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Impact of In-Hospital Major Bleeding on Late Clinical Outcomes After Primary Percutaneous Coronary Intervention in Acute Myocardial Infarction

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

Jung-Won Suh, MD, PHD,* Roxana Mehran, MD,*† Bimmer E. Claessen, MD,* Ke Xu, PHD,* Usman Baber, MD,† George Dangas, MD, PHD,† Helen Parise, SCD,* Alexandra J. Lansky, MD,*‡ Bernhard Witzenbichler, MD,§ Cindy L. Grines, MD,‖ Giulio Guagliumi, MD,¶ Ran Kornowski, MD,# Jochen Wöhrle, MD,** Dariusz Dudek, MD,†† Giora Weisz, MD,*‡ Gregg W. Stone, MD*‡

New York, New York; Berlin and Ulm, Germany; Royal Oak, Michigan; Bergamo, Italy; Petach Tikva, Israel; and Krakow, Poland

Objectives We aimed to investigate the long-term prognosis of patients with in-hospital major bleeding (IHMB).

Background The effect of IHMB on the long-term prognosis of patients undergoing primary percutaneous coronary intervention (PCI) for ST-segment elevation myocardial infarction is unknown.

Methods Primary PCI was performed in 3,345 (92.9%) of 3,602 patients in the HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) trial; in-hospital protocol-defined non–coronary artery bypass graft–related major bleeding developed in 231 (6.9%). We examined medication use at discharge, mortality, and major adverse cardiovascular events (composite of death, reinfarction, stroke, or ischemic target vessel revascularization) at 3-year follow-up in patients with and without IHMB.

Results At 3-year follow-up, patients with IHMB had higher mortality (24.6% vs. 5.4%, $p < 0.0001$) and major adverse cardiovascular events (40.3% vs. 20.5%, $p < 0.0001$). The deleterious effect of major bleeding was observed within 1 month, between 1 month and 1 year, and between 1 and 3 years. IHMB was an independent predictor of mortality (hazard ratio: 2.80; 95% confidence interval: 1.89 to 4.16, $p < 0.0001$) at 3-year follow up.

Conclusions Patients with IHMB after primary PCI have significantly increased 3-year rates of morbidity and mortality. Further investigation is warranted to understand the mechanisms underlying this relationship and to further improve outcomes in patients with ST-segment myocardial infarction. (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction [HORIZONS-AMI]; NCT00433966) (J Am Coll Cardiol 2011;58: 1750–6) © 2011 by the American College of Cardiology Foundation

From the *Cardiovascular Research Foundation, New York, New York; †Mount Sinai School of Medicine, New York, New York; ‡Columbia University Medical Center, New York, New York; §Charite Campus Benjamin Franklin, Berlin, Germany; ‖William Beamont Hospital, Royal Oak, Michigan; ¶Ospedali Riuniti di Bergamo, Bergamo, Italy; #Rabin Medical Center, Petach Tikva, Israel; **University of Ulm, Ulm, Germany; and the ††Jagiellonian University, Krakow, Poland. The main study (HORIZON-AMI) of this post-hoc analysis was supported by the Cardiovascular Research Foundation with grant support from Boston Scientific and the Medicines Company. Dr. Mehran reported receiving lecture fees from Boston Scientific and the Medicines Company; is a consultant for Abbott Vascular, AstraZeneca, and Regado Biosciences; and has received research support from BMS/Sanofi-Aventis. Dr. Dangas has received an institutional research grant from The Medicines Co., Sanofi-Aventis, and Bristol-Myers Squibb; has received speaker honoraria from Cordis; and his spouse is on the advisory board for Abbott and AstraZeneca. Dr. Witzenbichler has received lecture fees from The Medicines Co. and Boston Scientific. Dr. Grines is on the advisory board for Abbott Vascular. Dr. Guagliumi has received consulting fees from or serving on advisory boards for Abbott Vascular and Boston Scientific; and has received grant support from Medtronic and Boston Scientific. Dr. Stone has received consulting fees from Medtronic, GlaxoSmithKline, Eli Lilly-Daiichi Sankyo, Merck, AstraZeneca, Boston Scientific, Abbott Vascular, The Medicines Co., and Bristol-Myers Squibb-Sanofi; and has received grant support from Boston Scientific, the Medicines Company, and Abbott Vascular. Dr. Dudek has received research grants or served as a consultant/advisory board member for Abbott, Adamed, AstraZeneca, Biotronik, Balton, Bayer, BBraun, BioMatrix, Boston Scientific, Boehringer Ingelheim, Bristol-Myers Squibb, Cordis, Cook Eli Lilly, EuroCor, Glaxo, Invatec, Medtronic, The Medicines Co., MSD, Nycomed, Orbus-Neich, Pfizer, Possis, Promed, Sanofi-Aventis, Siemens, Solvay, Terumo, and Tyco. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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Although potent antiplatelet agents and early revascularization have improved the prognosis for patients with acute myocardial infarction (MI), bleeding complications may result in substantial morbidity or mortality. Major bleeding has been identified as an independent risk factor for mortality after acute MI (1,2). Previous reports have suggested that major bleeding in patients with acute coronary syndromes treated with an early invasive strategy confers an increased risk for both short-term and mid-term mortality (3–5). However, few studies have evaluated the impact of in-hospital major bleeding (IHMB) on longer-term outcomes in these patients.

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Accordingly, we sought to evaluate the clinical correlates and impact of IHMB on the 3-year outcomes after primary percutaneous coronary intervention (PCI) for acute MI among randomized participants in the HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) trial.

Methods

The design of the HORIZONS-AMI trial has been previously described (4). Endpoints for the current analysis included all-cause mortality, the composite endpoint of major adverse clinical events (MACE) (composite of death, reinfarction, target vessel revascularization for ischemia, or stroke), and stent thrombosis (ST, definite, or probable) at 3-year follow-up. Major bleeding was defined as the occurrence of any of the following: intracranial bleeding, intraocular bleeding, retroperitoneal bleeding, access site hemorrhage requiring surgery or radiologic or interventional procedure, hematoma ≥5 cm in diameter at the puncture site, reduction in hemoglobin concentration of ≥4 g/dl without an

Abbreviations and Acronyms

- **CI** = confidence interval
- **HR** = hazard ratio
- **IHMB** = in-hospital major bleeding
- **MACE** = major adverse cardiac event(s)
- **MI** = myocardial infarction
- **PCI** = percutaneous coronary intervention
- **ST** = stent thrombosis

Table 1 Baseline Clinical and Angiographic Characteristics of Patients With and Without In-Hospital Major Bleeding

	Major Bleeding (n = 218)	No Major Bleeding (n = 3,114)	p Value
Age, yrs	67.50 (56.1–77.3)	59.7 (52.4–69.3)	<0.0001
Female	37.6% (82/218)	21.9% (682/3,114)	<0.0001
Body mass index, kg/m^2	26.3 (23.8–29.5)	27.1 (24.6–30.3)	0.01
Anemia	18.5% (42/227)	9.9% (289/2,926)	<0.01
WBC count, baseline, giga/l	11.0 (8.5–14.2)	10.9 (8.8–13.4)	0.21
Hypertension	57.3% (125/218)	52.3% (1,629/3,112)	0.15
Hyperlipidemia	41.3% (90/218)	43.0% (1,337/3,112)	0.63
Current smoking	40.0% (86/215)	47.5% (1,471/3,100)	0.03
Diabetes mellitus	22.5% (49/218)	15.9% (496/3,112)	0.01
Insulin dependent	6.4% (14/218)	4.3% (135/3,112)	0.15
Previous MI	11.9% (26/218)	10.4% (324/3,112)	0.48
Previous PCI	10.6% (23/218)	10.5% (327/3,111)	0.99
Previous CABG	3.2% (7/218)	2.6% (81/3,112)	0.59
History of CHF	5.0% (11/218)	2.4% (75/3,112)	0.02
Renal insufficiency	8.3% (18/218)	2.4% (75/3,111)	<0.0001
Periprocedural characteristics			
Time from symptom onset to hospital arrival, h	2.5 (1.4–4.2)	2.1 (1.3–3.9)	0.10
Time from symptom onset to first balloon inflation, h	4.1 (3.0–5.8)	3.7 (2.7–5.6)	0.01
Killip class 2 to 4	17.4% (38/218)	7.9% (248/3,109)	<0.0001
Index PCI vessels			
LAD	42.4% (100/236)	40.6% (1,349/3,325)	0.59
Index procedure			
Balloon angioplasty only	7.4% (16/215)	3.9% (120/3,056)	0.01
Stent implanted	84.9% (185/218)	94.1% (2,929/3,114)	<0.0001
No. of stents, per patient	1.7 ± 1.0	1.5 ± 0.8	<0.007
Stent total length, mm	28 (20–44)	24 (20–36)	<0.003
Final TIMI flow grade after PCI			
0–1	6.4% (15/236)	2.0% (67/3,319)	<0.0001
2	12.7% (30/236)	5.5% (184/3,319)	<0.0001
3	80.9% (191/236)	92.4% (3,068/3,319)	<0.0001

Values are median (interquartile range) or % (n/N).

CABG = coronary artery bypass graft; CHF = congestive heart failure; LAD = left anterior descending artery; MI = myocardial infarction; PCI = percutaneous coronary intervention; TIMI = Thrombolysis In Myocardial Infarction; WBC = white blood cell.

Table 2 Medication Use in Patients With and Without In-Hospital Major Bleeding

	Major Bleeding (n = 218)	No Major Bleeding (n = 3,114)	p Value
Nonprotocol pre-procedure heparin	66.5% (145/218)	65.6% (2,042/3,112)	0.79
Use of GPI	76.0% (165/217)	54.6% (1,696/3,109)	<0.0001
Use of bivalirudin	34.9% (76/218)	51.0% (1,582/3,102)	<0.0001
Clopidogrel loading dose given	97.7% (213/218)	98.1% (3,054/3,112)	0.60
300 mg	42.7% (93/218)	33.3% (1,128/3,112)	0.005
600 mg	53.7% (117/218)	63.4% (1,972/3,112)	0.004
Aspirin use			
At discharge	97.4% (188/193)	98.8% (3,024/3,061)	0.10
At 30 days	96.7% (178/184)	98.1% (2,911/2,966)	0.17
At 1 yr	94.0% (156/166)	97.2% (2,773/2,854)	0.02
At 3 yrs	95.3% (142/149)	95.4% (2,631/2,759)	0.97
Thienopyridine use			
At discharge	96.9% (187/193)	98.1% (3,004/3,063)	0.28
At 30 days	96.8% (179/185)	97.3% (2,891/2,970)	0.64
At 1 yr	68.3% (114/167)	69.8% (1,995/2,858)	0.67
At 3 yrs	34.7% (52/150)	26.9% (744/2,765)	0.04
Other medication at discharge			
Beta-blocker	84.1% (180/214)	91.1% (2,826/3,103)	0.0007
ACEIs or ARBs	81.9% (158/193)	82.5% (2,527/3,063)	0.82
Statin	90.2% (174/193)	95.9% (2,938/3,063)	0.0002
Diuretics	30.6% (59/193)	20.6% (630/3,063)	0.001
Digoxin	3.1% (6/193)	1.1% (35/3,063)	0.03
Amiodarone	6.7% (13/193)	2.3% (70/3,063)	0.001
Nonstatin lipid-lowering agent	5.2% (10/193)	4.3% (131/3,061)	0.55
Warfarin	6.2% (12/193)	3.6% (109/3,063)	0.06
Cilostazol	0.5% (1/193)	0.6% (19/3,063)	1.0

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; GPI = glycoprotein IIb/IIIa inhibitor.

overt source of bleeding, reduction in hemoglobin concentration of ≥3 g/dl with an overt source of bleeding, reoperation for bleeding, or use of any blood product transfusion (4). Bleeding complications were adjudicated as either related or unrelated to coronary artery bypass (CABG) graft surgery. An independent clinical events

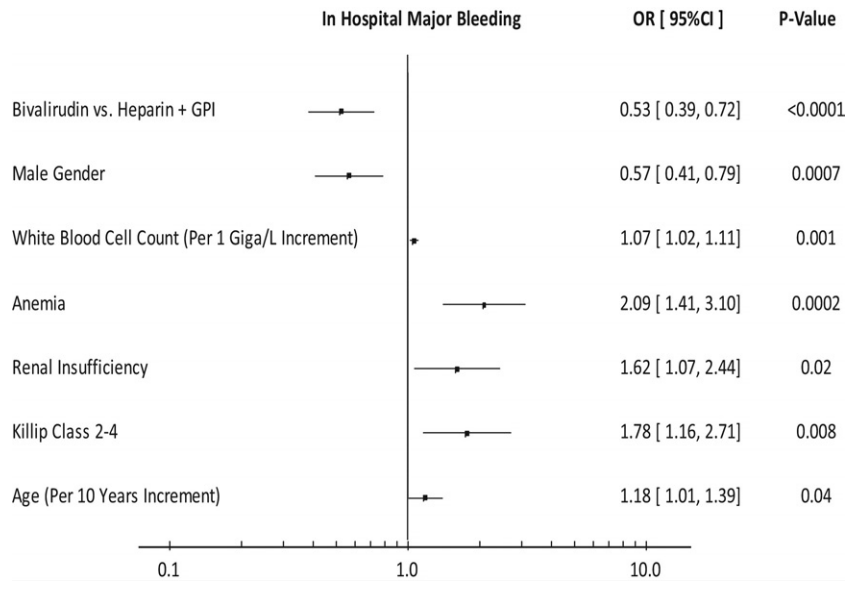

Figure 1 Independent Predictors of In-Hospital Major Bleeding by Logistic Regression

Boxes represent odds ratios (ORs) and **lines** 95% confidence intervals (CIs). GPI = glycoprotein IIb/IIIa inhibitor.

committee adjudicated all primary endpoints and ST events throughout the 3-year follow-up period.

For the current analysis, we compared the 3-year clinical outcomes in patients with a non–CABG-related major bleeding event as their first in-hospital adverse event after the index procedure with patients who did not have major bleeding during their hospital course.

Statistical methods. Categorical variables are presented as percentages and were compared with the chi-square test or Fisher exact test. Continuous variables are presented as medians with interquartile ranges and were compared using Mann-Whitney *U* test.

Predictors of IHMB were identified with logistic regression analyses. The following variables were entered: age, female sex, body mass index, hypertension, hyperlipidemia, smoking, diabetes, previous MI, previous CABG, previous angina, previous heart failure, baseline thrombocytopenia, baseline anemia, renal insufficiency (defined as estimated glomerular filtration rate <60 ml/min), use of pre-randomization heparin, antiplatelet medication use in the past 5 days, pharmacologic randomization arm, loading dose of clopidogrel, symptom to balloon time, and culprit lesion in left anterior descending artery.

Rates of clinical endpoints were compared between patients with and without IHMB cumulative to 3 years and within 3 separate time intervals (0 to 30 days, 30 days to 1 year, and 1 to 3 years). The results are displayed using Kaplan-Meier estimates and compared using the log-rank test.

Cox proportional hazards analysis was used to identify independent predictors of 3-year mortality. The multivariate model was built by stepwise variable selection with entry and exit criteria set at the p = 0.1 level, and we selected all relevant variables from previous studies as candidate variables for this model. Variables included in the multivariable model were age, sex, diabetes mellitus, Killip class, baseline anemia, white blood cell count, renal insufficiency, hypertension, hyperlipidemia, previous MI, smoking, pharmacologic randomization arm, loading dose of clopidogrel, culprit lesion in left anterior descending artery, symptom to first balloon time, and final Thrombolysis In Myocardial Infarction flow grade 3. IHMB and in-hospital ST were forced into the outcomes model.

As a secondary analysis, Cox proportional hazards analysis was repeated for in-hospital survivors only. In addition to the same variables used in the previous model, we included prescription of a statin, beta-blocker, or a thienopyridine at discharge as variables in this model. A p value <0.05 was considered statistically significant.

Results

Patient characteristics. Primary PCI was performed in 3,345 (92.9%) of 3,602 randomized patients; in-hospital protocol-defined non–CABG-related major bleeding developed in 231 (6.9%). Thirteen cases were excluded because the bleeding events developed after thrombotic complications (re-infarction, n = 1; stroke, n = 1; ischemic target vessel revascularization, n = 2; or ST, n = 9). Table 1 shows the baseline clinical, angiographic, and procedural characteristics of patients. Patients with IHMB were older, more often female, more often had a history of congestive heart failure, had a higher Killip class, and had a lower body mass index. Moreover, they were more likely to have diabetes mellitus, anemia, and renal insufficiency. IHMB occurred less frequently in patients randomized to bivalirudin. Table 2 shows antithrombotic medication use in patients. A 600-mg loading dose of clopidogrel and bivalirudin was administered less frequently, and glycoprotein IIb/IIIa inhibitors were more often used in patients with bleeding. Independent predictors of IHMB are presented in Figure 1.

Medications use at and after discharge. As shown in Table 2, there were no significant differences in the prescription rate of

Table 3 Cumulative Rates of Major Adverse Clinical Events in Patients With Versus Without In-Hospital Major Bleeding

	Major Bleeding (n = 218)	No Major Bleeding (n = 3,114)	p Value
MACE			
3 yrs, cumulative	40.3% (85)	20.5% (622)	<0.0001
≤30 days	14.7% (32)	4.4% (136)	<0.0001
30 days to 1 yr	16.2% (31)	6.7% (201)	<0.0001
1 to 3 yrs	21.8% (36)	11.2% (324)	<0.0001
Death			
3 yrs, cumulative	24.6% (52)	5.4% (163)	<0.0001
≤30 days	11.0% (24)	1.8% (57)	<0.0001
30 days to 1 yr	7.3% (14)	1.3% (38)	<0.0001
1 to 3 yrs	8.5% (14)	2.4% (68)	<0.0001
Cardiovascular death			
3 yrs, cumulative	14.2% (30)	3.2% (97)	<0.0001
≤30 days	9.7% (21)	1.8% (55)	<0.0001
30 days to 1 yr	3.2% (6)	0.5% (15)	<0.0001
1 to 3 yrs	1.9% (3)	1.0% (27)	0.25
Myocardial infarction			
3 yrs, cumulative	11.2% (22)	7.1% (209)	0.02
≤30 days	1.0% (2)	1.7% (53)	0.40
30 days to 1 yr	3.2% (6)	2.2% (66)	0.34
1 to 3 yrs	5.1% (8)	3.6% (101)	0.36
Ischemic TVR			
3 yrs, cumulative	19.9% (39)	13.4% (398)	<0.01
≤30 days	2.4% (5)	2.2% (67)	0.85
30 days to 1 yr	7.6% (14)	4.5% (136)	0.053
1 to 3 yrs	10.6% (17)	7.4% (213)	0.19
Stroke			
3 yrs, cumulative	5.0% (10)	1.4% (41)	<0.0001
≤30 days	1.4% (3)	0.4% (13)	0.04
30 days to 1 yr	1.6% (3)	0.4% (11)	0.01
1 to 3 yrs	1.9% (3)	0.6% (18)	0.07
Stent thrombosis			
3 yrs, cumulative	7.0% (12)	4.7% (135)	0.18
≤30 days	3.1% (6)	2.1% (61)	0.33
30 days to 1 yr	1.8% (3)	1.0% (29)	0.34
1 to 3 yrs	2.7% (4)	1.7% (48)	0.40

Values are % (n).

MACE = major adverse cardiac events (composite of death, myocardial infarction, ischemic target vessel revascularization and stroke); TVR = target vessel revascularization.

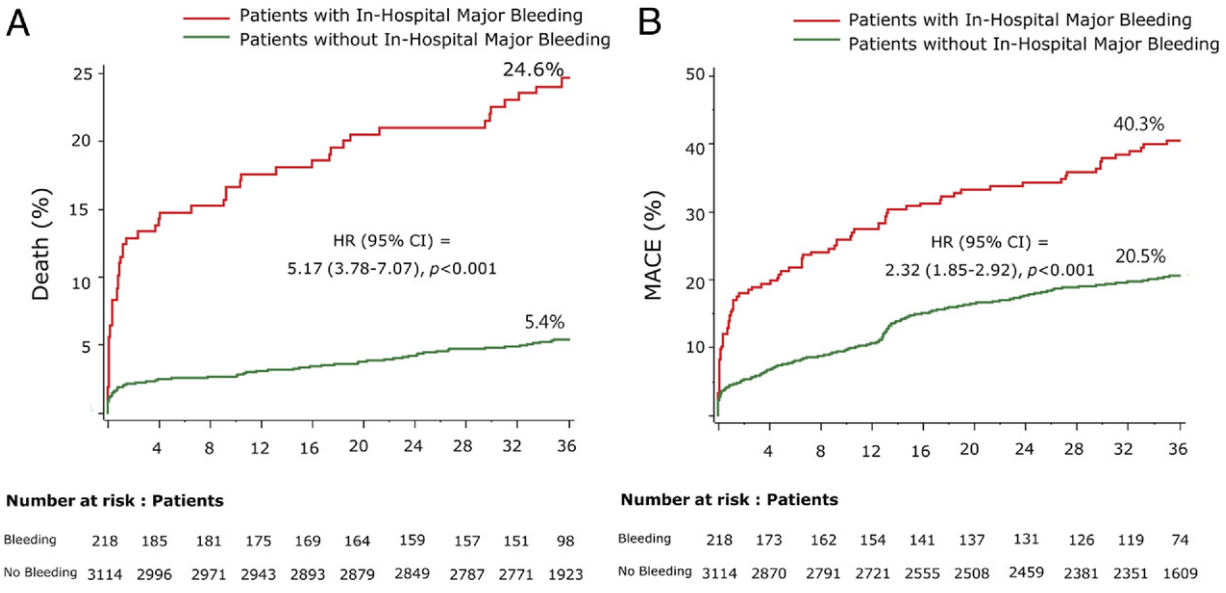

Figure 2 3-Year Mortality and MACE

Kaplan-Meier estimates of time to death **(A)** and major adverse cardiovascular events **(B)** in patients with and without in-hospital major bleeding.
CI = confidence interval; HR = hazard ratio; MACE = major adverse cardiovascular events.

aspirin between patients with and without IHMB at discharge, 1 month, and 3 years. At 1 year, however, patients with bleeding were less likely to be taking aspirin. There were no significant differences in thienopyridine use between both groups at discharge, 1 year, and 2 years. However, patients with IHMB were more likely to be taking a thienopyridine at 3 years. Patients with IHMB were less likely to receive a beta-blocker and statin at hospital discharge, but were more likely to receive diuretics, digoxin, and antiarrhythmic agents.

Major bleeding and clinical outcomes. Kaplan-Meier estimates of the incidence of MACE and their individual components at 3 years and between 0 to 30 days, 30 days to 1 year, and 1 to 3 years are shown in Table 3. Patients with IHMB had significantly higher 3-year rates of mortality (24.6% vs. 5.4%, $p < 0.0001$) (Fig. 2A) and MACE (40.3% vs. 20.5%, $p < 0.0001$) (Fig. 2B).

Moreover, the rates of mortality and MACE were significantly higher in patients with IHMB within each time interval (Fig. 3). The 3-year cumulative rates of MI, ischemic target vessel revascularization, and stroke were also significantly higher in patients with IHMB. Rates of stroke were significantly higher in the bleeding group within 30 days and between 30 days to 1 year, but not thereafter (Table 3). The 3-year cumulative rates of ST were not significantly increased in patients with compared to those without IHMB.

IHMB was still associated with 3-year mortality (Online Fig. A) and MACE (Online Fig. B) after exclusion of patients with large hematomas alone (n = 13).

Predictors of long-term mortality. IHMB was an independent predictor of 3-year mortality (hazard ratio [HR]: 2.80, 95% confidence interval [CI]: 1.89 to 4.16; $p < 0.0001$). Other independent predictors included in-hospital ST, age, male sex, diabetes mellitus, renal insufficiency, smoking, Killip classes 2 to 4 at admission, anemia, baseline white blood cell count, left anterior descending artery culprit lesion, and final Thrombolysis In Myocardial Infarction flow grade <3 (Table 4).

In the secondary analysis among in-hospital survivors (n = 3,260), IHMB remained an independent predictor of 3-year mortality (HR: 2.26, 95% CI: 1.43 to 3.54; p = 0.0004), while in-hospital ST was not a significant predictor (HR: 0.95; 95% CI: 0.13 to 6.93).

Discussion

In the present analysis from the HORIZONS-AMI trial, we found that the occurrence of IHMB in ST-segment elevation myocardial infarction patients treated with primary PCI confers a sustained risk of both mortality and MACE for at least 3 years. We also identified several important differences in pharmacotherapy at the time of discharge between patients with and without IHMB that may in part explain the effect on late mortality.

Although the incidence of both mortality and MACE among bleeding patients was greatest in the first 30 days following PCI, the risk of late mortality after IHMB continued to monotonically accrue over time. While the deleterious impact of thrombotic complications is principally evidenced in the acute stage after their occurrence (6), our findings do not suggest a similar attenuation of risk over time in patients with IHMB in the setting of STEMI.

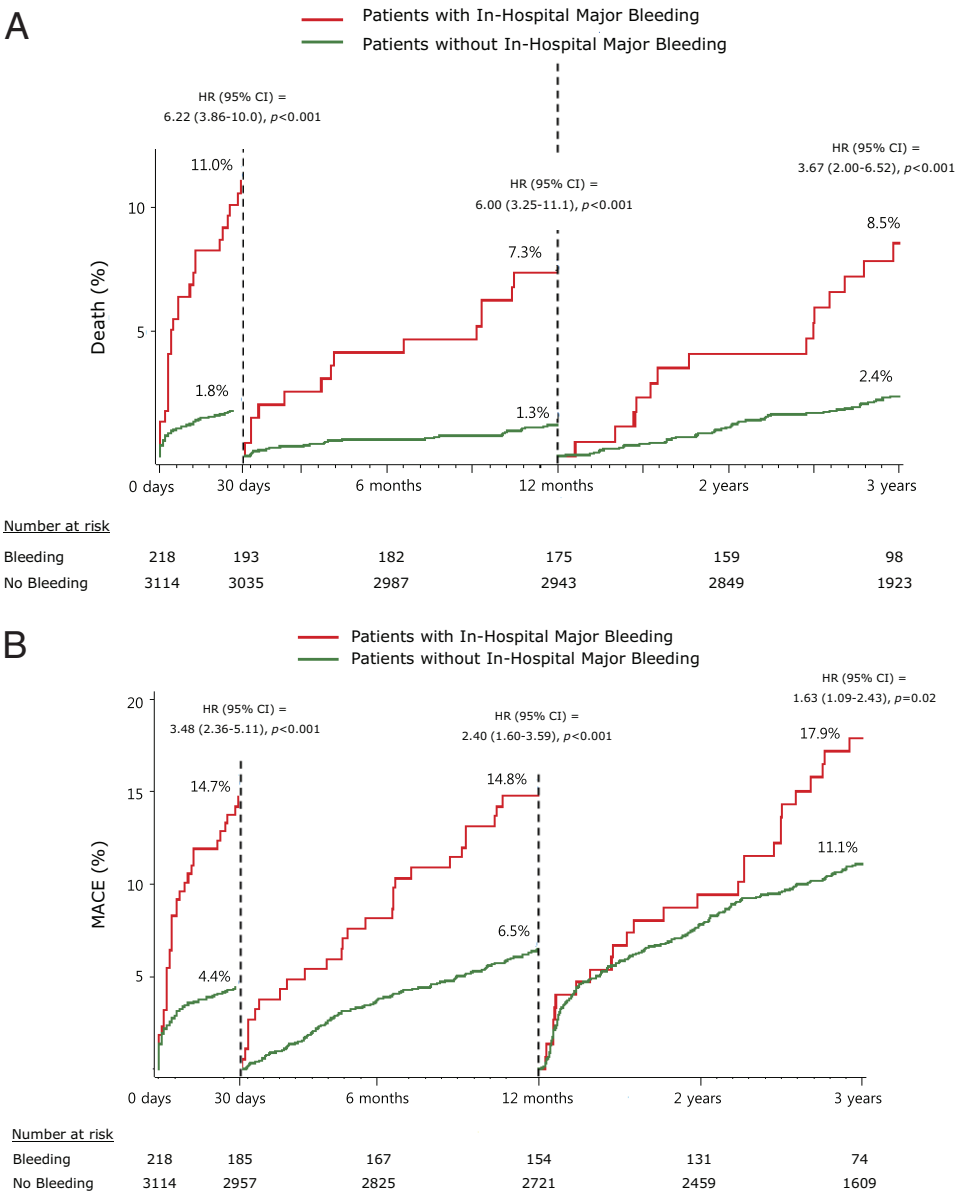

Figure 3 **3-Year Mortality and MACE at Different Time Intervals (Landmark Analysis)**

(A) Mortality within 1 month, between 1 month and 1 year, and between 1 and 3 years. **(B)** MACE within 1 month, between 1 month and 1 year, and between 1 and 3 years. Abbreviations as in Figure 2.

Indeed, IHMB was associated with an approximate 3.5-fold increased risk of mortality between 1 and 3 years.

In this study, IHMB was adjudicated according to the protocol definition used in the HORIZONS-AMI and ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trials (3,7). This report, therefore, validates the definition of major bleeding used in these studies as being clinically relevant and useful in predicting long-term prognosis.

The incidence of IHMB in the present study is higher than that reported from earlier analyses in other acute coronary syndrome studies (1,8). Differences in patient populations, treatment strategies, and bleeding definitions likely explain these discrepancies. Using the same protocol definition, the rate of IHMB among acute coronary syndrome patients treated with PCI in the ACUITY trial was 5.9% (9).

IHMB was associated with 3-year mortality and MACE after the exclusion of patients with large hematomas alone, and the influence of single large hematoma on subsequent mortality or MACE seems to be negligible, as in previous reports (10,11).

Bleeding complications after acute MI may have detrimental effects on long-term prognosis due to several reasons. Patients with IHMB were discharged less often on beta-blocker and

Table 4 Independent Predictors of 3-Year Mortality After Primary PCI in All Patients and In-Hospital Survivors

	HR (95% CI)	p Value
All patients		
In-hospital major bleeding	2.80 (1.89–4.16)	<0.0001
In-hospital stent thrombosis	13.0 (6.95–24.3)	<0.0001
Age, every 10-yr increase	1.93 (1.59–2.33)	<0.0001
Male	1.53 (1.06–2.22)	0.02
Diabetes	1.65 (1.17–2.34)	0.004
Renal insufficiency	1.57 (1.06–2.32)	0.02
History of smoking	1.67 (1.18–2.36)	0.004
Anemia at admission	1.79 (1.21–2.65)	0.004
WBC count at admission, per 1 giga/l	1.08 (1.04–1.12)	0.0001
Killip class 2 to 4	2.04 (1.40–2.96)	0.0002
Culprit lesion in LAD	1.64 (1.08–2.49)	0.02
Final TIMI flow grade 3 count	0.57 (0.40–0.83)	0.003
Hospital survivors		
In-hospital major bleeding	2.29 (1.43–3.67)	0.0006
Age, every 10-yr increase	2.22 (1.85–2.66)	<0.0001
Diabetes	1.76 (1.19–2.60)	0.004
History of smoking	1.96 (1.33–2.90)	0.0007
Anemia at admission	2.00 (1.31–3.06)	0.001
WBC count at admission, per 1 giga/l	1.08 (1.04–1.14)	0.0006
Culprit lesion in LAD	1.73 (1.10–2.71)	0.02
Statin prescription at discharge	0.49 (0.26–0.90)	0.02

CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

statin therapy, which are known to have a survival benefit after acute MI (12). Interestingly, we did not find a reduction in the use of antiplatelet agents in patients with IHMB, as has been reported in the PREMIER (Prospective Registry Evaluating Myocardial Infarction: Events and Recovery) registry (13). We speculate that this may be due to mandated, protocol-defined instructions to keep patients on dual antiplatelet therapy at discharge and for up to at least 1 year. Greater comorbidities in bleeding patients might have also contributed to higher cardiovascular risk. IHMB remained a strong and independent predictor of subsequent mortality, however, even after adjusting for these differences. Other mechanisms that might heighten cardiac risk after bleeding include hypovolemia, hypotension, anemia, impaired oxygen-carrying capacity, and inflammatory response caused by transfusion (3). These factors generate multiple hypotheses for future investigation.

Study limitations. The current analysis was not prespecified in the original study. Multivariate analysis might not account for unmeasured confounders that are associated with mortality after acute MI.

Conclusions

IHMB confers an independent and sustained risk of both mortality and MACE in patients with ST-segment elevation myocardial infarction treated with primary PCI. Further investigation is warranted to understand the mechanisms underlying this relationship and whether the prognosis of these patients may be improved by tailored follow-up and detailed attention to adjunctive pharmacotherapy.

Reprint requests and correspondence: Dr. Roxana Mehran, Mount Sinai Hospital, Cardiovascular Research Foundation, 111 East 59th Street, New York, New York 10022. E-mail: roxana.mehran@mssm.edu

REFERENCES

1. Eikelboom JW, Mehta SR, Anand SS, Xie C, Fox KA, Yusuf S. Adverse impact of bleeding on prognosis in patients with acute coronary syndromes. Circulation 2006;114:774–82.
2. Rao SV, O'Grady K, Pieper KS, et al. Impact of bleeding severity on clinical outcomes among patients with acute coronary syndromes. Am J Cardiol 2005;96:1200–6.
3. Manoukian SV, Feit F, Mehran R, et al. Impact of major bleeding on 30-day mortality and clinical outcomes in patients with acute coronary syndromes: an analysis from the ACUITY trial. J Am Coll Cardiol 2007;49:1362–8.
4. Mehran R, Lansky AJ, Witzenbichler B, et al. Bivalirudin in patients undergoing primary angioplasty for acute myocardial infarction (HORIZONS-AMI): 1-year results of a randomised controlled trial. Lancet 2009;374:1149–59.
5. Ndrepepa G, Berger PB, Mehilli J, et al. Periprocedural bleeding and 1-year outcome after percutaneous coronary interventions: appropriateness of including bleeding as a component of a quadruple end point. J Am Coll Cardiol 2008;51:690–7.
6. Mehran R, Pocock SJ, Stone GW, et al. Associations of major bleeding and myocardial infarction with the incidence and timing of mortality in patients presenting with non-ST-elevation acute coronary syndromes: a risk model from the ACUITY trial. Eur Heart J 2009;30:1457–66.
7. Mehran R, Brodie B, Cox DA, et al. The Harmonizing Outcomes with RevasculariZatiON and Stents in Acute Myocardial Infarction (HORIZONS-AMI) Trial: study design and rationale. Am Heart J 2008;156:44–56.
8. Rao SV, Eikelboom JA, Granger CB, Harrington RA, Califf RM, Bassand JP. Bleeding and blood transfusion issues in patients with non-ST-segment elevation acute coronary syndromes. Eur Heart J 2007;28:1193–204.
9. Stone GW, White HD, Ohman EM, et al. Bivalirudin in patients with acute coronary syndromes undergoing percutaneous coronary intervention: a subgroup analysis from the Acute Catheterization and Urgent Intervention Triage strategy (ACUITY) trial. Lancet 2007;369:907–19.
10. Mehran R, Pocock SJ, Nikolsky E, et al. A risk score to predict bleeding in patients with acute coronary syndromes. J Am Coll Cardiol 2010;55:2556–66.
11. White HD, Aylward PE, Gallo R, et al. Hematomas of at least 5 cm and outcomes in patients undergoing elective percutaneous coronary intervention: insights from the SafeTy and Efficacy of Enoxaparin in PCI patients, an internationaL randomized Evaluation (STEEPLE) trial. Am Heart J 2010;159:110–6.
12. Rasmussen JN, Chong A, Alter DA. Relationship between adherence to evidence-based pharmacotherapy and long-term mortality after acute myocardial infarction. JAMA 2007;297:177–86.
13. Wang TY, Xiao L, Alexander KP, et al. Antiplatelet therapy use after discharge among acute myocardial infarction patients with in-hospital bleeding. Circulation 2008;118:2139–45.

Key Words: bivalirudin ■ bleeding ■ clinical outcomes ■ prognosis.

APPENDIX

For supplementary figures, please see the online version of this article.