

CLINICAL RESEARCH

Interventional Cardiology

Reduction in Cardiac Mortality With Bivalirudin in Patients With and Without Major Bleeding

The HORIZONS-AMI Trial (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction)

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- Objectives** The purpose of this study was to determine whether, in patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI), the reduction in cardiac mortality in those taking bivalirudin compared with unfractionated heparin plus a glycoprotein IIb/IIIa inhibitor (UFH+GPI) can be fully attributed to reduced bleeding.
- Background** The association between hemorrhagic complications and mortality may explain the survival benefit with bivalirudin.
- Methods** A total of 3,602 STEMI patients undergoing primary PCI were randomized to bivalirudin versus UFH+GPI. Three-year cardiac mortality was analyzed in patients with and without major bleeding.
- Results** When compared with UFH+GPI, bivalirudin resulted in lower 3-year rates of major bleeding (6.9% vs. 10.5%, hazard ratio [HR]: 0.64 [95% confidence interval (CI): 0.51 to 0.80], $p < 0.0001$) and cardiac mortality (2.9% vs. 5.1%, HR: 0.56 [95% CI: 0.40 to 0.80], $p = 0.001$). Three-year cardiac mortality was reduced in bivalirudin-treated patients with major bleeding (20 fewer deaths with bivalirudin; 5.8% vs. 14.6%, $p = 0.025$) and without major bleeding (18 fewer deaths with bivalirudin; 2.6% vs. 3.8%, $p = 0.048$). In a fully-adjusted multivariable model accounting for major bleeding and other adverse events, bivalirudin was still associated with a 43% reduction in 3-year cardiac mortality (adjusted HR: 0.57 [95% CI: 0.39 to 0.83], $p = 0.003$).
- Conclusions** Bivalirudin reduces cardiac mortality in patients with STEMI undergoing primary PCI, an effect that can only partly be attributed to prevention of bleeding. Further studies are required to identify the nonhematologic benefits of bivalirudin. (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction; [NCT00433966](https://doi.org/10.1016/j.jacc.2013.09.027)) (J Am Coll Cardiol 2014;63:15–20) © 2014 by the American College of Cardiology Foundation

In the large-scale, prospective, randomized HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) trial, in patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI), anticoagulation with the direct thrombin inhibitor bivalirudin compared with unfractionated heparin (UFH)

plus a glycoprotein IIb/IIIa inhibitor (GPI) resulted in reduced 30-day and 3-year rates of all-cause death, a difference due to reduced cardiac mortality (1,2). Lower mortality with bivalirudin compared with UFH alone and UFH+GPI in patients with STEMI, non-STEMI, and stable coronary artery disease undergoing PCI has also been reported in meta-analyses of randomized trials and from large registry databases (3–6). The mechanism underlying the survival benefit observed with bivalirudin in these studies, although not known with certainty, has usually been ascribed to reduced major bleeding, the rates of which have consistently been 40% to 50% lower in patients treated with bivalirudin compared with UFH with or without GPI (1–11). This belief is based on the findings from numerous studies that have reported a strong relationship between hemorrhagic complications and subsequent mortality, with an associated hazard from bleeding at least as great as that after myocardial infarction (12–15).

We, therefore, sought to determine the extent to which the reduction in cardiac mortality after primary PCI

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**Abbreviations
and Acronyms****CI** = confidence interval**GPI** = glycoprotein IIb/IIIa inhibitor**HR** = hazard ratio**PCI** = percutaneous coronary intervention**STEMI** = ST-segment elevation myocardial infarction**UFH** = unfractionated heparin

with bivalirudin compared with UFH+GPI can be attributed to reduced bleeding.

Methods

Study design. The HORIZONS-AMI trial was a prospective, open-label, randomized, multicenter trial comparing bivalirudin alone with UFH+GPI (abciximab or eptifibatid) in 3,602 STEMI patients presenting within 12 h of symptom onset and undergoing

primary PCI (1). A total of 3,006 eligible patients were randomized again to either paclitaxel-eluting TAXUS Express (Boston Scientific, Natick, Massachusetts) stents or otherwise identical, uncoated bare-metal Express (Boston Scientific) stents. Aspirin 324 mg chewed or 500 mg intravenously was given upfront, and 75 to 81 mg was prescribed daily indefinitely after discharge. A 300- to 600-mg clopidogrel loading dose was followed with an oral 75-mg dose daily for at least 6 months. Clinical follow-up was performed through 3 years.

Endpoints and definitions. Cardiac mortality was defined as death due to myocardial infarction, cardiac perforation or pericardial tamponade, arrhythmia or conduction abnormality, stroke, procedural complications, or any death in which a cardiac cause could not be excluded. A post-hoc analysis of the principal etiology of cardiac death was performed by review of original source documents, blinded to the randomization arm. Noncardiac death was defined as a death not due to cardiac causes, including bleeding-related death. Non-coronary artery bypass graft major bleeding was defined as intracranial or intraocular hemorrhage, access site bleeding with ≥ 5 cm diameter hematoma or requiring intervention, hemoglobin decrease ≥ 4 g/dl without or ≥ 3 g/dl with overt bleeding, or blood transfusion. In-hospital acquired thrombocytopenia was defined as a nadir platelet count $< 150,000$ cells/mm³ in patients without baseline thrombocytopenia. An independent clinical events committee blinded to treatment assignment adjudicated all ischemic and bleeding events using original source documents.

Statistical methodology. Categorical variables were compared by chi-square or Fisher's exact test. Independent predictors of 3-year cardiac mortality were determined using Cox proportional hazards regression (Table 1). Treatment effects among patients with and without major bleeding were then modeled (Table 2). To investigate the effect of bivalirudin after accounting for adverse events that bivalirudin is known to reduce (including thrombocytopenia and reinfarction, as well as major bleeding), each event was entered into a time-updated covariate-adjusted Cox model (Table 3). Analyses were performed using STATA version 12.1 (StataCorp LP, College Station, Texas). All significance levels are 2-sided, and significance was set at $\alpha = 0.05$.

Table 1 Independent Predictors of 3-Year Cardiac Mortality

Risk Factor	HR (95% CI)	p Value
Age (per 5 yrs)	1.33 (1.21–1.45)	<0.001
White blood cell count (per 10 ⁹ cells/l)	1.12 (1.07–1.18)	<0.001
Serum creatinine (per 0.1 mg/dl)	1.11 (1.06–1.16)	<0.001
Killip class 2–4	2.28 (1.52–3.42)	<0.001
PCI of the left main artery	6.15 (2.26–16.76)	<0.001
PCI of the left anterior descending artery	1.65 (1.13–2.42)	0.01
Diabetes, medically-treated	1.58 (1.09–2.29)	0.02
Hemoglobin (per g/dl)	0.89 (0.79–1.00)	0.04
Bivalirudin (vs. UFH+GPI)	0.56 (0.40–0.80)	0.001

Other variables in the model that were not significantly associated with cardiac mortality: current smoker, female sex, prior myocardial infarction, and number of vessels treated.

CI = confidence interval; GPI = glycoprotein IIb/IIIa inhibitor; HR = hazard ratio; PCI = percutaneous coronary intervention; UFH = unfractionated heparin.

Results**Outcomes according to pharmacologic randomization.**

Baseline characteristics were well matched between patients allocated to bivalirudin and UFH+GPI (1,2). Treatment with bivalirudin compared with UFH+GPI resulted in lower 3-year rates of all-cause mortality (5.9% vs. 7.7%, hazard ratio [HR]: 0.75 [95% confidence interval (CI): 0.58 to 0.97], $p = 0.03$) and cardiac mortality (2.9% vs. 5.1%, HR: 0.56 [95% CI: 0.40 to 0.80], $p = 0.001$), with similar rates of noncardiac mortality (3.1% vs. 2.8%, $p = 0.62$). After adjusting for baseline characteristics, treatment with bivalirudin was associated with a 44% reduction in cardiac mortality (Table 1). Bivalirudin also resulted in lower 3-year rates of major bleeding (6.9% vs. 10.5%, HR: 0.64 [95% CI: 0.51 to 0.80], $p = 0.0001$) and reinfarction (6.2% vs. 8.2%, HR: 0.76 [95% CI: 0.59 to 0.99], $p = 0.04$), with nonsignificant differences in stroke (1.7% vs. 2.0%, $p = 0.50$), stent thrombosis (4.5%

Table 2 Independent Predictors of 3-Year Cardiac Mortality in Patients With and Without Major Bleeding at Any Time

Risk Factor	HR (95% CI)	p Value
Patients with major bleeding		
Age (per 5 yrs)	1.32 (1.10–1.57)	0.002
White blood cell count (per 10 ⁹ cells/l)	1.26 (1.13–1.40)	<0.001
Bivalirudin (vs. UFH+GPI)	0.31 (0.13–0.76)	0.005
Patients without major bleeding		
Age (per 5 yrs)	1.28 (1.15–1.43)	<0.001
Killip class 2–4	2.91 (1.85–4.57)	<0.001
PCI of the left main artery	10.56 (3.75–29.77)	<0.001
PCI of the left anterior descending artery	1.71 (1.10–2.67)	0.02
Serum creatinine (per 0.1 mg/dl)	1.14 (1.08–1.20)	<0.001
White blood cell count (per 10 ⁹ cells/l)	1.08 (1.02–1.15)	0.008
Diabetes, medically-treated	1.58 (1.03–2.44)	0.04
Hemoglobin (per g/dl)	0.86 (0.75–0.98)	0.04
Bivalirudin (vs. UFH+GPI)	0.65 (0.44–0.97)	0.03

Other variables in the bleeding model that were not significantly associated with cardiac mortality: diabetes, Killip class, PCI of the left anterior descending artery, baseline hemoglobin, serum creatinine, current smoker, female sex, prior myocardial infarction, and number of vessels treated (PCI of the left main artery was omitted due to low numbers). Other variables in the non-bleeding model that were not significantly associated with cardiac mortality: current smoker, female sex, prior myocardial infarction, and number of vessels treated.

Abbreviations as in Table 1.

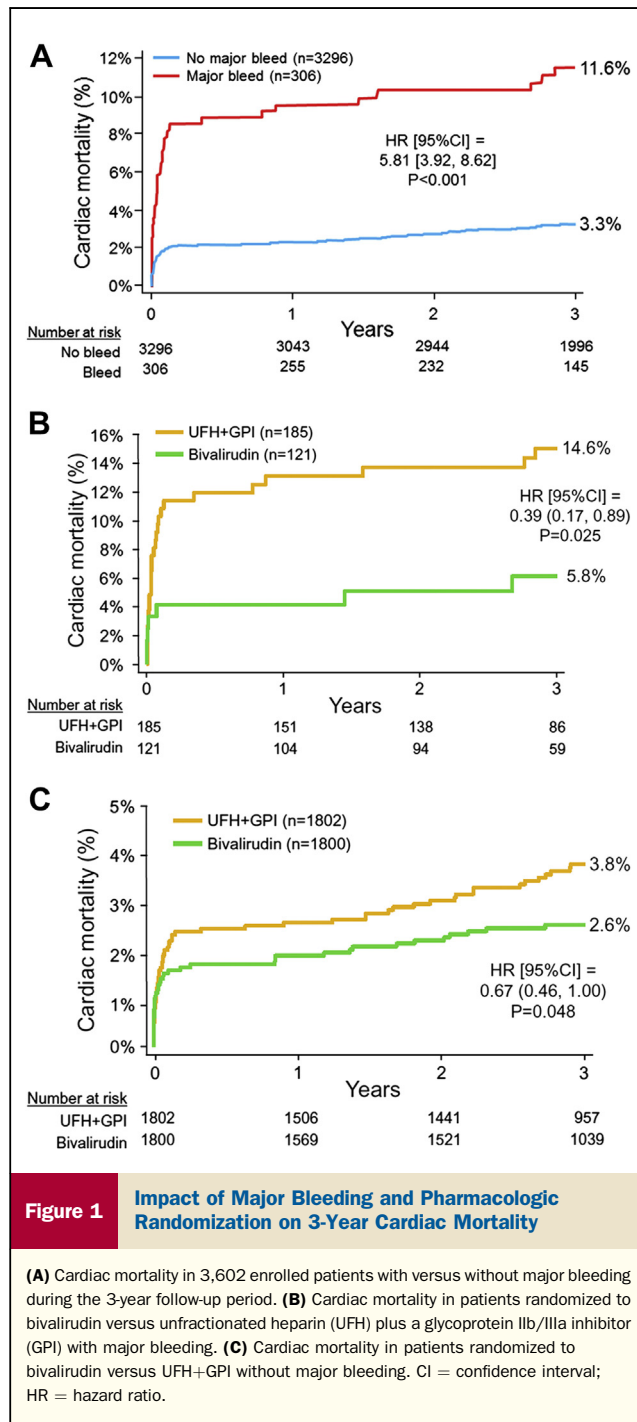
Table 3 Covariate-Adjusted Independent Predictors of 3-Year Cardiac Mortality*			
Risk Factor	HR (95% CI)	p Value	
Age (per 5 yrs)	1.33 (1.21-1.46)	<0.001	
White blood cell count (per 10 ⁹ cells/l)	1.14 (1.08-1.20)	<0.001	
Serum creatinine (per 0.1 mg/dl)	1.08 (1.03-1.14)	0.003	
Killip class 2-4	1.63 (1.04-2.56)	0.03	
PCI of the left main artery	6.47 (2.30-18.20)	<0.001	
PCI of the left anterior descending artery	1.62 (1.08-2.43)	0.02	
Diabetes, medically-treated	1.51 (1.01-2.25)	0.05	
Major bleed	2.53 (1.61-3.98)	<0.001	
Acquired thrombocytopenia	2.29 (1.49-3.52)	<0.001	
Reinfarction	7.88 (4.62-13.42)	<0.001	
Bivalirudin (vs. UFH+GPI)	0.57 (0.39-0.83)	0.003	

Other variables in the model that were not significantly associated with cardiac mortality: current smoker, female sex, prior myocardial infarction, number of vessels treated, and baseline hemoglobin. Model excludes 145 patients with thrombocytopenia at baseline. *Major bleed and reinfarction are fitted as time-updated covariates from the moment they occurred. Abbreviations as in Table 1.

vs. 5.1%, $p = 0.49$), and ischemia-driven TVR (14.2% vs. 12.1%, $p = 0.06$).

Cardiac mortality in patients with and without major bleeding. Major bleeding occurred in 258 patients (7.2%) within 30 days and in 306 patients (8.5%) during the 3-year follow-up period. Cardiac mortality occurred in 84 patients (2.3%) within 30 days and in 138 patients (3.8%) within 3 years. Three-year cardiac mortality was substantially higher in patients with versus without a major bleed at any time during follow-up (Fig. 1). Major bleeding was associated with higher 3-year mortality both in patients treated with UFH+GPI (14.6% vs. 3.8%, HR: 5.67 [95% CI: 3.59 to 8.96], $p < 0.0001$) and bivalirudin (5.8% vs. 2.6%, HR: 4.62 [95% CI: 2.04 to 10.45], $p = 0.002$). Bivalirudin resulted in lower mortality both in patients with and without major bleeding (Fig. 1). Three-year cardiac mortality occurred in 38 fewer patients treated with bivalirudin than UFH+GPI: 20 fewer cardiac deaths occurred among patients with major bleeding (27 of 185 [14.6%] on UFH+GPI vs. 7 of 121 [5.8%] on bivalirudin, $p = 0.02$) and 18 fewer cardiac deaths occurred among patients without major bleeding (61 of 1,617 [3.8%] on UFH+GPI vs. 43 of 1,679 [2.6%] on bivalirudin, $p = 0.048$). After multivariable adjustment for baseline differences, bivalirudin remained associated with reduced mortality both in patients with and without major bleeding (Table 2).

Infarct size, left ventricular function, and causes of cardiac death. Among patients randomized to bivalirudin versus UFH+GPI, there were no differences in median peak creatine phosphokinase (1,470 [628 to 2,795] ng/ml vs. 1,436 [604 to 2,671] ng/ml, respectively, $p = 0.58$) or creatine phosphokinase-MB (192 [88 to 355] ng/ml vs. 191 [82 to 364] ng/ml, respectively, $p = 0.86$). Similarly, among stented patients undergoing protocol-directed routine 13-month follow-up angiography, there was no significant difference in core laboratory-assessed median left ventricular ejection fraction with bivalirudin (63.8% [55.5% to 71.5%], $n = 413$) vs. UFH+GPI (63.2% [54.3%



to 70.3%], $n = 381$) ($p = 0.36$). Cardiac death was most commonly attributed to left ventricular failure or sudden cardiac death (Online Table 1). The etiology of cardiac death was similar with bivalirudin versus UFH+GPI in all patients and the cohorts with and without major bleeding (Online Table 2).

Severity of bleeding and role of blood transfusions. The mean decrease in hemoglobin from admission to nadir in UFH+GPI and bivalirudin-treated patients was 3.9 ± 1.7 g/dl vs. 3.7 ± 2.0 g/dl, respectively, in patients with major bleeding

($p = 0.31$) and 1.7 ± 1.4 g/dl vs. 1.5 ± 1.3 g/dl, respectively, in patients without major bleeding ($p = 0.0007$). In-hospital red blood cell transfusions were administered to 103 patients (5.7%) treated with UFH+GPI versus 83 patients (4.6%) treated with bivalirudin ($p = 0.13$), with mean 3.8 ± 3.9 U versus 4.2 ± 4.0 U administered, respectively ($p = 0.49$). Three-year cardiac mortality in patients transfused compared with those with major bleeding without transfusion was 26 of 186 (14.2%) versus 15 of 174 (8.6%), respectively ($p = 0.11$). In a fully-adjusted multivariable model, the HR for a major bleed with vs. without transfusion was 1.24 (95% CI: 0.64 to 2.38, $p = 0.52$).

Among those without major bleeding, minor bleeding occurred in 254 of 1,617 (15.7%) UFH+GPI-treated patients versus 141 of 1,679 (8.4%) bivalirudin-treated patients ($p < 0.0001$). Three-year cardiac mortality occurred in 11 of 254 (4.3%) versus 3 of 141 (2.1%) patients with minor bleeding treated with UFH+GPI versus bivalirudin ($p = 0.26$). After multivariable adjustment, minor bleeding was not significantly associated with cardiac mortality (HR: 0.98 [95% CI: 0.52 to 1.85], $p = 0.94$).

Impact of thrombocytopenia. In-hospital acquired thrombocytopenia developed in 404 of 3,457 patients (11.7%), and was strongly associated with 3-year cardiac mortality (8.1% vs. 3.1%, HR: 2.76 [95% CI: 1.85 to 4.14], $p = 0.0003$). In-hospital acquired thrombocytopenia occurred in 13.1% versus 10.4% of patients treated with UFH+GPI versus bivalirudin, respectively ($p = 0.004$). Among patients treated with UFH+GPI, acquired thrombocytopenia was strongly associated with 3-year cardiac mortality (12.3% vs. 3.5%, HR: 4.36 [95% CI: 2.73 to 6.95], $p < 0.0001$). In contrast, among bivalirudin-treated patients, 3-year cardiac mortality rates were similar in patients in whom thrombocytopenia did and did not develop (2.3% vs. 2.5%, HR: 1.44 [95% CI: 0.50 to 4.12], $p = 0.51$). The effects of major bleeding and acquired thrombocytopenia on cardiac

mortality were additive in patients treated with UFH+GPI but not in those treated with bivalirudin (Fig. 2).

Multivariable model accounting for clinical events. After accounting for baseline characteristics and the time-adjusted occurrence of adverse clinical events (major bleeding and reinfarction through 3 years and in-hospital acquired thrombocytopenia), treatment with bivalirudin compared with UFH+GPI was independently associated with a 43% reduction in 3-year cardiac mortality (Table 3).

Analysis of noncardiac mortality according to major bleeding. Three-year noncardiac mortality was more frequent in patients with versus without major bleeding (32 of 306 [10.5%] vs. 66 of 3,296 [2.0%], $p < 0.0001$). There were no significant differences in noncardiac mortality with UFH+GPI compared with bivalirudin either in patients with major bleeding (15 of 185 [8.1%] vs. 17 of 121 [14.0%], respectively, $p = 0.10$) or without major bleeding (31 of 1,617 [1.9%] vs. 35 of 1,679 [2.1%], respectively, $p = 0.73$).

Discussion

In the HORIZONS-AMI trial, anticoagulation with bivalirudin rather than UFH+GPI during primary PCI resulted in a 44% relative (2.2% absolute) reduction in 3-year cardiac mortality. The improved survival with bivalirudin in the present and earlier studies (3–6) has typically been attributed to prevention of major hemorrhagic complications. In this regard, the present report confirms prior studies (12–15) by demonstrating the strong association between major bleeding and subsequent mortality. However, although bivalirudin resulted in a 36% relative (3.6% absolute) reduction in major bleeding, this outcome did not fully account for the survival benefit of bivalirudin. First, among patients with major bleeding, a smaller proportion of bivalirudin-treated than UFH+GPI-treated patients died, an effect not explainable by less-severe bleeding or fewer blood transfusions. Second,

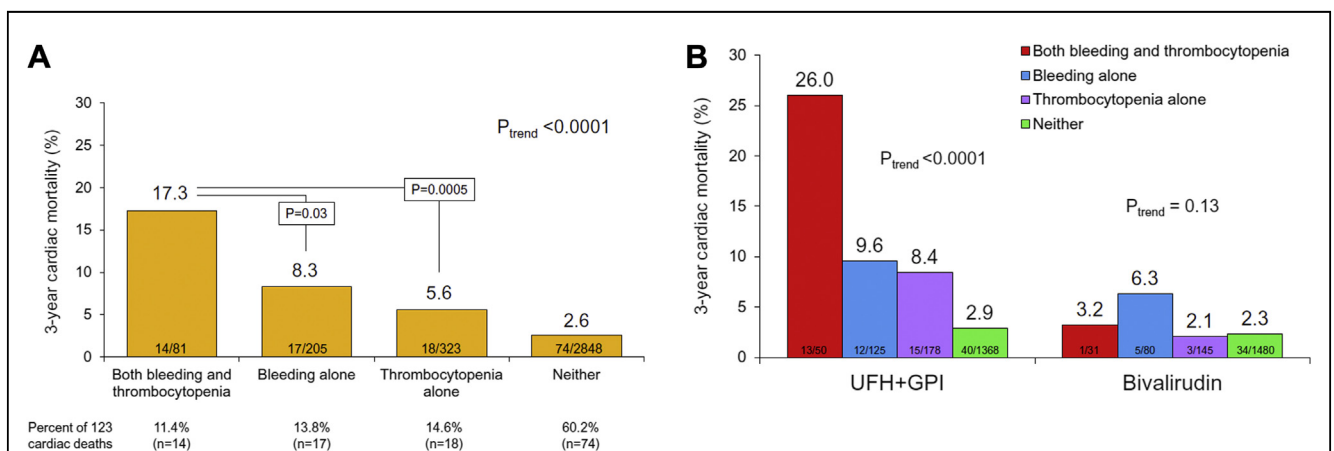


Figure 2 Interaction Between Major Bleeding and In-Hospital Acquired Thrombocytopenia on 3-Year Cardiac Mortality

(A) Both treatments combined. (B) Results according to randomization to UFH+GPI versus bivalirudin. Abbreviations as in Figure 1.

and more striking, fewer patients treated with bivalirudin versus UFH+GPI died even if overt bleeding did not occur. Indeed, 18 (47%) of the 38 fewer cardiac deaths with bivalirudin occurred in patients without major bleeding.

While the present study was not designed to determine the mechanisms underlying bivalirudin's survival benefit, we have explored several possibilities. In addition to major bleeding, in-hospital acquired thrombocytopenia has been linked to mortality in the present and prior studies (16–18). In the HORIZONS-AMI trial, thrombocytopenia developed less frequently with bivalirudin versus UFH+GPI, confirming previous reports (7,19). Notably, however, cardiac mortality was increased only in patients in whom thrombocytopenia developed after UFH+GPI; acquired thrombocytopenia in bivalirudin-treated patients was not associated with cardiac mortality. Moreover, the deleterious interaction between major bleeding and thrombocytopenia was marked in UFH+GPI-treated patients and was absent in bivalirudin-treated patients. The mechanisms underlying the development of thrombocytopenia with UFH+GPI (17,18,20) may be different than with bivalirudin, and the prognostic impact of thrombocytopenia may vary accordingly.

In addition to reducing major bleeding and thrombocytopenia, treatment with bivalirudin compared with UFH+GPI was also associated with reduced 3-year rates of reinfarction. Reinfarction is an important cause of mortality after primary PCI (21,22), and this reduction may have contributed to the survival benefit of bivalirudin. However, even after accounting for major bleeding, thrombocytopenia, and reinfarction in a time-adjusted multivariable model, treatment with bivalirudin remained independently associated with a 43% reduction in 3-year cardiac mortality, similar to the 44% reduction observed before these adverse events were taken into account.

Direct thrombin inhibition may reduce inflammation and apoptosis (23–25), improve post-ischemic myocardial function (24), and reduce infarct size (23). Thrombin blockade of protease-activated receptor-1 signaling may reduce cardiac remodeling and heart failure after STEMI (26), and protease-activated receptor-4 inhibition may reduce reperfusion injury (27). Bivalirudin may otherwise ameliorate reperfusion injury (28,29). UFH but not bivalirudin also increases circulating levels of antiangiogenic peptides, which may impair myocardial recovery (30). Intramyocardial hemorrhage can occur after UFH+GPI (31,32), which might be prevented by bivalirudin. Infarct size was nonsignificantly smaller with bivalirudin compared with UFH+GPI in the single-center HORIZONS-AMI cardiac magnetic resonance imaging substudy, and microvascular obstruction tended to be less (33). Consistent with this observation, post-PCI coronary flow reserve was greater in patients treated with bivalirudin rather than UFH+GPI in PROTECT-TIMI 30 (A Randomized Trial to Evaluate the Relative Protection Against Post-PCI Microvascular Dysfunction and Post-PCI Ischemia Among Anti-Platelet and Anti-Thrombotic Agents–Thrombolysis In Myocardial Infarction 30) (34).

However, post-PCI myocardial blush (35) and ST-segment resolution (36) were comparable in bivalirudin- and UFH+GPI-treated patients, and biomarker-assessed infarct size and follow-up left ventricular ejection fraction were also similar. Further studies are required to elucidate the non-hematologic attributes of bivalirudin that contribute to its survival benefit.

Study limitations. First, the present observations do not prove causality, and are hypothesis-generating. Second, to exclude the dilutional effects of noncardiac mortality (the rates of which were similar between groups), the present analysis was restricted to cardiac mortality. In this regard, the reduction in cardiac mortality with bivalirudin compared with UFH+GPI was robust (HR: 0.56 [95% CI: 0.40 to 0.80], $p = 0.001$), making type I error unlikely, although play of chance cannot totally be excluded. Third, although aspirin and thienopyridine usage was similar in the treatment arms throughout 3 years (2), as was use of beta-blockers, angiotensin-converting enzyme inhibitors, and statins at discharge (1), we did not assess nonantiplatelet agent usage beyond discharge. Finally, although femoral artery access was most common (1), the demonstration that the survival benefit of bivalirudin was present in patients without major bleeding suggests bivalirudin might reduce mortality after radial artery intervention. An adequately-powered randomized trial of primary PCI with radial access is required to test this hypothesis.

Conclusions

In the HORIZONS-AMI trial, treatment with bivalirudin rather than UFH+GPI resulted in a marked reduction in cardiac mortality after primary PCI, a benefit that was present by 30 days and increased in magnitude over 3 years (1,2). The mechanisms through which bivalirudin exerts this survival benefit are multifactorial, and cannot entirely be explained by prevention of bleeding. Notably, the impact of major bleeding occurring after treatment with bivalirudin compared with UFH+GPI on subsequent cardiac mortality was attenuated, despite the severity of bleeding being similar in magnitude. Moreover, bivalirudin was strongly associated with reduced cardiac mortality even in patients without any bleeding and even after accounting for all adverse events known to be reduced by bivalirudin (bleeding, thrombocytopenia, and reinfarction). Further studies are required to identify the nonhematologic benefits of bivalirudin in patients undergoing PCI.

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Key Words: angioplasty ■ bivalirudin ■ complications ■ myocardial infarction ■ prognosis.

▶ APPENDIX

For supplemental tables, please see the online version of this article.