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In-hospital major bleeding and its clinical relevance in patients with ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention

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ABSTRACT

Aims

Advances in antithrombotic therapy for ST-segment elevation myocardial infarction (STEMI) enhance the risk of bleeding. Therefore, the incidence, determinants and prognostic implications of in-hospital major bleeding after primary percutaneous coronary intervention for STEMI were investigated.

Methods

In 963 consecutive patients, the incidence of bleeding was evaluated according to commonly used classifications including Can Rapid risk stratification of Unstable angina patients Suppress Adverse outcomes with Early implementation of the ACC/AHA guidelines, Thrombolysis In Myocardial Infarction, Global Use of Strategies To Open coronary arteries, and Bleeding Academic Research Consortium. Multivariable regression analyses investigated determinants of bleeding and the relation between bleeding and 1-year all-cause mortality.

Results

Large variability in incidence existed depending upon classification (1.3% - 21%). Female gender, heart rate, creatinine, multivessel disease, cardiogenic shock and procedural failure were independently associated with bleeding. One-year mortality reached 10.2% in bleeders vs. 2.0% in non-bleeders ($p<0.001$). Bleeding was independently associated with an increased risk of 1-year mortality (HR2.41, $p<0.017$). Assessment of individual classifications confirmed the increased risk of mortality for BARC (HR2.27, $p=0.048$), but not for CRUSADE, TIMI and GUSTO bleeding. Thrombotic events occurred more frequently in bleeders (5.8% vs. 1.5%, $p<0.001$), however bleeding remained independently related to mortality with a negligible reduction in HR (2.25, $p=0.028$) after adjustment.

Conclusions

In-hospital major bleeding was frequently observed after STEMI but a widespread variation in incidence existed depending on the applied definition. Patient and procedural characteristics were related to bleeding, allowing identification of high-risk patients. In-hospital major bleeding was independently associated with 1-year all-cause mortality, however not all bleeding classifications proved equally relevant to prognosis. The relation between bleeding and mortality was shown not to be driven by the higher rate of thrombotic events among bleeders.

INTRODUCTION

In recent years, advances in mechanical revascularization and antithrombotic therapy led to a considerable progress in the prevention of thrombotic events after acute myocardial infarction (AMI). However, the increasingly aggressive treatment strategies enhance the risk of bleeding[1]. Although previously reported incidences strongly depend on the classification used, bleeding is undoubtedly a frequent complication, in particular after primary percutaneous coronary intervention (PCI), leading to high costs and worse prognosis[2]. Therefore, identifying patients at highest risk for bleeding might improve outcomes by individualized treatment. Although several baseline characteristics have been consistently related to bleeding after acute coronary syndrome[2-4], other factors may play a role in case of ST-segment elevation myocardial infarction (STEMI). In addition to an increase in morbidity and costs, previous literature reported an increased risk for death late after discharge in patients who suffered from in-hospital major bleeding[2], including access site bleeding[5] which traditionally has been considered relatively benign. However, late mortality conferred by bleeding and the mechanism behind this supposed phenomenon are subject of debate[6-8]. The purpose of the present study was firstly to investigate the incidence of in-hospital major bleeding after primary PCI for STEMI and its determinants by evaluating both the Can Rapid risk stratification of Unstable angina patients Suppress Adverse outcomes with Early implementation of the ACC/AHA guidelines (CRUSADE) bleeding risk score and individual potential risk factors. Secondly, the prognostic implications of bleeding according to commonly used bleeding classifications were studied.

METHODS

This was a single center analysis of prospectively collected data from consecutive STEMI patients enrolled in an ongoing clinical registry between January 2007 and January 2011.

Patients

All patients were treated according to the institutional STEMI protocol (MISSION!) up to one year after the index event[9]. This protocol is based upon the international guidelines and standard of STEMI care in the district Hollands-Midden, the Netherlands. Diagnosis of STEMI was made based on typical electrocardiographic ST-segment changes in combination with clinical symptoms of AMI and a rise and/or fall of cardiac biomarkers[10]. All patients underwent primary PCI using the femoral approach. Antithrombotic therapy included upfront abciximab (bolus of 25 μg/kg in-ambulance followed by 10 μg/kg/min for 12 hours), loading doses of aspirin (300 mg) and clopidogrel (600 mg), peri-procedural heparin (5,000 IU) and enoxaparin (1 mg/kg twice daily for 48 hours). Patients transferred

to another hospital during hospitalization for geographical reasons were excluded, as well as non-residents of the Netherlands and those without data on the CRUSADE risk score[3]. Patients without return of spontaneous circulation after out-of-hospital cardiac arrest are not enrolled in the MISSION! Registry.

Data collection and follow-up

Data on patient characteristics and adverse events were prospectively entered in the departmental electronic patient dossier (EPD-Vision 10.3.3.0, LUMC, Leiden, The Netherlands) by attending cardiologists not involved in the present study and were retrospectively analyzed. Vital status of the entire cohort was retrieved retrospectively from municipal civil registries. Patients in whom ≥2 months of clinical follow-up data (other than vital status) were lacking were considered lost to clinical follow-up. Data were included until the last date of follow-up.

Endpoints and definitions

The primary endpoints of the present study were major bleeding during the index hospitalization and all-cause mortality up to one year. Bleeding was categorized according to several pre-defined classifications using its criteria for major bleeding not related to coronary artery bypass grafting, including CRUSADE[3], Thrombolysis In Myocardial Infarction (TIMI)[11], Global Use of Strategies To Open coronary arteries (GUSTO)[12] and Bleeding Academic Research Consortium (BARC)[13]. Criteria for each of the classifications are listed in **Table 1**. Any bleeding was defined as bleeding according to at least one of the aforementioned bleeding classifications. Spontaneous recurrent AMI during one year follow-up was regarded as secondary endpoint for thrombotic risk and defined as a troponin-T concentration above the upper limit or a re-rise of >25% after recent AMI, both in the presence of ischemic complaints.

Statistical analysis

Categorical data are presented as counts and percentages and continuous data as mean ± SD or median and interquartile range. Data between groups were compared with a Pearson's chi-square test, a Fisher's Exact test (as appropriate) or a Student's *t* test. Receiver operating characteristics curves evaluated the discriminative capacity of the CRUSADE risk score for bleeding by means of the area under the curve. Multivariable logistic regression analysis was performed to identify factors associated with in-hospital major bleeding, incorporating baseline variables with p <0.10 in univariable analysis: age, gender, out-of-hospital cardiac arrest, history of hypertension, diabetes mellitus, current smoking, admission creatinine, hematocrit, weight, heart rate, systolic blood pressure and killip class, multivessel disease (≥50% stenosis in >1 major epicardial coronary vessel), peri-procedural cardiogenic shock (requiring therapy), proximity of the culprit lesion and procedural fail-

Table 1. Criteria for major bleeding not related to coronary artery bypass grafting

Classification	Criteria
CRUSADE	Intracranial hemorrhage
	Documented retroperitoneal bleed
	Hematocrit drop ≥12%
	Red blood cell transfusion when baseline hematocrit ≥28%
	Red blood cell transfusion when baseline hematocrit <28% with witnessed bleed
TIMI	Intracranial hemorrhage
	Signs of bleeding with drop of hemoglobin >5 g/dL or drop in hematocrit ≥15%
	Fatal bleeding (death within 7 days after bleeding)
GUSTO	Fatal bleeding
	Intracerebral hemorrhage
	Bleeding resulting in substantial hemodynamic compromise*
BARC (class ≥ 3)	Hemoglobin drop of ≥3 g/dL with overt bleeding
	Red blood cell transfusion with overt bleeding
	Cardiac tamponade
	Bleeding requiring surgical intervention
	Bleeding requiring intravenous vasoactive agents
	Intracranial hemorrhage
	Intraocular bleed compromising vision
	Fatal bleeding (probable or definite)

* Systolic blood pressure <90 mmHg requiring treatment (e.g. blood or fluid replacement, administration of vasopressor or inotropic agents, or surgical intervention).

ure (final thrombolysis in myocardial infarction flow <3). The Kaplan-Meier method was used to estimate cumulative incidences of events during follow-up, which were compared with the log-rank test. In order to adjust for potential confounders, multivariable Cox proportional hazard regression analysis was performed in a stepwise forward fashion, entering baseline variables based on clinical judgment and $p < 0.10$ in univariable analysis: age, diabetes mellitus, admission heart rate, admission creatinine, peri-procedural cardiogenic shock and peak creatine phosphokinase level during hospitalization. Bleeding status was forced to remain in the model. To assess the prognostic role of thrombotic events in bleeders, it was added as a dichotomous variable to the aforementioned multivariable Cox regression model. All p-values were 2-sided, and $p < 0.05$ was considered to be statistically significant. Analyses were conducted with IBM SPSS Statistics 20 (SPSS Inc., Chicago, Illinois).

RESULTS

In total 1212 patients were screened for eligibility, of whom 249 were excluded because of a transfer (219), non-residency (11) or missing data on the CRUSADE risk score (19).

Table 2. Baseline characteristics

Variable	N = 963
Age (years)	61 ± 12
Men	728 (76%)
Hypertension *	366 (38%)
Hyperlipidemia †	199 (21%)
Diabetes mellitus	111 (12%)
Current smoker	446 (47%)
Positive family history	416 (44%)
Previous acute myocardial infarction	100 (10.4%)
Previous percutaneous coronary intervention	73 (7.6%)
Previous coronary artery bypass grafting	27 (2.8%)
Symptoms-balloon time (min)	165 (122-256)
Diagnosis-balloon time (min)	79 (68-95)
Abciximab-balloon time (min)	57 (45-70)
Out-of-hospital cardiac arrest	44 (4.6%)
CRUSADE bleeding risk score	21 (14-29)
Admission systolic blood pressure (mmHg)	130 (116-150)
Admission heart rate (bpm)	70 (60-83)
Admission Killip class ≥2	20 (2.1%)
Admission hemoglobin (mmol/L)	8.8 (8.2-9.3)
Admission hematocrit (%)	41 (39-44)
Admission creatinine (μmol/L)	77 (67-89)
Renal insufficiency ‡	108 (11%)
Proximal lesion	424 (44%)
Culprit vessel left anterior descending	400 (42%)
Peri-procedural cardiogenic shock	29 (3.0%)
Intra-aortic balloon pump use	16 (1.7%)
Multivessel coronary artery disease	556 (58%)
Stent implantation	934 (97%)
Drug-eluting stent	831 (86%)
Initial Thrombolysis In Myocardial Infarction flow ≥2	233 (24%)
Post-procedural Thrombolysis In Myocardial Infarction flow 3	887 (93%)
Peak creatine phosphokinase (U/L)	1240 (567-2552)

Data are expressed as number (%) or mean ± standard deviation (SD) or median (interquartile range).

* Blood pressure ≥ 140/90 mmHg or previous pharmacological treatment; † Total cholesterol ≥ 190 mg/dl or previous pharmacological treatment; ‡ Estimated glomerular filtration rate < 60 (mL/min/1.73 m^2)

The final study population comprised 963 patients. Baseline characteristics are listed in **Table 2**.

Bleeding

In 216 patients (22%) any in-hospital major bleeding event was observed as defined by at least one of the examined bleeding classifications. In 73 patients (34%), bleeding was attributed to the vascular access site. The incidence of bleeding showed a large variability depending upon classification (**Table 3**). In all classifications, the event rate increased

Table 3. In-hospital major bleeding rates per CRUSADE bleeding risk category.

CRUSADE risk score categories	N	Any bleeders*	CRUSADE bleeders	TIMI bleeders	GUSTO bleeders	BARC bleeders
Very low	**448**	57 (13%)	50 (11%)	12 (2.7%)	4 (0.9%)	20 (4.5%)
Low	**303**	75 (25%)	73 (24%)	27 (8.9%)	4 (1.3%)	29 (9.6%)
Moderate	**136**	46 (34%)	42 (31%)	14 (10.3%)	1 (0.7%)	16 (12%)
High	**60**	26 (43%)	21 (35%)	7 (12%)	3 (5.0%)	8 (13%)
Very high	**16**	12 (75%)	11 (69%)	6 (38%)	1 (6.2%)	6 (38%)
Total	**963**	216 (22%)	197 (21%)	66 (6.9%)	13 (1.3%)	79 (8.2%)

Data are expressed as numbers (%).

* Patients who suffered from in-hospital major bleeding according to at least one of the pre-defined bleeding classifications (i.e. CRUSADE, TIMI, GUSTO or BARC)

Table 4. Receiver operating characteristics curves of CRUSADE bleeding risk score for in-hospital major bleeding

Classification	Area under curve (interquartile range)	P value
Any*	0.688 (0.649-0.728)	<0.001
CRUSADE	0.684 (0.644-0.725)	<0.001
TIMI	0.701 (0.640-0.762)	<0.001
GUSTO	0.662 (0.519-0.805)	0.045
BARC	0.666 (0.606-0.726)	<0.001

* Patients who suffered from in-hospital major bleeding according to at least one of the pre-defined bleeding classifications (i.e. CRUSADE, TIMI, GUSTO or BARC)

gradually with increasing CRUSADE bleeding risk category. However, this risk score was shown to have a modest capacity to discriminate bleeders from non-bleeders in all classifications (**Table 4**). Female gender (HR 2.58, 95%CI 1.70-3.92, p<0.001), admission heart rate (HR 1.16, 95%CI 1.06-1.27 [per 10bpm], p=0.001), admission creatinine (HR 1.08, 95%CI 1.00-1.16 [per 10 mmol/L], p=0.044), multivessel disease (HR 1.54, 95%CI 1.07-2.22, p=0.021), peri-procedural cardiogenic shock (HR 3.68, 95%CI 1.45-9.34, p=0.006) and procedural failure (HR 3.22, 95%CI 1.86-5.57, p<0.001) were individual parameters found to be independently associated with an increased risk of in-hospital major bleeding (any), whereas age (HR 1.09, 95%CI 0.93-1.28, p=0.31), weight (HR 1.00, 95%CI 0.94-1.07, p=0.94) and baseline hematocrit (HR 0.98, 95%CI 0.93-1.02, p=0.33) were not. Of all patients alive at time of discharge, the hospitalization duration was significantly longer in any bleeders vs. non-bleeders (5±5 days vs. 3±2 days, p<0.001).

Mortality

During one year follow-up, 37 patients (3.8%) deceased; in three the in-hospital major bleeding event was most likely the direct cause of death. The majority of deaths were attributable to a cardiac cause, i.e. heart failure (17), recurrent AMI (six), out-of-hospital

cardiac arrest resulting in anoxic encephalopathy (one) and rupture of the interventricular septum (one). Other causes of death included malignancy (five), fatal bleeding during follow-up (one intracranial and one related to coronary artery bypass grafting) and renal failure (one). In one patient, the cause of death was unknown. All-cause mortality was significantly increased in any bleeders compared to non-bleeders, not only in-hospital (4.2% vs. 0.8%, p=0.002), but also after 30 days (6.0% vs. 0.9%, p<0.001) and one year (10.2% vs. 2.0%, p<0.001, **Figure 1**). For separate classifications, 1-year all-cause mortality rates were 9.2% in CRUSADE and TIMI bleeders, 25% in GUSTO bleeders and 13% in BARC bleeders (**Figure 1**).

Cox proportional hazard regression adjusted for potential confounders demonstrated that any bleeding was independently associated with 1-year mortality with a more than two-fold risk (HR 2.41 [95% CI 1.17-4.95], p=0.017, **Figure 2**). Models incorporating bleeding status according to the individual classifications confirmed the independent association with excess mortality for BARC bleeding (HR 2.27 [95% CI 1.01-5.11], p=0.048), but not for bleeding classified by CRUSADE (HR 1.62 [95% CI 0.80-3.31],

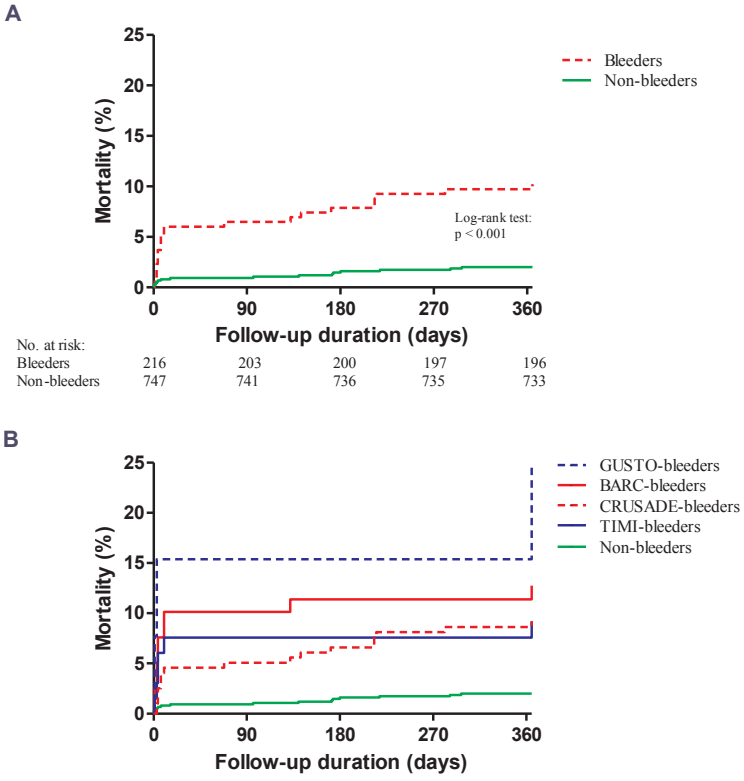

Figure 1. Kaplan-Meier time-to-event curve for 1-year all-cause mortality after in-hospital major bleeding according to A. any classification and B. all individual classifications

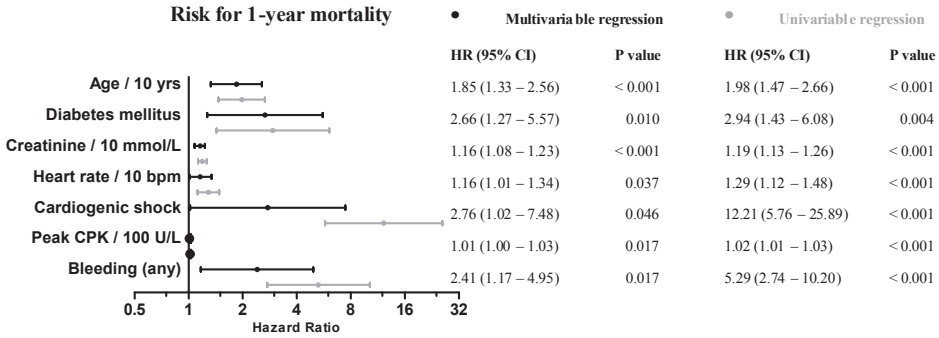

Figure 2. Cox proportional hazard regression for 1-year all-cause mortality
CI = confidence interval; CPK = creatine phosphokinase; HR = hazard ratio.

p=0.18), TIMI (HR 1.23 [95% CI 0.47-3.23], p=0.67) or GUSTO (HR 2.13 [95% CI 0.55-8.32], p=0.28).

Recurrent acute myocardial infarction

During follow-up, 23 patients (2.4%) suffered from recurrent AMI. Median duration to recurrence was 10 days (interquartile range 5-79). In 14 patients (1.5%), recurrent AMI was attributed to the culprit lesion of the index event and in all, but one, due to stent thrombosis. In the remaining nine patients, the culprit lesion was located elsewhere. In these patients, recurrent AMI was attributable to progression of a known lesion (seven), a new lesion (one) or stent thrombosis of a non-culprit lesion (one). All patients suffering from recurrent AMI, except for two, were on full protocol based pharmacotherapy[9] including dual antiplatelet therapy, statins, betablockers and angiotensin-converting-enzyme inhibitors. In two patients, betablockers were contraindicated because of conduction abnormalities. Recurrent AMI was more frequently observed in any bleeders vs. non-bleeders (5.8% vs. 1.5%, p<0.001). With the addition of recurrent AMI to the previously described Cox regression model for 1-year mortality, the relationship between bleeding and mortality remained significant though a minor reduction in hazard ratio of 2.41 to 2.25 (95%CI 1.09-4.64, p=0.028) was observed. Recurrent AMI was independently associated with 1-year mortality as well (HR 4.65 [95%CI 1.83-11.78], p=0.001). Of note, 16 patients (1.7%) were considered lost to clinical follow-up according to definition.

DISCUSSION

Key findings of the present study include: 1) In-hospital major bleeding is frequently observed after primary PCI for STEMI, although the incidence differs depending upon definition as described in the CRUSADE, TIMI, GUSTO and BARC bleeding

classifications. 2) The CRUSADE bleeding risk score is a modest discriminatory tool for bleeding after STEMI. Female gender, admission heart rate, creatinine, multivessel disease, peri-procedural cardiogenic shock and procedural failure were factors shown to be independently related to bleeding. 3) Any in-hospital major bleeding was independently associated with 1-year all-cause mortality. Assessment of individual classifications confirmed the relationship with mortality merely for BARC defined bleeding, stressing its clinical relevance. 4) The excess mortality among bleeders could not be ascribed to the concomitant higher thrombotic risk in these patients.

Incidence and determinants of bleeding

Although innovations in treatment have led to a considerable progression in the prevention of thrombotic events after STEMI, the risk of bleeding complications has simultaneously increased tremendously. Although most trials assessing novel antithrombotic agents currently acknowledge bleeding as a serious adverse event, the reported rates of major bleeding are hardly comparable between trials given the heterogeneity in definitions applied[14]. Data from the present study confirmed the large variability in incidence among different classifications. Interpretation of results would be facilitated by a standardized definition of major bleeding, proven to be clinically relevant regarding prognosis. To individualize treatment for patients particularly prone to bleeding, several studies identified baseline parameters related to in-hospital major bleeding. For identification of such high-risk patients in daily practice, the CRUSADE investigators developed a risk score to estimate the risk of bleeding in non-STEMI patients[3]. Assessment of this risk score in STEMI patients of the present study revealed a modest capacity to discriminate in the risk of bleeding, suggesting that in case of ST-elevation, other or additional factors may play a role in the predisposition for bleeding after AMI. Although the results of the CRUSADE bleeding risk score in this study were not similar to those of the original development and validation non-STEMI cohort, it is noteworthy that area under the curve values in the original cohort were already modest as well. Individual baseline parameters, largely consistent with prior studies[2-4;15], were found to be independently related to in-hospital major bleeding, including female gender, renal failure, admission heart rate and cardiogenic shock (or a substantially identical variable). Remarkably, age, weight and baseline hematocrit were not, nor was a previous stroke/transient ischemic attack. However, the influence of one or more of these factors might be obscured by the evident interaction between female gender and major bleeding, who are generally older, have a lower body weight and more comorbidities including hypertension[16]. In the present study, multivessel disease and procedural failure appeared to be of substantial influence on the incidence of bleeding. These findings may be attributed to 1) a prolonged procedural time and exposure to antithrombotic agents, and 2) more generalized vascular disease. Moreover, whether to treat patients with potent antithrombotic agents (e.g. abciximab), was at the discretion of the operator who might

be more likely to neglect a high risk profile for bleeding after performing a complicated procedure. It is not surprising that in the CRUSADE cohort procedural characteristics were not found to be of predictive value since almost half of the patients did not undergo PCI[3]. Based on findings in this and other studies, bleeding seems to have a multifactorial etiology. Factors consistently identified as correlates of bleeding should be acknowledged as part of a risk profile specifically for bleeding.

Mortality

In line with previous studies[7;17-22], the present study demonstrated that in-hospital major bleeding after primary PCI for STEMI was associated with increased mortality during one year follow-up with a more than two-fold risk. However of all classifications taken separately, only bleeding defined by the BARC classification was shown to independently predict 1-year mortality, in contrast to bleeding defined by CRUSADE, TIMI or GUSTO. The CRUSADE criteria for bleeding are fairly broad, what may explain the limited prognostic implications of the potentially less severe bleeding events as allocated by CRUSADE. The absent impact on adverse outcome of TIMI and GUSTO defined bleeding might more likely be ascribed to the small number of events in these classifications. However, it is remarkable that although the BARC classification employs broader criteria for bleeding compared to TIMI and GUSTO, just this is the one having an independent significant impact on late mortality. This suggests that the strict criteria for bleeding in the TIMI and GUSTO classifications may be too limited and potentially miss prognostically important events. Based on the results of the present study, the BARC definition of major bleeding events appears to be most accurate.

Although literature is quite consistent regarding the increase in mortality after bleeding, the nature of this relationship remains unclear. This study revealed that thrombotic events were significantly more frequent in bleeders. Since major bleeding and thrombotic events share multiple risk factors, a substantial number of STEMI patients are prone to increased risks of both adverse outcomes. It is unclear whether bleeding is merely an indication of advanced arterial disease, resulting in an increase of thrombotic events and subsequent mortality or instead, bleeding itself is the culprit of increased late mortality[23]. The occurrence of a major bleeding event may also affect patient's compliance and physician's clinical decision making, both of which may lead to inadequate antithrombotic therapy. However, the present study demonstrated that the increased hazard for mortality in bleeders was hardly affected when adjusted for the occurrence of a thrombotic event, suggesting that bleeding is of substantial influence on late mortality independent of the concomitant increased thrombotic risk in these patients. Although these results contribute to knowledge in this field, the nature of a potential causal relationship between bleeding and excess mortality remains to be clarified. A possible explanation for late mortality

conferred by bleeding, not involving a hypercoagulable state and thrombosis, might be harmful effects of blood transfusion[23;24]. Major bleeding should primarily be prevented given the magnitude of this emerging problem in current health care. Measures such as radial artery approach to invasive procedures[25], proper dosage of "safer" antithrombotics[26], minimizing sheath diameter[5], the use of vascular closure devices[27] and raised awareness in patients susceptible for bleeding may contribute to a lower incidence.

Limitations

The present study has some limitations. Since the design of the study was observational, we could not account for undocumented clinical variables which may possibly have influenced the outcomes. Although an observational designed study is more prone to bias of any kind, it should be noted that all data were collected prospectively and events were adjudicated by attending cardiologists not involved in the present study. Moreover, an observational study may properly reflect a real-world setting. Secondly, the sample size may possibly be too small for validation of all bleeding classifications. At last, results only apply to in-hospital major bleeding while an increased risk of bleeding may extend beyond the duration of hospitalization.

REFERENCE LIST

(1) Boden H, van der Hoeven BL, Karalis I, Schalij MJ, Jukema JW. Management of acute coronary syndrome: achievements and goals still to pursue. Novel developments in diagnosis and treatment. J Intern Med 2012 Jun;271(6):521-36.

(2) Steg PG, Huber K, Andreotti F, Arnesen H, Atar D, Badimon L, et al. Bleeding in acute coronary syndromes and percutaneous coronary interventions: position paper by the Working Group on Thrombosis of the European Society of Cardiology. Eur Heart J 2011 Aug;32(15): 1854-64.

(3) Subherwal S, Bach RG, Chen AY, Gage BF, Rao SV, Newby LK, et al. Baseline risk of major bleeding in non-ST-segment-elevation myocardial infarction: the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA Guidelines) Bleeding Score. Circulation 2009 Apr 14;119(14):1873-82.

(4) Mehran R, Pocock SJ, Nikolsky E, Clayton T, Dangas GD, Kirtane AJ, et al. A risk score to predict bleeding in patients with acute coronary syndromes. J Am Coll Cardiol 2010 Jun 8;55(23): 2556-66.

(5) Doyle BJ, Ting HH, Bell MR, Lennon RJ, Mathew V, Singh M, et al. Major femoral bleeding complications after percutaneous coronary intervention: incidence, predictors, and impact on long-term survival among 17,901 patients treated at the Mayo Clinic from 1994 to 2005. JACC Cardiovasc Interv 2008 Apr;1(2):202-9.

(6) Spencer FA, Moscucci M, Granger CB, Gore JM, Goldberg RJ, Steg PG, et al. Does comorbidity account for the excess mortality in patients with major bleeding in acute myocardial infarction? Circulation 2007 Dec 11;116(24):2793-801.

(7) 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 Aug 22;114(8): 774-82.

(8) Hochholzer W, Wiviott SD, Antman EM, Contant CF, Guo J, Giugliano RP, et al. Predictors of bleeding and time dependence of association of bleeding with mortality: insights from the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel—Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38). Circulation 2011 Jun 14;123(23):2681-9.

(9) Liem SS, van der Hoeven BL, Oemrawsingh PV, Bax JJ, van der Bom JG, Bosch J, et al. MISSION!: optimization of acute and chronic care for patients with acute myocardial infarction. Am Heart J 2007 Jan;153(1):14-1.

(10) Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. J Am Coll Cardiol 2012 Oct 16;60(16):1581-98.

(11) Rao AK, Pratt C, Berke A, Jaffe A, Ockene I, Schreiber TL, et al. Thrombolysis in Myocardial Infarction (TIMI) Trial—phase I: hemorrhagic manifestations and changes in plasma fibrinogen and the fibrinolytic system in patients treated with recombinant tissue plasminogen activator and streptokinase. J Am Coll Cardiol 1988 Jan; 11(1):1-11.

(12) An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. The GUSTO investigators. N Engl J Med 1993 Sep 2;329(10):673-82.

(13) Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation 2011 Jun 14; 123(23):2736-47.

(14) Quinlan DJ, Eikelboom JW, Goodman SG, Welsh RC, Fitchett DH, Theroux P, et al. Implications of variability in definition and reporting of major bleeding in randomized trials of oral P2Y12 inhibitors for acute coronary syndromes. Eur Heart J 2011 Sep;32(18):2256-65.

(15) Nikolsky E, Mehran R, Dangas G, Fahy M, Na Y, Pocock SJ, et al. Development and validation of a prognostic risk score for major bleeding

in patients undergoing percutaneous coronary intervention via the femoral approach. Eur Heart J 2007 Aug;28(16):1936-45.

(16) Velders MA, Boden H, van Boven AJ, van der Hoeven BL, Heestermans AA, Cannegieter SC, et al. Influence of Gender on Ischemic Times and Outcomes After ST-Elevation Myocardial Infarction. Am J Cardiol 2013 Feb 1;111(3): 312-8.

(17) Mehran R, Pocock S, Nikolsky E, Dangas GD, Clayton T, Claessen BE, et al. Impact of bleeding on mortality after percutaneous coronary intervention results from a patient-level pooled analysis of the REPLACE-2 (randomized evaluation of PCI linking angiomax to reduced clinical events), ACUITY (acute catheterization and urgent intervention triage strategy), and HORIZONS-AMI (harmonizing outcomes with revascularization and stents in acute myocardial infarction) trials. JACC Cardiovasc Interv 2011 Jun;4(6):654-64.

(18) Hermanides RS, Ottervanger JP, Dambrink JH, de Boer MJ, Hoorntje JC, Gosselink AT, et al. Incidence, predictors and prognostic importance of bleeding after primary PCI for ST-elevation myocardial infarction. EuroIntervention 2010 May;6(1):106-11.

(19) Lopes RD, Subherwal S, Holmes DN, Thomas L, Wang TY, Rao SV, et al. The association of in-hospital major bleeding with short-, intermediate-, and long-term mortality among older patients with non-ST-segment elevation myocardial infarction. Eur Heart J 2012 Aug; 33(16):2044-53.

(20) Barthelemy O, Silvain J, Brieger D, Mercadier A, Lancar R, Bellemain-Appaix A, et al. Bleeding complications in primary percutaneous coronary intervention of ST-elevation myocardial infarction in a radial center. Catheter Cardiovasc Interv 2012 Jan 1;79(1):104-12.

(21) Ndrepepa G, Schuster T, Hadamitzky M, Byrne RA, Mehilli J, Neumann FJ, et al. Validation of the Bleeding Academic Research Consortium definition of bleeding in patients with coronary artery disease undergoing percutaneous coronary intervention. Circulation 2012 Mar 20;125(11): 1424-31.

(22) Ndrepepa G, Berger PB, Mehilli J, Seyfarth M, Neumann FJ, Schomig A, 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 Feb 19;51(7): 690-7.

(23) Doyle BJ, Rihal CS, Gastineau DA, Holmes DR, Jr. Bleeding, blood transfusion, and increased mortality after percutaneous coronary intervention: implications for contemporary practice. J Am Coll Cardiol 2009 Jun 2;53(22):2019-27.

(24) Rao SV, Jollis JG, Harrington RA, Granger CB, Newby LK, Armstrong PW, et al. Relationship of blood transfusion and clinical outcomes in patients with acute coronary syndromes. JAMA 2004 Oct 6;292(13):1555-62.

(25) Mehta SR, Jolly SS, Cairns J, Niemela K, Rao SV, Cheema AN, et al. Effects of radial versus femoral artery access in patients with acute coronary syndromes with or without ST-segment elevation. J Am Coll Cardiol 2012 Dec 18;60(24):2490-9.

(26) Alexander KP, Peterson ED. Minimizing the risks of anticoagulants and platelet inhibitors. Circulation 2010 May 4;121(17):1960-70.

(27) Tavris DR, Wang Y, Jacobs S, Gallauresi B, Curtis J, Messenger J, et al. Bleeding and vascular complications at the femoral access site following percutaneous coronary intervention (PCI): an evaluation of hemostasis strategies. J Invasive Cardiol 2012 Jul;24(7):328-34.