Bleeding Risk Comparing Targeted Low-Dose Heparin With Bivalirudin in Patients Undergoing Percutaneous Coronary Intervention

Results From a Propensity Score–Matched Analysis of the Evaluation of Drug-Eluting Stents and Ischemic Events (EVENT) Registry

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Background—Prior randomized trials have shown reduced bleeding with bivalirudin compared with unfractionated heparin (UFH) in patients undergoing percutaneous coronary intervention (PCI). However, it is not known if this benefit is also present when UFH doses are more tightly controlled (as measured by activated clotting time, ACT).

Methods and Results—Patients enrolled in the EVENT (Evaluation of Drug-Eluting Stents and Ischemic Events) registry, were divided into 3 groups, based on the antithrombotic drug used during PCI (UFH monotherapy, UFH+glycoprotein IIb-IIIa receptor inhibitor [GPI], or bivalirudin alone). Propensity score matching was used to adjust for measured covariates (89 variables) and to compare bivalirudin versus UFH monotherapy and bivalirudin versus UFH+GPI groups. The UFH groups were stratified based on ACT achieved (optimal ACT defined as 250–300 for UFH monotherapy and 200–250 when GPI was also used). The primary bleeding outcome was in-hospital composite bleeding, defined as events of access site bleeding, Thrombolysis In Myocardial Infarction major/minor bleeding, or transfusion. Primary (in-hospital death/myocardial infarction) and secondary ischemic outcomes (death/MI/unplanned repeat revascularization at 12 months) were also evaluated. Propensity score matching yielded 3022 patients for the UFH monotherapy versus bivalirudin comparison and 3520 patients for the UFH+GPI versus bivalirudin comparison. Bivalirudin use was associated with numerically lower bleeding rates at all categories of achieved ACT when compared with UFH (low, optimal, high ACT: 2.5% versus 4.7%, 1.9% versus 6.0%, 3.1% versus 4.8%, respectively) or heparin+GPI groups (low, optimal, high ACT: 0.0% versus 2.7%, 2.7% versus 5.2%, 2.4% versus 6.1%, respectively) and was not associated with any statistically significant increase in either primary or secondary ischemic outcomes.

Conclusions—Among unselected patients undergoing PCI, bivalirudin use during PCI was associated with a lower risk of bleeding at all comparator ACT levels without an increase in ischemic outcomes. **(*Circ Cardiovasc Interv*. 2011;4:463-473.)**

Key Words: bivalirudin ■ bleeding ■ heparin ■ ischemia ■ percutaneous coronary intervention

Recent studies have shown association between bleeding, blood transfusion, and both short- and long-term mortality in patients with acute coronary syndromes (ACS) as well as in those undergoing percutaneous coronary intervention (PCI).[1–4] Bleeding complications remain a major challenge after PCI, despite better management of arterial access sites and modifications in anticoagulant regimen and are associated with increased length of stay and resource utilization.[5]

Some of the pharmacological strategies proposed to reduce the risk of bleeding include more judicious dosing of antithrombotics, provisional use of glycoprotein IIb-IIIa receptor inhibitor (GPI) drugs, or use of direct thrombin inhibitors such as bivalirudin. Current guidelines suggest that patients undergoing PCI who do not receive a GPI should receive unfractionated heparin (UFH) sufficient to prolong the activated clotting time (ACT) to 250–300 seconds.[6] When UFH

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Table 1. Baseline Characteristics of the UFH Monotherapy and Bivalirudin Groups Before and After Propensity Score Matching

	Unmatched			Propensity Score Matched		
	UFH (n=1767)	Bivalirudin (n=3318)	*P* Value	UFH (n=1511)	Bivalirudin (n=1511)	*P* Value
Clinical characteristics						
Age, y	65.3±11.7	65.5±11.1	0.69	65.6±11.5	65.4±11.4	0.75
Men, %	67.2	67.2	0.99	67.0	64.9	0.46
Diabetes, %	33.5	36.1	0.06	34.1	34.5	0.85
Indication for PCI, %						
Acute coronary syndrome	37.6	23.9	<0.001	33.4	34.9	0.53
Chronic stable angina or positive stress test	49.8	64.1	<0.001	54.6	53.0	0.88
Ejection fraction <25%, %	2.2	1.8	0.33	2.2	2.1	0.90
NYHA class IV, %	5.8	5.7	0.81	6.2	6.6	0.65
CCS class IV, %	14.6	8.4	<0.001	12.4	11.9	0.68
Baseline laboratory data						
Platelet count <100 100/μL, %	1.7	1.7	0.94	1.7	1.4	0.54
Angiographic characteristics						
No. of diseased vessels, %						
1	50.1	50.1	0.36	49.9	48.2	0.66
2	30.4	29.2		30.5	32.4	
3	19.5	20.6		19.6	19.4	
Most severe lesion classification, %			<0.001			0.94
A	9.9	10.6		10.6	11.4	
B1	29.1	34.4		30.8	31.2	
B2	35.3	38.7		36.1	34.9	
C	25.7	16.2		22.5	22.5	
Preprocedure TIMI flow, %			<0.001			0.96
0	9.2	4.0		7.5	7.3	
1	3.4	2.9		3.3	3.3	
2	8.4	7.9		8.1	8.5	
3	79.0	85.3		81.0	80.8	
Unprotected left main PCI, %	0.6	0.8	0.32	0.6	0.5	0.81
Bifurcation lesion, %	10.4	10.4	0.99	10.3	10.4	0.86
Angiographic thrombus, %	7.1	2.2	<0.001	4.8	4.2	0.44
Total stent length, mm	30.6±20.9	28.2±18.0	<0.001	29.7±20.3	29.6±19.4	0.97
Stents per patient	1.62±0.96	1.52±0.84	0.001	1.59±0.94	1.61±0.92	0.63
No. of vessels treated per patient	1.15±0.37	1.15±0.38	0.99	1.14±0.36	1.15±0.37	0.82
Clopidogrel loading,* %	49.9	47.1	0.06	48.4	48.2	0.94

UFH indicates unfractionated heparin; PCI, percutaneous coronary intervention; NYHA, New York Heart Association; CCS, Canadian Cardiovascular Society; and TIMI, Thrombolysis In Myocardial Infarction.

*Defined as chronic therapy >1 week before PCI or ≥300 mg at least 6 hours before PCI or ≥600 mg at least 2 hours before PCI.

is given with a GPI, the target ACT should be reduced to 200–250 seconds.[6] However, the reduced risk of bleeding has to be weighed against the increased risk of ischemic complications if anticoagulation is inadequate. In addition, the level of anticoagulation achieved with heparin is highly variable and difficult to predict.

In this regard, bivalirudin has been shown to produce lower rates of bleeding complications and have comparable anti-ischemic efficacy when compared with either UFH monotherapy or UFH+GPI. In patients with stable coronary artery disease and acute coronary syndromes,[7] bivalirudin (plus provisional GPI) was noninferior to UFH with or without GPI in suppressing ischemic events, while markedly reducing bleeding.[7–9] However, some of this bleeding advantage with bivalirudin seen in earlier trials has been criticized due to higher ACT achieved in the heparin arm.[7] In addition, in a randomized trial comparing bivalirudin and UFH+GPI in the setting of PCI for ST-elevation–myocardial infarction (MI), whereas the frequencies of overall major adverse cardiovascular events (MACE) were not different between bivalirudin

and UFH randomized treatment arms, acute stent thrombosis was more common with bivalirudin.[9] Moreover, it is unknown whether the reduced bleeding observed with bivalirudin is maintained when compared with lower dosage of UFH (with or without GPI). Our objectives were to use data from the EVENT (Evaluation of Drug Eluting Stents and Ischemic Events) registry to evaluate the bleeding and ischemic events with bivalirudin when compared with various degrees of anticoagulation with UFH (as measured by ACT) used in an unselected cohort of patients undergoing PCI.

WHAT IS KNOWN

- Randomized trials have shown reduced bleeding with bivalirudin compared with unfractionated heparin in patients undergoing percutaneous coronary intervention.
- However, some of this bleeding advantage with bivalirudin seen in earlier trials has been criticized due to higher activated clotting time achieved in the heparin arm.
- Moreover, limited studies have shown increased risk of ischemic outcomes with bivalirudin.

WHAT THE STUDY ADDS

- This analysis of data from the EVENT (Evaluation of Drug Eluting Stents and Ischemic Events) registry showed numerically lower bleeding rates with bivalirudin when compared across different activated clotting time strata for both heparin and heparin+glycoprotein inhibitor comparator strategies without any statistically significant increase in either in-hospital or long-term ischemic outcomes.

Methods

The design, methods, and population of EVENT have been described previously.[10] Briefly, EVENT is a collaborative effort to assess the contemporary practice of PCI by prospective evaluation of unselected patients undergoing attempted PCI using an approved intracoronary stent at more than 50 centers in the United States. To minimize selection bias, enrollment of patients was performed consecutively during each enrollment period (eg, on predetermined days of the week) during specified recruitment "waves." A total of 10 144 patients were enrolled in waves 1 through 4 between July 2004 and June 2007. The study protocol was approved by the institutional review board at each participating institution, and written informed consent was obtained from all patients before participation in the registry.

Study Population

Patients enrolled in any wave of the registry (waves 1 through 4) receiving either UFH mononotherapy, UFH+GPI, or bivalirudin monotherapy as antithrombotic strategy during PCI were eligible for this analysis. Eligible patients included those with either PCI for ACS or stable angina. The choice of the antithrombotic strategy was left to the discretion of the physician performing the PCI. Patients who received low-molecular-weight heparin (LMWH), direct thrombin inhibitor other than bivalirudin, combination of antithrombotics (example: LMWH before PCI with heparin or bivalirudin during PCI) or those receiving "bail-out" GPI (with either UFH or bivalirudin) were excluded from this study.

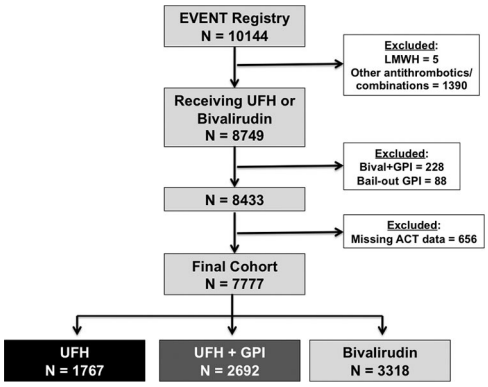

Figure 1. Patient selection.

Data Collection and Definitions

Data regarding patient baseline demographics, risk factors, presentation, angiographic characteristics, PCI procedural details, discharge medications, and outcomes were collected prospectively on standardized case report forms and submitted to the data coordinating center (Harvard Clinical Research Institute, Boston, MA). For the purposes of this analysis, clopidogrel loading was defined as chronic clopidogrel therapy >1 week before PCI or a loading dose of ≥300 mg at least 6 hours before PCI or ≥600 mg at least 2 hours before PCI. Troponin, creatinine kinase (CK), and CK-MB levels were assessed at baseline (within 1 hour before the procedure) and every 8 hours for a minimum of 2 samples after the procedure and assayed using the clinical laboratory and reference values for each site. If an MI was suspected clinically at a later point, additional biomarkers were obtained as clinically indicated. The definition of a procedural MI was elevation of CK-MB (or CK in the absence of CK-MB data) of at least 3 times the upper limit of normal (as determined by the local reference laboratory) or by new and persistent ST-segment elevation >1 mm in 2 contiguous limb leads or >2 mm in 2 contiguous precordial leads on the ECG. In addition, in patients with elevated biomarkers at baseline, biomarker elevation >2× baseline was required.

Patients were contacted by telephone at 6 and 12 months after the index PCI. Events ascertained at follow-up included death, MI, stent thrombosis, and revascularization. All clinical outcomes were adjudicated by 2 cardiologists blinded to baseline variables.

Outcomes

The primary bleeding outcome for this analysis was in-hospital composite bleeding, defined as clinically important access site bleeding, Thrombolysis In Myocardial Infarction (TIMI) major or minor bleeding, or transfusion. The primary ischemic outcome was death or MI, occurring in-hospital. The secondary ischemic outcome was a composite of death, MI, or any unplanned repeat revascularization at 12 months. Other outcomes included individual rates of in-hospital death, MI, or urgent repeat revascularization; ARC-defined[11] definite or probable stent thrombosis and postprocedure length of stay.

Activated Clotting Time

Peak ACT (in seconds) was recorded in all patients during the index PCI. Unlike UFH, in which ACT levels help quantify response to UFH, standard ACT tests for bivalirudin are used more qualitatively and correlate less well with the degree of anticoagulation.[12–14] Because we regarded heparin as the control group for our hypothesis, we therefore chose to use the ACT level in the UFH groups to further categorize the patient subsets.

Optimal ACT was defined as 250–300 for heparin alone and 200–250 when GPI was also used.[6,15] For the UFH monotherapy group, patients were stratified into 3 groups, based on peak ACT achieved: low ACT (<250), optimal ACT (250–300), and high ACT (>300). For the UFH+GPI, the 3 groups based on ACT were low ACT (<200), optimal ACT (200–250), and high ACT (>250).

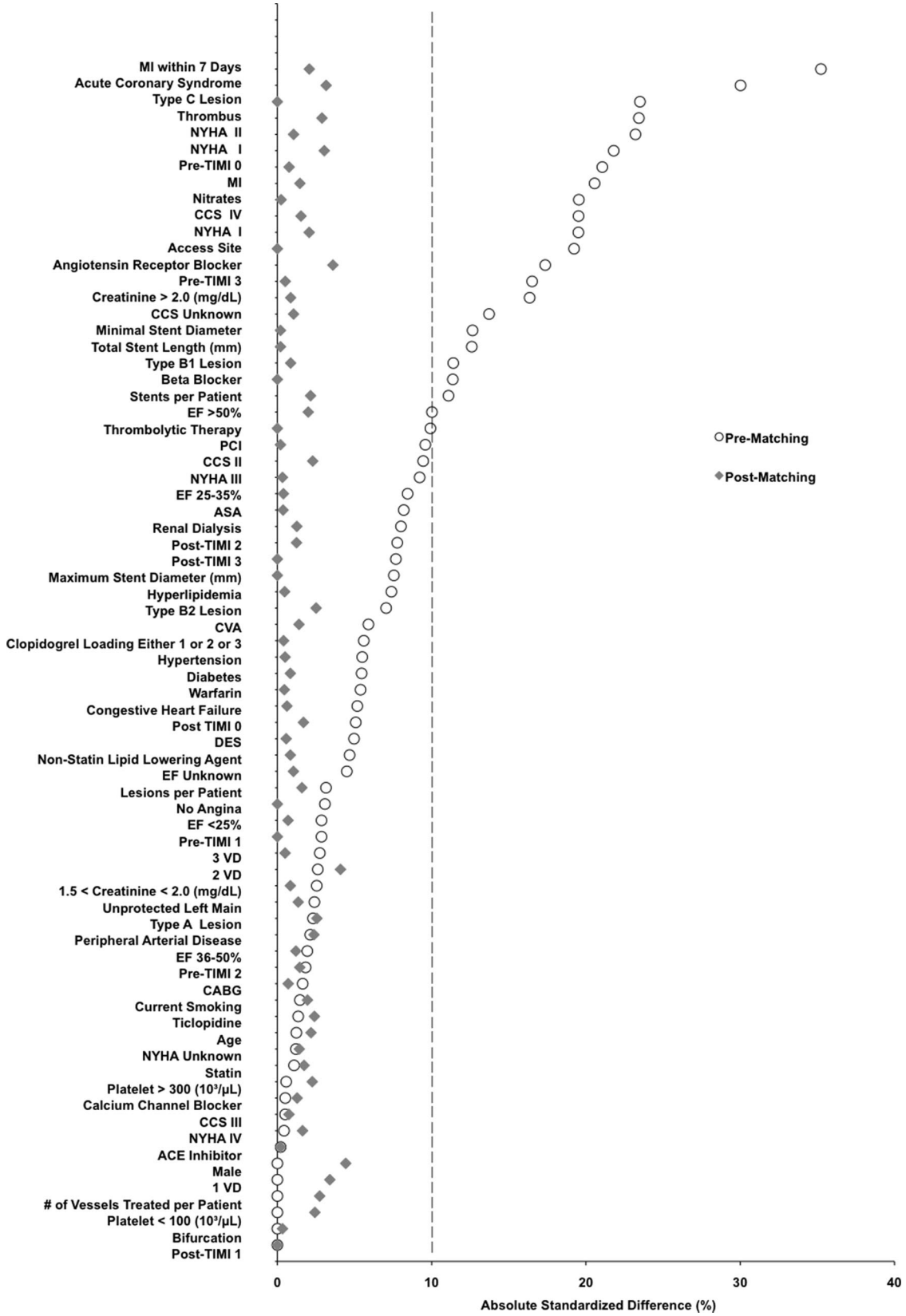

Figure 2. Absolute standardized differences in baseline covariates between unfractionated heparin monotherapy and the bivalirudin groups, before and after propensity score matching (postmatch standardized difference <10% indicates excellent covariate balance).

Table 2. Baseline Characteristics of the UFH+GPI and Bivalirudin Groups Before and After Propensity Score Matching

	Unmatched			Propensity Score Matched		
	UFH+GPI (n=2692)	Bivalirudin (n=3318)	*P* Value	UFH+GPI (n=1760)	Bivalirudin (n=1760)	*P* Value
Clinical characteristics						
Age, y	62.8±11.7	65.5±11.1	<0.0001	64.1±11.3	64.2±11.3	0.93
Men, %	71.9	67.2	<0.0001	68.6	68.9	0.93
Diabetes, %	32.4	36.1	0.002	34.6	34.0	0.75
Indication for PCI, %						
Acute coronary syndrome	39.8	23.9	<0.0001	30.4	32.1	0.41
Chronic stable angina or positive stress test	43.7	64.1	<0.0001	58.1	57.3	0.83
Ejection fraction <25%, %	2.7	1.8	0.02	2.2	1.9	0.64
NYHA class IV, %	11.9	5.7	<0.0001	7.3	6.4	0.33
CCS class IV, %	23.7	8.4	<0.0001	12.4	11.9	0.63
Baseline laboratory data, %						
Platelet <100 100/μL	0.8	1.7	0.01	1.1	1.1	0.74
Angiographic characteristics, %						
No. of diseased vessels			0.01			0.96
1	45.5	50.1		48.0	47.7	
2	32.0	29.2		30.8	30.6	
3	22.5	20.6		21.2	21.6	
Most severe lesion classification			<0.0001			0.92
A	8.3	10.6		9.9	9.5	
B1	25.7	34.4		29.3	30.0	
B2	36.9	38.7		38.5	39.0	
C	29.2	16.2		22.3	21.5	
Preprocedure TIMI flow			<0.0001			0.79
0	10.9	4.0		6.6	6.0	
1	3.2	2.9		2.6	2.9	
2	9.6	7.9		8.4	8.3	
3	76.2	85.3		82.4	82.8	
Unprotected left main, %	0.9	0.8	0.75	1.0	1.0	0.87
Bifurcation, %	14.0	10.4	<0.0001	11.8	11.9	0.92
Thrombus, %	13.7	2.2	<0.0001	4.4	4.0	0.56
Total stent length, mm	31.5±20.7	28.2±18.0	<0.0001	30.1±20.2	29.9±19.2	0.79
Stents per patient	1.68±0.96	1.52±0.84	<0.0001	1.62±0.91	1.61±0.90	0.87
No. of vessels treated per patient	1.14±0.37	1.15±0.37	0.41	1.14±0.36	1.15±0.37	0.43
Clopidogrel loading,* %	29.2	47.1	<0.0001	34.9	37.2	0.26

UFH indicates unfractionated heparin; GPI, glycoprotein IIb-IIIa receptor inhibitor; PCI, percutaneous coronary intervention; NYHA, New York Heart Association; CCS, Canadian Cardiovascular Society; and TIMI, Thrombolysis In Myocardial Infarction.

Defined as chronic therapy >1 week before PCI or ≥300 mg at least 6 hours before PCI or ≥600 mg at least 2 hours before PCI.

Statistical Analyses

All analyses were carried out using SPSS for Windows, Version 16.0 (SPSS Inc, Chicago, IL). Continuous variables are reported as mean±SD. Variables (before propensity score matching) were compared across groups using Student *t* test (for normally distributed variable) or the Wilcoxon rank-sum test (for other variables) for continuous variables and χ^2 test or Fisher exact tests for categorical variables.

Propensity Score Matching

Analyses were performed after dividing the cohort into 3 groups, based on the planned PCI anticoagulation strategy at index PCI: UFH monotherapy, UFH+GPI, or bivalirudin monotherapy. Paired comparisons were made between the UFH versus bivalirudin and UFH+GPI versus bivalirudin groups. Because of differences in key baseline characteristics between participants (Table 1), we used propensity score matching to assemble a cohort for each comparison in which all the measured covariates would be well balanced across comparator groups. The propensity score is the conditional probability of having a particular exposure (bivalirudin use), given a set of measured baseline covariates.[16,17] Propensity score matching was performed separately for the UFH versus bivalirudin groups and the UFH+GPI versus bivalirudin groups. Of note, bivalirudin treated patients could appear in both the analyses if they matched with the

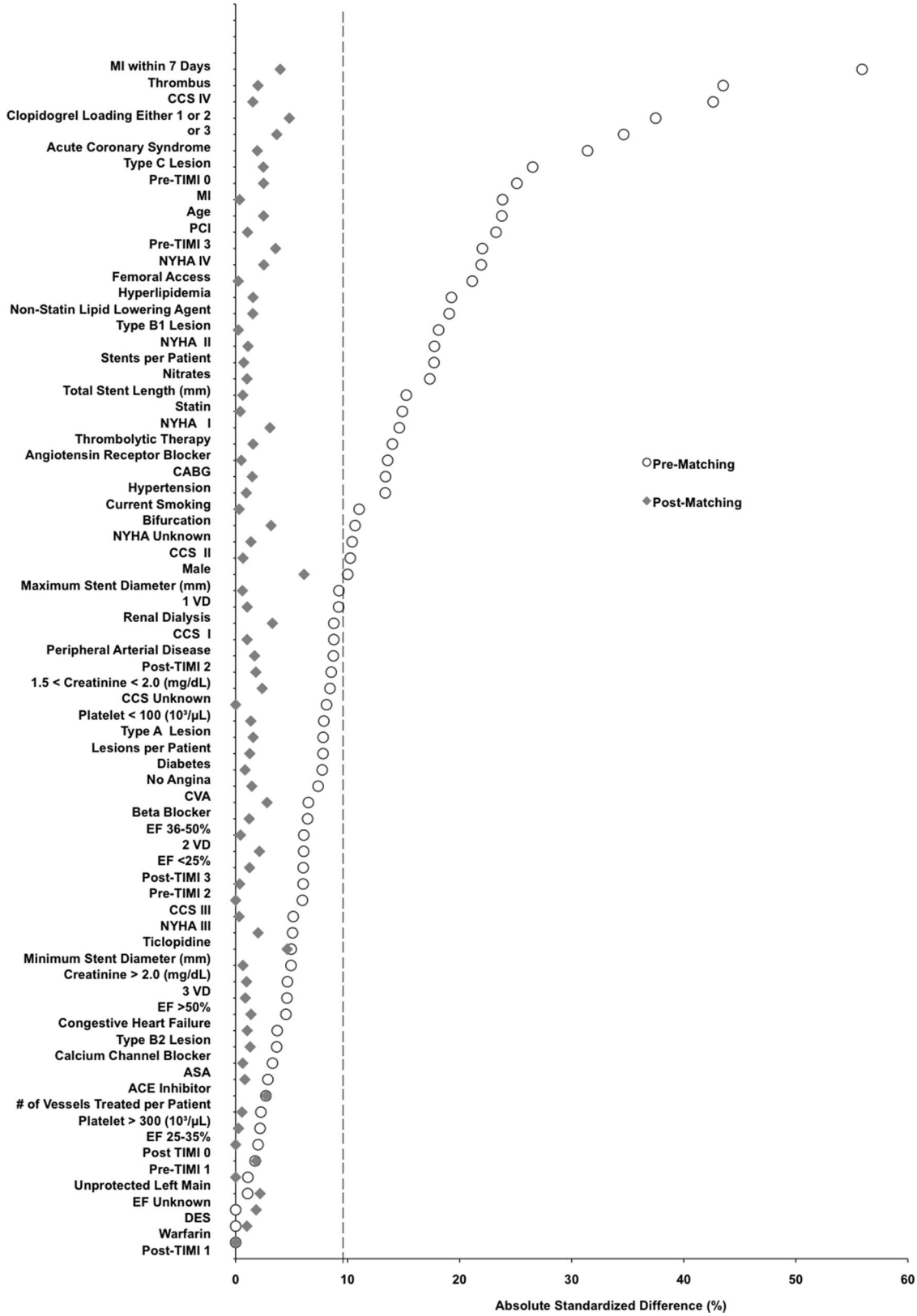

Figure 3. Absolute standardized differences in baseline covariates between unfractionated heparin plus glycoprotein IIb-IIIa receptor inhibitor (UFH+GPI) and the bivalirudin groups, before and after propensity score matching (postmatch standardized difference <10% indicates excellent covariate balance).

Table 3. Angiographic Complications, In-Hospital, and 12-Month Outcomes of the UFH Monotherapy Versus Bivalirudin Groups Before and After Propensity Score Matching

	Unmatched			Propensity Score Matched		
	UFH (n=1767)	Bivalirudin (n=3318)	*P* Value	UFH (n=1511)	Bivalirudin (n=1511)	*P* Value
Angiographic complications, %						
None	95.3	96.9	0.003	95.8	95.8	0.99
Abrupt closure	0.4	0.2	0.23*	0.3	0.3	0.74
No reflow	1.0	0.8	0.45	0.9	1.1	0.47
Thrombus	0.2	0.1	0.65*	0.1	0.1	0.99
Distal embolization	0.5	0.2	0.07*	0.5	0.1	0.12
Outcomes						
In-hospital						
Death or MI, %	5.8	5.4	0.57	5.7	5.6	0.88
Death, %	0.5	0.1	0.003*	0.5	0.1	0.53
Adjudicated MI, %	5.3	5.4	0.95	5.2	5.5	0.75
Composite bleeding, %	5.3	2.2	<0.001	5.2	2.5	<0.0001
Postprocedure length of stay, d	1.8±2.4	1.5±4.9	0.004	1.8±2.4	1.5±4.2	0.05
1 Year						
Death or MI or any unplanned repeat revascularization, %	16.2	14.8	0.19	16.3	15.2	0.46
Stent thrombosis, %	0.7	0.6	0.67	0.8	0.7	0.67

UFH indicates unfractionated heparin; MI, myocardial infarction.
*Fisher exact test used.

respective groups. Propensity scores were estimated using a nonparsimonious multivariable logistic regression model.[18] In the model, the antithrombotic strategy (UFH versus bivalirudin or UFH+GPI versus bivalirudin) was used as the dependent variable, and the 89 baseline characteristics displayed in Figures 1 and 2 were entered as covariates. Matching was performed using a greedy matching protocol (1:1 matching without replacement) with a caliper width of 0.6 of the standard deviation. We estimated standardized differences for all 89 covariates before and after matching, to assess prematch imbalance and postmatch balance.[19] Standardized differences <10% for a given covariate indicate a relatively small imbalance.[19] Matching was performed using NCSS 2007 (NCSS, Kaysville, UT).

The cohort of patients treated with UFH (with or without GPI) was then further divided into 3 strata, based on ACT achieved (as described above). The matched bivalirudin-treated patients formed the comparator for each subgroup. Paired comparisons were performed using conditional logistic regression analysis for categorical variables and paired *t* test for continuous variables. Conditional logistic regression involves analysis stratified on the matched pairs. A probability value <0.05 was considered statistically significant. The analyses were exploratory in nature, so no probability value adjustment for multiple testing was applied with the exception of subgroup analyses where we used the Bonferroni correction.

Results

The baseline demographics and clinical and angiographic characteristics between the UFH versus bivalirudin and the UFH+GPI groups are summarized in Tables 1 and 2. All results described are for the propensity score matched comparisons, unless otherwise stated. Among the 10 144 patients enrolled in EVENT waves 1 to 4, a total of 7777 (77%) met the inclusion criteria (Figure 1). Compared with the patients excluded for missing ACT data alone (656 patients), patients included in the analyses had similar rates of primary ischemic outcome (5.7% versus 6.4%; $P=0.47$).

Of the 7777 patients included, 1767 were treated with UFH monotherapy, 2692 with UFH+GPI, and 3318 with bivalirudin monotherapy. Although there were important differences in baseline characteristics between the bivalirudin and UFH groups (with or without GPI), after propensity matching these differences were no longer statistically significant. Moreover, after matching, standardized differences were <10% for all variables (Figures 2 and 3), suggesting a balanced distribution of characteristics between the paired comparison groups. For the bivalirudin versus UFH monotherapy comparison, the final cohort consisted of 1511 matched patients in each treatment group. For the comparison versus UFH+GPI, there were a total of 1760 matched patients in each treatment group.

Bivalirudin Versus UFH Comparison

In the matched cohorts, angiographic complications did not differ between the bivalirudin and UFH monotherapy groups (Table 3). Bivalirudin therapy was associated with a 30% reduction in the odds of composite bleeding (odds ratio [OR]=0.70; 95% confidence interval [CI], 0.57–0.85) compared with UFH without a statistically significant increase in either the primary (ie, in-hospital) (OR=0.88; 95% CI, 0.89–1.15) or secondary (ie, 12-month) ischemic outcomes (OR=0.97; 95% CI, 0.88–1.06) including stent thrombosis (Table 3).

The risks of bleeding and ischemic outcomes stratified by ACT in the UFH group are summarized in Figure 4A through 4C. Bivalirudin groups had numerically lower bleeding rates when compared with UFH across ACT strata (Figure 4A) without any statistically significant increase in either the primary (Figure 4B) or the secondary (Figure 4C) ischemic outcomes.

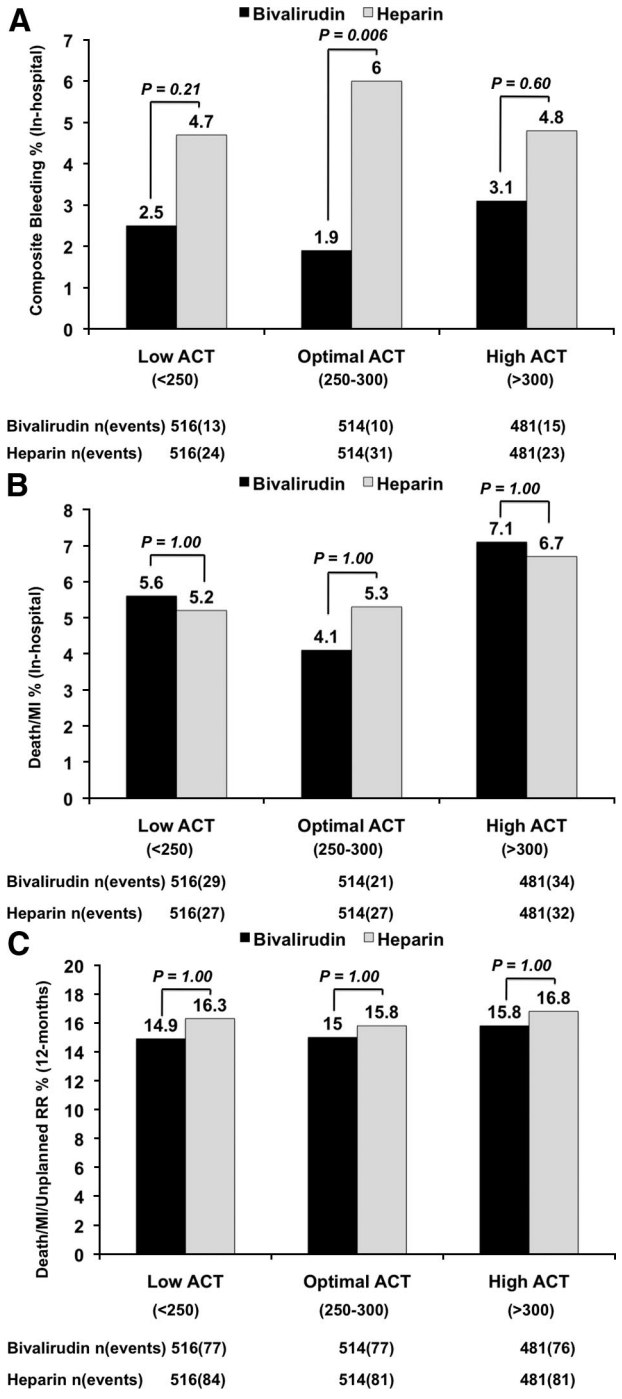

Figure 4. A, Risk of primary bleeding outcome between unfractionated heparin (UFH) monotherapy and bivalirudin groups, as a function of activated clotting time (ACT) achieved in the UFH monotherapy group. **B**, Risk of primary ischemic outcome (in-hospital) between UFH monotherapy and bivalirudin groups, as a function of ACT achieved in the UFH monotherapy group. **C**, Risk of secondary ischemic outcome (12 months) between UFH monotherapy and bivalirudin groups, as a function of ACT achieved in the UFH monotherapy group. All probability values are Bonferroni-adjusted values.

Bivalirudin Versus UFH+GPI Comparison

In the matched cohorts, angiographic complications or either in-hospital (OR=0.92; 95% CI, 0.70–1.20) or 1-year ischemic outcomes (OR=0.97; 95% CI, 0.83–1.15) did not differ between the bivalirudin and UFH+GPI groups (Table 4). In contrast, bivalirudin therapy was associated with a 57% reduction in the odds of composite bleeding rate (OR=0.43; 95% CI, 0.30–0.62) when compared with the UFH+GPI group. The use of bivalirudin versus UFH+GPI was also associated with a modest reduction in postprocedure length of stay (1.4 versus 1.6 days, $P<0.001$).

The risk of bleeding and ischemic outcomes stratified by ACT strata in the UFH+GPI arm are summarized in Figure 5A through 5C. The risk of bleeding with UFH+GPI increased with higher ACT strata. Bivalirudin groups had numerically lower bleeding rates when compared with UFH+GPI within each of the ACT strata (Figure 5A) without any statistically significant increase in either the primary (in-hospital) (Figure 5B) or the secondary ischemic outcomes (12-month) (Figure 5C) at any of the ACT strata. Of note, the risk of primary ischemic outcome with UFH+GPI strategy was lowest in the optimal ACT group.

Among the 2367 patients excluded from this study, the composite bleeding rate was 4.71% and the primary ischemic outcome rate was 6.73%—rates that were not dissimilar from those seen in the UFH monotherapy group in the analytic cohort. Among the patients included in this analysis, 468 patients (6.0%) in the overall cohort and 327 patients (5%) in the matched cohort had <330 days of follow-up. A sensitivity analysis performed using time-to-event analysis yielded results largely consistent with the main results (data not shown).

A post hoc power analysis on the key outcomes where we did not achieve statistical significance was performed. For 1-year composite of death, MI or unplanned repeat revascularization, there was 80% power to detect an effect characterized by an odds ratio of approximately 1.3–1.4. For the in-hospital composite of death or MI, we could detect an odds ratio of 1.5–1.8.

Discussion

This analysis of data from the EVENT registry sought to evaluate the efficacy and safety of bivalirudin use during PCI in a relatively unselected cohort of patients when compared with various levels of UFH activity (as measured by ACT) with or without adjunctive GPI. The results showed numerically lower bleeding rates with bivalirudin when compared across different ACT strata for both UFH and UFH+GPI comparator strategies without any statistically significant increase in either in-hospital or long-term ischemic outcomes.

Bivalirudin and Bleeding

Use of bivalirudin, a direct thrombin inhibitor, is recommended by various national and international guidelines and is a class I recommendation in patients with acute coronary syndrome undergoing PCI.[20–24] The efficacy and safety of bivalirudin has been tested in many prospective randomized trials. The initial dose of the comparator (UFH) used in these trials has varied from high dose in the Bivalirudin Angioplasty Trial (BAT) trial (175 U/kg bolus)[25] and Intracoronary Stenting and Antithrombotic Regimen—Rapid Early Action for Coronary Treatment 3 (ISAR-REACT 3) trial[26] (140 U/kg bolus; no infusion) to the more contemporary dosage (60-U/kg bolus when given in conjunction with a GPI) used in recent trials (HORIZONS-AMI, Acute Catheterization and Urgent Intervention Triage strategY (ACUITY) trial).[8,9]

Table 4. Angiographic Complications, In-Hospital, and 12-Month Outcomes of the UFH+GPI Versus Bivalirudin Groups Before and After Propensity Score Matching

	Unmatched			Propensity Score Matched		
	UFH+GPI (n=2692)	Bivalirudin (n=3318)	*P* Value	UFH+GPI (n=1760)	Bivalirudin (n=1760)	*P* Value
Angiographic complications, %						
None	93.8	96.9	<0.0001	95.3	97.0	0.62
Abrupt closure	0.3	0.2	0.70*	0.3	0.3	0.76
No reflow	1.3	0.8	0.08	0.6	1.0	0.26
Thrombus	1.0	0.1	<0.0001	0.5	0.2	0.13
Distal embolization	0.7	0.2	0.01*	0.4	0.1	0.12
Outcomes						
In-hospital						
Death or adjudicated MI, %	6.9	5.4	0.01	6.4	5.9	0.54
Composite bleeding, %	6.1	2.2	<0.0001	5.5	2.3	<0.0001
Death, %	0.1	0.1	0.28*	0.1	0.1	1.00
Adjudicated MI, %	6.8	5.4	0.02	6.3	5.9	0.58
Postprocedure length of stay, d	1.9±2.2	1.5±4.9	<0.0001	1.6±1.9	1.4±1.6	<0.001
12 Months						
Death or MI or any unplanned repeat revascularization, %	17.4	14.8	0.01	16.2	15.8	0.77
Stent thrombosis, %	0.9	0.6	0.32	0.7	0.9	0.71

UFH indicates unfractionated heparin; GPI, glycoprotein IIb–IIIa receptor inhibitor; and MI, myocardial infarction.
*Fisher exact test used.

These findings have led some to speculate as to whether the differences in bleeding observed in these studies relate primarily to use of higher doses of heparin, (reflected by a high ACT) in the heparin-treated groups.[7,27,28] Steinberg et al evaluated 1205 patients undergoing elective PCI. They found no difference between bivalirudin compared with targeted low dose UFH+GPI (targeted ACT of 250 seconds) for either in-hospital bleeding outcomes or 6-month MACE rates.[28] In addition, although bleeding rates have been consistently low with bivalirudin in randomized trials, there has been concern regarding trends toward increased ischemic outcomes in some studies. In the HORIZONS-AMI trial, acute stent thrombosis was 5.9 times more common with bivalirudin when compared with UFH+GPI,[9] suggesting that the reduction in bleeding came at the cost of an increase in ischemic outcomes.

Our analysis of 7777 patients from a relatively unselected cohort of patients undergoing PCI showed that (1) bleeding rates were numerically lower with bivalirudin when compared with UFH either with or without GPI and regardless of the ACT stratum; (2) there was no increase in acute thrombotic/ischemic complications during PCI with bivalirudin; (3) there was no increase in 12-month ischemic outcomes (including stent thrombosis); and (4) postprocedure length of stay was shorter in patients who received bivalirudin compared with UFH—possibly related to the impact of bleeding on resource utilization and length of stay.

Our study differs from that of Steinberg et al in several important ways. Specifically, our total sample size was 7 times larger; the events were systematically collected and adjudicated (including routine surveillance of cardiac biomarkers); we included patients who were given UFH alone; and we included patients regardless of the achieved ACT. Our results differ from those of Steinberg et al in that we observed numerically lower bleeding rates with bivalirudin across ACT stratum. Of note, the comparison of each ACT stratum in UFH-treated patients (with or without GPI) with the corresponding bivalirudin group preserved the postmatch balance shown in Figures 1 and 3, even at the ACT substrata level.

Whereas the HORIZONS-AMI trial showed an increase in acute stent thrombosis rates, we observed no increase in acute thrombotic complications or stent thrombosis rates when bivalirudin was compared with UFH with or without GPI. Our study differs from HORIZONS-AMI, however, by including patients with both ST-elevation and non–ST-elevation–ACS and also those undergoing elective PCI rather than ST-elevation–MI alone. Moreover, in our study nearly half the patients had clopidogrel loading before PCI, which may explain the lack of increase in thrombotic complications with bivalirudin. In fact, in a post hoc analysis of the HORIZONS-AMI trial, a 600 mg loading dose of clopidogrel was an independent predictor of reduced 30-day MACE rates,[29] and this loading dose has been proposed as a solution to prevent ischemic complications with bivalirudin. In the ISAR REACT 3 trial of patients with stable or unstable angina (with normal levels of troponin T and CK-MB) who were undergoing PCI after pretreatment with a 600-mg dose of clopidogrel at least 2 hours before the procedure, there was no increase in ischemia endpoints with bivalirudin when compared with UFH.[26]

Study Limitations

Our study uses data derived from a registry with prospective follow-up of patients and hence should be regarded as

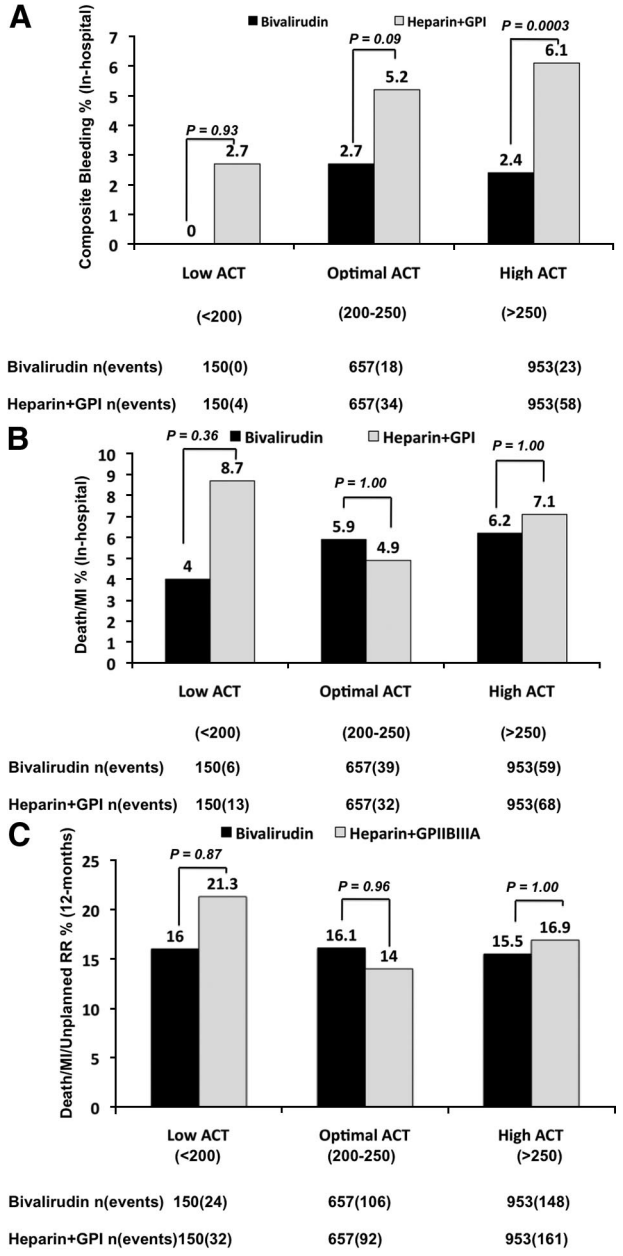

Figure 5. A, Risk of primary bleeding outcome between unfractionated heparin plus glycoprotein IIb-IIIa receptor inhibitor (UFH+GPI) and bivalirudin groups, as a function of activated clotting time (ACT) achieved in the UFH+GPI group. **B**, Risk of primary ischemic outcome (in-hospital) between UFH+GPI and bivalirudin groups, as a function of ACT achieved in the UFH+GPI group. **C**, Risk of secondary ischemic outcome (12 months) between UFH+GPI and bivalirudin groups, as a function of ACT achieved in the UFH+GPI group. All probability values are Bonferroni-adjusted values.

hypothesis generating. Because treatment allocation was not randomized, we used propensity score matching to adjust for selection bias. Despite this rigorous approach, we cannot exclude the possibility that our results were due to residual confounding. In addition, because the operators were not blinded to the antithrombotic drugs used, it is possible that there were differences in patient treatment that could have confounded the results. Moreover, there may be "responder bias" in that patients who had the highest ACTs probably were more sick, likely to metabolize heparin less efficiently, and thus were more likely to bleed. We excluded a small number of patients who received LMWH (n=5), because the intention of the present analysis was to evaluate the relationship between procedural complications and achieved ACT, which is not generally measured after treatment with LMWHs. We also excluded patients who received GPI with bivalirudin because prior studies have shown increased bleeding risk with this combination, and this combination is rarely used in contemporary practice.[8] Finally, we also excluded patients who received "bail-out" GPI (in the UFH+GPI group) because these are likely to be high-risk patients with increased risk of in-hospital cardiovascular outcomes. Inclusion of this subset probably would increase the observed reduction in bleeding that was associated with bivalirudin use. In addition, the peak ACT achieved may also be a reflection of patients' health, including hepatic function and antithrombin levels.

Conclusions

In a unselected cohort of patients undergoing PCI, use of bivalirudin during PCI was associated with lower bleeding rates when compared with heparin with or without GPI, regardless of the ACT strata of the heparin group, with no increase in either in-hospital or 12-month ischemic outcomes, including stent thrombosis.

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