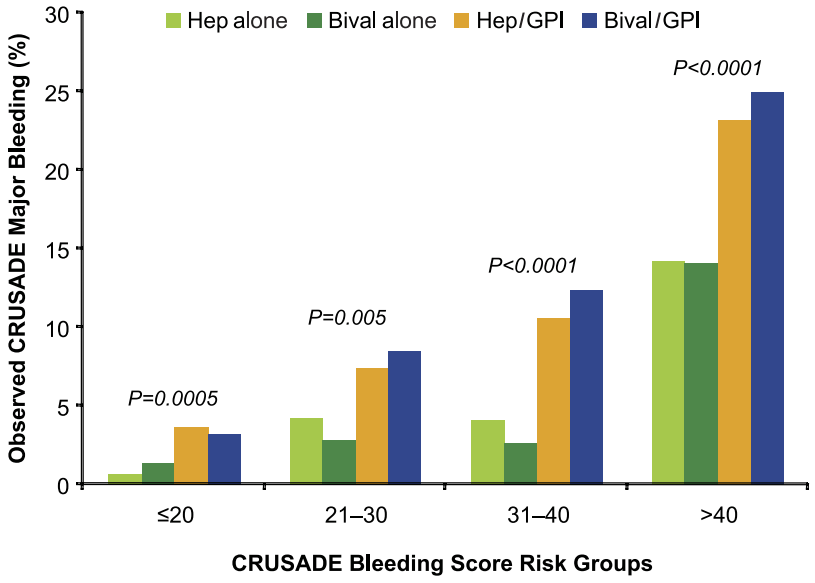

Figure 3. Unadjusted Rate of Major Bleeding Stratified by CRUSADE Bleeding Score Risk and Antithrombotic Strategy

CRUSADE = Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the American College of Cardiology/American Heart Association guidelines; other abbreviations as in Figure 1.

pared early (≥12 h before catheterization) eptifibatide to delayed provisional eptifibatide among 9,492 patients with non–ST-segment elevation acute coronary syndromes (6). No significant differences in death or MI at 30 days were noted between early and delayed eptifibatide (9.3% vs. 10.0%, respectively), but more major bleeding and transfusions were observed in the early-eptifibatide group. Similar findings were previously observed by the ACUITY investigators (18). In 9,207 patients with moderate-to-high-risk acute coronary syndromes undergoing an invasive treatment strategy, the use of GPI at the time of the angioplasty (delayed) was associated with a nonsignificant increase in the composite outcome of death, MI, and unplanned revascularization for ischemia at 30 days but significantly less major and minor bleeding when compared with those patients receiving GPI upstream (early). Therefore, the deferred use of GPI resulted in similar rates of net clinical outcomes but in better safety compared with upstream use. Although the provisional use of GPI is not the focus of the present analysis, we note in our population approximately 45% of those who received GPI did so before PCI as an upstream strategy.

Clopidogrel is recommended in all patients in advance of planned PCI and is particularly important when GPI is not part of the treatment strategy (19). It has been shown that pre-treatment with clopidogrel is clinically important in PCI patients treated with bivalirudin alone (19). Patients treated with bivalirudin alone who did not receive clopidogrel at the time of PCI experienced more ischemic events compared with those who received clopidogrel. In our study, the majority of patients received clopidogrel early; however, its recommended use in advance of PCI was lacking in approximately 20%. Patients treated with heparin or bivalirudin alone were slightly more likely to receive clopidogrel before PCI compared with those treated with either drug plus a GPI, suggesting that it might have been part of the initial treatment strategy. Furthermore, the bivalirudin-alone group received more clopidogrel (78%) than the heparin-alone group (73%), and this fact could have played a role in the lower mortality rates in the bivalirudin-alone group. Overall, focus upon better upstream use of clopidogrel might further improve outcomes, particularly among patients treated with heparin or bivalirudin alone.

Study limitations. Our study has several limitations. First, ACTION sites volunteered for this national quality improvement initiative and might not be representative of all U.S. practice. Second, all outcome comparisons were observational and might be subject to treatment selection bias. Although we did adjust our findings for most of the key measured confounders, unmeasured confounders could not be accounted for, and therefore causal relationships between treatment strategies and outcomes cannot be established. In addition, we observed some imbalances—such as time to cardiac catheterization/PCI and troponin levels—among the different groups for which we did not adjust. Third, we report in-hospital outcomes; therefore, caution should be taken when considering the long-term implications of these results. Fourth, we did not collect information about up-

stream versus bailout use of GPI, so all GPI use was considered together. Finally, we could not account for the exact timing or switching and crossing-over of antithrombotic strategies. For the sake of simplicity, strategies implemented before PCI were not considered further in this descriptive analysis.

Conclusions

Standard practice in patients with NSTEMI undergoing PCI is to use heparin/GPI, yet approximately 30% of NSTEMI patients receive heparin alone or bivalirudin alone at the time of PCI. There is a selection bias in favor of use of antithrombins alone in those patients at higher baseline risk for bleeding. This selection process seems to benefit this high-risk group, who go on to have lower rates of major bleeding during their hospital stay.

Reprint requests and correspondence: Dr. Renato D. Lopes, Duke Clinical Research Institute, Box 3850, 2400 Pratt Street, Room 0311, Terrace Level, Durham, North Carolina 27705. E-mail: renato.lopes@duke.edu.

REFERENCES

1. Bassand JP, Hamm CW, Ardissino D, et al. Guidelines for the diagnosis and treatment of non–ST-segment elevation acute coronary syndromes. The Task Force for the Diagnosis and Treatment of Non–ST-Segment Elevation Acute Coronary Syndromes of the European Society of Cardiology. Eur Heart J 2007;28:1598–660.
2. 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). J Am Coll Cardiol 2007;50:e1–e157.
3. Mehta SR, Granger CB, Boden WE, et al., TIMACS Investigators. Early versus delayed invasive intervention in acute coronary syndromes. N Engl J Med 2009;360:2165–75.
4. Stone GW, McLaurin BT, Cox DA, et al. Bivalirudin for patients with acute coronary syndromes. N Engl J Med 2006;355:2203–16.
5. Stone GW, Ware JH, Bertrand ME, et al. Antithrombotic strategies in patients with acute coronary syndromes undergoing early invasive management: one-year results from the ACUITY trial. JAMA 2007; 298:2497–506.
6. Giugliano RP, White JA, Bode C, et al., EARLY ACS Investigators. Early versus delayed, provisional eptifibatide in acute coronary syndromes. N Engl J Med 2009;360:2176–90.
7. Peterson ED, Roe MT, Rumsfeld JS, et al. A call to ACTION (Acute Coronary Treatment and Intervention Outcomes Continuous Quality Improvement for Acute Myocardial Infarction Network): a national effort to promote timely clinical feedback and support. Circ Cardiovasc Qual Outcomes 2009;2:491–9.
8. Subherwal S, Bach RG, Chen AY, et al. Baseline risk of major bleeding in non–ST-segment-elevation myocardial infarction: the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress Adverse outcomes with Early implementation of the ACC/AHA Guidelines) bleeding score. Circulation 2009;119:1873–82.
9. Roe MT, Chen AY, Delong ER, et al. Patterns of transfer for patients with non–ST-segment elevation acute coronary syndrome from community to tertiary care hospitals. Am Heart J 2008;156:185–92.
10. Tricoci P, Peterson ED, Chen AY, et al. Timing of glycoprotein IIb/IIIa inhibitor use and outcomes among patients with non–ST-segment elevation myocardial infarction undergoing percutaneous coronary intervention (results from CRUSADE). Am J Cardiol 2007;99: 1389–93.
11. Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. Biometrics 1986;42:121–30.
12. Bittl JA, Chaitman BR, Feit F, Kimball W, Topol EJ. Bivalirudin versus heparin during coronary angioplasty for unstable or postinfarction angina: Final report reanalysis of the Bivalirudin Angioplasty Study. Am Heart J 2001;142:952–9.
13. Lincoff AM, Bittl JA, Harrington RA, et al. Bivalirudin and provisional glycoprotein IIb/IIIa blockade compared with heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary intervention: REPLACE-2 randomized trial. JAMA 2003;289:853–63.
14. Kastrati A, Neumann FJ, Mehilli J, et al., ISAR-REACT 3 Trial Investigators. Bivalirudin versus unfractionated heparin during percutaneous coronary intervention. N Engl J Med 2008;359:688–96.
15. Bittl JA, Strony J, Brinker JA, et al., Hirulog Angioplasty Study Investigators. Treatment with bivalirudin (Hirulog) as compared with heparin during coronary angioplasty for unstable or postinfarction angina. N Engl J Med 1995;333:764–9.
16. Lopes RD, Alexander KP, Manoukian SV, et al. Advanced age, antithrombotic strategy, and bleeding in non–ST-segment elevation acute coronary syndromes: results from the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial. J Am Coll Cardiol 2009;53:1021–30.
17. Alexander KP, Chen AY, Roe MT, et al., CRUSADE Investigators. Excess dosing of antiplatelet and antithrombin agents in the treatment of non–ST-segment elevation acute coronary syndromes (erratum in: JAMA 2006;295:628). JAMA 2005;294:3108–16.
18. Stone GW, Bertrand ME, Moses JW, et al., ACUITY Investigators. Routine upstream initiation vs. deferred selective use of glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: the ACUITY timing trial. JAMA 2007;297:591–602.
19. Lincoff AM, Steinhubl SR, Manoukian SV, et al., ACUITY trial investigators. Influence of timing of clopidogrel treatment on the efficacy and safety of bivalirudin in patients with non–ST-segment elevation acute coronary syndromes undergoing percutaneous coronary intervention: an analysis of the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial. J Am Coll Cardiol Intv 2008;1:639–48.

Key Words: antithrombotic therapy ■ in-hospital major bleeding ■ mortality ■ non–ST-segment elevation myocardial infarction ■ percutaneous coronary intervention.