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Original Article

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

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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 in-hospital 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%).

RÉSUMÉ

Contexte : Le saignement majeur (SM) est un facteur prédictif indépendant de la mortalité chez les patients ayant eu un infarctus du myocarde avec élévation du segment ST (STEMI) qui subissent une intervention coronarienne percutanée primaire (ICPp). La prévention du SM lié à l'accès vasculaire a fait l'objet de nombreuses études. Toutefois, rares sont les données sur l'influence du SM lié à l'accès vasculaire par rapport au SM non lié à cet élément et sur son association avec des résultats indésirables intrahospitaliers subséquents chez des patients ayant subi une ICPp après un STEMI.

Méthodologie : Nous avons répertorié 1 494 patients ayant subi une ICPp après un STEMI entre 2012 et 2018. Nous avons évalué les différences non ajustées et ajustées entre les cas sans SM, les cas de SM liés à l'accès vasculaire et les cas de SM non liés à l'accès vasculaire, et les résultats cliniques intrahospitaliers. L'utilisation de

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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Ethics Statement: This study was approved by the Clinical Research Ethics Board of the University of British Columbia (No. H18-02217).

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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.

stratégies d'évitement des saignements et leurs effets sur le SM ont également été évalués.

Résultats : Un SM a été observé chez 121 (8,1 %) patients. Le SM lié à l'accès vasculaire touchait 34 (2,3 %) patients, et le SM non lié à l'accès vasculaire 87 (5,8 %) patients. La réduction médiane du taux d'hémoglobine était de 31 g/L (intervalle interquartile : 19 à 43) dans le cas du SM lié à l'accès vasculaire, et de 44 g/L (intervalle interquartile : 29 à 62) pour le SM non lié à l'accès vasculaire. Après ajustement multivarié, une association indépendante a été observée entre le SM non lié à l'accès vasculaire et le décès (rapport de cotes ajusté [RRa] 4,21; intervalle de confiance [IC] à 95 % : de 2,04 à 8,68), le choc cardiogénique (RRa 10,91; IC à 95 % : de 5,67 à 20,98), et l'arrêt cardiaque (RRa 5,63; IC à 95 % : de 2,88 à 11,01) intrahospitaliers. Inversement, le SM lié à l'accès vasculaire n'était associé à aucun résultat indésirable intrahospitalier. Les stratégies d'évitement des saignements avaient été utilisées fréquemment; toutefois, après ajustement multivarié, aucune stratégie particulière d'évitement des saignements n'était associée de façon significative à une réduction du SM.

Conclusions : Chez les patients subissant une ICPp après un STEMI, le SM non lié à l'accès vasculaire était associé de façon indépendante aux résultats indésirables intrahospitaliers, alors que le SM lié à l'accès vasculaire ne l'était pas. La poursuite des recherches sur les stratégies permettant de réduire l'incidence et les conséquences du SM non lié à l'accès vasculaire semble donc justifiée.

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.[8-14] 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 m^2 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 χ^2 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.[22] 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[23] 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.[4,24-28] The clinically important adjusted variables were selected a priori. Bleeding rates as defined by the National Cardiovascular Data Registry (NCDR) CathPCI Registry bleeding definition,[27] and the TIMI major and minor bleeding definitions,[23] 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 pPCI. 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 cointerventions 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 ($P < 0.001$;

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

	No major bleeding (n = 1373)	Access-site bleeding (n = 34)	Non-access-site bleeding (n = 87)	*P*
Baseline comorbidities				
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/m^2	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
History of or new-onset atrial fibrillation				0.013
New onset	26 (4.6)	5 (26.3)	4 (10.0)	
Prior	29 (5.1)	0 (0.0)	4 (10.0)	
Peripheral vascular disease	33 (2.4)	2 (5.9)	4 (4.7)	0.135
Chronic kidney disease				< 0.001
No (CrCl: ≥60)	970 (± 70.9)	16 (± 47.1)	41 (± 47.7)	
Mild (CrCl: 45−59)	203 (± 14.8)	11 (± 32.4)	16 (± 18.6)	
Moderate (CrCl: 30−44)	141 (± 10.3)	4 (± 11.8)	21 (± 24.4)	
Severe (CrCl: < 30)/currently on dialysis	55 (± 4.0)	3 (± 8.8)	8 (± 9.3)	
Prior myocardial infarction	195 (14.3)	0 (0.0)	14 (16.5)	0.049
Clinical features on presentation				
Initial heart rate, beats per minute	77.6 (± 23.3)	73.5 (± 23.1)	81.5 (± 24.3)	0.178
Initial systolic blood pressure, mm Hg	141.0 (121.5, 164.0)	138.5 (104.0, 157.0)	135.0 (108.0, 157.0)	0.057
Initial creatinine, mmol/L	94.0 (79.0, 109.0)	96.5 (70.0, 107.0)	115.0 (90.0, 134.0)	< 0.001
Heart failure on presentation	54 (3.9)	2 (5.9)	11 (12.8)	0.002
Cardiogenic shock on arrival	90 (6.6)	4 (11.8)	29 (33.3)	< 0.001
Prehospital cardiac arrest	104 (7.7)	2 (5.9)	27 (31.0)	< 0.001
Anterior infarct	650 (47.3)	15 (44.1)	47 (54.0)	0.441
Initial presentation to PCI hospital	973 (70.9)	24 (70.6)	71 (81.6)	0.098
FMC-to-device, min	103.0 (85.0, 130.0)	102.5 (84.0, 137.0)	109.0 (93.0, 139.0)	0.067
Bleeding-avoidance strategies				
None	224 (± 17.0)	12 (± 36.4)	23 (± 26.7)	0.002
Angiogram access site				0.220
Femoral	998 (72.7)	29 (85.3)	66 (75.9)	
Radial	375 (27.3)	5 (14.7)	21 (24.1)	
Vascular closure device	694 (53.5)	17 (51.5)	40 (47.6)	0.572
Bivalirudin before diagnostic angiogram	117 (± 8.6)	0 (± 0.0)	4 (± 4.7)	0.092

Values are given as n (%), median (interquartile range), or mean (±SD).
CrCl, creatinine clearance; FMC, first medical contact; PCI, percutaneous coronary intervention.

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 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
Interventions for bleeding episode				0.036
Unknown	—	0	1	—
None	—	19 (55.9)	28 (32.6)	—
RBC/whole blood transfusion	—	11 (32.4)	33 (38.4)	—
Surgical or procedural intervention	—	4 (11.8)	25 (29.1)	—

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

Odds ratios for each outcome were adjusted for age, sex, creatinine level, hemoglobin level, systolic blood pressure, heart failure on presentation, cardiogenic shock on presentation, prehospital cardiac arrest, vascular access site, prior myocardial infarction, anatomic territory of myocardial infarction, and prolonged time to reperfusion.

CI, confidence interval; OR, odds ratio.

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

† Too few events to perform adjusted analysis.

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 in-hospital 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

	Major bleeding, n (%)					
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 (0.32-3.67)	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

Odds ratios were adjusted for age, sex, initial creatinine level, admission hemoglobin level, initial systolic blood pressure, heart failure on presentation, cardiogenic shock on arrival, prehospital cardiac arrest, prior myocardial infarction, anatomic territory of myocardial infarction, prolonged time to reperfusion, use of intra-aortic balloon pump, and use of glycoprotein IIb/IIIa inhibitors. Analysis performed for each individual bleeding-avoidance strategy vs no bleeding-avoidance strategy.

CI, confidence interval; OR, odds ratio.

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

† Radial access site vs femoral access site.

‡ Any 1 of: bivalirudin before diagnostic angiogram, vascular closure device, or radial access.

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,[15,16,20-22] 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.[30] 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.[12,33]

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 events compared to the primary analyses using the VCHA MB definition. Furthermore, we found similar associations between in-hospital oucomes 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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References

1. Suh JW, Mehran R, Claessen BE, 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;58:1750-6.

2. Moghaddam N, Wong GC, Cairns JA, et al. Association of anemia with outcomes among ST-segment-elevation myocardial infarction patients receiving primary percutaneous coronary intervention. Circ Cardiovasc Interv 2018;11:1-10.

3. Rao SV, Dai D, Subherwal S, et al. Association between periprocedural bleeding and long-term outcomes following percutaneous coronary intervention in older patients. JACC Cardiovasc Interv 2012;5. 958-5.

4. Mehta SK, Frutkin AD, Lindsey JB, et al. Bleeding in patients undergoing percutaneous coronary intervention: the development of a clinical risk algorithm from the national cardiovascular data registry. Circ Cardiovasc Interv 2009;2:222-9.

5. Kwok CS, Ao SV, Myint PK, et al. Major bleeding after percutaneous coronary intervention and risk of subsequent mortality: a systematic review and meta-analysis. Open Heart 2014;1:e000021.

6. Eikelboom JW, Mehta SR, Anand SS, et al. Adverse impact of bleeding on prognosis in patients with acute coronary syndromes. Circulation 2006;114:774-82.

7. Ndrepepa G, Berger PB, Mehilli J, et al. Periprocedural bleeding and 1-year outcome after percutaneous coronary interventions. Appropriateness of including bleeding as a component of a quadruple end point. J Am Coll Cardiol 2008;51:690-7.

8. Stone GW, Witzenbichler B, Guagliumi G, et al. Bivalirudin during primary PCI in acute myocardial infarction. N Engl J Med 2008;358:2218-30.

9. Jolly SS, Yusuf S, Cairns J, et al. Radial versus femoral access for coronary angiography and intervention in patients with acute coronary syndromes (RIVAL): a randomised, parallel group, multicentre trial. Lancet 2011;377:1409-20.

10. Romagnoli E, Biondi-Zoccai G, Sciahbasi A, et al. Radial versus femoral randomized investigation in st-segment elevation acute coronary syndrome: the rifle-steacs (radial versus femoral randomized investigation in st-elevation acute coronary syndrome) study. J Am Coll Cardiol 2012;60:2481-9.

11. Bernat I, Horak D, Stasek J, et al. ST-segment elevation myocardial infarction treated by radial or femoral approach in a multicenter randomized clinical trial: the STEMI-RADIAL trial. J Am Coll Cardiol 2014;63:964-72.

12. Sanborn TA, Tomey MI, Mehran R, et al. Femoral vascular closure device use, bivalirudin anticoagulation, and bleeding after primary angioplasty for STEMI: results from the HORIZONS-AMI trial. Catheter Cardiovasc Interv 2015;85:371-9.

13. Hermanides RS, Ottervanger JP, Dambrink JHE, et al. Closure device or manual compression in patients undergoing percutaneous coronary intervention: a randomized comparison. J Invasive Cardiol 2010;22:562-6.

14. Biancari F, D'Andrea V, Di Marco C, et al. Meta-analysis of randomized trials on the efficacy of vascular closure devices after diagnostic angiography and angioplasty. Am Heart J 2010;159:518-31.

15. Verheugt FWA, Steinhubl SR, Hamon M, et al. Incidence, prognostic impact, and influence of antithrombotic therapy on access and nonaccess site bleeding in percutaneous coronary intervention. JACC Cardiovasc Interv 2011;4:191-7.

16. Vavalle JP, Clare R, Chiswell K, et al. Prognostic significance of bleeding location and severity among patients with acute coronary syndromes. JACC Cardiovasc Interv 2013;6:709-17.

17. Chhatriwalla AK, Amin AP, Kennedy KF, et al. Association between bleeding events and in-hospital mortality after percutaneous coronary intervention. JAMA 2013;309:1022-9.

18. Kikkert WJ, Delewi R, Ouweneel DM, et al. Prognostic value of access site and nonaccess site bleeding after percutaneous coronary intervention: a cohort study in ST-segment elevation myocardial infarction and comprehensive meta-analysis. JACC Cardiovasc Interv 2014;7:622-30.

19. Vranckx P, Campo G, Anselmi M, et al. Does the site of bleeding matter? A stratified analysis on location of TIMI-graded bleedings and their

impact on 12-month outcome in patients with ST-segment elevation myocardial infarction. EuroIntervention 2012;8:71-8.

20. Fordyce CB, Cairns JA, Singer J, et al. Evolution and impact of a regional reperfusion system for ST-elevation myocardial infarction. Can J Cardiol 2016;32:1222-30.

21. Wenner JB, Wong GC, Cairns JA, et al. Impact of patient- and system-level delays on reperfusion among patients with ST-elevation myocardial infarction. CJC Open 2020;2:94-103.

22. Morrow DA, Antman EM, Charlesworth A, et al. TIMI risk score for ST-elevation myocardial infarction: a convenient, bedside, clinical score for risk assessment at presentation: an Intravenous nPA for treatment of infarcting myocardium early II trial substudy. Circulation 2000;102:2031-7.

23. Chesebro JH, Knatterud G, Roberts R, et al. Thrombolysis in myocardial infarction (TIMI) trial, phase I: a comparison between intravenous tissue plasminogen activator and intravenous streptokinase. Clinical findings through hospital discharge. Circulation 1987;76:142-54.

24. Moscucci M, Fox KAA, Cannon CP, et al. Predictors of major bleeding in acute coronary syndromes: the Global Registry of Acute Coronary Events (GRACE). Eur Heart J 2003;24:1815-23.

25. Kinnaird TD, Stabile E, Mintz GS, et al. Incidence, predictors, and prognostic implications of bleeding and blood transfusion following percutaneous coronary interventions. Am J Cardiol 2003;92:930-5.

26. Feit F, Voeltz MD, Attubato MJ, et al. Predictors and impact of major hemorrhage on mortality following percutaneous coronary intervention from the REPLACE-2 Trial. Am J Cardiol 2007;100:1364-9.

27. Rao SV, McCoy LA, Spertus JA, et al. An updated bleeding model to predict the risk of post-procedure bleeding among patients undergoing percutaneous coronary intervention: a report using an expanded bleeding definition from the national cardiovascular data registry CathPCI registry. JACC Cardiovasc Interv 2013;6:897-904.

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

29. Kwok CS, Khan MA, Rao SV, et al. Access and non-access site bleeding after percutaneous coronary intervention and risk of subsequent mortality and major adverse cardiovascular events. Circ Cardiovasc Interv 2015;8:1-11.

30. Riley RF, Newby LK, Don CW, et al. Guidelines-based treatment of anaemic STEMI patients: practice patterns and effects on in-hospital mortality: a retrospective analysis from the NCDR. Eur Heart J Acute Cardiovasc Care 2013;2:35-43.

31. Sehested TSG, Carlson N, Hansen PW, et al. Reduced risk of gastrointestinal bleeding associated with proton pump inhibitor therapy in patients treated with dual antiplatelet therapy after myocardial infarction. Eur Heart J 2019;40:1963-70.

32. US National Library of Medicine/clinical trials.gov. Myocardial Ischemia and Transfusion (Mint) Trial. Available at: https://clinicaltrials.gov/ct2/show/NCT02981407. Accessed January 24, 2021.

33. Aronow HD, Peyser PA, Eagle KA, et al. Predictors of length of stay after coronary stenting. Am Heart J 2001;142:799-805.

Supplementary Material

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