Simple Risk Algorithm to Predict Serious Bleeding in Patients With ST-Segment Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention

– RISK-PCI Bleeding Score –

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**Background:** Bleeding is a potentially catastrophic complication after primary percutaneous coronary intervention (PPCI). It occurs most frequently within the first 30 days following the intervention. The aim of this study was to generate a simple and accurate risk model for the prediction of bleeding after PPCI.

**Methods and Results:** The training set included 2,096 patients enrolled in the RISK-PCI trial. The model was validated using a database of 961 patients enrolled in the ART-PCI trial. Bleeding was defined as type ≥3a bleeding according to the Bleeding Academic Research Consortium definition. Multivariate logistic regression was used to evaluate the predictors of outcome. A sum of weighted points for specific predictors was calculated to determine the final score. The model included 5 independent predictors of 30-day bleeding: gender (female); history of peptic ulcer; creatinine clearance at admission (<60 ml/min); hemoglobin at presentation (<125 g/dl); and Killip class >1 heart failure at admission. The model showed good discrimination and calibration for the prediction of bleeding in the derivation set (C-statistic, 0.79; goodness of fit, P=0.12) and in the validation set (C-statistic, 0.76; goodness of fit, P=0.37). Patients were classified into 3 risk classes and the observed incidence of 30-day bleeding of 1.0%, 3.5% and 10.7% corresponded to the low-, intermediate- and high-risk classes, respectively.

**Conclusions:** A simple risk model was developed that has a reasonably good capacity for the prediction of 30-day bleeding after PPCI. (Circ J 2013; 77: 1719–1727)

**Key Words:** Primary percutaneous coronary intervention; Risk score; Serious bleeding

The aggressive use of antiplatelet and anti-thrombin agents in patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI) has led to an increased risk of bleeding, as the most common non-cardiac complication of therapy.\(^1,2\) A significantly worse outcome has been found in patients with hemorrhagic events after PCI.\(^3,4\) Patients who bleed often have their antiplatelet agents discontinued, which further increases the risk of thrombosis and death.\(^5\) A number of recent reports has found that bleeding in ACS patients is associated with increased risk of death, myocardial infarction and stroke at 30 days,\(^5\) as well as at 6 months and beyond.\(^6-8\) It is noteworthy that not only major bleeding, but also moderate bleeding were significantly associated with 1-year mortality.\(^5,7\)

An accurate bleeding prediction model might help to determine treatment strategies in patients presenting with ST-segment elevation myocardial infarction (STEMI). Measures aimed at reducing the risk of bleeding might also help to reduce the adverse impact of bleeding on clinical outcomes.\(^9,10\) This highlights the importance of taking the risk of bleeding into account before making decisions on management. Because the radial approach appeared to be associated with a

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significant reduction in vascular complications compared with the femoral approach, the predicted risk for bleeding following primary PCI (PPCI) should also influence the decision on access in invasive procedures.

No universally accepted simple risk score exists for the prediction of bleeding in STEMI patients undergoing PPCI. We therefore performed the present study in order to generate and validate a simple risk model for the prediction of bleeding after PPCI.

**Methods**

The training set included data from 2,096 patients enrolled in the RISK-PCI trial between February 2006 and December 2009. The score was validated using a database from 961 patients enrolled in the ART-PCI trial between February 2008 and June 2011. The design and methods of the RISK-PCI and ART-PCI trials have been previously published. Briefly, the RISK-PCI (http://www.controlled-trials.com/ISRCTN83474650) was an observational, single-center trial specifically designed to generate and validate an accurate risk model to predict 30-day major adverse coronary events (MACE) after contemporary PPCI in patients pretreated with 600 mg clopidogrel. The study enrolled 2,096 consecutive patients aged ≥18 years, who presented with clinical and electrocardiographic signs of acute STEMI within 12 h after the onset of symptoms. Independent predictors of MACE at 30 days were assigned a risk score based on their regression coefficients. A patients aged ≥600 mg clopidogrel. The study enrolled 2,096 consecutive patients whose antiplatelet regimen was modified in accordance with platelet reactivity. The trial included 961 consecutive patients aged ≥18 years, who presented with clinical and electrocardiographic signs of STEMI within 12 h after the onset of symptoms. Independent predictors of MACE at 30 days were assigned a risk score based on their regression coefficients. A summary of weighted points for 12 independent predictors was calculated to define the total score for each patient with a range of 0–20. Risk strata with low (0–2.5 points), intermediate (2.5–9 points), high (9–6 points) and very high (≥6 points) risk classes were defined to optimize the discrimination ability of the model.

The aim of the ART-PCI trial (http://www.controlled.trials.com/ISRCTN64082539) was to investigate the impact of high on-treatment platelet reactivity on clinical outcomes in PPCI patients whose antiplatelet regimen was modified in accordance with platelet reactivity. The trial included 961 consecutive STEMI patients. Multiple electrode aggregometry has been used to measure platelet aggregation in response to various agonists. The ART-PCI specified co-primary endpoints were: MACE as an efficacy composite endpoint, and Thrombolysis In Myocardial Infarction (TIMI) major bleeding as a key safety endpoint. Patients were followed up for adherence to antiplatelet therapy and adverse events at 30 days after enrollment.

**Patient Selection and Management**

Both trials enrolled consecutive patients aged ≥18 years, who presented with clinical and electrocardiographic signs of acute STEMI within 12 h after the onset of symptoms. PPCI was performed via a femoral approach, using standard 6F or 7F guiding catheters. Stenting was performed whenever anatomically suitable (ie, vessel ≥2.0 mm in diameter, no excessive tortuosity and no extremely angulated lesions). Angioplasty without stenting was performed in selected patients who were candidates for urgent surgery or who had small, tortuous or highly calcified infarction-related artery. Drug-eluting stents (DES) were encouraged in selected patients with diabetes mellitus and complex lesions (long lesions >20 mm; bifurcation lesions; small vessels <2.75 mm in diameter; in-stent restenosis or saphenous vein grafts). The decision on DES implantation was left at the discretion of the operator. Flow grades were assessed according to TIMI criteria.

Before PPCI, 300 mg aspirin and 600 mg clopidogrel were given. Unfractionated heparin was started as 100 IU/kg bolus (60 IU/kg if glycoprotein (GP)IIb/IIIa receptor inhibitor was used); the 12 IU·kg⁻¹·h⁻¹ infusion followed if clinically indicated (atrial fibrillation; left ventricular [LV] thrombus or aneurysm; recent or recurrent venous thromboembolism; defected sheath removal). A proton-pump inhibitor, pantoprazole, or H2-blocker, ranitidine, were given to selected patients at risk for gastrointestinal hemorrhage. The GPIIb/IIIa receptor inhibitor ticlofiban was encouraged in patients with visible residual thrombus, no (slow) reflow, threatening or acute vessel closure and complex lesions. LV ejection fraction (LVEF) was assessed on echocardiography according to Simpson in classical 2- and 4-chamber apical projections, between 48 h and 72 h from the intervention. Creatinine clearance rate was estimated using the Cockcroft-Gault formula.

**Study Outcomes, Definitions and Follow-up**

Patients were followed up at 30 days after enrollment via scheduled telephone interview and/or outpatient visit. An independent Clinical Event Committee adjudicated the occurrence of major adverse events and bleeding. The primary endpoint was defined as type ≥3 bleed in accordance with the Bleeding Academic Research Consortium (BARC) definition, not related to coronary artery bypass graft surgery. Therefore, bleeding was defined as an overt non-coronary artery bypass graft surgery-related bleed with hemoglobin drop ≥3 g/dl; any transfusion with overt bleeding; cardiac tamponade; bleeding requiring surgical intervention for control; bleeding requiring i.v. vasoactive agents; intracranial bleeding; intracranial bleed compromising vision or fatal bleeding. Secondary endpoints included total mortality, non-fatal reinfarction, non-fatal stroke and definite stent thrombosis at 30 days following PPCI. Non-fatal reinfarction was defined as (1) recurrent ischemic chest pain >20 min; (2) ST deviation >0.1 mV or new pathognomonic Q waves (≥0.04 s) in at least 2 contiguous electrocardiographic leads; and (3) increase of cardiac troponin above the upper reference limit. Stroke was defined as a new onset of focal or global neurological deficit lasting >24 h. Definite stent thrombosis was defined in accordance with the Academic Research Consortium definition as an angiographic or autopsy confirmation of thrombus originating in the stent or in the segment 5 mm proximal or distal to the stent with the presence of ACS within a 48-h time window. Subacute stent thrombosis was defined in a time window from 24 h to 30 days after index procedure.

**Statistical Analysis**

The sample size of 2,096 patients enabled detection of the significant ≥1.80 relative risk of bleeding associated with a study power of 80% at a 2-sided significance level of 0.05, a prevalence of exposure to risk factor of 50% and incidence of 30-day BARC type ≥3 bleeding of 3.4%. Multiple missing data imputation was performed for creatinine, hemoglobin, leukocyte and glycemia (0.5–1.9% of data were missing). The single hot-deck imputation method, which matches individuals with missing data with those having similar values in a set of other variables, was used to estimate the missing values for LVEF. Continuous variables are expressed as median and 25th–75th percentiles, whereas categorical variables are expressed as frequency and percentage. Analysis for normality of data was performed using the Kolmogorov-Smirnov test. Baseline differences between groups were analyzed using the Mann-Whitney test for continuous variables, and Pearson chi-square
multivariate analysis) were transformed into categorical data. Receiver operating characteristics (ROC) curve analysis was used to identify the best threshold values and guide the cut points toward the nearest widely accepted values (hemoglobin 125 g/dl, creatinine clearance 60 ml/min). Bootstrapping based on 1,000 bootstrap samples was applied to the validation set to estimate 95% confidence intervals (95% CIs) for the c-statistics. Risk scores were constructed by dividing the β coefficients for categorical variables. Time-to-event outcomes are presented using Kaplan-Meier curves.

Individual risk factors that were significantly related to the primary endpoint on univariate analysis (P<0.1) were entered into the multiple logistic regression using backward stepwise least-squares elimination with a set to 0.05 for entry into the model and 0.10 for retention in the model. The model was rerun after the continuous variables (independent predictors on Table 1. Baseline RISK-PCI Trial Patient Characteristics vs. Presence of Serious Bleeding

|                          | Bleeding                  | P-value     |
|--------------------------|---------------------------|-------------|
|                          | Yes (n=74)                | No (n=2,022) |
| Demographics             |                           |             |
| Age (years)              | 69 (60–75)                | 59 (51–69)  | <0.001      |
| Female                   | 34 (45.9)                 | 540 (26.7)  | <0.001      |
| Body mass index          | 25.1 (23.7–27.7)          | 26.3 (24.5–29.3) | 0.004      |
| Medical history          |                           |             |
| Diabetes                 | 16 (21.6)                 | 363 (17.9)  | 0.35        |
| Hypertension             | 50 (67.6)                 | 1,316 (65.0) | 0.44       |
| Hyperlipidemia           | 23 (31.1)                 | 992 (49.0)  | 0.004      |
| Current smoking          | 32 (43.2)                 | 1,095 (54.1) | 0.11      |
| MI                       | 10 (13.5)                 | 190 (9.4)   | 0.20        |
| PCI                      | 4 (5.4)                   | 43 (2.1)    | 0.06        |
| Stroke                   | 2 (2.7)                   | 85 (4.2)    | 0.55        |
| Peptic ulcer             | 5 (6.7)                   | 41 (2.0)    | 0.005      |
| Clinical features†       |                           |             |
| Time from symptoms to FMC (h) | 2.7 (1.4–6.0) | 2.5 (1.5–4.0) | 0.56      |
| Systolic blood pressure (mmHg) | 127.5 (105–150) | 140 (120–150) | 0.003  |
| Heart rate (beats/min)   | 80 (60–90)                | 77 (68–88)  | 0.51        |
| Killip >1 heart failure  | 23 (31.1)                 | 237 (11.7)  | <0.001      |
| Electrocardiogram†       |                           |             |
| Anterior infarction      | 30 (40.5)                 | 812 (40.1)  | 0.81        |
| Inferior infarction      | 42 (56.7)                 | 1,212 (59.9) | 0.81      |
| Complete AV block        | 14 (18.9)                 | 91 (4.5)    | <0.001      |
| Atrial fibrillation      | 15 (20.2)                 | 114 (5.6)   | <0.001      |
| Laboratory analysis†     |                           |             |
| Peak creatine kinase (U/L) | 1,818 (928–3,923)    | 1,893 (1,035–3,460) | 0.86 |
| Hemoglobin (g/dl)        | 132 (121–145)             | 143 (132–152) | <0.001  |
| CrCl <80 ml/min          | 32 (44.4)                 | 301 (14.9)  | <0.001      |
| Leukocytes (10 ×10/L)    | 11.4 (9.8–14.7)           | 11.2 (9.3–13.7) | 0.21 |
| Fibrinogen (g/L)         | 4.3 (3.4–5.2)             | 4.0 (3.4–4.9) | 0.35      |
| Platelets (10 ×10/L)     | 235 (196–271)             | 235 (198–273) | 0.97     |
| LVEF (%)                 | 45 (35–50)                | 50 (41–55)  | <0.001      |
| Angiographic features†   |                           |             |
| 3-vessel disease         | 27 (36.5)                 | 536 (26.5)  | 0.04        |
| Left main disease        | 9 (12.1)                  | 135 (6.7)   | 0.06        |
| Pre-procedure IRA occlusion | 57 (77.0)              | 1405 (69.4) | 0.09      |
| Bifurcation lesion       | 4 (5.4)                   | 64 (3.2)    | 0.26        |
| Procedure data†          |                           |             |
| FMC to balloon time (min) | 90 (60.171)              | 82 (40.143) | 0.27       |
| Stent implanted          | 64 (86.5)                 | 1,901 (93.9) | 0.09     |
| DES                      | 5 (6.8)                   | 118 (5.8)   | 0.64        |
| Temporary pacemaker      | 10 (13.5)                 | 50 (2.5)    | <0.001      |
| Post-procedural TIMI flow <3 | 7 (9.5)              | 108 (5.3)   | 0.11        |
| IRA dissection           | 4 (5.4)                   | 41 (2.0)    | 0.04        |

Data given as mean (IQR) or n (%). †At presentation. AV, atrioventricular; CrCl, creatinine clearance; DES, drug-eluting stent; FMC, first medical contact; IRA, infarction-related artery; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; TIMI, Thrombolysis In Myocardial Infarction.
cossitively significant. P<0.05 was considered statistically significant.

IBM SPSS version 19 was used for statistical analysis. P<0.05 was considered statistically significant.

Outcome. Low, intermediate, and high classes of risk were defined using classification tree analysis to optimize the discrimination ability of the model. The accuracy of the estimates of probability of risk was assessed using the Hosmer-Lemeshow chi-square test. Discrimination of the model was measured by the area under the ROC curve (AUC) as an index of model performance. Agreement or difference between predicted and observed events (goodness of fit) was assessed using the Hosmer-Lemeshow chi-square test. Sensitivity analysis was also done to investigate the effect of significant covariates from univariate analysis (Table 1) that did not enter the score. The accuracy of the estimates of probability was described in terms of the Brier accuracy score, which directly measures how close the prediction is to the observed outcome. Low, intermediate, and high classes of risk were defined using classification tree analysis to optimize the discrimination ability of the model. IBM SPSS version 19 was used for statistical analysis. P<0.05 was considered statistically significant.

Results

Patient Characteristics

Baseline patient characteristics according to 30-day bleeding status are listed in Table 1. Patients with bleeding were older, more frequently female with a history of peptic ulcer. They presented more often with atrial fibrillation, heart failure, complete atrioventricular block, lower body mass index, systolic blood pressure, EF, hemoglobin level and creatinine clearance at admission. Angiographic and procedural features were also less favorable in the bleeding group. Medical treatment during hospitalization in the coronary unit is given in Table 2.

Thirty-day bleeding occurred in 74 patients (3.5%) in the derivation set and in 28 (2.9%) in the validation set. The most frequent overt bleeding was gastrointestinal hemorrhage and bleeding from the femoral access site (Table 3). Bleeding was fatal in 3 patients (0.1%). Immediate surgery was necessary in 7 (0.3%). I.v. vasoactive agents were used in 4 patients (0.2%), and endoscopic management of bleeding was necessary in 1 (0.5%). One patient had intracranial bleeding.

The time distribution of bleeding is shown in Figure 1. Fifty-four per cent of total bleeds occurred within 24 h from admission, 19% occurred within 48 h, and 9% occurred within 72 h from presentation. Fifty-three per cent of gastrointestinal bleeds and 58% of bleeds from the access site occurred within first 24 h from presentation.

Antiplatelet therapy was withdrawn because of bleeding in 31 patients (aspirin was withdrawn in 14 patients, clopidogrel in 2 patients, and both aspirin and clopidogrel were withdrawn in 15 patients). After the control of bleeding, aspirin and/or clopidogrel were restarted in 14 patients (aspirin was restarted in 7 patients, clopidogrel in 1 patient and both agents were restarted in 6 patients). Kaplan-Mayer curves according to bleeding showed a much higher cumulative hazard for 30-day mortality, non-fatal infarction, non-fatal stroke and definite subacute stent thrombosis (DST) in the bleeding group, compared to the non-bleeding control (Figure 2).

Score Development and Validation

Risk score for the prediction of 30-day bleeding was developed using a derivation set of 2,096 patients enrolled in the RISK-PCI trial. Multivariate logistic regression identified 5 independent predictors of 30-day bleeding: gender (female); history of peptic ulcer; creatinine clearance (<60 ml/min) at admission; hemoglobin at presentation (<125 g/dl); and Killip class >1 heart failure at admission (Table 4).

The algorithm used to determine the predicted probability of a 30-day bleed corresponding to total risk points and risk classes is shown in Figure 3.

All variables included in the final model fulfilled the criteria for absence of serious multicollinearity (detection tolerance >0.2, variance inflation factor <10, condition index <30). Sensitivity analyses indicated that the derived score was robust (OR, 1.65; 95% CI: 1.48–1.84; P<0.001, Wald 77.88).

The independent predictors of bleeding at 30 days were assigned a risk score based on their regression coefficients (Table 4). A sum of weighted points for the 5 independent predictors was calculated to define the total score for each

| Table 2. Medical Treatment During Hospitalization in the Coronary Unit |
|-----------------------------|-------------|------------|-----------|
|                          | Percentage | No bleeding | P-value   |
| Tirofiban                  | 39 (52.7)  | 848 (41.9) | 0.07      |
| Heparin                    | 17 (23.0)  | 144 (71.1) | <0.001    |
| β-blocker                  | 40 (54.1)  | 1,755 (86.7)| <0.001   |
| ACEI                       | 36 (48.7)  | 1,455 (71.9)| <0.001   |
| Statins                    | 50 (67.6)  | 1,906 (94.2)| <0.001   |
| Diuretics                  | 27 (36.5)  | 290 (14.3) | <0.001    |
| Digitalis                  | 9 (12.2)   | 54 (2.7)   | <0.001    |
| Inotropes                  | 30 (40.5)  | 113 (5.6)  | <0.001    |
| Anti-arrhythmics           | 10 (13.5)  | 106 (5.2)  | 0.03      |
| PPIs or H2RAs              | 10 (13.5)  | 62 (3.1)   | <0.001    |

ACEI, angiotensin-converting enzyme inhibitor; H2RA, H2-receptor antagonist; PPI, proton-pump inhibitor.

Table 3. Source of Bleeding and Treatment During 30-Day Follow-up

| Hb drop (d/L) | Gastrointestinal | Puncture site† | Retroperitoneal | Others | No obvious site | Intracranial | VAA | Transfusion | EM | Surgery | Fatal |
|---------------|------------------|----------------|-----------------|--------|----------------|--------------|-----|-------------|----|---------|-------|
| ≥5            | 14               | 8              | 5               | 6      | 1              | 1            | 8   | 3           | 19 | 2       | 1     |
| 3–5           | 18               | 20             | 1               | 6      | 1              |              | 20  | 2           | 14 | 2       |       |
|               |                  |                |                 |        |                |              |     |             |    |         |       |
| Total         | 28               | 46             | 7               | 38     | 1              |              |     |             |    | 7       | 3     |

†Femoral approach. EM, endoscopic management of bleeding; Hb, hemoglobin; VAA, vasoactive agents.
Figure 1. Time distribution of bleeds.

Figure 2. Kaplan-Meyer curves according to serious bleeding for 30-day mortality, non-fatal reinfarction (RelM), stroke (CVI) and definite subacute stent thrombosis (DSST).
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indicated good calibration of the model. The score was predictive for access site-related bleeds (AUC, 0.80; 95% CI: 0.73–0.88; goodness of fit, $\chi^2=3.37$, $P=0.34$) as well as for bleeds not related to access site (AUC, 0.77; 95% CI: 0.69–0.84, goodness of fit, $\chi^2=6.10$, $P=0.11$). Estimates of probability of bleeding were reasonably accurate (mean Brier accuracy score $0.13 \pm 0.04$).

Risk Stratification

We classified the patients into 3 risk strata for bleeding, and identified a 1.0%, 3.5% and 10.7% incidence of observed 30-day bleeding in the low-risk (0 points), intermediate-risk (1–2 points) and high-risk ($\geq 3$ points) classes, respectively. Mean predicted probability of bleeding according to risk class is shown in Figure 3. The corresponding mortality at 30 days according to risk class was 1.7%, 5.2% and 14.6%, respectively. An 11-fold graded increase in the primary endpoint was observed between patients in the low-risk class and those in the high-risk class, $P(trend)<0.0001$. The c-statistic of the 3-strata model was 0.75 (95% CI: 0.70–0.81) for 30-day bleeding in the derivation set and 0.74 (95% CI: 0.65–0.84) in the validation set. The non-significant goodness-of-fit estimates for 30-day bleeding in the derivation set ($\chi^2=0.20$, $P=0.88$) and in the validation set ($\chi^2=0.03$, $P=0.95$) indicated good calibration of the 3-strata model.

Discussion

The present trial derived 5 independent predictors of bleeding at 30 days after PPCI. The model’s discrimination and calibration for the prediction of bleeding and TIMI major bleeding was reasonably good. Furthermore, this analysis has demonstrated the significant adverse impact of bleeding on 30-day mortality, non-fatal reinfarction, ischemic stroke and DSST after PPCI. Bleeding in the present analysis was classified using the BARC diagnostic criteria, allowing for comparisons with other studies.$^{16}$ Bleeding occurred in 2.9–3.5% of the present patients, which is in accordance with the pooled data from previous studies suggesting that the risk of bleeding is between 1% and 6%.$^{4,5,16,17}$ The rate of bleeding reported in registries, however, is higher than that of clinical trials.$^{3,18}$

The gastrointestinal tract was the most common source of bleeding in the present study. Data from recent trials showed that dual antiplatelet therapy increased the rate of major gastrointestinal bleeding in the year after a PCI, compared with aspirin monotherapy.$^1$ Analysis of patients experiencing gas-

### Table 4. Independent Predictors of 30-Day Serious Bleeding

| Risk factor                              | B     | OR    | 95% CI   | P-value | Score points | Bootstrap P-value | Bootstrap 95% CI |
|-----------------------------------------|-------|-------|----------|---------|--------------|-------------------|-----------------|
| Demographic                             |       |       |          |         |              |                   |                 |
| Female gender                           | 0.62  | 1.86  | 0.99–3.47| 0.05    | 1            | 0.02              | 0.02–1.85       |
| Medical history                         |       |       |          |         |              |                   |                 |
| Peptic ulcer                            | 0.89  | 2.43  | 1.01–7.51| 0.04    | 1            | 0.05              | 0.10–2.53       |
| Laboratory values at presentation       |       |       |          |         |              |                   |                 |
| Creatinine clearance <60 ml/min         | 1.16  | 3.21  | 1.83–5.34| <0.001  | 2            | 0.03              | 0.07–1.86       |
| Hemoglobin <125 g/dl at presentation    | 1.02  | 2.82  | 1.69–4.70| 0.0001  | 2            | 0.007             | 0.06–1.87       |
| Heart failure at presentation           |       |       |          |         |              |                   |                 |
| Killip class $>$1                       | 1.06  | 2.89  | 1.71–4.87| <0.001  | 2            | 0.02              | 0.07–1.45       |
| Constant                                | −4.28 |       |          |         |              |                   | −4.19 to −4.59  |

B, regression coefficient; CCU, coronary care unit; CI, confidence interval; OR, odds ratio.

The score showed a strong association with bleeding observed at 30 days, with a graded 33-fold increase in 30-day bleeding with increasing risk score from 0 (1%) to 7 (33.3%; $P<0.0001$). The model’s discrimination for the prediction of 30-day bleeding, tested on c-statistic, was reasonably good in the derivation group (c-statistic, 0.79; 95% CI: 0.72–0.85, $P<0.001$) and in the validation group (c-statistic, 0.76; 95% CI: 0.67–0.86, $P<0.001$).

In addition, the non-significant Hosmer–Lemeshow goodness-of-fit estimates for 30-day bleeding in the derivation set ($\chi^2=4.49$, $P=0.12$) and in the validation set ($\chi^2=3.17$, $P=0.37$)
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Table 5. Variables Included in the RISK-PCI Score for Bleeding in and/or Other Risk Models for Bleeding in Patients Presenting With ACS Undergoing PCI

| Authors            | Mehta et al | Kinnaird et al | Nikolsky et al | Subherwal et al | Fuchs et al | Hermanides et al | Pocock et al |
|--------------------|-------------|----------------|----------------|-----------------|-------------|------------------|-------------|
| Bleeds Patients    | Serious ACS | Major ACS      | Major ACS      | Major AIM       | Major STEMI | Major Minor STEMI | Major ACS + STEMI |
| Variables          |             |                |                |                 |             |                  |              |
| Female gender†     | +           | +              | +              | +               | +           |                  |              |
| Heart failure†     | +           | +              | +              | +               | +           |                  |              |
| Basal anemia†      | +           | +              | +              | +               | +           |                  |              |
| Renal dysfunction† | +           | +              | +              | +               | +           |                  |              |
| Age                | +           | +              | +              | +               | +           |                  |              |
| Low blood pressure | +           | +              | +              | +               | +           |                  |              |
| Prior peripheral VD| +           | +              | +              | +               | +           |                  |              |
| IABP               | +           | +              | +              | +               | +           |                  |              |
| GPI IIB/IIIa inhibitors | +   | +              | +              | +               | +           |                  |              |
| Anticoagulants     | +           | +              | +              | +               | +           |                  |              |

†Included in the RISK-PCI score for bleeding. ACS, acute coronary syndrome; CV, cerebrovascular; GPI, glycoprotein inhibitor; IABP, intra-aortic balloon pump; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

Gastrointestinal bleeding reported mortality up to 5.4% in ACS patients and up to 10% in PPCI patients. Furthermore, proton-pump inhibitors are likely to reduce only upper gastrointestinal bleeding. This is consistent with the present finding that despite the use of protective doses of H2 blockers or proton-pump inhibitors in all patients at risk for gastrointestinal bleeding, the history of peptic ulcer remained an independent predictor of bleeding in the present trial.

Variables incorporated into the RISK-PCI score for bleeding and other bleeding risk models in patients presenting with ACS and/or STEMI undergoing PCI are shown in Table 5. Importantly, none of the previously published models examined bleeding in accordance with BARC classification. Some scores analyzed ACS patients while some models examined STEMI patients undergoing PPCI. Furthermore, a majority of models examined the occurrence of serious or major bleeds, but some scores included major and minor bleeding events.

We created a simple risk score consisting of only 5 clinical and laboratory variables that can be easily obtained upon patient presentation. Some risk models incorporated angiographic and interventional variables, which have made their scores more difficult to obtain. Other more complex models included significantly more variables compared with the present model. Nevertheless, the present score performed comparably with other risk models shown in Table 5.

The present study identified a number of independent correlates of bleeding. These include female gender, heart failure at presentation, baseline renal function and anemia at presentation, all of which are of known prognostic significance. Importantly, some variables that were incorporated into the present risk model, such as history of peptic ulcer, have not been shown previously to predict bleeding in patients undergoing PPCI. The present model, however, did not include some risk factors for bleeding previously identified in ACS patients. Because the goal was to develop a prediction model that would facilitate decision-making on the most adequate treatment at patient presentation, the variables related to medical therapy following PPCI were not included in the analysis. Therefore, we did not assess the impact of periprocedural tirofiban on 30-day bleeding. Prior analyses have demonstrated that the use of i.v. GPIIb/IIIa inhibitors almost doubled the rate of non-intracranial bleeding complications, predominantly from the gastrointestinal tract. Moreover, the use of GPIIb/IIIa inhibitors has been incorporated in some risk models for bleeding after PCI. In addition, major bleeding was higher in the upstream GPIIb/IIIa inhibitor arm under 600-mg clopidogrel pretreatment compared with provisional use in STEMI. In multivariate analysis, the use of heparin after PPCI did not appear to be an independent predictor of bleeding in the present study. Other authors have shown that early use of heparin resulted in improved initial TIMI flow grade, angiographic thrombus burden and rate of slow-flow during the primary angioplasty procedure. But, as in the present study, the use of heparin did not reduce the rate of in-hospital adverse cardiac events. In addition, women, older patients and patients with body mass index <25 had a higher risk of being over-anticoagulated during treatment with heparin.

Heart failure at presentation was a powerful predictor of bleeding in the present study. Indeed, LVEF <30% was an independent predictor of periprocedural bleeding after PCI in the EXCITE trial. Also, LVEF (OR, 0.65 per 10% increase) was a predictor of late severe bleeding after PCI in the BASKET trial. In addition, pre-existing anemia has been shown to predict major bleeding in previous models.

Implications

A simple and accurate risk model might help clinicians to stratify individual STEMI patients according to risk of bleeding, thus ensuring that the most effective treatment options are considered. Patients in the low-risk class might be treated via a femoral approach, using bare-metal stent or DES and optimal doses of antiplatelet drugs. In contrast, patients in the high-risk class should be treated preferably with bare-metal stents and/or a radial approach, which appeared to be associated with a significant reduction in vascular complications compared with the femoral approach. Concerning anti-thrombotic drugs, the excessive doses and more potent thienopyridines should be avoided; doses should be adjusted for renal function; and bivalirudin might be used in place of heparin and GPIIb/IIIa inhibitor. Furthermore, unnecessary co-inter-
ventions should be avoided, and the prevention of gastrointestinal hemorrhage in patients at high risk for gastrointestinal bleeding is essential. A radial approach to PCI and the use of smaller sheath sizes should be considered in those patients.

Study Limitations

The potential limitations of this study should be considered. First, the model requires further external validation in order to be generally applied to a broader sample of STEMI patients. Second, due to the presence of many significant differences between the present patients with and without bleeding, certain unmeasured confounders of bleeding may not be controlled for in the multivariate analysis. Third, although the observed rate of bleeding in the present study was similar to that observed in the recent large PCI trials, we cannot for sure exclude underreporting of minimal bleeding events. In addition, patients with cardiogenic shock were excluded from the study, but cardiogenic shock was a predictor of major hemorrhage in some risk models for bleeding.\(^\text{18}\) Next, we did not collect data on the past history of bleeding, which was a predictor of bleeding in some risk models.\(^\text{19}\) In addition, we used the femoral approach in the majority of the present patients. Therefore, the score should not be applied to patients who are treated exclusively by a radial approach. We also did not use bivalirudin in the acute phase of STEMI, which was used the femoral approach in the majority of the present patients. Moreover, ticagrelor and prasugrel were not approved in Serbia at the time of patient enrollment. Only 6% of the present patients were treated invasively with DES, therefore the present results apply mainly to patients with bare-metal stents. Next, because a modified antplatelet regimen was used in the ART-PCI trial, a lower rate of bleeding in this trial was registered compared with the RISK-PCI trial. Last, because thrombus aspiration was used only sporadically in the RISK-PCI trial, it was not analyzed in univariate analysis as a separate variable.

Conclusions

A novel simple risk model for the prediction of 30-day bleeding after PCI has been derived using a femoral approach. An accurate prediction of this potentially catastrophic complication following PCI might help physicians to consider the available prevention strategies. It can also aid the choice of the most balanced therapeutic option, targeting the reduction of bleeding and improving the short- and long-term prognosis.

Author Contributions

I.M. had full access to all of the data in the study and takes responsibility for the integrity of the data, study concept and design. L.S., M.A., J.P., R.L., N.D. and N.B. participated in the acquisition of data. J.M. and N.K. performed statistical analysis. I.M., L.S. and M.A. drafted the manuscript. J.M., N.K. and J.P. participated in the analysis and interpretation of data. All authors contributed to the final version of the manuscript.

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Disclosures

The authors report no conflicts of interest in this work.

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