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Aetiology and predictors of major bleeding events in patients with heart failure with reduced ejection fraction undergoing percutaneous coronary intervention

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ABSTRACT

Objectives We sought to determine the relationship between the degree of left ventricular ejection fraction (LVEF) impairment and the frequency and type of bleeding events after percutaneous coronary intervention (PCI).

Design This was an observational retrospective cohort analysis. Patients who underwent PCI from 2009 to 2017 were identified from our institutional National Cardiovascular Disease Registry (NCDR) CathPCI database. Patients were stratified by pre-PCI LVEF: preserved (≥50%), mildly reduced (41%–49%) and reduced (≤40%) LVEF.

Primary outcome measures The outcome was major bleeding, defined by NCDR criteria. Events were classified based on bleeding aetiology and analysed by multivariable logistic regression.

Results Among 13 537 PCIs, there were 817 bleeding events (6%). The rate of bleeding due to any cause, blood transfusion, gastrointestinal bleeding and coronary artery perforation or tamponade each increased in a stepwise fashion comparing preserved, mildly reduced and reduced LVEF reduction ($p<0.05$ for all comparisons). However, there were no differences in bleeding due to asymptomatic drops in haemoglobin, access site haematoma or retroperitoneal bleeding. After multivariable adjustment, mildly reduced and reduced LVEF remained independent predictors of bleeding events (OR 1.36, 95% CI 1.06 to 1.74, $p<0.05$ and OR 1.73, 95% CI 1.45 to 2.06, $p<0.0001$).

Conclusions The degree of LV dysfunction is an independent predictor of post-PCI major bleeding events. Patients with mildly reduced or reduced LVEF are at greatest risk of post-PCI bleeding, driven by an increased need for blood transfusion, major GI bleeding events and coronary artery perforation or tamponade. Pre-PCI LV dysfunction does not predict asymptomatic declines in haemoglobin, access site haematoma or retroperitoneal bleeding.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Patients with reduced left ventricular ejection fraction (LVEF) who undergo percutaneous coronary intervention (PCI) are at high risk for adverse outcomes.

⇒ The utility of coronary revascularisation in this patient population is unknown, due to increased periprocedural risks including major bleeding events and mortality, and limited information on which patients may receive improvement in left ventricular function.

WHAT THIS STUDY ADDS

⇒ In this analysis of a large cohort study of patients undergoing PCI at a quaternary referral centre, we use a robust dataset with high-quality patient-level data.

⇒ We provide in-depth analysis of the specific aetiologies of post-PCI bleeding events, stratified by degree of preprocedural left ventricular dysfunction. We show that the degree of preprocedural left ventricular dysfunction is an independent predictor of post-PCI major bleeding events in a stepwise manner, driven by an increased risk of blood transfusion, gastrointestinal (GI)/genitourinary (GU) bleeds and coronary artery perforation or tamponade.

⇒ To our knowledge, this is the first study to signal that there may be an interaction between the acuity of PCI and left ventricular function in predicting major bleeding events.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings suggest that targeting patients with reduced LVEF with GI/GU protective measures and reconsideration of periprocedural anticoagulant strategies may be warranted to protect this patient population from adverse outcomes post-PCI.

INTRODUCTION

Current guidelines on revascularisation strategies for patients with reduced left ventricular ejection fraction (LVEF) are limited. According to the 2021 American College of Cardiology (ACC), American

Heart Association (AHA), Society for Cardiovascular Angiography and Interventions (SCAI) Guidelines for Coronary Artery Revascularisation,[1] there are insufficient data to make recommendations regarding the utility of percutaneous coronary intervention (PCI) in patients with severe left ventricular (LV) dysfunction. This is in part due to the lack of evidence showing a benefit with regard to improvement in LVEF and increased periprocedural risks, including major bleeding and mortality, in this patient population.[2–4]

Several risk scores to predict post-PCI bleeding events exist; however, not all include pre-PCI LVEF as a predictive variable. Among the most widely used, the SCAI/BMC2 Cardiovascular Consortium PCI Risk Assessment Tool[5 6] includes pre-PCI LVEF as a predictor for major bleeding per the National Cardiovascular Data Registry (NCDR) definition (including a composite of blood transfusion, access site haematoma, major gastrointestinal (GI) bleeding, retroperitoneal bleeding, coronary artery perforation or tamponade or an asymptomatic decline in haemoglobin (Hgb) ≥30 g/L within 72 hours after PCI). While the SCAI/BMC2 risk model has good predictive accuracy of major bleeding events (C statistic 0.89),[7] to date, no study has evaluated whether there is a relationship between the degree of LV function and the type of major bleeding when stratified by aetiology.

Accordingly, we conducted a study to determine the relationship between the degree of LV dysfunction and the frequency and aetiology of major bleeding events post-PCI. This information may be especially important to providers and inform optimal bleeding avoidance strategies pre-PCI and post-PCI.

METHODOLOGY

Study design and data collection

We conducted a retrospective observational cohort study of patients who underwent PCI at the Cleveland Clinic from 2009 to 2017, identified using the institutional NCDR CathPCI database. The study population includes all patients who underwent PCI at Cleveland Clinic. Patients who underwent only diagnostic or right-heart catheterisation were excluded.

Procedural characteristics and 30-day outcomes were obtained from the institutional CathPCI database. Further granular-level patient information, including demographics, baseline characteristics and laboratory values, was obtained from electronic medical records. Preprocedural LVEF was obtained from echocardiographic data. The study was approved by the institutional review board.

Definition of exposures and outcomes

Patients were stratified by pre-PCI LVEF, obtained from a transthoracic or transoesophageal echocardiogram. LVEF categories were defined as preserved (≥50%), mildly reduced (41%–49%) and reduced (≤40%). The outcome was major in-hospital bleeding events due to any cause, defined by NCDR criteria as any of the following occurring within 72 hours after PCI or before hospital discharge (whichever occurred first):

1. An asymptomatic postprocedure Hgb decrease of ≥30 g/L in patients with a preprocedure Hgb ≤160 g/L.
2. Postprocedure non-bypass surgery-related blood transfusion in patients with a preprocedure Hgb level ≥80 g/L without overt blood loss other than from the procedure.
3. Arterial access site bleeding producing a meaningful haematoma (>10 cm for femoral access, >5 cm for brachial access and >2 cm for radial access).
4. Significant retroperitoneal, GI or genitourinary (GU) bleeding.
5. Coronary artery perforation causing pericardial effusion, cardiac tamponade or other serious organ bleeding (including intracranial haemorrhage).

Statistical analysis

Tests for significant variations in baseline and procedural characteristics were performed using the Student's t-test (for continuous, normally distributed variables), the Mann-Whitney U test (for continuous, non-parametric distributed variables), the χ^2 test (for categorical variables) and the Fisher's exact test (for categorical, non-parametric distributed variables). A p value of <0.05 was considered statistically significant.

Events were classified based on bleeding source and analysed by multivariable logistic regression. The analyses were adjusted for age, sex, body mass index (BMI), pre-PCI Hgb levels, access site and coronary artery disease (CAD) presentation. Statistical analysis was performed on JMP Pro (JMP, V.16. SAS Institute, Cary, North Carolina, USA) and RStudio (R Core Team, Vienna, Austria).

Patient and public involvement

There was no patient or public involvement in the design, conduct, or reporting of this work.

RESULTS

Baseline and procedural characteristics

The patient characteristics stratified by LVEF presentation are presented in table 1. Overall, of all patients who presented for PCI (both elective and non-elective procedures), the majority presented with preserved LVEF (68.9% of patients). Fewer presented with some degree of LV dysfunction (mild reduction (10.6%) and reduced (20.5%)). Across all degrees of LV presentation, patients had an average age over 65 years, an average BMI greater than 29 (overweight or obese categories) and the majority were Caucasian and male. Though there were statistical differences in the distribution of baseline characteristics between groups with reduced LVEF correlated with increased prevalence of diabetes, prior myocardial infarction, prior heart failure and haemodialysis use, the differences were relatively small and not likely to be clinically significant. A larger proportion of individuals with reduced LVEF presented with a worsened degree of baseline kidney function (chronic kidney disease stages 3a–5),

Table 1 Baseline characteristics of patients undergoing PCI at Cleveland Clinic from 2009 to 2017

Pre-PCI left ventricular ejection fraction				
	Preserved (≥50%)	**Mildly reduced (41%–49%)**	**Reduced (≤40%)**	**P value**
n	9329	1437	2771	
Age (years) (mean (SD))	65.7 (11.8)	66.0 (12.0)	67.1 (12.2)	<0.0001*
Sex—male (%)	6450 (69.1)	1044 (72.7)	2030 (73.3)	<0.0001*
Race (%)†				0.0049*
White	7578 (81.2)	1156 (80.4)	2181 (78.7)	
Black	1263 (13.6)	220 (15.3)	445 (16.1)	
Other	488 (5.2)	61 (4.2)	144 (5.2)	
Body mass index (kg/m^2) (mean (SD))	30.3 (6.3)	29.9 (6.3)	29.4 (6.5)	<0.0001*
Smoker (%)‡	1970 (21.1)	370 (25.7)	791 (28.5)	<0.0001*
Essential hypertension (%)	8177 (87.7)	1278 (88.9)	2469 (89.1)	0.0676
Diabetes (%)	3590 (38.4)	629 (43.8)	1338 (48.3)	<0.0001*
Dyslipidaemia (%)	8466 (90.7)	1273 (88.6)	2484 (89.6)	0.0156*
Family history of coronary artery disease (%)	2842 (30.5)	381 (26.5)	698 (25.2)	<0.0001*
Prior history of myocardial infarction (%)	3227 (34.6)	764 (53.2)	1686 (60.8)	<0.0001*
Prior history of heart failure (%)	1329 (14.3)	499 (34.7)	1640 (59.2)	<0.0001*
Prior history of PCI (%)	4216 (45.2)	695 (48.4)	1297 (46.8)	0.0428*
Prior history of coronary artery bypass grafting (%)	2664 (28.6)	503 (35.0)	997 (36.0)	<0.0001*
Chronic kidney disease (%)				<0.0001*
Stage 1 (estimated glomerular filtration rate ≥90 mL/min/1.73 m^2)	3309 (35.5)	455 (31.7)	738 (26.6)	
Stage 2 (60–89)	3949 (42.3)	575 (40.0)	1034 (37.3)	
Stage 3a (45-5–9)	1165 (12.5)	201 (14.0)	436 (15.7)	
Stage 3b (30–44)	528 (5.7)	103 (7.2)	307 (11.1)	
Stage 4 (15–29)	147 (1.6)	36 (2.5)	104 (3.8)	
Stage 5 (≤15)	30 (0.3)	4 (0.3)	18 (0.7)	
Current dialysis (%)	201 (2.2)	63 (4.4)	134 (4.8)	<0.0001*
Prior history of cardiovascular disease (%)	1712 (18.4)	300 (20.9)	637 (23.0)	<0.0001*
Prior history of peripheral artery disease (%)	1533 (16.4)	293 (20.4)	681 (24.6)	<0.0001*
Chronic lung disease (%)	1314 (14.1)	273 (19.0)	642 (23.2)	<0.0001*
Cardiac transplant recipient (%)	33 (0.4)	3 (0.2)	9 (0.3)	0.6717

*Denotes statistical significance at p<0.05.
†Missing values for race: reduced (1).
‡Current or past smoker.
PCI, percutaneous coronary intervention.

compared with patients with preserved or mildly reduced LVEF (p<0.05).

Procedural characteristics and NCDR-reported outcomes post-PCI are provided in table 2. The largest frequency of PCI procedures was performed using the femoral artery as the access site. Across all LVEF presentations, most patients presented with unstable angina/non-ST elevated myocardial infarction. The majority of individuals received procedural anticoagulants (unfractionated heparin, low molecular weight heparin and direct thrombin inhibitors) and dual antiplatelet therapy (DAPT). Few patients received GpIIb/IIIa inhibitors for anticoagulant therapy (n=126, 0.93% of total patients). Among individuals who presented with reduced LVEF, a higher percentage presented with acute kidney injury. These individuals had slightly lower Hgb levels, both before and after PCI. Of these individuals, a significant number had also experienced cardiogenic shock or cardiac arrest prior to PCI.

Prevalence and type of bleeding events

Among the 13 537 PCIs, there were 817 bleeding events due to any cause (6%) (figure 1). The majority of bleeding events were due to packed red blood cell transfusions (n=382), followed by asymptomatic drops

Table 2 Procedural characteristics of PCI procedures at Cleveland Clinic from 2009 to 2017

Pre-PCI left ventricular ejection fraction				
	Preserved (≥50%)	Mildly reduced (41%–49%)	Reduced (≤40%)	P value
n	9329	1437	2771	
Access site (%)				<0.0001*
Femoral	6680 (71.6)	1038 (72.2)	2150 (77.6)	
Radial	2568 (27.5)	391 (27.2)	593 (21.4)	
Brachial	73 (0.8)	8 (0.6)	25 (0.9)	
Other	8 (0.09)	0 (0.0)	3 (0.1)	
Fluoroscopy time (min) (median (IQR))	21 (13.9–32.4)	22.5 (15.0–35.3)	23.2 (15.2–36.6)	<0.0001*
Fluoroscopy dose (mGy) (median (IQR))	1754 (1042–2873.5)	1787 (1041–2921)	1893 (1119–3100)	<0.0001*
Contrast volume (mL) (median (IQR))	170 (130–225)	170 (120–225)	165 (120–220)	<0.0001*
Coronary artery disease presentation (%)				<0.0001*
Stable angina	2750 (29.5)	393 (27.3)	398 (14.4)	
Unstable angina/non-ST elevated myocardial infarction	4861 (52.1)	768 (53.4)	1626 (58.7)	
ST elevated myocardial infarction	1254 (13.4)	218 (15.2)	398 (14.4)	
Pre-PCI creatinine (mg/dL) (median (IQR))	1 (0.8–1.2)	1 (0.8–1.3)	1.1 (0.9–1.4)	<0.0001*
Post-PCI creatinine (mg/dL) (median (IQR))	1 (0.8–1.2)	1 (0.8–1.3)	1.1 (0.9–1.5)	<0.0001*
Pre-PCI Hgb (g/dL) (mean (SD))	13.4 (1.9)	13.0 (2.2)	12.6 (2.2)	<0.0001*
Post-PCI Hgb (g/dL) (mean (SD))	12.4 (2.0)	11.9 (2.1)	11.6 (2.3)	<0.0001*
Anticoagulant therapy (%)†	9300 (99.7)	1429 (99.4)	2749 (99.2)	0.0024*
Dual antiplatelet therapy (%)‡	9142 (98.0)	1408 (98.0)	2700 (97.4)	0.1937
Acute kidney injury (%)§	599 (6.4)	145 (10.1)	426 (15.4)	<0.0001*
Cardiogenic shock prior to PCI (%)¶	149 (1.6)	55 (3.8)	232 (8.4)	<0.0001*
Cardiac arrest prior to PCI (%)	152 (1.6)	42 (2.9)	102 (3.7)	<0.0001*

*Denotes statistical significance at p<0.05.
†Includes direct thrombin inhibitors, unfractionated heparin, low molecular weight heparin
‡Includes aspirin + P2Y12 inhibitor (clopidogrel, prasugrel, ticagrelor)
§AKI (Acute Kidney Injury) stages defined by NCDR Criteria as relative increase of 50% in serum creatinine (Cr) from baseline or absolute increase in Cr by 0.3 mg/dL, within 72 hours after PCI. Missing values for AKI: Preserved (2), Mildly Reduced (2), Reduced (2)
¶Missing values for Cardiogenic Shock Prior to PCI: Preserved (5), Mildly Reduced (1)
PCI, percutaneous coronary intervention.

in Hgb (n=220), GI or GU bleeding (n=59), access site haematoma (n=65), coronary artery perforation or tamponade (n=76) and retroperitoneal bleeding (n=15). Stratification of bleeding events by CAD presentation is provided in online supplemental table S1. Regardless of CAD presentation, the majority of bleeding events were asymptomatic or the need for packed red blood cell transfusion (S1).

The rate of any (composite) bleeding, blood transfusion, GI/GU bleeding and coronary artery perforation or tamponade increased in a stepwise fashion comparing preserved, mildly reduced and reduced LVEF (p<0.0001, p<0.0001 and p<0.05, respectively) (figure 2). There were no differences in events due to asymptomatic drops in Hgb, access site haematoma or retroperitoneal bleeding (p=non-significant for all comparisons) when stratified by pre-PCI LVEFs.

LVEF is an independent predictor of bleeding events

Logistic regression models were used to compare the risk of bleeding events among individuals presenting with different degrees of LV dysfunction (table 3). After multivariable adjustment, mildly reduced LVEF (OR 1.36, 95% CI 1.06 to 1.74, p<0.05) and reduced LVEF (OR 1.73, 95% CI 1.45 to 2.06, p<0.0001) remained independent predictors of major in-hospital bleeding events.

Additional models were created to test for interaction between acuity of presentation and degree of LVEF dysfunction (online supplemental table S2). In a model including only CAD presentation (defined as ST elevated myocardial infarction (STEMI) vs other presentations), LVEF (defined as preserved or mildly reduced LVEF (>40%) vs reduced LVEF (≤40%)) and their interaction, there was evidence for effect modification (CAD presentation × LVEF; p<0.0001).

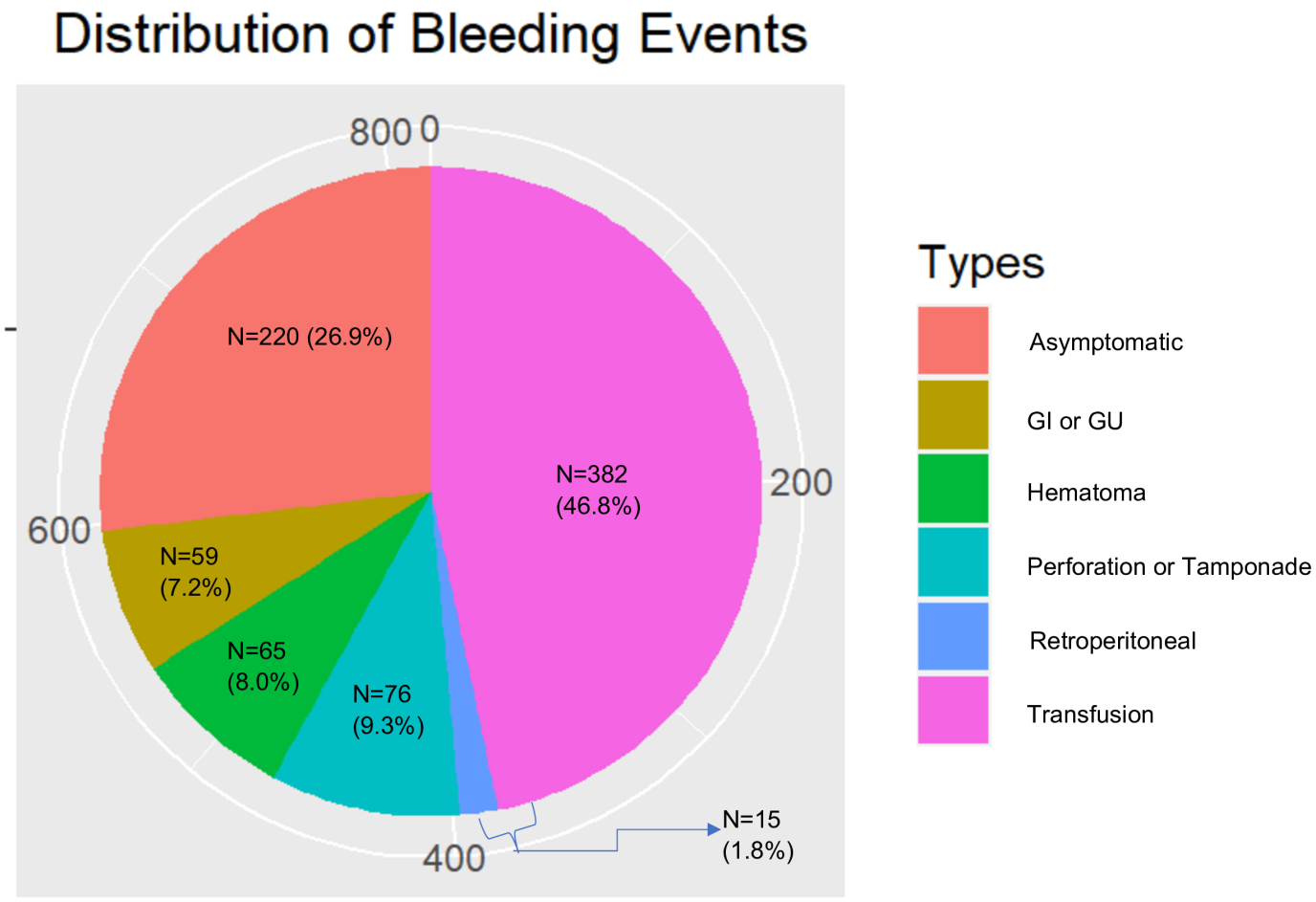

Figure 1 Distribution of bleeding events, stratified by type of event; n=817 total bleeding events. GI, gastrointestinal and GU, genitourinary.

Revised definition of asymptomatic drop in Hgb

In 2021, the NCDR changed the definition of an asymptomatic bleeding event to include a fall in Hgb ≥40 g/L (previously ≥30 g/L) in an individual with pre-PCI Hgb ≤160 g/L. Using this threshold, the rate of bleeding declined slightly to 636 events (4.7%), and the number of asymptomatic bleeding events fell to n=39 (22 with preserved LVEF, 11 with mildly reduced LVEF dysfunction and 6 with reduced LVEF dysfunction). After multivariable adjustment, our key results did not change, as pre-PCI LVEF remained an independent predictor of major bleeding events, with mildly reduced LVEF (OR 1.44, 95% CI 1.09 to 1.90, p<0.01) and reduced LVEF (OR 1.87, 95% CI 1.53 to 2.27, p<0.0001).

DISCUSSION

In our study, we demonstrate that despite robust adjustment for variables known to be associated with bleeding, pre-PCI LV dysfunction is an independent predictor of bleeding events post-PCI. Moreover, we observed a strong relationship between the degree of pre-PCI LV dysfunction and post-PCI bleeding events, with a stepwise relationship between reduction in LVEF pre-PCI and risk of post-PCI bleeding. To our knowledge, this is the first study to demonstrate that the degree of pre-PCI LV dysfunction independently strongly predicts bleeding events in the first 72 hours after PCI and that this relationship varies among the different causes of bleeding. This knowledge may help providers stratify patients into risk categories for post-PCI bleeding based on the magnitude of LVEF reduction prior to the case. Possible mechanisms linking LV dysfunction to the risk of bleeding are multifactorial. Patients with LV dysfunction are inherently a higher-risk patient population. The combination of advanced patient age, concomitant medication use (eg, non-steroidal anti-inflammatory drugs use), comorbidities (including atrial fibrillation with concurrent anticoagulant use or history of PCI with concurrent DAPT use), as well as physiological stress during PCI may predispose patients with reduced LVEF to increased bleeding risk. Knowledge of the patient's LVEF prior to the procedure may help providers anticipate which patients are at the highest risk of bleeding events.

We found that the stepwise increase in bleeding events in patients with reduced LVEF is driven by an increased risk of blood transfusion, GI/GU bleeding and coronary artery perforation or tamponade rather than other bleeding aetiologies. In specific, asymptomatic falls in Hgb, access site bleeding and retroperitoneal haemorrhage did not vary when stratified by LVEF. Our results are

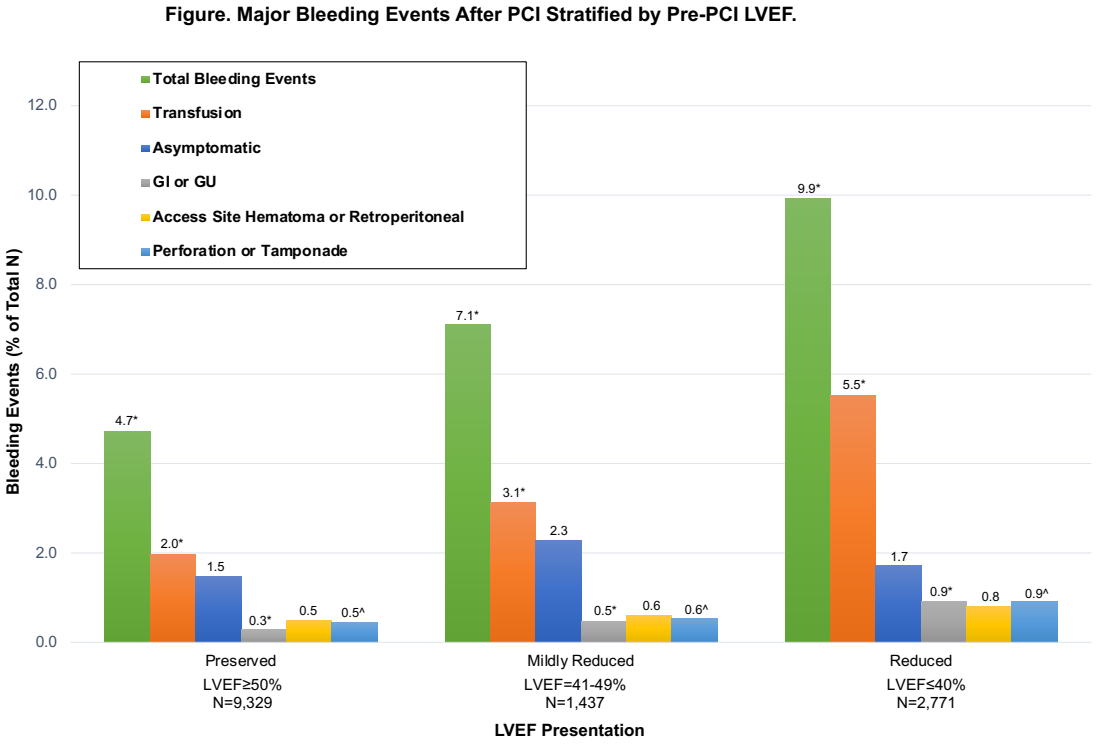

Figure 2 Major bleeding events after PCI, stratified by preprocedural LVEF. *Denotes statistical significance at p<0.0001 (comparing preserved, mildly reduced and reduced LVEF presentations); ^Denotes statistical significance at p<0.05 (comparing all LVEF presentations). GI, gastrointestinal; GU, genitourinary; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention.

consistent with previous studies, including data suggesting that coronary artery perforation or tamponade is more common in high-risk patients undergoing complex PCI and is associated with adverse outcomes, including periprocedural mortality.[8] Our data suggest that targeting patients who have reduced LVEF with GI and GU protective measures may be especially effective at reducing the risk of bleeding in patients post-PCI. This may include the use of proton pump inhibitors, H2-receptor blockers or consideration of anticoagulant strategies associated with fewer bleeding events, such as bivalirudin, compared with unfractionated heparin.[9] In our model, we adjusted for procedural anticoagulant and DAPT use and found that DAPT use plays a protective role in lowering bleeding risk (OR 0.48, 95% CI 0.32 to 0.72, p<0.001). We created additional models stratifying by type of anticoagulant and DAPT and found that procedural P2Y12 inhibitor and direct thrombin inhibitor therapies play a protective role against bleeding after PCI (online supplemental table S3). All patients followed standard protocol for anticoagulation during PCI, including targeting an activated coagulation time of 250–300 s. While we did not adjust for the presence of atrial fibrillation or anticoagulant use pre-PCI due to the unavailability of these data in our database, our findings suggest that a cautious approach of slow reinitiation of anticoagulation in patients on it prior to PCI may be warranted. Likewise, discontinuation of aspirin and de-escalation to P2Y12 inhibitor therapy in patients also on anticoagulation should be considered to reduce the risk of post-PCI bleeding, especially in patients with reduced LVEF.

Our approach to including the magnitude of reduction in LVEF as a predictor of bleeding events is novel. The Academic Research Consortium for High Bleeding Risk (ARC-HBR)[10] criteria capture the most up-to-date consensus on risk stratification for postprocedural bleeding events. This score defines factors for high-risk bleeding after PCI, including older age (over 75 years), bleeding history, central nervous system issues and renal and liver disease comorbidities.[11] The ARC-HBR score has been validated in prospective cohort studies, which have concluded that this score is more sensitive in identifying future bleeding events in patients compared with other contemporary risk scores, including the Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy (PRECISE-DAPT) and Patterns of non-Adherence to Anti-Platelet Regimen in Stented Patients (PARIS) risk scores.[12] The ARC-HBR score has also been validated as a measure that is able to identify patients' risk of experiencing bleeding, thrombotic events and all-cause mortality.[13] However, while this score captures several critical patient characteristics and comorbidities in its risk score, it does not include a measure of LVEF dysfunction.

Two periprocedural risk calculators are available to determine a patient's bleeding risk during PCI, including

Table 3 Multivariable-adjusted ORs for composite bleeding events

	Model 1 (Pre-PCI LVEF defined continuously)		Model 2 (Pre-PCI LVEF defined categorically)	
	OR (95% CI)	P value	OR (95% CI)	P value
Pre-PCI LVEF (%)	0.983 (0.978 to 0.988)	<0.0001*		
Pre-PCI LVEF			1.36 (1.06 to 1.74)	0.0143*
Mildly reduced (LVEF 41%–49%)				
Reduced (LVEF ≤40%)			1.73 (1.45 to 2.06)	<0.0001*
Age (years)	1.02 (1.01 to 1.02)	<0.0001*	1.02 (1.01 to 1.02)	<0.0001*
Female sex	1.30 (1.11 to 1.54)	0.0017*	1.29 (1.09 to 1.52)	0.0025*
BMI (kg/m^2)	0.98 (0.97 to 0.99)	0.0031*	0.98 (0.97 to 0.99)	0.0026*
Pre-PCI Hgb (g/dL)	0.79 (0.76 to 0.82)	<0.0001*	0.79 (0.76 to 0.82)	<0.0001*
Access site				
Radial	0.79 (0.65 to 0.95)	0.0128*	0.78 (0.64 to 0.94)	0.0094*
CAD presentation				
Stable angina/other	0.95 (0.59 to 1.52)	0.8307	0.95 (0.59 to 1.51)	0.8138
Unstable angina/non-ST elevated myocardial infarction	1.43 (0.92 to 2.21)	0.1138	1.42 (0.92 to 2.21)	0.1165
ST elevated myocardial infarction	7.80 (4.97 to 12.23)	<0.0001*	7.84 (5.00 to 12.30)	<0.0001*
Chronic kidney disease				
Stage 2 (estimated glomerular filtration rate 60–89 mL/min/1.73m^2)	1.06 (0.86 to 1.31)	0.5989	1.06 (0.85 to 1.31)	0.6108
Stage 3a (45–59)	1.37 (1.05 to 1.77)	0.0188*	1.37 (1.06 to 1.77)	0.0176*
Stage 3b (30–44)	1.92 (1.44 to 2.55)	<0.0001*	1.94 (1.46 to 2.57)	<0.0001*
Stage 4 (16–29)	2.56 (1.77 to 3.70)	<0.0001*	2.59 (1.80 to 3.75)	<0.0001*
Stage 5 (≤15)	1.99 (0.89 to 4.45)	0.0941	2.03 (0.91 to 4.54)	0.0858
Anticoagulant therapy	2.33 (0.65 to 8.27)	0.1919	2.21 (0.63 to 7.79)	0.2173
DAPT	0.48 (0.32 to 0.72)	0.0004*	0.48 (0.32 to 0.71)	0.0003*

After multivariable adjustment for age, sex, BMI, pre-PCI Hgb, baseline kidney function, access site, pre-PCI LVEF, procedural anticoagulant and DAPT therapy, and CAD presentation.
*Denotes statistical significance at p<0.05.
BMI, body mass index; DAPT, dual antiplatelet therapy; Hgb, haemoglobin; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention.

the SCAI/BMC2 PCI Risk Calculator[5 6] and the ACC CathPCI Bleeding Risk Calculator.[14] However, of these two periprocedural risk calculators, the SCAI/BMC2 PCI Risk Calculator is the only one that includes a pre-PCI LVEF presentation. We expand on this as we demonstrate that certain types of bleeding are associated with reduced LV function post-PCI.

In our study, we also assessed for possible effect modification between the acuity of CAD presentation and the magnitude of LVEF dysfunction pre-PCI. In a model including CAD presentation and LVEF dysfunction, defined as dichotomised variables, there was evidence of an interaction between CAD presentations and LVEF. This suggests an additive risk in patients with reduced LVEF (≤40%) presenting with STEMI and that patients without STEMI presentations and preserved or mildly reduced LVEF (>40%) may have lower bleeding events. Importantly, this interaction was not seen while dichotomising CAD presentation and LVEF in other ways, or when including other terms for multivariable adjustment, suggesting that the interaction may be weak or that we were not well-powered for this assessment. However, ours is the first study to signal there may be an interaction between the acuity of PCI and LV function and suggests additional studies are needed to further assess this relationship.

In our study, we defined an asymptomatic bleeding event as a decline in Hgb ≥30 g/L in an individual with a pre-PCI Hgb <160 g/L, based on the criteria outlined by Rao *et al*.[3] However, during the course of the study, the NCDR changed the working definition of an asymptomatic bleeding event to require a decline in Hgb ≥40 g/L. As such, we provide a secondary analysis using this threshold, which did not significantly change results.

Importantly, in our study, the majority of patients received femoral access for PCI. The reason for this is that our data includes patients from 2007 to 2017; radial access was not yet widely used until halfway through this time frame. Between 2011 and 2018, radial access for PCI increased from 14% to approximately 52% nationally,

based on data from the Clinical Assessment, Reporting and Tracking Programme, regardless of the indication for PCI.[15] In our current practice, approximately 75% of patients undergo radial access for PCI at our institution.

The current study has certain limitations. This was a retrospective, observational cohort study that was performed for quality assessment purposes. There is a possibility for selection bias; however, to adjust for this, we do create multivariable models. In addition, while we uncovered a possible interaction between acuity of presentation and LVEF, this was not seen after multivariable adjustment, suggesting a weak relationship or that our study was not powered to assess for interaction. In addition, while we do have some missing values, they are randomly selected among the patient groups and few in number, underscoring the high-quality nature of our patient-level data. As this study was performed between 2009 and 2017, we use older NCDR definitions that have since been updated. Therefore, in our analysis, we were unable to include information regarding stent type and rates of haemostatic or compression devices used in patients after PCI. Nonetheless, only 8% of bleeding events were access site haematoma, and 1.8% were retroperitoneal bleeding. There are data to suggest that stent type may affect bleeding and mortality in patients undergoing PCI.[16–18] However, as this was an analysis of in-hospital outcomes, it is unlikely that stent type would have impacted acute bleeding events. We did not have data regarding access site crossover or the number of puncture attempts performed until the artery access site was achieved. We also did not have data regarding the level of operator experience and how many procedures were performed during on-hours versus off-hours. Previously published data suggests that higher operator experience in radial artery access might be associated with worse outcomes in scenarios requiring femoral artery access.[19] Furthermore, timing of primary PCI for STEMI during on-hours and off-hours may lead to differing procedural characteristics, including radiation dose, and adverse outcomes, including rates of periprocedural mortality.[20]

CONCLUSIONS

There is a strong relationship between post-PCI bleeding and mortality, and as such, it is imperative to carefully assess a patient's risk factors for postprocedural bleeding events. Pre-PCI LV dysfunction independently predicts an increased risk of post-PCI major bleeding events in a stepwise manner. This is driven by an increased risk of blood transfusion, GI/GU bleeding and coronary artery perforation or tamponade, rather than other bleeding aetiologies. GI and GU protective measures may be especially relevant to reduce the risk of bleeding in patients with reduced LV function post-PCI.

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