Access-Site vs Non-Access-Site Major Bleeding and In-Hospital Outcomes Among STEMI Patients Receiving Primary PCI

Michael J. Thibert, MD, a,b Christopher B. Fordyce, MDCM, MHS, MSc, a,b John A. Cairns, MD, MSc, a,b Ricky D. Turgeon, BSc(Pharm), ACPR, PharmD, b,c,d Martha Mackay, PhD, RN, e,f,g Terry Lee, PhD, d,h Wendy Tocher, RN, i Joel Singer, PhD, d,h Michele Perry-Arnesen, MHA, RN, d,j and Graham C. Wong, MD, MPH, b

a Division of Cardiology, University of British Columbia, Vancouver, British Columbia, Canada
b Centre for Cardiovascular Innovation, University of British Columbia, Vancouver, British Columbia, Canada
c University of British Columbia Faculty of Pharmaceutical Sciences, Vancouver, British Columbia, Canada
d Centre for Health Evaluation and Outcome Sciences, Vancouver, British Columbia, Canada
e Providence Health Care Research Institute, University of British Columbia, Vancouver, British Columbia, Canada
f St Paul’s Hospital Heart Centre, Vancouver, British Columbia, Canada
g University of British Columbia School of Nursing, Vancouver, British Columbia, Canada
h School of Population and Public Health, University of British Columbia, Vancouver, British Columbia, Canada
i Vancouver Coastal Health Authority, Vancouver, British Columbia, Canada
j Burnaby Hospital, Fraser Health Authority, Burnaby, British Columbia, Canada

ABSTRACT

Background: Major bleeding (MB) is an independent predictor of mortality among ST-elevation myocardial infarction (STEMI) patients undergoing primary percutaneous coronary intervention (pPCI). Prevention of access-site MB has received significant attention. However, limited data have been obtained on the influence of access-site MB vs non-access-site MB and association with subsequent adverse in-hospital outcomes in the STEMI population undergoing pPCI.

Methods: We identified 1494 STEMI patients who underwent pPCI between 2012 and 2018. Unadjusted and adjusted differences among patients with no MB, access-site MB, non-access-site MB, and inhospital clinical outcomes were assessed. The use of bleeding-avoidance strategies and their effects on MB were also evaluated.

Results: MB occurred in 121 (8.1%) patients. Access-site MB occurred in 34 (2.3%) patients, and non-access-site MB occurred in 87 (5.8%).

Patients undergoing primary percutaneous coronary intervention (pPCI) are exposed to an increased risk of bleeding owing to a variety of factors, including impaired renal function, anemia, advanced age, female sex, heart failure, and use of heparin and glycoprotein IIb/IIIa inhibitors. 1,2 Although PCI is the preferred reperfusion modality for ST-elevation myocardial infarction (STEMI), STEMI as the indication for PCI has also been independently associated with an

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Corresponding author: Dr Graham C. Wong, Vancouver General Hospital, Level 9-2775 Laurel St, Vancouver, British Columbia V5Z1M9, Canada. Tel.: +1-604-875-5735; fax: +1-604-875-5735. E-mail: gcwong@mail.ubc.ca

Please see page 870 for disclosure information.
The median reduction in hemoglobin was 31 g/L (interquartile range: 19-43) with access-site MB, and 44 g/L (interquartile range: 29-62) with non-access-site MB. After multivariable adjustment, non-access-site MB was independently associated with in-hospital death (adjusted odds ratio [aOR] 4.21; 95% confidence interval [CI] 2.04-8.68), cardiogenic shock (aOR 10.91; 95% CI 5.67-20.98), and cardiac arrest (aOR 5.63; 95% CI 2.88-11.01). Conversely, access-site MB was not associated with adverse in-hospital outcomes. Bleeding-avoidance strategies were used frequently; however, after multivariable adjustment, no single bleeding-avoidance strategy was significantly associated with reduced MB.

Conclusions: In STEMI patients undergoing pPCI, non-access-site MB was independently associated with adverse in-hospital outcomes, whereas access-site MB was not. Additional study of strategies to reduce the incidence and impact of non-access-site MB appears to be warranted.

Increased risk for major bleeding (MB), compared with that in patients undergoing elective PCI,3,4 MB in patients undergoing PCI occurs frequently and is associated with significant adverse outcomes, including short-term and long-term mortality.5,7 STEMI patients who experience MB after pPCI are at an increased risk of death, myocardial infarction, stroke, and ischemic target revascularization.1 Although risk is greatest in the short term, MB remains associated with adverse outcomes for up to 3 years post-pPCI.1 As a result of the known adverse outcomes associated with bleeding, bleeding-avoidance strategies, including use of bivalirudin, radial access for PCI, and use of vascular closure devices, have been developed and studied in an attempt to reduce PCI-related bleeding.3-14 Although bleeding-avoidance strategies are mostly intended to reduce access-site bleeding, non-access-site bleeding may have a stronger association with long-term mortality than does access-site bleeding.3,15-19 Non-access-site bleeding has also been associated with an increased requirement for blood transfusions and surgery related to bleeding.18 However, the immediate, in-hospital consequences of non-access-site bleeding on in-hospital mortality, hemodynamic stability, and adverse outcomes have not been fully explored.

The aim of the present study was to describe the frequency and clinical implications of access-site vs non-access-site MB in STEMI patients post-pPCI.

Methods

Study population

This study was approved by the Clinical Research Ethics Board of the University of British Columbia (No. H18-02217). This was a retrospective analysis based on the prospectively collected Vancouver Coastal Health Authority (VCHA) STEMI Database.20,21 STEMI patients aged >18 years presenting to hospitals in the VCHA between April 1, 2012 and March 31, 2018 were identified. We excluded patients who had ischemic times greater than 12 hours, those who had unsuccessful pPCI, or those for whom PCI was not the initial revascularization plan.

Definitions

Outcome events included only those occurring during the index hospitalization. MB was defined by the VCHA MB definition—a documented overt bleeding event that requires transfusion of whole blood, packed red blood cells, or use of a surgical or procedural intervention to manage the bleeding, or is associated with a hemoglobin reduction of at least 30 g/L. Access-site MB included any MB originating from the femoral or radial arterial puncture site. Retroperitoneal bleeds were categorized as access-site bleeding if the participant had a femoral arterial puncture for pPCI access. Non-access-site MB included all other MB. Mortality was defined as death from any cause. Cardiogenic shock was defined as a cardiac index of < 2.2 ml/min per m² or systolic blood pressure of < 90 mm Hg determined to be secondary to cardiac dysfunction persisting for > 30 minutes or the requirement for parenteral inotropic or vasopressor agents or mechanical support to maintain blood pressure and cardiac index above those specified levels. Cardiac arrest was defined as any loss of pulse occurring after pPCI requiring chest compressions that was associated with a shockable or non-shockable rhythm. Stroke was defined as abnormality of neurologic function caused by an ischemic or hemorrhagic event with residual symptoms lasting at least 24 hours or leading to death. Reinfarction was defined as clinical signs and symptoms of ischemia that were temporally distinct.
from the presenting event supported by electrocardiogram changes, angiographic evidence, or an elevation of troponin or creatine kinase by at least 50% above the most recent post-PCI value. The composite endpoint comprised mortality, cardiogenic shock, cardiac arrest, reinfarction, and stroke.

**Statistical analysis**

Patients were grouped into those in whom there was no MB and those in whom there was any MB, who were further divided into access-site MB or non-access-site MB groups. Univariate comparisons among no MB, access-site MB, and non-access-site MB groups were performed using the Kruskal-Wallis test or analysis of variance for continuous variables, and the Pearson’s χ² test or Fisher’s exact test for categorical variables, as appropriate. Continuous variables were expressed as medians with interquartile range (IQR), or means (±standard deviation); categorical variables were expressed as percentages. The impact of MB (access-site and non-access-site vs no MB) on in-hospital outcomes was assessed using a logistic regression model. Unadjusted and adjusted odds ratios (aORs) were calculated. Adjustment variables for the MB and in-hospital outcomes model included the following prognostically important clinical characteristics: age, sex, initial creatinine, admission hemoglobin, initial systolic blood pressure, heart failure on presentation, cardiogenic shock on arrival, prehospital cardiac arrest, angiogram access site, prior myocardial infarction, anatomic territory of myocardial infarction, and prolonged reperfusion times. The clinically important adjusted variables were selected a priori. Additional analyses of any MB (access-site or non-access-site) and their association with in-hospital outcomes using the thrombolysis in myocardial infarction (TIMI) definition for MB were also performed. All data were analyzed with SAS software version 9.4 (SAS Institute, Cary, NC).

The relationship between MB and use of a single bleeding-avoidance strategy (use of bivalirudin before angiogram, radial access, and use of vascular closure devices) vs no bleeding-avoidance strategy was assessed using logistic regression. Unadjusted and aORs were calculated. Adjustment variables for the use of a bleeding-avoidance strategy and MB included the following, known to be associated with an increased risk of bleeding: age, sex, initial creatinine, admission hemoglobin, initial systolic blood pressure, heart failure on presentation, cardiogenic shock on arrival, prehospital cardiac arrest, prior myocardial infarction, anatomic territory of myocardial infarction, prolonged reperfusion times, use of an intra-aortic balloon pump, and use of glycoprotein IIb/IIIa inhibitors. The clinically important adjusted variables were selected a priori. Bleeding rates as defined by the National Cardiovascular Data Registry (NCDR) CathPCI Registry bleeding definition, and the TIMI major and minor bleeding definitions, were also calculated and compared with overall MB rates using the VCHA MB definition. Statistical significance was defined as a P value of <0.05.

**Results**

This analysis included 1494 patients with STEMI undergoing PCI. Eighty-six patients were excluded due to ischemic time >12 hours; 456 were excluded for unsuccessful or unplanned PCI. Of the 1494 included, 121 (8.1%) experienced VCHA MB during the index hospitalization. Using the TIMI major and NCDR CathPCI definition, overall MB rates were 5.2% and 13.9%, respectively (Supplemental Fig. S1). Access-site MB occurred in 34 patients (2.3%) and non-access-site MB occurred in 87 patients (5.8%). Specific sites of bleeding can be found in Supplemental Figure S2. The rate of VCHA MB stratified by predicted risk using the NCDR CathPCI bleeding risk model can be found in Supplemental Figure S3.

**Baseline characteristics**

The baseline characteristics, by group, are presented in Table 1. There were significant between-group differences for age, body mass index, sex, diabetes, atrial fibrillation, and chronic kidney disease. There were also significant differences in initial creatinine level, heart failure on arrival, cardiogenic shock on arrival, and pre-hospital cardiac arrest. The baseline characteristics and therapeutic coninterventions of all patients who developed MB (access-site and non-access-site), compared with those with no MB, are presented in Supplemental Table S1 and Supplemental Table S2, respectively.

Overall, 1052 (74.9%) patients had benefit of the use of at least one bleeding-avoidance strategy. Of the 1494 patients included for analysis, 121 (8.2%) patients received bivalirudin before pPCI, 401 (26.8%) had radial access for pPCI, and 751 (53.1%) received a vascular closure device.

**Magnitude of MB and interventions**

The admission hemoglobin, change in hemoglobin, and lowest hemoglobin in those with no MB, access-site MB, and non-access-site MB are presented in Table 2. The median reduction in hemoglobin for patients with access-site MB was 31 g/L (IQR 19-43) and was 44 g/L (IQR 29-62) for those with non-access-site MB. The hemoglobin nadir was a median of 130 g/L (IQR 117-140) in those with no MB, 93 g/L (IQR 84-113) in patients with access-site MB, and 84 g/L (IQR 70-104) in those with non-access-site MB. Patients with non-access-site MB also more often received transfusions or surgical or procedural interventions to stop bleeding than did those with access-site MB (Table 2).

**In-hospital outcomes of access-site MB and non-access-site MB**

The unadjusted and adjusted association of MB (access-site MB and non-access-site MB vs no MB) with in-hospital outcomes is presented in Table 3. After multivariable adjustment, non-access-site MB was independently associated with all-cause mortality (aOR 4.21; 95% confidence interval [CI] 2.04-8.68), cardiogenic shock (aOR 10.91; 95% CI 5.67-20.98), in-hospital cardiac arrest (aOR 5.63; 95% CI 2.88-11.01), and the composite outcome (aOR 10.96; 6.00-20.03). However, access-site MB was not associated with all-cause mortality (aOR 0.61; 95% CI 0.10-3.77), cardiogenic shock (aOR 2.64; 95% CI 0.67-10.39), in-hospital cardiac arrest (aOR 0.67; 95% CI 0.09-4.83), or the composite outcome (aOR 2.54; 95% CI 0.77-8.73). Median length of stay was significantly different in those with no MB, compared with access-site MB, and non-access-site MB (P < 0.001). Median length of stay was longest in those with non-access-site MB (10.0 days, IQR 7.0-22.8), compared to 3.8 days (IQR 2.8-7.6) for access-site MB and 3.0 days (IQR 2.4-3.7) for no MB (P < 0.001;
Supplemental Table S3). Similar associations of most in-hospital outcomes with access-site and non-access-site bleeding were also noted when bleeding was defined using the NCDR CathPCI bleeding definition (Supplemental Table S4). However, the association of all-cause mortality with all MB and non-access-site bleeding was not at the level of statistical significance using this definition (Supplemental Tables S5 and S6).

### Bleeding-avoidance strategies

The unadjusted and adjusted associations of bleeding-avoidance strategy use with the occurrence of MB are presented in Table 4. After multivariable adjustment, there was no significant association between MB and the use of bivalirudin (aOR 1.08; 95% CI 0.32-3.67), use of a vascular closure device (aOR 0.83; 95% CI 0.49-1.38), or radial access for pPCI (aOR 0.69; 95% CI 0.37-1.28).

### Table 1. Baseline characteristics and clinical features on presentation, by bleeding status

| Baseline characteristics | No major bleeding (n = 1373) | Access-site bleeding (n = 34) | Non-access-site bleeding (n = 87) | P |
|--------------------------|-----------------------------|-----------------------------|---------------------------------|---|
| Age (y)                  | 64.7 (56.0, 73.8)           | 72.0 (62.8, 81.7)           | 68.4 (58.7, 77.9)              | 0.009 |
| Body mass index, kg/m²   | 26.2 (23.7, 28.8)           | 24.5 (22.5, 26.2)           | 25.8 (22.3, 29.5)              | 0.022 |
| Female                   | 269 (19.6)                  | 12 (35.3)                   | 22 (25.3)                      | 0.039 |
| Hypertension             | 754 (55.1)                  | 15 (44.1)                   | 58 (67.4)                      | 0.033 |
| Diabetes mellitus        | 280 (20.5)                  | 2 (5.9)                     | 26 (31.0)                      | 0.007 |
| Current/recent smoker    | 326 (23.8)                  | 10 (29.4)                   | 16 (18.6)                      | 0.393 |

### Table 2. Major bleeding characteristics, by bleeding status

| Hemoglobin features, g/L | No major bleeding (n = 1373) | Access-site bleeding (n = 34) | Non-access-site bleeding (n = 87) | P |
|--------------------------|-----------------------------|-----------------------------|---------------------------------|---|
| Admission                | 143 (133–154)               | 131 (113–151)               | 137 (127–150)                   | < 0.001 |
| Change                   | −13 (−20 to −5)             | −31 (−43 to −19)            | −44 (−62 to −29)                | < 0.001 |
| Lowest                   | 130 (117–140)               | 93 (84–113)                 | 84 (70–104)                     | < 0.001 |

### Values

- Values are given as n (%), median (interquartile range), or mean (±SD).
- CrCl, creatinine clearance; FMC, first medical contact; PCI, percutaneous coronary intervention.
- Values are median (interquartile range) or n (%).
- RBC, red blood cell.
Table 3. Association between major bleeding and in-hospital outcomes of ST-elevation myocardial infarction patients with primary percutaneous coronary intervention

| Outcome | Patients, n | Unadjusted OR (95% CI) | P  | Adjusted OR (95% CI) | P  |
|---------|-------------|-------------------------|----|----------------------|----|
| All-cause mortality | | | | | |
| No major bleeding | 61 | — | — | — | — |
| All major bleeding | 25 | 5.60 (3.37–9.32) | < 0.001 | 3.15 (1.59–6.25) | < 0.001 |
| Access-site bleeding | 2 | 1.34 (0.31–5.74) | 0.69 | 0.61 (0.10–3.77) | 0.592 |
| Non-access-site bleeding | 23 | 7.73 (4.50–13.28) | < 0.001 | 4.21 (2.04–8.68) | < 0.001 |
| Cardiac arrest | | | | | |
| No major bleeding | 47 | — | — | — | — |
| All major bleeding | 24 | 6.94 (4.07–11.83) | < 0.001 | 4.19 (2.21–7.94) | < 0.001 |
| Access-site bleeding | 1 | 0.84 (0.11–6.28) | 0.866 | 0.67 (0.09–4.83) | 0.69 |
| Non-access-site bleeding | 23 | 10.13 (5.79–17.72) | < 0.001 | 5.63 (2.88–11.01) | < 0.001 |
| Cardiogenic shock | | | | | |
| No major bleeding | 87 | — | — | — | — |
| All major bleeding | 46 | 9.18 (5.99–14.08) | < 0.001 | 8.10 (4.46–14.72) | < 0.001 |
| Access-site bleeding | 5 | 2.55 (0.96–6.74) | 0.060 | 2.64 (0.67–10.39) | 0.166 |
| Non-access-site bleeding | 41 | 13.46 (8.36–21.65) | < 0.001 | 10.91 (5.67–20.98) | < 0.001 |
| Reinfarction | | | | | |
| No major bleeding | 5 | — | — | — | — |
| All major bleeding | 2 | 4.63 (0.89–24.12) | 0.069 | — | — |
| Access-site bleeding | 1 | 8.28 (0.94–72.84) | 0.057 | — | — |
| Non-access-site bleeding | 1 | 3.21 (0.37–27.82) | 0.289 | — | — |
| Stroke | | | | | |
| No major bleeding | 15 | — | — | — | — |
| All major bleeding | 13 | 10.98 (5.09–23.68) | < 0.001 | — | — |
| Access-site bleeding | 1 | 2.74 (0.35–21.35) | 0.336 | — | — |
| Non-access-site bleeding | 12 | 14.66 (6.62–32.44) | < 0.001 | — | — |
| Composite outcome* | | | | | |
| No major bleeding | 107 | — | — | — | — |
| All major bleeding | 54 | 9.51 (6.31–14.34) | < 0.001 | 7.82 (4.56–13.39) | < 0.001 |
| Access-site bleeding | 6 | 2.49 (1.01–6.15) | 0.048 | 2.54 (0.77–8.37) | 0.125 |
| Non-access-site bleeding | 48 | 14.69 (9.19–23.48) | < 0.001 | 10.96 (6.00–20.03) | < 0.001 |

* In-hospital cardiac arrest, reinfarction, stroke, cardiogenic shock, or death.

Discussion

In this contemporary cohort of STEMI patients receiving successful pPCI, MB occurred frequently and was predominantly located in non-access sites. Compared to access-site MB, non-access-site MB resulted in a greater decrease in hemoglobin and a lower nadir than access-site MB. We observed an independent association of non-access-site MB with inhospital all-cause mortality, cardiac arrest, and cardiogenic shock post-pPCI. These associations were not present with access-site MB, although event rates with access-site MB were low. These results demonstrate the significant risk of non-access-site MB following pPCI for STEMI and emphasize

Table 4. Association of major bleeding with bleeding-avoidance strategies

| Bleeding-avoidance strategy | No (n = 1373) | Yes (n = 121) | Unadjusted OR (95% CI) | P  | Adjusted OR (95% CI) | P  |
|-----------------------------|--------------|--------------|------------------------|----|----------------------|----|
| Bivalirudin before angiogram | 39 (3.0) | 3 (2.6) | 0.56 (0.18–1.79) | 0.328 | 1.08 (0.52–2.07) | 0.903 |
| Vascular closure device* | 608 (47.2) | 55 (46.6) | 0.57 (0.36–0.89) | 0.013 | 0.83 (0.49–1.38) | 0.471 |
| Angiogram access site | | | | | |
| Radial | 375 (27.3) | 26 (21.5) | 0.42 (0.24–0.73) | 0.002 | 0.69 (0.37–1.28) | 0.235 |
| Femoral | 998 (72.7) | 95 (78.5) | — | — | — | — |
| Number of strategies used | | | | | |
| 1 | 974 (75.6) | 78 (67.2) | 0.51 (0.33–0.78) | 0.002 | 0.79 (0.48–1.28) | 0.335 |
| > 1 | 90 (7.0) | 3 (2.6) | 0.24 (0.08–0.76) | 0.015 | 0.40 (0.13–1.29) | 0.127 |

* Vascular closure device status unknown for 79 patients. Patients with radial access excluded from analysis.

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the need to consider strategies for both bleeding avoidance and early detection to lessen morbidity from non-access-site MB in the STEMI population.

Our findings are consistent with those of previous studies that have also demonstrated a stronger association of mortality with non-access-site MB compared with access-site MB,\(^5,16,20-22\) and they extend our understanding on the prognostic value of non-access-site MB in the STEMI population.\(^18,19\) In a previous study of 744 STEMI patients undergoing pPCI, MB was associated with death or myocardial infarction at 1 year, driven by non-access-site bleeds.\(^19\) Similarly, in a cohort of 2002 STEMI patients undergoing pPCI, non-access-site bleeding was associated with a higher risk of 1-year mortality compared with no bleeding, whereas access-site bleeding was not.\(^18\) However, neither of these previous studies evaluated in-hospital mortality or morbidity outcomes that may lead to increased short-term mortality. A large propensity-matched population of all patients undergoing PCI (elective or for acute coronary syndromes) found that non-access-site bleeding was associated with an increased risk of in-hospital mortality; however, findings also indicated an increased risk of in-hospital mortality with access-site bleeding, which differs from our findings.\(^17\) Similar differences are described in a large meta-analysis evaluating access-site and non-access-site bleeding among patients undergoing PCI.\(^29\) Pooled results of 4 studies and a total of 281,670 patients demonstrated a significant increase in mortality with non-access-site and access-site bleeding. However, the relative risk of mortality was 2.4 times higher with non-access-site bleeds compared with access-site bleeds. Additionally, only 1 of the 4 studies was limited to patients presenting with STEMI. The low access-site bleeding rates and the inclusion of only STEMI patients in our study may explain these differences.

There are multiple mechanisms by which non-access-site MB may lead to increased risk of in-hospital morbidity and mortality. We showed that non-access-site MB led to a greater reduction in hemoglobin and a lower nadir, which may contribute to the development of shock by compromising oxygen-carrying capacity and potentiating end-organ dysfunction.\(^24\) Impaired oxygen delivery to injured myocardium may also lead to reduced myocardial function, subsequent cardiogenic shock, and the creation of a substrate for ventricular arrhythmias, perhaps accounting for our findings of increased cardiogenic shock and cardiac arrest post-pPCI in the non-access-site MB group. In one study, antiplatelet agents were discontinued more frequently during non-access-site MB than with access-site MB,\(^18\) which may have contributed to the worse outcomes with non-access-site MB, although few reinfarctions occurred in our cohort, and in-hospital antiplatelet discontinuation was not captured. We also observed that patients with non-access-site MB more often received transfusions, which have been independently associated with in-hospital and 1-year mortality in patients undergoing PCI.\(^25\) Lastly, non-access-site MB is usually less apparent than access-site MB, which may result in delayed recognition of the former and the consequences of a lower nadir. Non-access-site MB is also likely to be anatomically less accessible than access-site MB for immediate intervention to control bleeding.

We found that bleeding-avoidance strategies were not associated with reduced MB, after adjusting for known confounders, although event rates were low and a trend toward reduction was seen with radial access and vascular closure devices. The predominance of non-access-site MB may partially explain this finding, as bivalirudin use was the only bleeding-avoidance strategy that had the potential to decrease non-access-site MB. These observations emphasize the importance of developing new strategies to prevent, identify, and treat non-access-site MB. The use of proton pump inhibitors has been shown to reduce upper gastrointestinal bleeding in the long term,\(^31\) which may be a potential strategy to reduce in-hospital upper-gastrointestinal bleeding events. Although blood transfusions have previously been associated with worse outcomes,\(^25\) multiple randomized controlled trials are currently underway investigating the role of restrictive vs liberal transfusion strategies in the acute myocardial infarction population.\(^32\) More liberal transfusion could potentially lead to improved outcomes in patients with MB associated with greater degrees of anemia, such as non-access-site MB.

Lastly, in addition to worsened in-hospital clinical outcomes, we also demonstrated that non-access-site MB was associated with greater lengths of stay than those of patients with no MB, whereas access-site MB was not. To our knowledge, this is the first study to differentiate lengths of stay by location of bleed; overall, our length of stay results are consistent with previous analyses of patients undergoing PCI who experience all types of MB.\(^32,33\)

We acknowledge that our study has limitations. First, this was a prospective observational study, and therefore causation cannot be inferred. Although we adjusted for most of the variables known to confer poor outcomes in patients with STEMI, residual and unmeasured confounders might be present in our model that could influence the observed outcomes. Second, the VCHA definition of MB used in this study differs from other commonly used bleeding definitions. However, it includes many core components used in these definitions, and additional analyses using the TIMI MB definition yielded similar outcomes for in-hospital and long-term events compared to the primary analyses using the VCHA MB definition. Furthermore, we found similar associations between in-hospital outcomes and access-site and non-access-site bleeding using the NCDR CathPCI bleeding definition. The only major difference was that non-access-site bleeding was not associated with a significant increase in all-cause mortality when using the NCDR CathPCI definition. This is likely a result of the inclusion of less-significant bleeds in the broader NCDR CathPCI definition. Third, the location of many non-access-site bleeding events was not documented. Fourth, 73% of patients underwent pPCI via femoral access in this cohort, which is likely a higher percentage than would be found in contemporary practice. However, the number of access-site bleeds was low. Fifth, the number of events associated with access-site MB was small, which may limit the significance of the access-site MB results. Lastly, we did not capture long-term outcomes, as our database was limited to in-hospital events and there was no adjudication for cause of death.
Conclusions

In a contemporary STEMI cohort receiving pPCI, MB was predominately caused by non-access-site bleeding and was independently associated with in-hospital mortality, cardiogenic shock, and cardiac arrest post-PCI. Non-access-site MB resulted in a greater decrease in hemoglobin and a lower nadir than access-site MB and was associated with longer hospital length of stay. Bleeding-avoidance strategies were not associated with fewer MB events, although trends toward reduction were seen with the use of radial access and vascular closure devices. Additional study of strategies to reduce the incidence and impact of bleeding should also focus on non-access-site bleeding.

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**Supplementary Material**

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