



Incidence, predictors and prognostic implications of bleeding complicating primary percutaneous coronary intervention

Učestalost, prediktori i prognozni značaj krvarenja kao komplikacije primarne perkutane koronarne intervencije

Dragan M. Matić*, Milika R. Ašanin[†], Sanja Dj. Stanković[‡], Igor B. Mrdović[†], Jelena M. Marinković[§], Nikola I. Kočev[§], Nebojša M. Antonijević[†], Marija M. Marjanović*, Zorica I. Nešić^{||}, Milica S. Prostran^{||}, Goran R. Stanković^{*†}

*Clinic for Cardiology, [‡]Center for Medical Biochemistry, Clinical Center of Serbia, Belgrade, Serbia;

[†]Faculty of Medicine, University of Belgrade, Belgrade, Serbia; [§]Institute for Medical Statistics and Health Research, ^{||}Department of Pharmacology, Clinical Pharmacology and Toxicology, Faculty of Medicine, University of Belgrade, Belgrade, Serbia

Abstract

Background/Aim. Data about bleeding complicating primary percutaneous coronary intervention (PCI) are more frequently obtained from randomized clinical trials on patients with acute coronary syndromes (ACS), but less frequently from surveys or registries on patients with ST-elevation myocardial infarction (STEMI). The aim of this study was to investigate the incidence, predictors and prognostic impact of in-hospital major bleeding in the population of unselected real-world patients with acute STEMI undergoing primary PCI. **Methods.** All consecutive patients presenting with STEMI who underwent primary PCI at a single large tertiary healthcare center between January 2005 and July 2009, were studied. Major bleeding was defined according to the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) study criteria. We examined the association between in-hospital major bleeding and death or major adverse cardiac events (MACE) in patients treated with PCI. The primary outcomes were in-hospital and 6-month mortality and MACE. **Results.** Of the 770 STEMI patients treated with primary PCI, in-hospital major bleeding occurred in 32 (4.2%) patients. Independent pre-

dictors of major bleeding were advanced age (≥ 65 years), female gender, baseline anemia and elevated white blood cell (WBC) count and signs of congestive heart failure at admission (Killip class II–IV). In-hospital and 6-month mortality and MACE rates were more than 2.5-fold-higher in patients who developed major bleeding compared with those who did not. Major bleeding was a predictor of 6-month MACE, independent of a few risk factors (previous MI, previous PCI, diabetes mellitus and hypertension); (OR = 3.02; 95% CI for OR 1.20–7.61; $p = 0.019$), but was not a true independent predictor of MACE and mortality in the fully adjusted models. **Conclusion:** Patients of advanced age, female gender, with baseline anemia and elevated WBC count and those with Killip class II–IV at presentation are at particularly high risk of bleeding after primary PCI. Bleeding is associated with adverse outcome and may be an important marker of patient frailty, but it is not a true independent predictor of mortality/MACE.

Key words:

angioplasty, transluminal, percutaneous coronary; postoperative complications; hemorrhage; risk factors; prognosis; mortality; fibrinolytic agents.

Apstrakt

Uvod/Cilj. Podaci o krvarenju kao komplikaciji perkutanih koronarnih intervencija (PCI) češće se dobijaju putem randomizovanih kliničkih studija kod bolesnika sa akutnim koronarnim sindromima (ACS), a ređe putem popisa i registara bolesnika sa infarktom miokarda sa ST-elevacijom (STEMI). Cilj ove studije bio je da se ispita učestalost, prediktori i prognozni značaj velikog intrahospitalnog krvarenja kod populacije neselektovanih bolesnika sa STEMI lečenih metodom primarne PCI. **Metode.** U studiju su bili uključeni svi po redos-

ledu primljeni bolesnici sa STEMI, podvrgnuti primarnoj PCI u velikom tercijarnom zdravstvenom centru u periodu između januara 2005. i jula 2009. godine. Veliko krvarenje definisano je prema kriterijumima studije *Global Use of Strategies to Open Occluded Coronary Arteries* (GUSTO). Ispitali smo povezanost između velikog krvarenja nastalog tokom hospitalizacije i smrtnog ishoda, kao i glavnih neželjenih kardijalnih događaja (*major adverse cardiac events* – MACE) kod bolesnika lečenih metodom primarne PCI. Primarni ciljevi bili su bolnički i 6-mesečni mortalitet i glavni neželjeni kardijalni događaji. **Rezultati.** Od 770 bolesnika lečenih metodom primarne PCI,

veliko krvarenje tokom hospitalizacije nastalo je kod 32 (4,2%) bolesnika. Nezavisni prediktori velikog krvarenja bili su odmaklo životno doba (≥ 65 godina), ženski pol, anemija i povećan broj leukocita na prijemu, kao i zastoja srčana insuficijencija klase Killip II–IV. Učestalost bolničke i 6-mesečne smrtnosti i MACE bila je više nego 2,5 puta veća kod bolesnika koji su imali veliko krvarenje nego kod bolesnika bez krvarenja. Veliko krvarenje bilo je prediktor 6-mesečnog MACE, nezavisno od nekoliko faktora rizika (prethodni MI, prethodni PCI, dijabetes melitus i hipertenzija), (OR 3,02; 95% CI 1,20 do 7,61; $p = 0,019$), ali nije bilo nezavisan prediktor MACE u modelu korigovanom za sve faktore rizika.

Introduction

The widespread use of potent antithrombotic and fibrinolytic drugs for treatment of patients with acute coronary syndromes (ACS), coupled with the use of invasive procedures, has considerably reduced rates of recurrent ischemic events and death. However, the uses of multiple antiplatelet agents and anticoagulants have increased the risk of bleeding complications. Rates of bleeding in ACS and primary percutaneous coronary interventions (PCI) trials and registries have been reported to occur in up to 30% of patients^{1,2}. The incidence of major bleeding in recent large randomized trials ranged from as low as 0.2% to as high as 9.1%³.

Most of data refer to bleeding complications among patients presenting with non-ST-elevation ACS (NSTEMI) and those undergoing elective PCI. Much less data reported about bleeding complicating primary PCI^{4–6}. In addition, data about bleeding complicating primary PCI are mostly obtained from randomized clinical studies of specific patients populations; however, limited data obtained from real-world patients with ST-elevation myocardial infarction (STEMI). Both data, from registries and randomized trials, have indicated that bleeding is associated with worse clinical outcomes^{1,7,8}.

The aim of this study was to investigate the incidence, predictors and prognostic impact of periprocedural major bleeding in the population of unselected, consecutive patients undergoing contemporary primary PCI for STEMI in a single high-volume healthcare center in Serbia.

Methods

Study population

We analyzed 770 consecutive STEMI patients who underwent primary PCI between January 1, 2005 and July 30, 2009 at the Cardiology Clinic, Clinical Center of Serbia, Belgrade. Data was obtained from the computerized registry format of the ACS patients admitted to the Coronary Care Unit A, Emergency Center of Belgrade, Serbia.

Study definitions

Acute STEMI definition was based on the history of chest pain/discomfort lasting for at least 20 min attributed to myocardial ischemia, accompanied by persistent ST-segment elevation of ≥ 1 mm in ≥ 2 contiguous limb leads or ≥ 2 mm

Zaključak. Bolesnici odmaklog životnog doba, ženskog pola, sa anemijom i povećanim brojem leukocita na prijemu kao i Killip klasom II–IV su u posebno povećanom riziku od krvarenja posle primarne PCI. Krvarenje je udruženo sa nepovoljnim ishodom i može biti značajan marker bolesnikovog nestabilnog stanja, ali nije u potpunosti nezavisan prediktor smrtnosti i MACE.

Ključne reči:

angioplastika, translumenska, perkutana, koronarna; postoperativne komplikacije; krvarenje; faktori rizika; prognoza; mortalitet; fibrinoliti.

in precordial leads; or presumable new left bundle branch block; or true posterior MI with ST depression of ≥ 1 mm in ≥ 2 contiguous anterior leads⁹.

In this study, major bleeding definition was modified from the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) study criteria to include both severe (life-threatening) and moderate GUSTO bleeding categories^{3,10}. The GUSTO system defines moderate bleeding as the loss of blood requiring blood transfusion and defines severe or life-threatening bleeding as intracerebral bleeding or bleeding resulting in substantial hemodynamic compromise requiring treatment¹⁰.

Re-myocardial infarction (re-MI) was defined using the standard criteria for Q-wave and non-Q-wave myocardial infarction¹¹.

Cardiogenic shock was defined as systolic blood pressure of < 90 mmHg for at least 30 min or when inotropic support was needed to maintain systolic blood pressure over 90 mmHg^{9,12}.

Percutaneous coronary intervention procedure and subsequent antithrombotic medications

All the patients underwent coronary angioplasty and intracoronary stent implantation using standard percutaneous techniques only via the femoral artery. None of the patients had a non-femoral access. Unfractionated heparin (UFH) was administered as an intravenous bolus of 100 IU *per* kilogram of body weight or 50–60 IU/kg, if glycoprotein IIb/IIIa inhibitor (GPI) had given^{12,13}. Aspirin (300 mg orally) was pre-loaded in all the patients, after which 100–300 mg was given orally every day during the first 30 days and 100 mg every day thereafter indefinitely. Clopidogrel was given as a loading dose of 600 mg before insertion of the catheter, and 75 mg orally every day for 1 year^{12,13}. The GPI was administered based on operator discretion. The only GPI used in our study was tirofiban, given as an intravenous bolus of 10 μ g *per* kilogram followed by an infusion of 0.15 μ g *per* kilogram *per* minute, adjusted for renal impairment according to the label, and was continued for 24 hours. After removal of the sheath, hemostasis was secured with manual compression.

End points and follow-up data

The primary composite end point included in-hospital and 6-month mortality from any cause, and in-hospital and 6-

month major adverse cardiac events (MACE). MACE were defined as a composite of death, re-MI, and repeated target vessel vascularization (TVR)¹⁴. Out-of-hospital clinical outcomes were obtained by telephone interviews conducted by educated medical doctors or in the outpatient clinic at 6-month follow-up visit. Follow-up data were available for 89% of the patients at 6 months.

Statistical analysis

Descriptive statistics was computed as mean values and standard deviation (SD) for continuous variables (or median values and interquartile range – IQR if skewed) and as absolute frequencies and percent values for categorical variables. Analysis of normality of the continuous variables was performed with the Kolmogorov–Smirnov test.

The patients were divided into two groups: those with in-hospital major bleeding and those without major bleeding, and also those with in hospital and 6-month death/MACE and those without it. Two group comparisons were performed using independent Student's *t*-test or Mann-Whitney *U*-test for continuous variables and the χ^2 -test for categorical variables. Potential collinearity between variables was assessed using Pearson's correlations.

Multivariate logistic regression analysis was performed to determine the independent predictors of in-hospital major bleeding, as well as in hospital and 6-month death and MACE. The criterion for the entry and removal of variables was set at 0.05 and 0.20, respectively. Only the noncollinear variables that were significant at the 20% level at univariate analysis were included in the multivariate models.

The variables included in the prediction of major bleeding were age, gender and weight; history of myocardial infarction, history of PCI, diabetes mellitus, systemic hypertension, smoking and chronic renal failure; hemoglobin baseline and white blood cell count; Killip class II-IV; use of GPI.

In order to better assess and analyze different groups of possible predictors of mortality and MACE, besides bleeding, three models of logistic regression analysis were developed. The first model was adjusted for demographic variables (age and gender), the second model was adjusted for risk factors (previous MI, previous PCI, diabetes mellitus and hypertension). The third model, termed fully adjusted, was adjusted for any of the additionally important potential confounding variables as age, gender, history of MI, history of PCI, diabetes mellitus and hypertension.

The performance of the multivariate models was studied with respect to discrimination and calibration. Model discrimination was assessed with the *c*-statistic, and model calibration was assessed with the Hosmer–Lemeshow statistic. To test the stability of the stepwise selection process of the regression models and assess the robustness of the variables, the bootstrap resampling procedure (1000 bootstrap samples) was used.

A two-sided *p*-value of 0.05 was considered statistically significant. All analyses were performed using Statistical Package for Social Sciences for Windows, release 18.0.2 (SPSS Inc., Chicago, IL).

Results

Patients' characteristics

Of 770 patients treated with primary PCI because of STEMI, 32 (4.2%) patients developed major bleeding. The patients with major bleeding were older, more frequently female gender and of lower body weight. They also had higher rate of systemic hypertension and chronic renal failure, more likely to have lower level of baseline hemoglobin, and less likely to be current smokers. The patients with major bleeding more often presented with heart failure estimated as Killip class II–IV and elevated white blood cell count compared with those without major bleeding (Table 1).

Table 1

Baseline characteristics of the patients with and without major bleeding

Patients' characteristics	Major bleeding (n = 32)	No major bleeding (n = 738)	<i>p</i>
Mean age (years), $\bar{x} \pm SD$	67.8 $\pm$ 11.3	58.6 $\pm$ 11.2	< 0.0001
Female gender (%)	56.3	24.1	< 0.0001
Previous MI (%)	18.8	12.9	0.337
Previous PCI (%)	3.1	3.4	0.936
Previous CABG (%)	0.0	2.0	0.415
Diabetes mellitus (%)	21.9	15.6	0.340
Systemic hypertension (%)	78.1	61.4	0.05
Current smoking (%)	40.6	62.5	0.01
Chronic renal failure* (%)	60.0	27.3	< 0.0001
Weight (kg), [median (IQR)]	75.0 (68.0, 80.0)	81.0 (73.0, 90.5)	0.002
Hemoglobin at admission (g/dL), [median (IQR)]	13.6 (12.3, 14.4)	14.6 (13.5, 15.5)	< 0.0001
Anemia at admission† (%)	28.1	10.9	0.003
White blood cell count (1,000/mm ³), [median (IQR)]	11.8 (10.2, 15.9)	11.4 (9.2, 13.9)	0.130
Killip class II-IV (%)	25.0	5.4	< 0.0001
Cardiogenic shock (%)	9.4	2.7	0.03

*Chronic renal failure defined as creatinine clearance of < 60 mL/min estimated by the Cockcroft-Gault formula;

†Anemia was defined as hemoglobin levels of < 120g/L for women and < 130 g/L for men; IQR – interquartile range.

MI – myocardial infarction; PCI – percutaneous coronary intervention; CABG – coronary artery bypass grafting.

Angiographic and procedural results

At angiography, patients with major bleeding had similar proportion of right, left and circumflex coronary artery as a target coronary artery, compared with those without major bleeding (Table 2). In the present study, the application of GPI was infrequent and there was no difference in the use of this agent between patients with and without major bleeding.

Predictors of major bleeding

In multivariate logistic regression analysis, predictors of major bleeding in patients undergoing primary PCI were: age > 65 years, female gender, Killip class II–IV, anemia and elevated white blood cell count at admission. The strongest predictor of bleeding was heart failure estimated as Killip class II–IV (Table 3). Chronic renal failure and lower body

Table 2
Angiographic results and additional therapy

Variable	Major bleeding (n = 32)	No major bleeding (n = 738)	<i>p</i>
Target coronary artery (%)			0.642
right coronary artery	50.0	41.7	
left anterior descendent	43.8	45.1	
left circumflex	12.7	6.3	
by-pass graft	0.0	0.4	
Additional therapy (%)			
GP IIb/IIIa inhibitors	21.9	20.6	0.861

Table 3
Predictors of major bleeding

Variable (Major bleeding)	Univariate logistic regression analysis		Multivariate logistic regression analysis	
	OR (95%CI)	<i>p</i>	OR (95%CI)	<i>p</i>
Age ≥ 65 years	4.83 (2.17–10.72)	0.000	2.72 (1.01–7.33)	0.049
Female gender	3.99 (1.86–8.54)	0.000	3.08 (1.20–7.94)	0.020
Current smoking	0.41 (0.19–0.87)	0.021		
Chronic renal failure	3.99 (1.79–8.86)	0.001		
Anemia at admission	3.18 (1.39–7.29)	0.006	3.68 (1.47–9.18)	0.005
WBC per 1000/mm ³				
increase	1.06 (1.02–1.11)	0.008	1.10 (1.03–1.18)	0.003
Body weight per 1 kg				
increase	0.96 (0.93–0.99)	0.004		
Systemic hypertension	2.25 (0.86–5.89)	0.100		
Killip class II–IV, %	5.82 (2.46–13.76)	0.000	5.11 (1.74–15.03)	0.003

WBC – white blood cell count.

Clinical bleeding characteristics

In all the patients with major bleeding, clinical bleeding was identified. According to the bleeding localization, 11 (34.4%) patients had hematemesis, 3 (9.4%) patients developed melena, 7 (21.9%) experienced hematuria, 2 (6.2%) had retroperitoneal bleeding, and 9 (28.1%) had large access site hematoma. Two patients who experienced gastrointestinal bleeding had prior gastritis, but none of them had prior gastric ulcer. Immediately gastroscopy was performed in only one patient showing multiple gastric erosions. The patients with gastrointestinal bleeding had discontinuation of dual antiplatelet therapy and were treated with proton pump inhibitors. Three patients with gastrointestinal bleeding experienced subacute stent thrombosis that occurred after discontinuation of dual antiplatelet therapy. Reintervention was done successfully and all three patients survived the next 6 months. The patients with retroperitoneal hematomas had temporary discontinuation of dual antiplatelet therapy. Among patients with hematuria, discontinuation of dual antiplatelet therapy was evidenced in 1 patient and of clopidogrel in 1 patient, too. Two patients with site hematomas had discontinuation of dual antiplatelet therapy and one patient had discontinuation of clopidogrel only.

weight were found to be predictors of major bleeding by univariate but not by multivariate analysis.

Major bleeding and outcomes

The patients with versus without major bleeding had 3-fold higher rates of in-hospital mortality [9.4 % (cardiac 6.3%, non-cardiac 3.1%) vs 2.8%; *p* = 0.03] and 2.5-fold higher rates of 6-month mortality [15.6% (cardiac 9.4%, non-cardiac 6.2%) vs 5.8%, *p* = 0.03]. The patients with major bleeding had higher rates of in-hospital and 6-month MACE (15.6% vs 6.0%; *p* = 0.03 and 28.1% vs 10.3%; *p* = 0.002, respectively) versus those without major bleeding. All bleeding patients died during the first 6 months of gastrointestinal bleeding.

The association of in-hospital bleeding with in-hospital and 6-month mortality and MACE was evaluated using multivariate regression analysis (Table 4). Three models were used for multivariate analysis. The c-statistics was significant among most of the logistic regression models. The Hosmer-Lemeshow statistics was non significant for all models indicating good model fit, except for risk factors adjusted in-hospital and 6-month mortality. Major bleeding was found to be an important predictor of MACE after six months, inde-

Table 4

Association of in-hospital bleeding with all-cause mortality and MACE during follow up

Parameters	In-hospital		6- month	
	No bleeding	Major bleeding	No bleeding	Major bleeding
All cause mortality events/number at risk	21/717	3/29	38/653	5/32
	Reference	OR (95% CI)	Reference	OR (95% CI)
Unadjusted	1.00	3.53 (1.02–12.22)	1.00	3.00 (0.96–9.36)
Demographic adjusted*	1.00	1.57 (0.39–6.35)	1.00	1.46 (0.40–5.31)
Risk factors adjusted†	1.00	2.75 (0.76–9.98)	1.00	2.50 (0.76–8.25)
Fully adjusted‡	1.00	1.36 (0.30–6.06)	1.00	1.34 (0.35–5.21)
MACE events/number at risk	44/738	5/32	67/653	9/32
	Reference	OR (95% CI)	Reference	OR (95% CI)
Unadjusted	1.00	2.92 (0.93–9.13)	1.00	3.42 (1.40–8.39)
Demographic adjusted*	1.00	1.68 (0.46–6.17)	1.00	2.09 (0.73–5.95)
Risk factors adjusted†	1.00	2.50 (0.82–7.66)	1.00	3.02 (1.20–7.61)
Fully adjusted‡	1.00	1.50 (0.40–5.63)	1.00	1.95 (0.67–5.67)

* Adjusted for age and gender;

† Adjusted for previous myocardial infarction, previous percutaneous coronary intervention, diabetes mellitus and hypertension;

‡ Adjusted for age, gender, previous myocardial infarction, previous percutaneous coronary intervention, diabetes mellitus, hypertension; MACE – major adverse cardiac events.

pendent of a few risk factors (previous MI, previous PCI, diabetes mellitus and systemic hypertension); (OR 3.02, 95% CI 1.20 – 7.61; $p = 0.019$). However, in the fully adjusted model, bleeding was not a predictor of either MACE or mortality.

Discussion

The main findings of our study show that major bleeding occurred in 4.2% of 770 unselected consecutive STEMI patients who underwent primary PCI. The age ≥ 65 years, female gender, anemia and elevated white blood cell count at admission, as well as heart failure (Killip class II-IV) independently predicted major bleeding. Major bleeding was associated with 3-fold-higher in-hospital and 6-months mortality and 2.5-fold-higher MACE rates. In addition, chronic renal failure and lower body weight were found to be predictors of major bleeding in our univariate analysis.

The rates of major bleeding complications are highly variable, generally higher in registries than those of clinical trials^{1,14}. The incidence of bleeding depends mainly on the clinical setting and on the definition of bleeding events². Fuchs et al.⁶ reported major bleeding in 3.5% of 831 consecutive patients underwent primary PCI for STEMI. Kinnaid et al.¹⁵ found major bleeding in 5.4% of 10 974 unselected patient underwent PCI using TIMI classification of bleeding.

In our study, the patients of ≥ 65 years old were at almost 3-fold increased risk of major bleeding compared with younger patients. Manoukian and al.⁸ found that elderly patients (≥ 75 years old) of Acute Catheterization and Urgent Intervention Triage strategy (ACUITY) trial population were at 1.64-fold increased risk of major bleeding. The reasons for the higher bleeding risk in the elderly are likely multifactorial, including reduced renal function, greater sensitivity to anticoagulant agents as well as concomitant peripheral vascular disease with more frequent access site bleeding¹⁶.

In the current study the patients with anemia at admission were at 3.68-fold increased risk of major bleeding.

In trials Randomized Evaluation in Percutaneous Coronary Intervention Linking Angiomax to Reduced Clinical Events-2 (REPLACE) and both ACUITY and Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI), the risk of major bleeding was doubled in patients presenting with baseline anemia^{16,17}. Therefore, more common major bleeding, especially gastrointestinal in anemic patients, emphasizes the importance of a thorough search for predisposing bleeding sites and hemorrhagic diathesis.

Our results show that elevated white blood cell count was strongly associated with in-hospital bleeding, independent of other risk factors. With such increase in white blood cell count *per* 1000 cells/mm³ the patients were in 1.1 higher risk of major bleeding. In both ACUITY and HORIZONS-AMI trials, Mehran et al.¹⁷ presented that higher white blood cell count in patients with STEMI and high-risk ACS treated with PCI predicts in-hospital major bleeding¹⁷. Recent analysis of the HORIZONS-AMI patient population confirmed that elevated baseline white blood cell count ($> 11,000$ *per* 1 mm³) drawn at the time of presentation with STEMI was an independent predictor of infarction size as assessed by peak creatinine phosphokinase level, and of 1-year cardiac mortality, noncardiac mortality, and major bleeding¹⁸. Palmerini et al.¹⁸ discussed that these data suggest that a high level of systemic inflammation in the early phase of STEMI (as reflected by the white blood cell count) is strongly associated with 1-year mortality. Leukocytes may have prothrombotic effects and may also result in release of proinflammatory and vasculotoxic factors which effects may contribute to reperfusion injury and subsequent extension of myocardial necrosis. However, the mechanisms linking high white blood cell count with major bleeding are unknown and warrant further study¹⁸.

Female gender maybe associated with an increased risk for mayor bleeding compared with male gender, bud data are inconsistent^{6,7,19}. The present study provides evidence that women are at 3-fold higher risk of major bleeding after

primary PCI by multivariate analysis. Mehran et al.¹⁷ combined databases of ACUTY (patients with unstable angina or NSTEMI) and HORIZONS-AMI trials and found that female gender was an independent predictor of 2.32-fold increase in major bleeding. The exact mechanisms for the hemorrhagic risk in women are unknown. These findings may be related to smaller vessels size and therefore higher incidence of vascular access-site-related complications. In addition, because of smaller body mass, there is the tendency to over-anticoagulation in women¹⁶.

In the present study renal impairment was associated with major bleeding, but was not found to be an independent predictor of this complication. The reason for this finding could be a small number of participants in our study. In registries and trials which include several thousand patients [Global Registry of Acute Coronary Events (GRACE), REPLACE-2, ACUTY], renal impairment is consistently associated with a high risk of bleeding^{8, 19, 20}.

In this study congestive heart failure at admission estimated as Killip class II-IV was strongly associated with major bleeding. In a randomized clinical study HORIZONS-AMI patients with Killip class II-IV were at 1.78 higher risk of in-hospital major bleeding than patients without congestive heart failure²¹. In the GRACE the risk of bleeding in patients with STEMI and Killip class IV was 1.73-fold higher than in patients with STEMI but without Killip class IV. Hypotension with subsequent tissue hypoperfusion may cause gastritis or ulceration and increase the likelihood of gastrointestinal bleeding. Affecting renal and liver function, hypoperfusion adversely affects the coagulation system and platelet function¹⁵. In our study cardiogenic shock was significantly associated with major bleeding, but was not the independent predictor of major bleeding.

Several scoring systems have been developed to predict major bleeding in patients treated with PCI. Mehran et al.¹⁷ developed a practical integer risk score for NSTEMI and STEMI patients undergoing PCI to predict the risk and implications of major bleeding in ACS. This risk score consists of 7 variables estimated as the independent predictors of major bleeding within 30 days: female sex, advanced age, elevated serum creatinine and white blood cell count, anemia, presentation (STEMI or NSTEMI) and treatment with GPI. Mrdović et al.²² developed a simple and accurate risk model for predicting the risk of 30-day bleeding after primary PCI. The model included 5 independent predictors of bleeding: female gender, history of peptic ulcer, creatinine clearance at admission (< 60 mL/min), hemoglobin at presentation (< 125g/dL), and Killip class II-IV at admission²².

Although several concordant reports have shown that bleeding complicating PCI is associated with increased mortality rates, the association between bleeding and mortality or MACE are as yet poorly understood^{5, 6, 8, 15}. In the combined ACUTY/HORIZONS-AMI data-base, major bleeding was an independent predictor of a 3.2-fold increase in 1-year mortality. The negative impact of bleeding in many

patients who survive the bleeding event itself develops over-time, and is clearly visible at 30 days, but expands to 6 months and beyond^{8, 17}. We observed 3-fold increase in in-hospital and 6-month mortality rates and 2.5-fold higher rates of MACE among patients with major bleeding.

In our study, using multivariate regression analysis, major bleeding was an important predictor of MACE at 6-month follow-up, independent of risk factors such as previous MI, previous PCI, diabetes mellitus and systemic hypertension. However, the important fact is that bleeding was not a true independent predictor of MACE or mortality in the fully adjusted models. What this means it that bleeding is a very important marker of future MACE/mortality, but not the independent predictor and that it is unlikely to be a direct cause. The real possibility is that bleeding is a marker for the frailty of patient and their clinical likelihood of suffering from a poor outcome for other reasons. Indeed, in multivariable analysis, we identified older age, female gender, anemia, elevated white cell count and Killip class II-IV at admission as independent predictors of bleeding. These are all markers of frail, sick patients that are intrinsically more likely to suffer adverse outcome such as MACE or mortality.

Study limitation

Our study had some limitations. First, these study observations were derived from a retrospective analysis, thus had carry the inherent limitations of such mode of evaluation. Second, in anemic patients, a relative lesser drop in hemoglobin would trigger blood transfusion (moderate bleeding according to the GUSTO criteria), but might not actually represent "major bleeding". Third, in our primary PCI procedure, the access was exclusively trans-femoral, and the use of radial access may have changed the finding of this study.

Conclusion

Major bleeding in STEMI patients treated with primary percutaneous coronary intervention is associated with 3-fold-higher in-hospital and 6-month mortality/major adverse cardiac events rates. Patients of advanced age and female gender, those with anemia, elevated white blood cell count and heart failure on admission are at particularly high risk of bleeding. Although major bleeding is the predictor of 6-month major adverse cardiac events independent of some risk factors (previous MI, previous PCI, diabetes mellitus and hypertension), it is not a true independent predictor of major adverse cardiac events or mortality, but may be an important marker for the frailty of patients that are more likely to suffer an adverse outcome.

Conflict of interest

None declared.

R E F E R E N C E S

1. Rao SV, O'Grady K, Pieper KS, Granger CB, Newby L, Mahaffey KW, et al. A comparison of the clinical impact of bleeding measured by two different classifications among patients with acute coronary syndromes. *J Am Coll Cardiol* 2006; 47(4): 809–16.
2. Wallace TW, Rao SV. The challenge of defining bleeding among patients with acute coronary syndromes. *Clin Cardiol* 2007; 30(10 Suppl 2): II16–23.
3. Steinhubl SR, Kastrati A, Berger PB. Variation in the definitions of bleeding in clinical trials of patients with acute coronary syndromes and undergoing percutaneous coronary interventions and its impact on the apparent safety of antithrombotic drugs. *Am Heart J* 2007; 154(1): 3–11.
4. Stone GW, Witzenbichler B, Guagliumi G, Peruga JZ, Brodie BR, Dudek D, et al. Bivalirudin during primary PCI in acute myocardial infarction. *N Engl J Med* 2008; 358(21): 2218–30.
5. Mehran R, Lansky AJ, Witzenbichler B, Guagliumi G, Peruga JZ, Brodie BR, 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(9696): 1149–59.
6. Fuchs S, Kornowski R, Teplinsky I, Brosh D, Lev E, Vakenin-Assa H, et al. Major bleeding complicating contemporary primary percutaneous coronary interventions-incidence, predictors, and prognostic implications. *Cardiovasc Revasc Med* 2009; 10(2): 88–93.
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; 114(8): 774–82.
8. Manoukian SV, Feit F, Mehran R, Voeltz MD, Ebrahimi R, Hamon M, et al. Impact of major bleeding on 30-day mortality and clinical outcomes in patients with acute coronary syndromes: an analysis from the ACUTY Trial. *J Am Coll Cardiol* 2007; 49(12): 1362–8.
9. Van de Werf F, Ardissino D, Betriu A, Cokkinos DV, Falk E, Fox KA, et al. Management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2003; 24(1): 28–66.
10. The GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med* 1993; 329(10): 673–82.
11. Thygesen K, Alpert JS, White HD. Universal definition of myocardial infarction. *Eur Heart J* 2007; 28(20): 2525–38.
12. Van de Werf F, Bax J, Betriu A, Blomstrom-Lundquist C, Crea F, Falk V, et al. Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation: the Task Force on the Management of ST-Segment Elevation Acute Myocardial Infarction of the European Society of Cardiology. *Eur Heart J* 2008; 29(23): 2909–45.
13. Silber S, Albertsson P, Avilés FF, Camici PG, Colombo A, Hamm C, et al. Guidelines for percutaneous coronary interventions. The Task Force for Percutaneous Coronary Interventions of the European Society of Cardiology. *Eur Heart J* 2005; 26(8): 804–47.
14. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, et al. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation* 2007; 115(17): 2344–51.
15. Kinnaird TD, Stabile E, Mintz GS, Lee CW, Canos DA, Gevorkian N, et al. Incidence, predictors, and prognostic implications of bleeding and blood transfusion following percutaneous coronary interventions. *Am J Cardiol* 2003; 92(8): 930–5.
16. 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; 28(16): 1936–45.
17. 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; 55(23): 2556–66.
18. Palmerini T, Mehran R, Dangas G, Nikolsky E, Witzenbichler B, Guagliumi G, et al. Impact of leukocyte count on mortality and bleeding in patients with myocardial infarction undergoing primary percutaneous coronary interventions: analysis from the Harmonizing Outcome with Revascularization and Stent in Acute Myocardial Infarction trial. *Circulation* 2011; 123(24): 2829–37.
19. Manoukian SV, Voeltz MD, Eikelboom J. Bleeding complications in acute coronary syndromes and percutaneous coronary intervention: predictors, prognostic significance, and paradigms for reducing risk. *Clin Cardiol* 2007; 30(10 Suppl 2): 4–34.
20. Chew DP, Lincoff A, Gurm H, Wolski K, Cohen DJ, Henry T, et al. Bivalirudin versus heparin and glycoprotein IIb/IIIa inhibition among patients with renal impairment undergoing percutaneous coronary intervention (a subanalysis of the REPLACE-2 trial). *Am J Cardiol* 2005; 95(5): 581–5.
21. Sub J, Mehran R, Claessen BE, Xu K, Baber U, Dangas G, et al. 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. *J Am Coll Cardiol* 2011; 58(17): 1750–6.
22. Mrdovic I, Savic L, Krjancic G, Asanin M, Lasica R, Djuricic N, et al. Simple risk algorithm to predict serious bleeding in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention: RISK-PCI bleeding score. *Circ J* 2013; 77(7): 1719–27.

Received on February 23, 2014.

Revised on June 8, 2014.

Accepted on June 26, 2014.

Online First October, 2014.