Major bleeding events in Jordanian patients undergoing percutaneous coronary intervention (PCI): Incidence, associated factors, impact on prognosis, and predictability of the CRUSADE bleeding risk score. Results from the First Jordanian PCI Registry (PCR1)

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ABSTRACT

Objective: Determine the incidence of major bleeding events, their risk factors, and their impact on prognosis in Jordanian patients undergoing percutaneous coronary intervention (PCI). Evaluate the ability of the CRUSADE bleeding risk score (BRS) to predict major bleeding.

Methods: Major bleeding events were defined according to the CRUSADE classification and their incidence was evaluated from hospital admission to one year of follow-up. The CRUSADE bleeding risk score was calculated for each patient during the index admission. Incidence of major bleeding events was evaluated in each of the bleeding score quintiles. JoPCR1 is a prospective, observational, multicenter registry of consecutive patients who underwent PCI at 12 tertiary care centers in Jordan. A case report form was used to record data prospectively at hospital admission, at discharge, and at 1 and 12 months of follow-up.

Results: The study included 2426 consecutive patients who underwent PCI. During the index hospitalization, major and minor bleeding events occurred in 0.95% and 2.6% of patients, respectively. Multivariate analysis showed that only two variables were significantly associated with major bleeding: female gender (OR=3.7; 95% CI 1.6, 8.5; p=0.002) and past history of cardiovascular disease (OR=2.6; 95% CI 1.1, 5.9; p=0.026). Patients who had in-hospital major bleeding events had higher cardiac mortality during index hospitalization (13.0% vs. 0.7%, p<0.005) and at one year of follow up (13.0% vs. 1.8%, p<0.005) compared to those who had no such events. Receiver operating characteristic curve analysis showed that the CRUSADE BRS has a high ability to predict major bleeding.

Conclusion: Major bleeding events were uncommon in this ME registry of a contemporary cohort of patients undergoing PCI but were associated with a higher mortality rate compared with those who did not have major bleeding events. CRUSADE BRS was highly predictive of the incidence of major bleeding events. (Anatol J Cardiol 2017; 17: 445-51)

Keywords: major bleeding events, percutaneous coronary intervention, CRUSADE bleeding risk score

Introduction

Bleeding is the most important non-ischemic complication after percutaneous coronary intervention (PCI) and can potentially lead to significant mortality and morbidity (1–3). Predicting the risk of major bleeding events in patients undergoing PCI is an essential component of an effective and safe PCI procedure (4, 5). Several bleeding risk scores (BRSs) including the Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines (CRUSADE) BRS have been demonstrated to accurately predict risks of major bleeding events (6–11).

The predictive value of the CRUSADE BRS might not apply to patients admitted with acute coronary syndrome (ACS) and/or undergoing PCI in regions other than those where the risk score was developed or tested due to differences in baseline clinical features and/or availability of medical and invasive therapeutic strategies. The objective of this study (the First Jordanian PCI Registry (JoPCR1)) was to determine the incidence of major bleeding events, their risk factors, and their impact on prognosis in Jordanian patients undergoing PCI. The ability of the CRUSADE BRS to predict major bleeding was also evaluated.
Methods

JoPCRI is a prospective, observational, multicenter registry of consecutive patients who underwent PCI at 12 tertiary care Amman Surgical Hospital, Amman, Jordan; Arab Medical Center, Amman, Jordan; Essra Hospital, Amman, Jordan; Ibn Haitham Hospital, Amman, Jordan; Islamic Hospital, Amman, Jordan; Istishari Hospital, Amman, Jordan; Jordan Hospital, Amman, Jordan; Jordan University Hospital, Amman, Jordan; Khalidi Medical Center, Amman, Jordan; King Abdullah University Hospital, Irbid, Jordan; Prince Hamza Hospital, Amman, Jordan; Specialty Hospital, Amman, Jordan, in two major cities of Jordan (Amman and Irbid) between January 2013 and February 2014. A case report form was used to record data prospectively at hospital admission, at discharge, and at 1 and 12 months of follow-up. Data were collected during follow-up visits or phone calls to the patient, a household relative, or a primary care physician at 1, 6, and 12 months after discharge. The study was approved by the Institutional Review Board of each participating hospital. Baseline data included clinical, laboratory, electrocardiographic, echocardiographic, and coronary angiographic features. Details of the PCI procedure and its outcome were also recorded. Creatinine clearance (CrCl) was estimated using the Cockcroft-Gault equation (12).

All PCI procedures were performed according to current standard guidelines. The arterial access site, type and number of stents, and the use of intravenous glycoprotein inhibitors (GPI) IIb/IIIa inhibitors were left to the operator’s discretion. All patients received dual oral antiplatelet therapy (aspirin and 300–600 mg clopidogrel or 180 mg ticagrelor loading dose, and a loading dose of unfractionated heparin (100 IU/kg body weight). The activated clotting time was maintained >300 seconds throughout or immediately at the conclusion of the PCI procedure. PCI was indicated for either ACS or stable coronary disease (SC). ACS was classified as (1) acute ST-segment elevation myocardial infarction (STEMI); defined by the presence of cardiac ischemic chest pain, ST-segment elevation of >2 mm in at least 2 contiguous leads on the 12-lead electrocardiogram (ECG), and elevated cardiac biomarkers (troponin or creatinine kinase-myocardial band) greater than the upper limit of the normal, or (2) non-ST elevation ACS (NSTEMI), which included non ST-segment elevation MI (NSTEMI); defined by the presence of cardiac ischemic chest pain, ST-segment depression, inverted T wave or normal ECG, and elevated cardiac biomarkers as above, and (3) unstable angina (UA); defined by the presence of ischemic cardiac pain, ST-segment depression, inverted T wave or normal ECG, and no elevation of cardiac biomarkers on admission and 8–12 hours later. SC was defined by the presence of either (1) chronic stable angina (CSA); i.e., ischemic cardiac pain on effort that did not change in severity for the past 3 months, and absence of resting ECG ischemic changes or elevated cardiac biomarkers, or (2) silent ischemia (SI); defined by the absence of angina in the presence of signs of myocardial ischemia on ECG, echocardiography, or nuclear myocardial scan.

PCI for STEMI was (1) primary, i.e., PCI as reperfusion strategy with no thrombolysis, (2) rescue; after failure of thrombolysis, or (3) elective; after successful thrombolysis. PCI for NSTEMI was (1) urgent, i.e., done within 2 hours after admission for ongoing chest pain, hemodynamic instability, life-threatening ventricular arrhythmia, or heart failure, (2) early invasive; within 24 hours after admission, or (3) invasive; within 24–72 hours after admission.

Major bleeding events were defined according to the CRUSADE study classification (6) and included intracranial hemorrhage, retroperitoneal bleeding, haematocrit (Hct) drop >12% from baseline, any red blood cell (RBC) transfusion when baseline Hct was >28%, or any RBC transfusion when baseline Hct was <28% with witnessed bleeding. Minor bleeding was defined as any non-major bleeding. Cardiac mortality was defined as any death not attributed to a clear noncardiac cause.

The CRUSADE BRS was calculated for each patient by assigning certain number of points for weighted integers of each of the eight independent predictors of in-hospital major bleeding events. These predictors include the patient’s features [gender, diabetes mellitus (DM), and peripheral arterial disease (PAD)], clinical variables [heart rate (HR), systolic blood pressure (SBP), and heart failure], and admission laboratory data (Hct and CrCl). The sum of these points comprises the patient’s score that ranges from 1 to 100 (6). The scores of all patients were grouped into 5 quintiles, Q1; very low risk, Q2; low risk, Q3; intermediate risk, Q4; high risk, and Q5; very high risk. Incidence rates of major and minor bleeding events and cardiac mortality were assessed during admission and after 1 and 12 months of follow up.

Statistical analysis

Data were described using mean values [±standard deviation (SD)] for continuous variables, frequencies, and percentages for categorical variables. The differences between proportions were tested using chi-square tests and the differences between two means were analyzed using independent t-test. Multivariate analysis of factors associated with in-hospital major bleeding was performed using logistic regression analysis. The variables were included in the model step by step and those with p<0.10 in the univariate analysis were included in the model. Receiver operating characteristic (ROC) curve analyses were used to examine the overall discriminatory power of CRUSADE BRS to predict in-hospital major bleeding. The overall performance of the CRUSADE BRS was assessed by calculating the area under the curve (AUC). A p value of <0.05 was considered statistically significant. Statistical analyses were performed using the IBM SPSS 20 (SPSS Inc., Chicago, USA).

Results

Patients' characteristics

The study included 2426 consecutive patients who underwent PCI and were followed up for one year. Follow up information was obtained directly from patients in 92% (clinic visits in
45% and by phone calls in 47%), from primary care physicians in 6%, and from household relatives in 2%.

Their baseline demographic and clinical characteristics at admission are shown in Table 1. Of the whole group, 24.7% were <50 years old, 48% had DM, and 77.4% were overweight or obese. 77.1% had ACS as the admission diagnosis. Table 2 shows the coronary arteriography findings, PCI procedures and indications, and medications used during hospitalization and at discharge. The vascular access was the femoral artery in the majority of procedures. Dual antiplatelet agents and GPI were administered in 99% and 13.5% of patients, respectively. Only 3.3% of patients were treated with thrombolysis.
Incidence rate of bleeding

The incidence rates of major and minor bleeding events among the studied patients are detailed in Table 3. During the index hospitalization, major and minor bleeding events occurred in 0.95% and 2.6% of patients, respectively. Most of the major bleeding events were transfusion-requiring or associated with an Hct drop (19/23 (82.6%). All vascular access bleeding events were minor. In-hospital major bleeding among patients who received thrombolytic agents (2.5%) was not different from that among patients who did not receive thrombolysis (0.9%), p=0.39. At one year, the incidence rate of major bleeding events was 1.29%, which implied that only a small number of patients had bleeding events after discharge up to 1 year of follow up. Patients who had PCI for ACS had more major bleeding events than patients with stable coronary disease (1.1% vs. 0.5%), but this observation was not significant (p=0.53).

Factors associated with in-hospital major bleeding

The incidence rates of in-hospital major bleeding according to significant variables in univariate analysis are shown in Table 4. Major bleedings during hospitalization were significantly higher among females, patients older than 65 years, and those who have diabetes, hypertension, CrCl <90, or past PCI. Multivariate analysis showed that only two variables were significantly associated with major bleeding: female gender (OR=3.7; 95% CI 1.6, 8.5; p=0.002) and past history of cardiovascular disease (OR=2.6; 95% CI 1.1, 5.9; p=0.026).

Major bleeding and cardiac mortality

Patients who had in-hospital major bleeding events had higher cardiac mortality during index hospitalization (13.0% vs. 0.7%, p<0.005) and at one year of follow up (13.0% vs. 1.8%, p<0.005) compared to those who had no such events.

Predictive power of CRUSADE BRS

CRUSADE BRS ranged from 1 to 94 with a mean of 23.3 ± 13.8. Patients who developed in-hospital major bleeding had significantly higher CRUSADE score compared to those who had no bleeding (31.9% vs. 22.3%, p<0.005). The incidence of major bleeding events in each quintile of the CRUSADE score is shown in Table 5, and ranged from 0.4% in the lowest quintile to 1.8% in the highest quintile. There was a significant increasing trend

### Table 3. Incidence rates of major and minor bleeding events among the studied patients

<table>
<thead>
<tr>
<th>Bleeding events</th>
<th>During admission (2426 patients)</th>
<th>From discharge to 30 days (2387 patients)</th>
<th>From 1 to 6 months (2343 patients)</th>
<th>From 6 to 12 months (2297 patients)</th>
<th>All n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding</td>
<td>23 (0.95%)</td>
<td>4 (0.17%)</td>
<td>1 (0.04%)</td>
<td>3 (0.13%)</td>
<td>31</td>
</tr>
<tr>
<td>ICH</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Retroperitoneal</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Transfusion-requiring</td>
<td>3</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Hematocrit drop</td>
<td>16</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>64 (2.6%)</td>
<td>10 (0.42%)</td>
<td>1 (0.04%)</td>
<td>2 (0.08%)</td>
<td>77</td>
</tr>
<tr>
<td>Vascular access site</td>
<td>64</td>
<td>8</td>
<td>1</td>
<td>2</td>
<td>75</td>
</tr>
<tr>
<td>Hematuria</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>ICH - intracranial haemorrhage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 4. Incidence rates of in-hospital major bleeding according to important and significant variables in univariate analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Major bleeding during admission</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (n)</td>
<td>%</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1914</td>
<td>99.4</td>
</tr>
<tr>
<td>Female</td>
<td>489</td>
<td>97.8</td>
</tr>
<tr>
<td>Age, year</td>
<td></td>
<td>0.017</td>
</tr>
<tr>
<td>≤65</td>
<td>1781</td>
<td>99.3</td>
</tr>
<tr>
<td>&gt;65</td>
<td>622</td>
<td>98.3</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td>0.050</td>
</tr>
<tr>
<td>Yes</td>
<td>1283</td>
<td>98.7</td>
</tr>
<tr>
<td>No</td>
<td>1120</td>
<td>99.5</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td>0.014</td>
</tr>
<tr>
<td>No</td>
<td>912</td>
<td>99.7</td>
</tr>
<tr>
<td>Yes</td>
<td>1491</td>
<td>98.7</td>
</tr>
<tr>
<td>eGFR</td>
<td></td>
<td>0.017</td>
</tr>
<tr>
<td>&lt;60</td>
<td>293</td>
<td>98.3</td>
</tr>
<tr>
<td>60–89</td>
<td>674</td>
<td>98.4</td>
</tr>
<tr>
<td>≥90</td>
<td>1434</td>
<td>99.5</td>
</tr>
<tr>
<td>Past PCI</td>
<td></td>
<td>0.031</td>
</tr>
<tr>
<td>No</td>
<td>1824</td>
<td>99.3</td>
</tr>
<tr>
<td>Yes</td>
<td>579</td>
<td>98.3</td>
</tr>
<tr>
<td>Past CVD</td>
<td></td>
<td>0.090</td>
</tr>
<tr>
<td>No</td>
<td>1462</td>
<td>99.3</td>
</tr>
<tr>
<td>Yes</td>
<td>941</td>
<td>98.6</td>
</tr>
</tbody>
</table>

CVD - cardiovascular disease; eGFR - estimated glomerular filtration rate; PCI - percutaneous coronary intervention
higher than those who did not have major bleeding event (Table 6).

In-hospital 3 13.0 16 0.7 <0.005
1-month death 3 13.0 27 1.1 <0.005
6-month death 3 13.0 36 1.5 <0.005
1-year death 3 13.0 44 1.8 <0.005

Table 6. Differences in mortality between patients who developed major bleeding and those who did not

in the rate of bleeding with the higher quintiles of the CRUSADE score. ROC analysis showed that the CRUSADE score has a high ability to predict major bleeding events.

Furthermore, cardiac mortality during index hospitalization was higher among patients who had major bleeding and high scores (mortality 0% in the three lower quintiles, 14.3% in the high quintile, and 22.2% in the very high quintile, p-trend <0.0001).

Mortality among patients who had major bleeding events from hospital admission to one year of follow up was significantly higher than those who did not have major bleeding event (Table 6).

Discussion

This is the first study that evaluated the incidence, risk factors, and impact on prognosis of major bleeding events, and the CRUSADE BRS predictability in Jordanian patients undergoing PCI in Jordan. The main findings were: (1) major bleeding events are uncommon but are associated with higher in-hospital and one-year cardiac mortality compared with patients who did not have major bleeding, (2) most of the major bleeding events occurred during hospitalization, (3) several factors were associated with an increased risk of bleeding, but only female gender and past history of cardiovascular disease (CVD) were independent predictors of major bleeding in the multivariate analysis, and (4) CRUSADE BRS was highly predictive for the incidence of in-hospital major bleeding events.

Major bleeding events

Traditionally, the outcome after PCI has been evaluated by measuring the classical 3 endpoints of death, MI, and urgent repeat revascularization. Recently, bleeding has been integrated in outcome analysis of clinical studies and registries because peri-procedural bleeding in patients undergoing PCI is associated with an increased risk of recurrent ischemic complications and can adversely affect both short- and long-term mortality (1-4, 13-17).

This study enrolled patients who underwent PCI; a risk factor for bleeding by itself. Moreover, the majority of the enrolled patients (77%) had ACS; another risk factor for bleeding and most of the patients who had PCI for stable coronary disease (23%) had several risk factors associated with increased bleeding risk. Despite this clinical background, the incidence of major bleeding events was low. It is essential to adopt strategies that can reduce the incidence of bleeding, including the usage of a BRS to estimate the risk of major bleeding events and identify high-risk patients, use of appropriate antiplatelet and antithrombotic agents with maximal antithrombotic profile and minimal bleeding risk, choice of arterial access site, types and sizes of devices used in the PCI procedure, ACT monitoring, and closer surveillance for bleeding after the procedure (18-25).

The list of risk factors for bleeding in patients admitted with ACS or who underwent PCI includes old age, female gender, hypertension, DM, lower body weight, prior vascular disease [PAD, chronic renal disease and heart failure, and lower body weight. We observed a sharp decrease in the incidence of major bleeding events after discharge. Most of these events were minor vascular access hematomas that occurred in the first month of follow up.

The association of bleeding with excess long-term mortality in this study concurs with other studies and implies that bleeding is not simply a side effect of the medications and PCI procedure, or an acute event with no long-term prognostic impact (1, 25, 31). The excess bleeding-related mortality is multifactorial. These factors include the common risk factors mortality and bleeding share (age, diabetes mellitus, hypertension, past history of CVD, and renal insufficiency), hemodynamic effects of massive bleeding, higher mortality associated with intracranial bleeding, neurohormonal activation associated with hypotension, and bleeding-related imaging procedures and surgical interventions under general anesthesia that may independently increase cardiac mortality (32-38).

CRUSADE bleeding risk score

Clinical studies have shown that the CRUSADE BRS has a relatively high accuracy for estimating bleeding risk by incorpo-
rating admission and treatment variables. Although age is one of the predictors of major bleeding that is not directly considered in calculating the risk score, it is incorporated in calculating the 
CrCI. Each of the bleeding risk scores in clinical use has been utilized in specific patient population, including STEMI patients treated with fibrinolysis (GUSTO score) (39), STEMI and NSTEMI patients (GRACE score) (9), ACS patients planned to have urgent or early intervention (Phase III ACUITY study) (7), elective or urgent PCI via the femoral artery access (5), PCI with combination antiplatelet and antithrombotic agents (REPLACE 2 study) (40), and NSTEMI patients (CRUSADE study) (6).

The CRUSADE BRS was originally developed from NSTEMI patients’ data, but its predictive value was unchanged when patients with UA were included. Moreover, analysis of the ACTION Registry-GWTG suggested that the CRUSADE BRS can be applied in STEMI patients (41). The CRUSADE BRS evaluated the score’s predictability of in-hospital major bleeding events and mortality. Our study further demonstrated that this predictability persists up to one year after discharge, similar to other studies (25). The observed high predictability for major bleeding events of the CRUSADE BRS supports its expanded applicability in other geographical regions than those where the score was developed.

Study limitations

This registry had limitations inherent to observational studies (42). It may be subject to selection bias, collection of non-randomized data, and missing or incomplete information. Participation was voluntary and the enrolment of consecutive patients was encouraged, but this was not verified, as it is the case with similar registries (43). The accuracy of recall of the patients or their relatives of major events, such as major bleeding, is unlikely to be underreported. The registry included high volume tertiary care center; thus, it may not fully represent the PCI practice and outcome in all areas in the country or region.

Conclusions

Major bleeding events were uncommon in this Jordanian registry of a contemporary cohort of patients undergoing PCI but were associated with a higher mortality rate compared with those who did not have major bleeding events. CRUSADE BRS was highly predictive of the incidence of major bleeding events. We recommend incorporating CRUSADE BRS in the care of patients undergoing PCI to identify high-risk patients for bleeding events.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.


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