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Original Citation:

STEMI patients--the more you bleed, the more you die: a comparison between classifications / S.Valente; C.Lazzeri; M.Chiostri; L.Osmanagaj; C.Giglioli; G.F.Gensini. - In: CLINICAL CARDIOLOGY. - ISSN 0160-9289. - STAMPA. - 34:(2011), pp. 90-96.

Availability:

This version is available at: 2158/592568 since:

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(Article begins on next page)

12 October 2024

Clinical Investigations

STEMI Patients — The More You Bleed, the More You Die: A Comparison Between Classifications

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ABSTRACT

Background: In patients with acute coronary syndromes, an increase in hemorrhagic complications has been observed, and bleeding is now the most frequent noncardiac complication in these patients. Clinical trials and registries have used different scales to classify the severity of bleeding; so far, none of them has been developed for ST-segment elevation myocardial infarction (STEMI) patients in the era of primary percutaneous coronary intervention.

Methods: We analyzed data from our Intensive Cardiac Care Florence STEMI Registry, comprising 991 STEMI patients consecutively admitted to our intensive cardiac care unit after mechanical revascularization, to assess the clinical impact of both Thrombolysis In Myocardial Infarction (TIMI) and Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) classifications in identifying patients with major bleeding at higher risk for in-hospital mortality.

Results: Major bleeding events occurred in 8.9% of patients (88/991) in the TIMI classification and in 17.2% of patients (170/991) in the ACUITY classification. Among patients with major bleeding classified according to ACUITY, 82 patients did not meet the TIMI criteria for major bleeding. These patients represent the so-called gray zone, where no transfusion was performed and only 1 patient died.

Conclusions: In STEMI patients who undergo primary percutaneous coronary intervention and receive dual antiplatelet therapy, TIMI is more capable than ACUITY in identifying patients with major bleeding at higher risk for early mortality. The presence of renal failure represents an independent predictor for major bleeding.

Introduction

Percutaneous coronary intervention (PCI), along with the widespread adoption of newer antithrombotic and antiplatelet regimens, has resulted in significant improvement in ischemic outcomes of patients with acute coronary syndromes (ACS) and ST-segment elevation myocardial infarction (STEMI).[1,2] However, an increase in hemorrhagic complications has been observed, and bleeding is now the most frequent noncardiac complication of patients with ACS.[1–4] Major bleeding events are known to negatively influence prognosis, prolong the hospital stay, and increase costs.[1,3]

Clinical trials and registries of patients with ACS have used different scales to classify the severity of bleeding; so far, none has been developed for STEMI patients in the era of primary PCI. In the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction trial (HORIZONS-AMI),[5] major bleeding events were classified according to the criteria of the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial,[6] which enrolled patients with moderate- and high-risk ACS. Differences in various classifications can account for differences in the estimated prevalence of major bleeding.[1,3,5–8] The Thrombolysis In Myocardial Infarction (TIMI) classification[7] for major bleeding is one of the most commonly used, whereas the ACUITY criteria[6] have been developed in ACS patients subjected to invasive treatment and antiplatelet and antithrombotic therapies.

We analyzed data from our Intensive Cardiac Care Florence STEMI Registry, comprising 991 STEMI patients consecutively admitted to our intensive cardiac care unit (ICCU) after PCI, to assess the clinical impact of both TIMI and ACUITY classifications in identifying patients with major bleeding at higher risk for in-hospital mortality.

Methods

The clinical, angiographic, and in-hospital outcomes of 991 consecutive patients with STEMI (within 12 hours from symptom onset) who were admitted at our ICCU from January 1, 2004 to December 31, 2008 were stored prospectively in a dedicated database (Intensive Cardiac Care Florence STEMI Registry). All STEMI patients

The authors have no funding, financial relationships, or conflicts of interest to disclose.

Clin. Cardiol. 34, 2, 90–96 (2011)
Published online in Wiley Online Library (wileyonlinelibrary.com)
DOI:10.1002/clc.20842 © 2011 Wiley Periodicals, Inc.
Received: July 21, 2010
Accepted with revision: August 19, 2010

underwent primary PCI and then were admitted to the ICCU.[9–11]

The diagnosis of STEMI was based on the American College of Cardiology/American Heart Association criteria.[12]

Coronary angiography and angioplasty were performed using standard techniques by percutaneous femoral approach (using 6-Fr sheaths). Before PCI, a 70-IU/kg intravenous bolus of unfractionated heparin was administered (maximum 5000 IU), followed by additional weight-adjusted doses, in order to maintain an activated clotting time ≥250 seconds throughout the procedure. All patients were given 500 mg of aspirin and 300–600 mg of clopidogrel. Glycoprotein IIb/IIIa inhibitors (GPI) were administered according to the operator's judgment.

A successful PCI was defined as an infarct-artery stenosis <20% associated with TIMI grade 3 flow. Failure PCI was defined as resulting in TIMI grade 0–2 flow, regardless of the residual stenosis.[13]

Upon ICCU admission, blood samples were obtained for cell count, cardiac biomarkers, serum glucose and creatinine levels, high-sensitivity C-reactive protein (hs-CRP), erythrocyte sedimentation rate (ESR), and platelet counts. For the present analysis, the following hemoglobin (Hb) values were used: Hb on ICCU admission and nadir Hb (the lowest Hb value during the ICCU stay). Estimated glomerular filtration rate (eGFR) was calculated according to the Levey modified Modification of Diet in Renal Disease (MDRD) formula.[14] Transthoracic 2-dimensional echocardiography was performed on admission in order to measure left ventricular ejection fraction (LVEF).

Definition of Major Bleeding

TIMI[5]: Intracranial hemorrhage, a ≥5 g/dL decrease in Hb concentration, or a ≥15% absolute decrease in hematocrit. ACUITY[6]: Intracranial or intraocular bleeding; access-site hemorrhage requiring intervention, ≥5-cm-diameter hematoma, clinically overt blood loss with hemoglobin decrease ≥3 g/dL, any hemoglobin decrease ≥4 g/dL, or blood-product transfusion.

Statistical Analysis

Statistical analysis was performed using SPSS 13.0 for Windows (SPSS Inc., Chicago, IL). Data are reported as frequencies and percentages or medians (25th and 75th percentiles) and analyzed by means of χ^2 test (or Fisher exact text and Mann-Whitney U test, respectively; in χ^2 calculations, when appropriate, post hoc tests were performed taking into account standardized residuals). A multivariate backward stepwise logistic regression analysis was performed to determine the independent predictors of major bleeding. Variables that, in the univariate analysis, resulted in a significant difference between subgroups at a probability level <0.01 were entered into the multivariable model; namely age, weight, gender, admission systolic blood pressure (SBP), admission heart rate (HR), Killip class, MI location, LVEF, PCI failure, eGFR, admission Hb, intra-aortic balloon pump (IABP), ultrafiltration, and mechanical ventilation. A 2-tailed P value <0.05 was considered significant.

Results

Table 1 shows the baseline characteristics of the 991 STEMI patients included in the study, all treated with primary PCI. The overall population was classified according to TIMI major bleeding (left side of table) and ACUITY (right side of table). Major bleeding events occurred in 8.9% of patients (88/991) in the TIMI classification and in 17.2% of patients (170/991) in the ACUITY classification.

TIMI Major Bleeding Classification

The STEMI patients who experienced major bleeding were older ($P < 0.001$), more frequently female ($P = 0.007$), leaner ($P = 0.008$), and had chronic renal failure ($P < 0.001$) (Table 1). On admission (Table 2), STEMI patients who experienced major bleeding showed higher HR ($P < 0.001$), lower SBP ($P = 0.003$), and a lower percentage of ST decrease ($P = 0.013$). In these patients, anterior MI was more frequent ($P = 0.002$), as well as Killip class IV ($P < 0.001$), whereas LVEF was lower ($P < 0.001$). The use of a bare-metal stent was higher in patients who experienced major bleeding (Table 2). The rate of bleeding was higher ($P = 0.004$) among patients who had PCI failure. The use of GPIs was higher in patients who had no bleeding events ($P = 0.039$). Major bleeding was associated (Table 3) with higher values of TnI ($P < 0.001$), glucose ($P < 0.001$), positive hs-CRP ($P < 0.001$), and ESR ($P = 0.004$), and with lower values of eGFR ($P < 0.001$), admission Hb ($P < 0.001$), and, obviously, nadir Hb ($P < 0.001$). No difference was observed in platelet count on admission. The use of devices was more frequent in patients who experienced major bleeding events ($P < 0.001$) (Table 4). All blood transfusions were performed in major bleeding events (67/88, 76%; $P < 0.001$). Intra-ICCU mortality was higher in patients who had major bleeding (20% vs 3%; $P < 0.001$).

ACUITY Classification

Major bleeding was observed in older and leaner patients ($P = 0.004$ and 0.001, respectively), in females ($P = 0.016$), and in patients with chronic renal failure ($P = 0.010$) (Table 1). Patients who experienced major bleeding events showed, on ICCU admission, higher HR ($P < 0.001$) and lower percentage of ST decrease ($P = 0.023$), together with a higher Killip class ($P < 0.001$), a higher incidence of anterior MI ($P < 0.001$), and a lower LVEF ($P < 0.001$). In these patients, PCI failure was more frequent ($P = 0.012$), and they showed (Table 3) higher values of TnI ($P < 0.001$), glucose ($P < 0.001$), positive hs-CRP ($P < 0.001$), and ESR ($P = 0.015$), and lower values of eGFR ($P < 0.001$) as well as nadir Hb ($P < 0.001$). No difference was observed in admission Hb and in platelet count. Major bleeding was associated with a more frequent use of devices ($P < 0.001$) (Table 4).

All blood transfusions were performed in major bleeding events (67/170, 39.4%; $P < 0.001$). Intra-ICCU mortality was higher in patients who had major bleeding (11.2% vs 3.2%, $P < 0.001$).

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DOI:10.1002/clc.20842 © 2011 Wiley Periodicals, Inc.

Table 1. Baseline Characteristics of the 991 STEMI Study Patients

	TIMI-I			ACUITY		
	No Major Bleeding, n = 903 (91.9%)	Major Bleeding, n = 88 (8.9%)	*P* Value	No Major Bleeding, n = 821 (82.8%)	Major Bleeding, n = 170 (17.2%)	*P* Value
Demographics						
Median age, y (25th, 75th percentiles)	67 (58, 76)	75 (64, 80)	<0.001	67 (58, 76)	72 (60, 78)	0.004
Female sex	24.6	38.6	0.007	24.2	33.5	0.016
Median weight, kg (25th, 75th percentiles)	75 (65, 83)	70 (62, 80)	0.008	75 (65, 83)	70 (63, 80)	0.001
Medical history						
DM	24.7	31.8	0.158	25.1	26.8	0.628
Hypertension	52.4	51.1	0.824	51.0	58.3	0.090
Dyslipidemia	36.7	29.5	0.202	36.0	36.3	0.930
Smoking	63.3	48.9	0.011	63.0	56.8	0.139
Chronic renal failure	3.4	12.5	<0.001	3.4	8.2	0.010
COPD	8.0	11.4	0.307	8.2	8.8	0.761
Prior MI	14.3	20.5	0.156	14.4	17.1	0.406
Prior stroke	3.5	8.0	0.075	3.5	5.9	0.190
Prior PCI	13.5	19.3	0.147	13.8	15.3	0.628
Prior CABG	2.2	2.3	1	2.0	3.5	0.247

Abbreviations: ACUITY, Acute Catheterization and Urgent Intervention Triage Strategy; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; MI, myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; TIMI-I, Thrombolysis In Myocardial Infarction-I.
Numbers are percentages unless otherwise noted.

Gray Zone

Among patients with major bleeding events classified according to ACUITY, 82 patients did not meet the TIMI criteria for major bleeding. These patients represent a subgroup that we named the gray zone (Table 5). The patients included in the gray zone showed major bleeding according to the ACUITY criteria, but no transfusion was performed and only 1 patient died.

Major Bleeding Sites

Clinical bleeding was identified in 66 (75%) of the patients with major bleeding according to TIMI criteria. The most frequent bleeding events were femoral groin hematoma (44.3%), gastrointestinal hemorrhage (10.2%) and retroperitoneal bleeding (4.5%), urinary tract hemorrhage (2.3%), cerebral hemorrhage (1.1%), cardiac tamponade (4.5%), respiratory tract hemorrhage (4.5%), and disseminated intravascular coagulopathy (3.4%).

Clinical bleeding was identified in 100 (59%) of the patients with major bleeding according to ACUITY criteria. The most frequent bleeding events were femoral groin hematoma (40.6%), gastrointestinal hemorrhage (6.5%) and retroperitoneal bleeding (2.4%), urinary tract hemorrhage (1.8%), cerebral hemorrhage (0.6%), cardiac tamponade (2.9%), respiratory tract hemorrhage (2.4%), and disseminated intravascular coagulopathy (1.8%).

Logistic Regression Analysis

At backward stepwise logistic regression analysis, performed until all covariates resulted statistically significant, the following variables were independent predictors of intra-ICCU major bleeding according to TIMI criteria: IABP (odds ratio [OR]: 2.96, 95% confidence interval [CI]: 1.39–6.34, $P = 0.005$), mechanical ventilation (OR: 5.08, 95% CI: 2.19–11.78, $P < 0.001$), eGFR (OR: 0.97, 95% CI: 0.95–0.98, $P < 0.001$), admission Hb (OR: 0.82, 95% CI: 0.69–0.97, $P = 0.022$), and Hosmer-Lemeshow test (4.80, $P = 0.779$).

At the same statistical analysis, the following variables resulted as independent predictors of intra-ICCU major bleeding according to ACUITY criteria: IABP (OR: 3.59, 95% CI: 2.14–6.02, $P < 0.001$), weight (OR: 0.98, 95% CI: 0.96–0.99, $P = 0.011$), eGFR (OR: 0.98, 95% CI: 0.97–0.99, $P < 0.001$), ultrafiltration (OR: 5.95, 95% CI: 1.91–18.5, $P = 0.002$), and Hosmer-Lemeshow test (9.98, $P = 0.266$).

Discussion

The main finding of the present investigation is that, in 991 consecutive STEMI patients treated with primary PCI, TIMI classification is able to identify patients with major bleeding at higher risk for intra-ICCU mortality, whereas the ACUITY classification includes also a subgroup of patients (the gray zone) showing bleeding events not able to affect their outcomes in the short term.

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DOI:10.1002/clc.20842 © 2011 Wiley Periodicals, Inc.

Table 2. Clinical Characteristics of the 991 STEMI Study Patients

	TIMI-I			ACUITY		
Presenting Signs	No Major Bleeding, n = 903 (91.9%)	Major Bleeding, n = 88 (8.9%)	*P* Value	No Major Bleeding, n = 821 (82.8%)	Major Bleeding, n = 170 (17.2%)	*P* Value
Median HR, bpm (25th, 75th percentiles)	77 (66, 87)	80 (71, 100)	<0.001	77 (65, 86)	80 (70, 96)	<0.001
Median SBP, mm Hg (25th, 75th percentiles)	130 (115, 145)	120 (98, 140)	0.003	130 (115, 145)	130 (104, 150)	0.106
ST decrease >50%	64.6	47.3	0.013	65.1	53.2	0.023
Killip class			<0.001			<0.001
I	82.6	48.3[a]		83.0	62.7[a]	
II	8.4	14.9		8.4	11.8	
III	2.7	4.6		2.6	4.1	
IV	6.3	32.2[a]		6.0	21.3[a]	
AMI location			0.002			<0.001
Inferior	39.7	23.3[a]		40.8	26.2[a]	
Lateral	8.1	4.7		8.2	6.0	
Anterior	52.2	72.1[a]		51.0	67.9[a]	
Median LVEF, % (25th, 75th percentiles)	45 (38, 50)	35 (30, 45)	<0.001	45 (38, 50)	40 (30, 45)	<0.001
CAD			0.500			0.122
No disease	0.2	0.0		0.2	0.0	
1-vessel	39.8	32.2		40.8	31.4	
2-vessel	34.0	40.2		33.7	38.5	
3-vessel	26.0	27.6		25.3	30.2	
Left main	7.3	13.1	0.083	6.9	12.1	0.036
CABG	1.6	2.3	0.609	1.5	2.4	0.499
IRA			<0.001			<0.001
RCA	33.7	17.6[a]		34.7	20.7[a]	
CX	12.2	14.0		12.4	12.1	
DA	52.4	61.3		51.3	62.3	
Left main	0.7	5.9[a]		0.7	3.1[a]	
CABG	1.0	1.2		0.9	1.8	
Stent implantation	89.4	85.2	0.313	89.6	86.2	0.284
BMS	46.9	61.4		47.1	53.5	
DES	42.8	28.4	0.024	42.4	37.6	0.293
POBA	10.3	10.2		10.5	8.9	

Table 2. *Continued*

Presenting Signs	TIMI-I			ACUITY		
	No Major Bleeding, n = 903 (91.9%)	Major Bleeding, n = 88 (8.9%)	*P* Value	No Major Bleeding, n = 821 (82.8%)	Major Bleeding, n = 170 (17.2%)	*P* Value
TIMI flow post-PCI			0.002			0.041
III	94.6	86.0		94.8	89.3	
II	3.4	10.5[a]		3.5	6.5	
I	0.9	0.0		0.7	1.2	
0	1.1	3.5		1.0	3.0	
PCI failure	5.4	13.8	0.004	5.2	10.7	0.012
GPI	70.2	59.1	0.039	69.4	68.2	0.784

Abbreviations: ACUITY, Acute Catheterization and Urgent Intervention Triage Strategy; AMI, acute myocardial infarction; BMS, bare-metal stent; CABG, coronary artery bypass graft; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CX, circumflex coronary artery; DA, descending anterior coronary artery; DES, drug-eluting stent; DM, diabetes mellitus; GPI, glycoprotein IIb/IIIa inhibitor; HR, heart rate; IRA, infarct-related artery; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; POBA, plain old balloon angioplasty; RCA, right coronary artery; SBP, systolic arterial blood pressure; ST, ST segment; STEMI, ST-elevation myocardial infarction; TIMI-I, Thrombolysis In Myocardial Infarction-I. Numbers shown are percentages unless otherwise noted. [a]$P < 0.05$.

Table 3. Biochemical Data on the 991 STEMI Study Patients

	TIMI-I			ACUITY		
	No Major Bleeding, n = 903 (91.9%)	Major Bleeding, n = 88 (8.9%)	*P* Value	No Major Bleeding, n = 821 (82.8%)	Major Bleeding, n = 170 (17.2%)	*P* Value
TnI, ng/mL (25th, 75th percentiles)	84.1 (37.8, 168.2)	129.0 (55.4, 370.0)	<0.001	82.0 (37.3, 164.0)	123.3 (50.1, 255.3)	<0.001
Glycemia, g/L (25th, 75th percentiles)	1.30 (1.11, 1.62)	1.65 (2.32, 2.40)	<0.001	1.29 (1.10, 1.62)	1.52 (1.24, 2.02)	<0.001
eGFR mL/min/1.73 m² (25th, 75th percentiles)	81.2 (67.0, 98.2)	57.0 (37.3, 74.5)	<0.001	81.3 (68.1, 98.1)	68.8 (45.7, 83.7)	<0.001
ESR, mm/h (25th, 75th percentiles)	25 (14, 42)	32 (18, 69)	0.004	25 (14, 42)	30 (18, 51)	0.015
Positive hs-CRP, %	53.8	76.1	<0.001	52.6	70.8	<0.001
Admission Hb, g/dL (25th, 75th percentiles)	13.8 (12.7, 14.7)	12.2 (10.2, 14.1)	<0.001	13.7 (12.6, 14.6)	13.4 (11.6, 14.8)	0.355
Nadir Hb, g/dL (25th, 75th percentiles)	12.0 (10.7, 13.0)	8.2 (7.6, 9.3)	<0.001	12.1 (11.0, 13.0)	9.3 (8.1, 10.5)	<0.001
Platelet count, *1000/ mL (25th, 75th percentiles)	210 (176, 253)	233 (181, 294)	0.204	210 (175, 253)	223 (180, 268)	0.184

Abbreviations: ACUITY, Acute Catheterization and Urgent Intervention Triage Strategy; eGFR, estimated glomerular filtration rate; ESR, erythrocyte sedimentation rate; Hb, hemoglobin; hs-CRP, high-sensitivity C-reactive protein; STEMI, ST-elevation myocardial infarction; TnI, troponin I; TIMI-I, Thrombolysis In Myocardial Infarction-I.
Numbers shown are percentages unless otherwise noted.

Bleeding rates are known to depend mainly on the clinical setting[15–17] and on the definition of bleeding events.[1,3] Taking into account that our series comprises a homogeneous population of STEMI patients, all treated with primary PCI by femoral approach, we confirm that classification type does influence the prevalence of bleeding events (8.9% according to TIMI I; 17.8% according to ACUITY).

On a clinical ground, the role of classifications is to provide tools to identify patients at higher risk. Our findings strongly suggest that, in STEMI patients who undergo primary PCI and receive dual antiplatelet therapy, TIMI is more capable

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Table 4. Device Use in the 991 STEMI Study Patients

	TIMI-I			ACUITY		
	No Major Bleeding, n = 903 (91.9%)	Major Bleeding, n = 88 (8.9%)	*P* Value	No Major Bleeding, n = 821 (82.8%)	Major Bleeding, n = 170 (17.2%)	*P* Value
IABP	24.1	60	<0.001	22.1	52.4	<0.001
CVVHDF	2.1	26.8	<0.001	1.6	17.4	<0.001
Mechanical ventilation	5.4	35.3	<0.001	5.2	21.7	<0.001
NIV	3.8	30.8	<0.001	3.2	20.3	<0.001
Blood transfusion	0.0	76.1	<0.001	0.0	39.4	<0.001
In-ICCU deaths	3.0	20.5	<0.001	3.2	11.2	<0.001

Abbreviations: ACUITY, Acute Catheterization and Urgent Intervention Triage Strategy; CVVHDF, continuous venovenous hemodiafiltration; IABP, intra-aortic balloon pump; ICCU, intensive coronary care unit; NIV, noninvasive ventilation; STEMI, ST-elevation myocardial infarction; TIMI-I, Thrombolysis In Myocardial Infarction-I.
Numbers shown are percentages.

Table 5. Comparison Between the Gray Zone and TIMI Major Bleeding

	Gray Zone	TIMI Major Bleeding	*P* Value
Number	82	88	
Mortality	1 (1.2%)	18 (20.4%)	<0.001
Blood transfusion	0 (0%)	67 (76.1%)	<0.001
PCI failure	6 (7.3%)	12 (13.6%)	NS
IABP	36 (43.9%)	51 (58.0%)	<0.001
NIV	7 (8.5%)	24 (27.2%)	<0.001
Mechanical ventilation	6 (7.3%)	30 (34.1%)	<0.001
CVVHDF	6 (7.3%)	22 (25.0%)	<0.001

Abbreviations: CVVHDF, continuous venovenous hemodiafiltration; IABP, intra-aortic balloon pump; NIV, noninvasive ventilation; NS, not significant; PCI, percutaneous coronary intervention; TIMI, Thrombolysis In Myocardial Infarction.

than ACUITY in identifying patients with major bleeding events at higher risk for mortality.

Moreover, according to our data, the entity of bleeding, and not only "bleeding" itself, affects prognosis, because patients in the gray zone, though classified as "major bleeding," did not show an increased rate of mortality and were not transfused.

According to both classifications (TIMI and ACUITY) and in agreement with the investigations by Nikolsky et al[18] and by Mehran et al,[19] the presence of chronic renal failure was an independent predictor of in-ICCU major bleeding. As recently reported,[20] GFR should be systematically measured for every single patient and monitored during treatment to guide the choice of drug and dose.

The severity of critical illness, as inferred by the presence of devices (ultrafiltration, IABP, mechanical ventilation), represents an independent predictor for major bleeding according to both classifications. Besides, ultrafiltration and IABP require heparin.

It is interesting to note that GPI administration was not associated with an increased incidence of bleeding. On the other hand, ACUITY,[6,21–22] in agreement with the Global Registry of Acute Coronary Events (GRACE) registry,[23] reported that GPI, among other factors, independently predicted major bleeding. Discrepancies between our study and previous ones can be related to the fact that our investigation is not a randomized one and it can be speculated that GPI use was administered by cardiologists to patients believed to be at lower risk for bleeding. Similarly, the higher use of bare-metal stents observed in patients who experienced major bleeding according to TIMI classification can be related to cardiologists' decisions to use them in patients believed to be at higher risk for bleeding.

In our series, in regard to bleeding sites, in both classifications about half of the clinical bleeding events were related to femoral groin hematoma. The transradial approach is supposed to substantially reduce the rate of this complication.[24]

A possible limitation of the study is that it is retrospective. However, it included a large series of STEMI patients all subjected to primary PCI with no age or gender restriction, thus mirroring the real-world scenario.

Conclusion

In STEMI patients who undergo primary PCI and receive dual antiplatelet therapy, TIMI is more capable than ACUITY in identifying patients with major bleeding at higher risk for early mortality. The presence of renal failure represents an independent predictor for major bleeding.

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DOI:10.1002/clc.20842 © 2011 Wiley Periodicals, Inc.