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Incidence, Prognostic Impact, and Influence of Antithrombotic Therapy on Access and Nonaccess Site Bleeding in Percutaneous Coronary Intervention

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Objectives The aim of this study was to evaluate the relative frequency of access and nonaccess site bleeding, the association of these events with 1-year mortality, and the impact of randomized antithrombotic therapy.

Background Post-percutaneous coronary intervention (PCI) bleeding has been strongly associated with subsequent mortality. The extent to which access versus nonaccess site bleeding contributes to this poor prognosis and the role of antithrombotic therapies remains poorly understood.

Methods The incidence and impact of Thrombolysis In Myocardial Infarction (TIMI) major/minor 30-day bleeding and randomized antithrombotic therapy were examined in a combined dataset from the REPLACE-2 (Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events), Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY), and HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) trials in 17,393 PCI patients.

Results The TIMI major/minor bleeding occurred in 5.3% of patients, 61.4% of which (3.3%) were nonaccess site bleeds. After multivariable adjustment, TIMI bleeding was associated with an increased risk of 1-year mortality (hazard ratio [HR]: 3.17, 95% confidence interval [CI]: 2.51 to 4.00, $p < 0.0001$). The HR of a nonaccess site bleed was approximately 2-fold that of an access site bleed: HR: 3.94, 95% CI: 3.07 to 5.15, $p < 0.0001$ versus HR: 1.82, 95% CI: 1.17 to 2.83, $p = 0.008$, respectively. Randomization to bivalirudin versus heparin + a glycoprotein IIb/IIIa inhibitor resulted in 38% and 43% relative reductions in TIMI major/minor and TIMI major bleeding, respectively ($p < 0.0001$ for both), with significant reductions in both access and nonaccess site bleeding.

Conclusions Nonaccess site bleeding after PCI is common, representing approximately two-thirds of all TIMI bleeding events, and is associated with a 4-fold increase in 1-year mortality. Use of bivalirudin rather than heparin + a glycoprotein IIb/IIIa inhibitor significantly decreases both nonaccess site as well as access site bleeding events by approximately 40%. (J Am Coll Cardiol Intv 2011;4:191–7)

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The most common in-hospital complications of percutaneous coronary intervention (PCI) are myocardial infarction (MI) and bleeding (1–4). Both of these adverse events are independently and strongly associated with long-term mortality, with comparable prognostic impact (1,2). The consistent association between these modifiable complications and survival highlights the importance of selecting pharmacological therapies and interventional techniques that minimize both.

A frequent source of bleeding for PCI patients is the arterial access site, in particular femoral artery access. Although radial artery access has been associated with a significant reduction in overall bleeding (3), most patients enrolled in trials examining the outcomes of antithrombotic agents have undergone PCI with femoral artery access (4–9). In such patients bleeding might arise from either the femoral access site or other sources. The relative frequency and contribution of hemorrhagic complications from femoral versus nonfemoral bleeding sites to the long-term prognosis of patients after PCI has not been determined.

Abbreviations and Acronyms

GPI = glycoprotein IIb/IIIa inhibitor

MI = myocardial infarction

PCI = percutaneous coronary intervention

STEMI = ST-segment elevation myocardial infarction

TIMI = Thrombolysis In Myocardial Infarction

In the current analysis the data from 3 large-scale, prospective, randomized trials of bivalirudin versus heparin plus a glycoprotein IIb/IIIa inhibitor (GPI) were pooled to evaluate the relative incidence of access site and nonaccess site bleeding, the association of these events with 1-year mortality, and the relative impact of randomized antithrombotic therapy on each type of bleeding. These studies span the whole spectrum of clinical settings for PCI, ranging from patients undergoing elective PCI (in the REPLACE-2 [Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events] trial) to non–ST-segment elevation acute coronary syndromes (in the ACUITY [Acute Catheterization and Urgent Intervention Triage Strategy] trial) and primary PCI for ST-segment elevation myocardial infarction (STEMI) (in the HORIZONS-AMI [Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction] trial).

Methods

The current study population consists of 17,393 patients who underwent PCI as part of the REPLACE-2 (5), ACUITY (6), and HORIZONS-AMI (7) trials. The details of the study designs, end points, definitions, and results for each study have been previously described. A brief summary of these trials follows.

The REPLACE-2 trial included 6,010 patients undergoing elective or urgent PCI. Patients were randomized to heparin (65 U/kg bolus) plus a GPI or bivalirudin (0.75 mg/kg bolus before PCI with 1.75 mg/kg/h infusion during procedure) with provisional GPI use. All patients received aspirin, whereas pretreatment with clopidogrel with daily administration for at least 30 days after intervention was strongly encouraged. A PCI was performed only via the femoral approach. The ACUITY trial enrolled 13,819 patients with moderate- to high-risk acute coronary syndrome and in whom an invasive approach was planned. Patients were randomized to either heparin (unfractionated or enoxaparin) plus GPI, bivalirudin with planned GPI, or bivalirudin with provisional GPI. Unfractionated heparin was administered as an intravenous bolus of 60 U/kg followed by a 12 U/kg/h infusion to target an activated partial thromboplastin time of 50 to 75 s before angiography and an activated clotting time of 200 to 250 s during PCI. Bivalirudin was administered as an intravenous bolus of 0.1 mg/kg with an infusion of 0.5 mg/kg before PCI, which was subsequently increased to 1.75 mg/kg/h during PCI. Aspirin was administered daily during the hospital stay, whereas clopidogrel use was left to the discretion of the individual investigators, although a loading dose of 300 mg or more was required in all patients no later than 2 h after PCI.

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After angiography 7,789 patients underwent PCI. Only these patients are included in the present analysis; choice of vascular access site was left to the discretion of the investigator. The HORIZONS-AMI trial enrolled 3,602 patients with STEMI being treated with primary PCI. Patients were randomized to either heparin (60 IU/kg bolus with subsequent boluses targeting an activated clotting time of 200 to 250 s) with planned GPI therapy or to a bivalirudin (0.75 mg/kg bolus and 1.75 mg/kg/h infusion) with provisional GPI therapy. Again, all patients received aspirin and clopidogrel before and after PCI, and choice of vascular access site was left to the investigator.

End points and definitions. This study focuses on bleeding end points measured at 30 days. The 30-day protocol-defined bleeding differed among the 3 trials, with their specific definitions noted in their original reports. Thrombolysis In Myocardial Infarction (TIMI) major and minor bleeding was assessed in all 3 trials, however. Therefore, the occurrence of TIMI major or minor bleeding was chosen as the primary end point for the present study. The TIMI major bleeding was defined as a reduction of hemoglobin of ≥5 g/dl (or >15% in hematocrit), with or without overt bleeding, or any intracranial bleeding. A TIMI minor bleeding was defined as a 3 to 5 g/dl decrease in hemoglobin (or 10% to 15% in hematocrit) with an observed source of bleeding or a hemoglobin drop of 4 to 5 g/dl (or 12% to 15% hematocrit) without an observed source. A transfusion of a unit of whole blood or packed red blood cells was factored into the evaluation of blood loss and considered the equivalent of 1 g/dl of hemoglobin or 3% in hematocrit.

Bleeding location was determined locally by the investigators and recorded on the case report form. For the present analysis, access site bleeding was defined a priori as any bleeding identified as arising only from the access or puncture site or retroperitoneal in origin. Nonaccess site bleeding was defined as bleeding that was not confined to the access site only. Nonaccess site bleeding was further subdivided into 3 mutually exclusive cohorts: patients with both an access site and nonaccess bleed, patients with a nonaccess site bleed only, and those patients in whom no source for bleeding was identified.

Statistical analysis. Continuous variables were summarized by means and SD. Categorical variables were summarized by frequencies and percentage. A p value of <0.05 was considered statistically significant. Comparisons among treatment groups were made with the normal approximation test for population proportions.

The rates of 1-year mortality as a function of access site and nonaccess site bleeding were determined. To evaluate the adjusted association between bleeding site and 1-year mortality, we constructed a Cox proportional hazards regression model that adjusted for baseline characteristics. Covariates were selected with a forward stepwise procedure from a large number of candidate variables with $p < 0.20$ as the criterion for entry into the model. The following variables were included in the model: age as a continuous variable, anemia, baseline myocardial enzyme (creatine kinase-myocardial band or troponin) elevation, baseline creatinine clearance <60 ml/min, current smoker, diabetes mellitus, previous MI, and STEMI as presenting diagnosis. Pertinent candidate variables evaluated but not generally selected included randomized therapy, race, hypertension, sex, weight, previous PCI, multivessel intervention, and baseline platelet count <100,000. Adjusted hazard ratios (HRs) of the risk for mortality with 95% confidence intervals (CIs) are presented. We performed, as a secondary analysis, an analysis to examine the effect of different pharmacological regimens on both access site and nonaccess site bleeding by constructing a model that examined the effect of the different pharmacological regimens. All statistical analyses were performed by SAS (version 8.2, Cary, North Carolina).

Results

Of the 23,431 patients enrolled in the REPLACE-2, ACUITY, and HORIZONS-AMI trials, 17,393 were treated with PCI and were included in the present analysis. Patient demographic data and treatment characteristics are representative of the diverse patient populations enrolled in the 3 trials (Table 1). A TIMI major/minor bleeding occurred in 925 patients (5.3%), including TIMI major bleeding in 279 (1.6%) and minor bleeding in 646 (3.7%) patients. Overall TIMI bleeding rates were 2.9%, 6.9%, and 5.8% in the REPLACE-2, ACUITY, and HORIZONS-AMI trials, respectively.

Sites of bleeding. Access site bleeding occurred in 2.1% of all patients (1.1%, 2.9%, and 1.9% in the REPLACE-2, ACUITY, and HORIZONS-AMI trials, respectively), whereas the rate of nonaccess site bleeding was 3.3% overall (1.8%, 4.1%, and 3.9% in the REPLACE-2, ACUITY, and HORIZONS-AMI trials, respectively). Among the 925 patients with a TIMI major/minor bleed, access site-related bleeding occurred in 357 (38.6%), and nonaccess site-related bleeding occurred in 568 (61.4%) (Fig. 1). The median time (interquartile range) from enrollment until a TIMI bleeding event was 1.0 (IQR: 0.0 to 1.0) day for access site bleeding and 2.0 (IQR: 1.0 to 2.0) days for nonaccess site-related bleeding.

The origin and classification of the site of bleeding among the 925 patients with a TIMI bleeding event is shown in Figure 1. Among the 568 patients with a nonaccess TIMI bleed, a total of 621 bleeding sites were documented with the breakdown of locations shown in Figure 2. The incidence of access site bleeding was as in the following text.

Association between bleeding etiology and 1-year mortality. Compared with patients without TIMI major/minor bleeding within 30 days, the unadjusted relative risk of 1-year mortality among patients in whom any TIMI major/minor

bleeding occurred was 4.22 (95% CI: 3.44 to 5.19), p < 0.001. Unadjusted mortality rates and relative risks by bleeding location are shown in Table 2.

After adjustment for baseline and procedural characteristics, TIMI major/minor bleeding still remained significantly associated with 1-year mortality (HR: 3.17, 95% CI: 2.51 to 4.00), p < 0.0001). The adjusted mortality risk associated with an access site-only bleed compared with no bleeding (HR: 1.82, 95% CI: 1.17 to 2.83, p = 0.008) was significant but lower than that associated with nonaccess site bleeding (HR: 3.94, 95% CI: 3.07 to 5.15, p < 0.0001). When the adjusted 1-year mortality risk of a nonaccess site bleed was compared with that of an access site bleed, the hazard associated with a nonaccess site bleed was significantly greater than that of an access site bleed (HR: 2.27, 95% CI: 1.42 to 3.64, p = 0.0007). Similar to the unadjusted data, the source of nonaccess bleeding did not alter the risk: 1-year mortality was strongly associated with nonaccess only bleeding (HR: 2.78, 95% CI: 1.62 to 4.78, p = 0.0002); combined access and nonaccess bleeding (HR: 3.64, 95% CI: 2.25 to 5.90, p < 0.0001); and indeterminate bleeding location (HR: 4.72, 95% CI: 3.38 to 6.59, p < 0.0001).

Table 1. Patient Demographic Data and Procedural Characteristics (n = 17,393)

Demographic data	
Age (yrs)	62.3 ± 11.4
Age ≥75 yrs	16.0%
Weight (kg)	85.6 ± 17.8
Female	25.7%
Diabetes	25.1%
Current smoker	32.3%
Creatinine clearance <60 ml/min	17.0%
Hypertension (on medication)	63.5%
Anemia	8.9%
Prior PCI	31.6%
Prior CABG	14.8%
Presenting diagnosis	
STEMI	20.7%
NSTEMI	30.0%
Unstable angina	29.5%
Stable angina	8.6%
Other	11.2%
Procedural characteristics	
Balloon/atherectomy only	6.5%
Stent	
Bare-metal only	50.9%
Any drug-eluting	58.2%
Multivessel intervention	12.6%
Femoral artery access site*	92.9%
Radial artery access site*	7.1%
Baseline medications	
Aspirin pre-angiography	98.0%
Thienopyridine pre-angiography	80.0%
Statins	49.9%

Values are mean ± SD or %. *Access site in the REPLACE-2 (Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events) trial was not documented but assumed to be 100% femoral for this analysis.

CABG = coronary artery bypass graft surgery; NSTEMI = non–ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

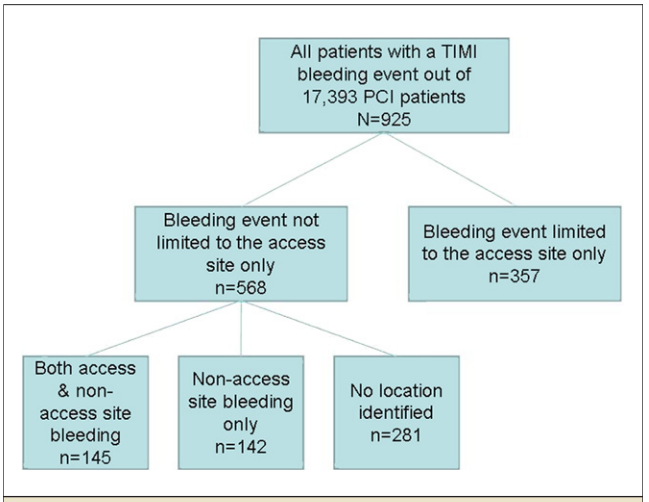

Figure 1. Study Patient Categorization

Classification of patients with a Thrombolysis In Myocardial Infarction (TIMI) major or minor bleeding event. PCI = percutaneous coronary intervention.

Influence of randomized therapy. To determine the impact of antithrombotic therapy on the incidence of access and nonaccess site-related bleeding, 14,784 patients who had been randomized to either bivalirudin alone or heparin plus a GPI were evaluated. Randomization to bivalirudin resulted in a 38% relative reduction in TIMI major/minor bleeding (Fig. 3) and a 43% reduction in TIMI major bleeding. Bivalirudin decreased both access and nonaccess site-related TIMI major/minor and TIMI major bleeding events compared with treatment with heparin plus a GPI

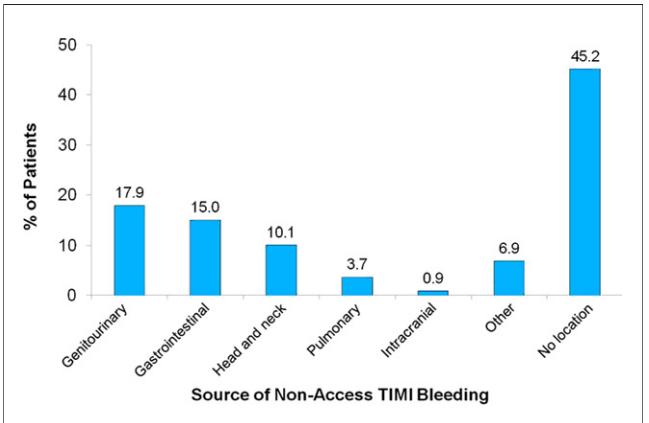

Figure 2. Distribution of Locations of Nonaccess Site Bleeding Events

TIMI = Thrombolysis In Myocardial Infarction.

Table 2. Unadjusted 1-Year Mortality Rates and RRs Associated With Experiencing a 30-Day TIMI

	1-Yr Mortality (%)	RR (95% CI) Compared With No Bleed	p Value
No bleed	2.54	—	—
Access site only	6.16	2.33 (1.53–3.53)	<0.001
All nonaccess site	14.4	5.40 (4.32–6.74)	<0.0001
Nonaccess only	14.1	5.52 (3.62–8.40)	<0.001
Both access and nonaccess	14.5	5.70 (3.78–8.61)	<0.001
Indeterminate	14.6	5.18 (3.82–7.03)	<0.001

Unadjusted 1-year mortality rates and relative risks (RRs) associated with experiencing a 30-day Thrombolysis In Myocardial Infarction (TIMI) (major + minor) bleed on the basis of the source of bleeding.
CI = confidence interval.

(Fig. 3). Similar levels of reduction in bleeding with bivalirudin were found for all bleeding sites (Fig. 4). The number needed-to-treat was 71 to prevent 1 nonaccess site-related TIMI bleeding event, considering noncoronary artery bypass graft surgery TIMI major/minor bleeding only, and 74 to prevent 1 access site-related TIMI bleeding event by use of bivalirudin rather than heparin plus a GPI.

Discussion

Bleeding, like peri-procedural MI, is a frequent complication of PCI and has been strongly associated with subsequent mortality (8,9). The present analysis is the largest to date describing the anatomic origin of bleeding after PCI. We found that, whereas access site-only bleeding was a frequent source of bleeding in patients undergoing PCI, most patients (61.4%) with TIMI major/minor bleeding had a bleeding source other than the access site. Moreover, although the present study confirmed bleeding as a powerful independent predictor of long-term (1-year) mortality, novel to this analysis is the finding that the degree of risk associated with bleeding is dependent upon the bleeding source: nonaccess site TIMI bleeding events were associated with a nearly 4-fold increase in 1-year mortality compared with patients without any bleeding event, representing an approximate 2-fold increase in the mortality risk compared with access site-only TIMI bleeds. These findings reinforce the need to identify treatment strategies that diminish not only access site bleeding but, even more importantly, nonaccess site bleeding.

Arterial access via the radial artery might improve both the safety and post-procedural comfort of patients undergoing PCI. Although the randomized trials required to determine whether radial artery compared with femoral artery access improves overall outcomes in PCI have not yet been performed, numerous observational studies have shown that the transradial approach might reduce the incidence of access site-related hemorrhagic complications (10). In the present study of more than 17,000 PCI, most patients (61.4%) with TIMI major/minor bleeding had a bleeding source other than the access site. Although radial artery access (used in only 7.9% of patients) might reduce most access site bleeds, it would not be expected to reduce nonaccess site-related bleeding events, which not only constitute a significant proportion of TIMI bleeds but are also associated with an even greater risk of subsequent 1-year mortality than access site bleeds.

Certain antithrombotic agents in a variety of clinical settings have been shown to be able to significantly reduce bleeding while effectively suppressing ischemic complications (5–7,11,12). This overall improvement of net adverse clinical events has been found to translate into improvements in long-term outcomes, including survival (12,13). Although bivalirudin compared with unfractionated heparin alone (4) or heparin plus a GPI (5–7) has been shown to significantly reduce overall major bleeding complications in patients undergoing a PCI, its influence on reducing access

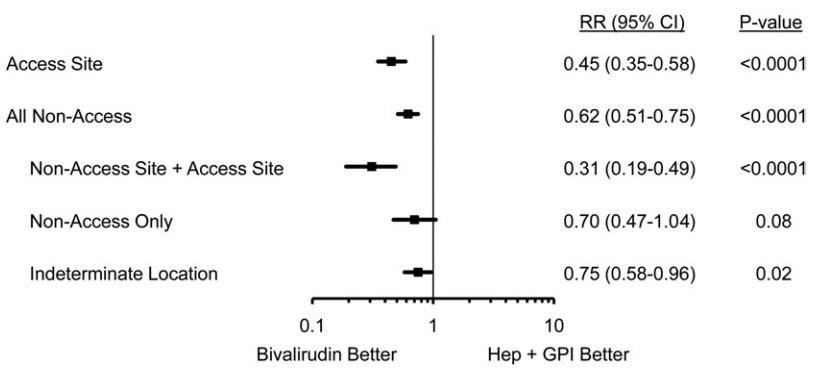

Figure 3. RR of Location-Specific TIMI Bleeding by Randomized Therapy

Influence of randomized therapy, bivalirudin alone versus heparin plus glycoprotein IIb/IIIa inhibitor (GPI), on the relative risk (RR) of 30-day Thrombolysis In Myocardial Infarction (TIMI) major plus minor bleeding on the basis of the etiology of the bleed. CI = confidence interval.

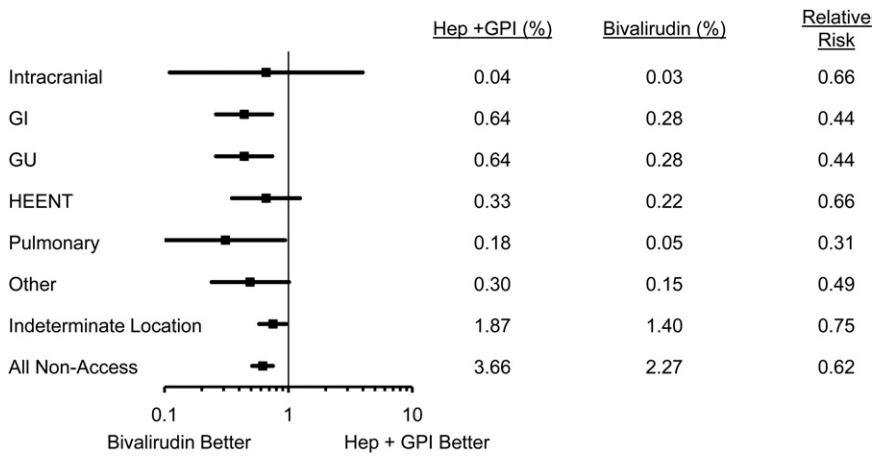

Figure 4. Relative Risk of TIMI Bleeding in Different Organ Systems by Randomized Therapy

Influence of randomized therapy, bivalirudin alone versus heparin plus GPI, on the relative risk of 30-day nonaccess TIMI major plus minor bleeding on the basis of the location. GI = gastrointestinal; GU = genitourinary; HEENT = head, eyes, ears, nose, and throat; other abbreviations as in Figure 3.

and nonaccess site major bleeding has not been previously reported. In the current analysis of nearly 15,000 PCI patients randomized to either bivalirudin or heparin plus a GPI, bivalirudin was equally effective in decreasing both access and nonaccess site-related bleeding, with an approximately 40% relative reduction in combined TIMI major/minor bleeding and TIMI major bleeding alone. Although the relative reduction in bleeding with bivalirudin is independent of bleeding location, the absolute mortality benefit of bivalirudin might be greatest from the prevention of nonaccess site-related bleeds. In this regard, even if all access bleeding were eliminated by the use of radial artery access, the number needed-to-treat with bivalirudin to prevent a single nonaccess site related TIMI major/minor bleed that is associated with a 4-fold increase in mortality at 1-year is only 71 patients.

After access site bleeding, the genitourinary and gastrointestinal systems represented the most common specific locations associated with TIMI bleeding events, perhaps not unexpected due to comorbidities, stress ulcers among acutely ill patients, and the use of bladder catheterization. What might be less commonly appreciated is the relatively high incidence of "indeterminate location" major bleeding events, representing patients with substantial decreases in hemoglobin (4 to 5 g/dl) and/or transfusions with no clear source of bleeding. Such bleeding events represented 30% of all TIMI bleeding in the present study and almost one-half of all such events unrelated to the access site. The etiology of such non-overt blood loss is unclear. Frequent or complex exchanges of PCI equipment, dilution due to various infusions, and frequent blood sampling are potential contributors to peri-procedural blood loss, the magnitude of which is frequently underappreciated. Baseline anemia is associated with an increased risk of in-hospital major bleeding, death, and MI (14,15) and is also likely to lower the clinical threshold for blood transfusions (16). In the ABOARD (Acute Coronary Syndromes Randomized for an Immediate or Delayed Intervention) trial in which 84% of patients underwent early invasive management of acute coronary syndrome via a radial approach, there was no clinical evidence of a source of bleeding in 37% of patients (17), consistent with our findings. Thus many or most of these "indeterminate location" bleeding events are likely nonaccess site-related in origin.

Study limitations. First, in patients who were found to have both access and nonaccess site bleeding events, it was not possible to determine the severity of each and therefore which location contributed more to the individual bleeding event. Second, as previously discussed, the bleeding site was indeterminate in 281 patients in the present study. However, even if all of these patients were excluded from the analysis, nonaccess site bleeding still accounted for 287 of 638 bleeds (45.0%), confirming the necessity to select therapies that mitigate both access site and nonaccess site bleeding. Third, the associations noted between type, severity, and site of bleeding and subsequent mortality are observational and subject to potential confounding.

Conclusions

On the basis of the present analysis of over 17,000 patients undergoing PCI across the spectrum of coronary artery disease (ranging from stable ischemic syndromes to STEMI), almost two-thirds of patients with TIMI major or minor bleeding will involve a source other than the arterial access site. Although all bleeding, irrespective of the source, is

independently associated with a significant increase in mortality at 1 year, the risk associated with bleeding originating from locations other than the access site were found to be 2-fold the risk of an access site bleed and 4-fold the risk of no bleed. Bivalirudin compared with heparin plus a GPI significantly reduces all TIMI bleeding events to a comparable degree, regardless of the bleeding location, and thus would be expected to improve patient outcomes irrespective of the individual patient risk for access site bleeding or use of transradial versus femoral access.

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