In-Hospital Outcome Comparing Bivalirudin to Heparin in Real-World Primary Percutaneous Coronary Intervention

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Randomized controlled trials have shown conflicting results regarding the outcome of bivalirudin in primary percutaneous coronary intervention (PPCI). The aim of this study was to evaluate the in-hospital outcomes of patients receiving heparin or bivalirudin in a real-world setting of PPCI: 7,023 consecutive patients enrolled in the Austrian Acute PCI Registry were included between January 2010 and December 2014. Patients were classified according to the peri-interventional anticoagulation regimen receiving heparin (n = 6430) or bivalirudin (n = 593) with or without GpIIb/IIIa inhibitors (GPIs). In-hospital mortality (odds ratio [OR] 1.13, 95% confidence interval [CI] 0.57 to 2.25, p = 0.72), major adverse cardiovascular events (OR 1.18, 95% CI 0.65 to 2.14, p = 0.59), net adverse clinical events (OR 1.01, 95% CI 0.57 to 1.77, p = 0.99), and TIMI non–coronary artery bypass graft-related major bleeding (OR 0.41, 95% CI 0.09 to 1.86, p = 0.25) were not significantly different between the groups. However, we detected potential effect modifications of anticoagulants on mortality by GPIs (OR 0.12, 95% CI 0.01 to 1.07, p = 0.06) and access site (OR 0.25, 95% CI 0.06 to 1.03, p = 0.06) favoring bivalirudin in femoral access. In conclusion, this large real-world cohort of PPCI, heparin-based anticoagulation showed similar results of short-term mortality compared with bivalirudin. We observed a potential effect modification by additional GPI use and access favoring bivalirudin over heparin in femoral, but not radial, access. **(Am J Cardiol 2017;120:2135–2140)**

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In the HORIZONS-AMI trial, anticoagulation with bivalirudin showed reduced major bleedings and mortality after 30 days and 3 years compared with unfractionated heparin (UFH) in combination with glycoprotein IIb/IIIa inhibitors (GPIs) in primary percutaneous coronary intervention (PPCI).[1,2] Since that time randomized controlled trials have shown inconsistent effects of bivalirudin on mortality,[3–6] whereas a reduction in bleeding was repeatedly confirmed.[3–5,7,8] Significantly lower rates of GPI use in bivalirudin-treated patients may have influenced these results. The MATRIX trial addressed this limitation and showed a decrease in mortality and bleeding after 1 month, if GPI use was optional.[5] However, the single-center HEAT-PPCI trial failed to show the superiority of bivalirudin over UFH regarding mortality and has led to considerable uncertainty regarding the benefits of bivalirudin over heparin in daily clinical practice.[4] We therefore performed an analysis comparing procedural anticoagulation with bivalirudin or heparin, both with or without GPIs during PPCI in a large, unselected real-world cohort.

Methods

The Austrian Acute PCI Registry was implemented in 2005 as a prospective, multicenter registry of interventional reperfusion therapy in acute myocardial infarction (MI) in Austria. The majority of PPCI-capable centers (18 of 25)

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participated in the registry, with all Austrian states being represented. Data management, storage, and analysis were performed by the Department of Medical Statistics, Informatics, and Health Economics at the Medical University Innsbruck. The registry is conducted in accordance with the Declaration of Helsinki, and the study protocol was approved by the Ethical Committee of the Medical University Innsbruck (UN2467).

A total of 7,023 patients admitted to one of the participating centers within 24 hours of symptom onset and considered for PPCI for reperfusion of STEMI between January 2010 and December 2014 were included. The patients' history was recorded, as were all events occurring during intervention and the index hospitalization. Patients were excluded if they were treated conservatively, received thrombolytic therapy for the index event, received upstream GPIs before reaching the catheterization laboratory, or underwent coronary artery bypass graft (CABG) as primary or urgent revascularization strategy. We classified patients according to the periprocedural anticoagulation regimen into 2 groups: those treated with heparin (UFH or low molecular weight heparin) and those treated with bivalirudin. Anticoagulation and platelet inhibition were performed according to regional STEMI protocols. Peri-interventional GPIs were at the physician's discretion.

Data were recorded according to Cardiology Audit and Registration Data Standards, as reported previously.[9–11] STEMI was diagnosed in the presence of persistent angina pectoris for at least 20 minutes and ST-segment elevation ≥1 mm in at least 2 standard leads or ≥2 mm in at least 2 continuous precordial leads or the presence of a presumable new left bundle–branch block.[9] Reinfarction was defined as the reoccurrence of ischemic symptoms with new ST-elevation/left bundle–branch block or angiographic evidence of the reocclusion of a previously patent vessel or an increase in cardiac markers (≥20%) after reaching stable or decreasing values.[12] Stroke or transient ischemic attack were defined as regional, ischemia-induced neurologic deficits excluding neurologic impairment due to intracranial hemorrhage or general hypoxemia after resuscitation or shock.[9] Major bleeding was diagnosed according to the TIMI classification and included any intracranial hemorrhage, a decrease in hemoglobin of ≥5g/dL (decrease in hematocrit of ≥15% if hemoglobin was unavailable), the need for blood transfusion, or surgical intervention.[9,11] The primary outcome of the present study was in-hospital all-cause mortality. Secondary end points were major adverse cardiovascular events (MACEs; composite of death, reinfarction, or stroke), net adverse clinical events (NACEs; composite of MACE and TIMI non–CABG-related major bleeding), and TIMI non–CABG-related major bleedings. The patients were followed until hospital discharge with a median follow-up duration of 5.1 (interquartile range [IQR] 2.3 to 7.6) days.

A detailed overview of the data collected in the Austrian Acute PCI Registry was previously published.[11] Data were recorded using an Internet-based data entry form and included demographic data, risk factors, previous coronary revascularization (PCI or CABG), previous MI, the occurrence of cardiogenic shock or resuscitation before or during the interventional procedure of the index event, and the mode of admission and several relevant time delays. Antithrombotic treatment before arrival in the catheterization laboratory includes standard therapy with heparin (either UFH or low molecular weight heparin), aspirin, and $P2Y_{12}$ inhibitors (clopidogrel, prasugrel, ticagrelor). Peri-interventional treatment data include revascularization strategy (drug-eluting stent, bare metal stent, bioabsorbable vascular scaffolds, plain old balloon angioplasty), TIMI flow before and after the intervention, and the use of thrombus aspiration.

Categorical variables are shown in numbers with corresponding percentages of nonmissing values in parentheses. Continuous variables are summarized by the mean with the SD or by the median with twenty-fifth and seventy-fifth percentiles (IQR), respectively. Pearson's chi-squared test, Fisher's exact test, the t-test, or the Mann–Whitney test were applied as appropriate. To adjust for associations of baseline characteristics, multivariable logistic regression analysis stratified by PCI center was performed to compare the treatment groups. The following covariates potentially influencing the anticoagulation regimen and mortality as well as MACEs, NACEs, or major bleeding were predefined: age (completed years), gender, cardiogenic shock, resuscitation for the index event, diabetes mellitus, previous MI, pretreatment with $P2Y_{12}$ inhibitors, delay from pain to PCI (long vs short, with a cutoff at 4 hours), and vascular access site (femoral vs radial). Furthermore, we evaluated the impact of GPI use and access site as potential modifiers of the effect of anticoagulation on in-hospital mortality, as well as on the combined outcome parameters (MACEs, NACEs), by adding interaction terms in the regression model. For all reported tests, a 2-sided p value of <0.05 was considered statistically significant. The statistical analyses were performed in Stata/MP 11.2 (StataCorp LLC, 4905 Lakeway Drive, College Station, Texas, USA).

Results

A total of 7,023 patients were included in the study: 6,430 patients (92%) received heparin with or without GPIs and 593 (8%) received bivalirudin with or without GPIs. An overview of the baseline characteristics and adjunctive antithrombotic medication is shown in Tables 1 and 2. A GPI at the physician's discretion was more frequent in the heparin-based treatment group, whereas thrombus aspiration was more

Table 1
Baseline patient characteristics by treatment group

Variable	Heparin (n = 6,430)	Bivalirudin (n = 593)	p-*Value*
Age (years)	62.4 (SD 13.3)	61.1 (SD 13.3)	0.02
Men	4659 (72%)	444 (75%)	0.21
Diabetes mellitus	929 (14%)	96 (16%)	0.25
Current smoker	2714 (51%)	286 (56%)	0.02
Prior myocardial infarction	596 (11%)	53 (10%)	0.71
Prior percutaneous intervention	734 (13%)	61 (12%)	0.38
Prior transient ischemic attack or stroke	183 (5%)	13 (3%)	0.17
Cardiogenic shock	584 (9%)	61 (10%)	0.33
Resuscitation	579 (9%)	53 (9%)	1.00
Atrial fibrillation	466 (9%)	32 (7%)	0.19

Age is presented as mean and standard deviation, categorical variables are presented as numbers and percentages of non-missing values.

Table 2
Antithrombotic management by treatment group

Variable	Heparin *(n = 6,430)*	Bivalirudin *(n = 593)*	p-*Value*
Antithrombotic pre-treatment			
Aspirin	6263 (97%)	543 (92%)	<0.01
Heparin	5411 (84%)	451 (76%)	<0.01
Unfractioned heparin	4660 (72%)	426 (72%)	0.29
Low molecular weight heparin	874 (14%)	33 (6%)	<0.01
$P2Y_{12}$—inhibitor	5682 (88%)	508 (86%)	0.05
Clopidogrel	3147 (49%)	246 (41%)	<0.01
Prasugrel	1621 (25%)	202 (34%)	<0.01
Ticagrelor	837 (13%)	74 (12%)	0.19
Peri-interventional antithrombotic management			
GP IIb/IIIa inhibitor	2562 (40%)	86 (15%)	<0.01
Bivalirudin	0 (0%)	593 (100%)	—

Categorical variables are presented as numbers and percentages of non-missing values in parentheses.

Table 3
Peri-interventional characteristics by treatment group

Variable	Heparin *(n = 6,430)*	Bivalirudin *(n = 593)*	p-Value
Femoral access	4736 (74%)	496 (84%)	<0.01
Radial access	1692 (26%)	97 (16%)	<0.01
Target vessel			
LAD	2958 (46%)	289 (49%)	0.21
CX	751 (12%)	43 (7%)	<0.01
RCA	2598 (40%)	252 (42%)	0.34
Others	121 (2%)	9 (2%)	0.63
TIMI flow before Intervention			
0–I	4499 (75%)	452 (77%)	0.10*
II	1019 (17%)	92 (16%)	
III	455 (8%)	32 (5%)	
TIMI flow after Intervention			
0–I	141 (2%)	6 (1%)	0.78*
II	310 (5%)	25 (4%)	
III	5386 (91%)	533 (92%)	
No reflow	27 (0%)	3 (1%)	
TIMI II + III	5696 (97%)	558 (96%)	0.08
Intervention			
Bare metal stent	1588 (25%)	129 (22%)	<0.01*
Drug eluting stent	4442 (69%)	433 (73%)	
Bioabsorbable scaffold	15 (0%)	16 (3%)	
Balloon angioplasty only	385 (6%)	15 (3%)	
Intraaortic balloon pump	73 (1%)	10 (2%)	0.15
Thrombus aspiration	1823 (29%)	195 (35%)	<0.01

* These p-values represent intracategory differences.

Categorical variables are presented as numbers with percentages of non-missing values in parentheses.

often applied in the bivalirudin group (Table 3). Concerning interventional management, the 2 groups differed slightly in the type of stents used for intervention but showed similar angiographic success rates (Table 3). The median delay from symptom onset until arrival at the catheterization laboratory was 195 minutes (IQR 126 to 360) in the heparin group versus 180 minutes (IQR 125 to 312) in patients treated with bivalirudin. Patient-related delay from symptom onset to first medical contact was 85 minutes (IQR 39 to 195) for heparin-treated patients versus 87 minutes (IQR 38 to 174) for patients treated with bivalirudin. Transfer times from first medical contact to catheterization laboratory (heparin 80 minutes [IQR 57 to 120] vs bivalirudin 79 minutes [IQR 50 to 112]), as well as the delay from arrival at the PCI hospital until catheter laboratory (heparin 20 minutes [IQR 10 to 45] vs bivalirudin 20 minutes [IQR 8 to 39]), were comparable in both groups. Concerning the mode of admission, rates for primary transfer to a PCI hospital was 59% in heparin-treated patients and 62% in bivalirudin-treated patients. Self-admission or spontaneous in-hospital MI at a PCI center were rare and comparable in both groups (heparin 9% and bivalirudin 8%).

Mortality, MACEs, and NACEs were comparable in the 2 treatment groups (Figure 1). This also applies to differences in event rates of reinfarction and transient ischemic attack or stroke. TIMI non–CABG-related major bleeding was low in both groups and, although statistically not significantly different, 3 times more common in the heparin group than in the bivalirudin group.

In-hospital mortality was not influenced by the choice of periprocedural anticoagulation in the adjusted regression model (OR 1.13, 95% CI 0.57 to 2.25, p = 0.72; Table 4). The most important independent factors associated with death were age, cardiogenic shock, resuscitation, and bleeding. TIMI non–CABG-related major bleeding did not significantly differ between the 2 treatment groups (OR 0.41, 95% CI 0.09 to 1.86, p = 0.25; Table 5). Considering adverse cardiovascular events, heparin treatment was similar compared with bivalirudin (MACE OR 1.18, 95% CI 0.65 to 2.14, p = 0.59; NACE OR 1.01, 95% CI 0.57 to 1.77, p = 0.99). We observed potential and borderline significant modifications of the effect of anticoagulation on mortality and MACEs by GPI co-administration in the catheterization laboratory (mortality OR 0.12, 95% CI 0.01 to 1.07, p = 0.06; MACE OR 0.23, 95% CI 0.05 to 1.17, p = 0.08) and on mortality, MACEs, and NACEs by access site (mortality OR 0.25, 95% CI 0.06 to 1.03, p = 0.06; MACE OR 0.34, 95% CI 0.10 to 1.16, p = 0.09; NACE OR 0.33, 95% CI 0.10 to 1.03, p = 0.05). These interactions favor bivalirudin in femoral access or if a GPI is co-administered, but not in radial access. Table 6 shows the ORs for mortality of therapeutic combinations according to the observed effect modification when heparin without (–) GPIs or heparin plus (+) radial access are used as the references. According to comparable effect modifications, the odds for MACEs and NACEs in subgroups were equivalent to those observed for mortality and not presented separately. Testing for the effect modification of GPIs with access did not show significant results (data not shown).

Discussion

The main finding of the present study is a lack of significant differences in in-hospital outcomes comparing anticoagulation with bivalirudin to heparin. These include overall mortality, TIMI non–CABG-related major bleeding, and the composite end points MACEs and NACEs. Furthermore, we observed a potential modification of the treatment effect of anticoagulation on mortality favoring bivalirudin if the GPI was co-administered and in femoral, but not in radial, access. However,

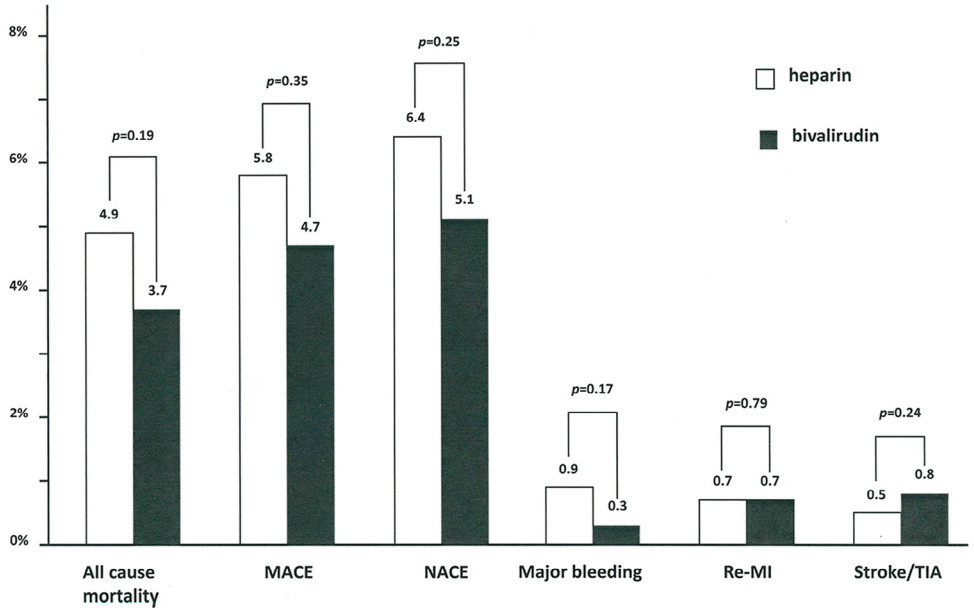

Figure 1. Univariate analyses of in-hospital outcomes. Re-MI = re-myocardial infarction; TIA = transient ischemic attack.

Table 4
Multivariable analyses of outcomes

Variable	Death		MACE		NACE	
	OR	95% CI	OR	95% CI	OR	95% CI
Age *yrs.*	1.07	1.05 to 1.08	1.05	1.04 to 1.07	1.05	1.04 to 1.06
Male sex	1.03	0.73 to 1.44	0.89	0.66 to 1.20	0.75	0.57 to 0.98
Cardiogenic shock *yes vs. no*	10.94	7.66 to 15.61	8.46	6.08 to 11.77	7.12	5.20 to 9.76
Resuscitation *yes vs. no*	3.01	2.02 to 4.51	2.52	1.74 to 3.67	2.66	1.88 to 3.78
Prior myocardial infarction *yes vs. no*	1.86	1.26 to 2.76	1.59	1.11 to 2.29	1.45	1.02 to 2.04
Delay *long vs. short*	1.23	0.89 to 1.69	1.03	0.77 to 1.37	1.00	0.77 to 1.31
Diabetes mellitus *yes vs. no*	1.66	1.17 to 2.37	1.41	1.02 to 1.95	1.33	0.98 to 1.80
Access site *femoral vs. radial*	1.50	0.90 to 2.50	1.26	0.81 to 1.96	1.24	0.82 to 1.88
Major bleeding *yes vs. no*	5.93	2.70 to 13.02	5.14	2.45 to 10.78	—	—
$P2Y_{12}$-inhibitor *yes vs. no*	0.62	0.42 to 0.93	0.71	0.49 to 1.03	0.63	0.45 to 0.89
Bivalirudin vs. heparin	1.13	0.57 to 2.25	1.18	0.65 to 2.14	1.01	0.57 to 1.77
GP IIb/IIIa inhibitor *yes vs. no*	1.34	0.97 to 1.85	1.28	0.96 to 1.70	1.40	1.07 to 1.82

Table 5
Multivariable analysis of major bleeding

	Major bleeding	
	OR	95% CI
Age *yrs.*	1.01	0.99 to 1.03
Male sex	0.53	0.30 to 0.94
Cardiogenic shock *yes vs. no*	1.24	0.55 to 2.79
Resuscitation *yes vs. no*	3.65	1.74 to 7.66
Myocardial infarction *yes vs. no*	0.69	0.24 to 1.97
Delay *long vs. short*	0.91	0.50 to 1.65
Diabetes mellitus *yes vs. no*	1.01	0.48 to 2.12
Access site *femoral vs. radial*	1.41	0.53 to 3.77
$P2Y_{12}$-inhibitor *yes vs. no*	0.35	0.18 to 0.65
Bivalirudin vs. heparin	0.41	0.09 to 1.86
GP IIb/IIIa inhibitor *yes vs. no*	1.95	1.11 to 3.42

Table 6
Effect modification of anticoagulant by GP IIb/IIIa inhibitor and access site on mortality

Treatment	OR	95% CI
Heparin – GP IIb/IIIa inhibitor	1.00	—
Heparin + GP IIb/IIIa inhibitor	1.34	0.97 to 1.85
Bivalirudin – GP IIb/IIIa inhibitor	1.13	0.57 to 2.25
Bivalirudin + GP IIb/IIIa inhibitor	0.19	0.02 to 1.63
Heparin + radial	1.00	—
Heparin + femoral	1.74	1.01 to 2.98
Bivalirudin + radial	2.41	0.69 to 8.39
Bivalirudin + femoral	1.15	0.48 to 2.79

these results of real-world practice did not reflect the superiority of bivalirudin over heparin regarding overall mortality, as it was shown in large RCTs before.

HORIZONS-AMI was the first large prospective trial to show a reduced short- and long-term mortality of bivalirudin-treated patients compared with heparin-treated patients with routine administration of GPIs in the setting of STEMI (30 days 2.1% vs 3.1%, p = 0.047, and 3 years 5.9% vs 7.7%, p = 0.03).[1,2,13] The beneficial effect on NACEs in this study (9.2% vs 12.1%, p = 0.005) was mainly driven by a reduction of bleeding events (4.9% vs 8.3%, p < 0.001).[2] The EUROMAX trial also showed a reduction in major bleedings (bivalirudin vs heparin + routine GPIs 2.6% vs 5.9%, p < 0.001 and bivalirudin vs heparin + bailout GPIs 2.6% vs 6.3%, p < 0.001), but not in mortality in STEMI patients.[6] As the use of GPIs has become rare and restricted to bailout situations and high thrombus burden in daily clinical practice, the different rates of GPIs in HORIZONS-AMI (routine use) or EUROMAX (69% GPI) make it difficult to draw firm conclusions for current clinical practice from these randomized trials.

These concerns were addressed in the largest and most recently published trial, MATRIX. In this study all-cause mortality (1.7% vs 2.3%, p = 0.04), as well as bleeding complications (BARC type 3 or 5, 1.4% vs 2.5%, p < 0.001), was significantly reduced with bivalirudin compared with a "heparin-only" strategy.[5] In contrast, in the all-comers HEAT-PPCI trial, in which a GPI was used in bailout situations (13% vs 15%), no significant differences between bivalirudin and heparin concerning mortality (5.1% vs 4.3%, p = 0.43) or bleeding (3.5% vs 3.0%, p = 0.59) were detected.[4] So far HORIZONS-AMI and MATRIX are the only 2 RCTs that described an overall mortality benefit with bivalirudin. Whether this is mainly explained by reduced bleeding complications or influenced by the rate of GPIs remains unclear.

Recent analyses from the "United Kingdom national PCI registry" and the National Cardiovascular Data Registry (NCDR) addressed this issue.[14,15] In the British registry adjusted 30-day mortality remained higher in the heparin-only group compared with the bivalirudin-treated patients (heparin only vs bivalirudin OR 1.23, 95% CI 1.02 to 1.47), whereas mortality was similar in patients with bivalirudin compared with those with heparin + GPIs (OR 1.01, 95% CI 0.84 to 1.21). In the NCDR (heparin 75%, bivalirudin 24%) adjusted mortality was similar in bivalirudin- and heparin-treated patients but was significantly different when GPIs were accounted for (risk difference −0.78, 95% CI −1.00 to −0.44).[14] This mortality benefit in the overall group of the NCDR when accounting for GPIs was based on a beneficial effect of bivalirudin in patients undergoing transfemoral access. There was no difference in any outcome, irrespective of adjustment for GPI use, for the transradial approach in that cohort.[14]

In our cohort with moderate rates of GPI use (heparin 40%, bivalirudin 15%) all-cause mortality was not significantly different between the 2 groups. Of note, access site and GPI co-administration appeared to modify the treatment effect of anticoagulation. Although only borderline significant, this observation may point to a favorable effect of bivalirudin in those situations where additional potent platelet inhibition by GPIs is used and in patients with femoral, but not radial, access.

In a recent updated meta-analysis of 6 RCTs bivalirudin's association with reduced bleedings varied depending on the GPI strategy (routine GPI: RR 0.44, 95% CI 0.23 to 0.81, p = 0.009; bailout GPI: RR 0.73, 95% CI 0.42 to 1.25, p = 0.252).[16] In the present study, major bleedings were 3 times higher for heparin than for bivalirudin, but the absolute rate was low (bivalirudin 0.3%; heparin 1.0%) and not significantly different. Although the bleeding rate is comparable with the rate reported in the British registry (bivalirudin 0.91%, heparin + GPI 0.78%, heparin only 0.5%), the stringent bleeding definition and the likelihood of underreporting may have influenced this. In contrast, the NCDR used a more extended bleeding definition, leading to higher rates of major bleeding favoring bivalirudin over heparin (heparin 15%, bivalirudin 11%). However, the beneficial effect of bivalirudin on bleeding reduction remained after adjustment for GPIs in that cohort.[14]

The present study has several limitations inherent to registries, most importantly the inability to correct for unidentified or unmeasured confounders. Imbalances in the treatment groups are unavoidable and, by virtue of the study design, may have influenced the comparisons in our study. The reasons for the operators' choice for one of the 2 anticoagulants or for additional use of GPIs (planned, high thrombus burden, or bailout) were not recorded and may have resulted in some heterogeneity of the treatment groups. The lack of on-site monitoring probably resulting in underreporting may have influenced the low number of major bleedings. Furthermore, stent thrombosis is not an outcome event in the Austrian Acute PCI Registry. Follow-up was limited to the in-hospital period, and we could not exclude treatment effects beyond this. Although information on some baseline characteristics was incomplete (smoker, stroke, previous MI or coronary intervention, atrial fibrillation, and TIMI flow), there were no missing data in outcomes and the most relevant co-variables including antithrombotic treatment, cardiogenic shock, and resuscitation. Finally, there was no on-site monitoring to assess data accuracy. Therefore suboptimal quality of data is possible.

In conclusion, in this large real-world cohort of PPCI, heparin-based anticoagulation showed similar results of short-term mortality compared with bivalirudin. However, bleeding complications, although not statistically significant, were higher with heparin. We observed potential interactions of GPIs and access site with the effect of anticoagulation on mortality favoring bivalirudin over heparin in selective situations with additional platelet inhibition by GPIs in the femoral, but not the radial, approach.

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Disclosures

All listed authors have no conflict of interest in connection with the submitted article. Conflicts of interest not related to the submitted article are as follows: JD: consulting and lectures fees: Astra Zeneca, Daiichi-Sankyo, Eli Lilly, MSD, and Novartis and Servier; HA: consulting, lecture, and personal fees from St. Jude Medical, Biotronik, AstraZeneca, Daiichi-Sankyo, Eli Lilly, Menarini, Pfizer, MSD, BMS, Servier, Sandoz, Boehringer Ingelheim, Bayer, Amgen, Sanofi, and Sanova; RB: grant from Abbott Cardiovascular and personal fees from Abbott Cardiovascular, Eli Lilly, Boehringer-Ingelheim,

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Supplementary Data

Supplementary data associated with this article can be found, in the online version, https://doi.org/10.1016/j.amjcard.2017.08.037.

Appendix

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