Implications of Bleeding and Blood Transfusion in Percutaneous Coronary Intervention

Sunil V. Rao, MD

Duke Clinical Research Institute, Durham, NC

For patients undergoing percutaneous coronary intervention (PCI), bleeding complications are a major clinical concern. With advances in pharmacotherapy and devices over the past 2 decades, the risk of ischemic outcomes, such as myocardial infarction or death, has decreased. Bleeding complications have more recently become a clinical and research priority. Determining the incidence of and risk factors for bleeding is complicated by the multiple systems used to classify bleeding severity and report bleeding events. The origin of the data, clinical trials versus registries, also influences the incidence of reported bleeding events. Registry data suggest that risk of bleeding among patients undergoing PCI is higher in clinical practice than the incidence observed in clinical trials. Another clinical concern is the possible association between PCI-related bleeding complications and myocardial infarction, stroke, or death. Reduction in bleeding risk is a desirable goal that may potentially improve survival and increase comfort for patients undergoing PCI. Using strategies such as careful vascular access, alternative radial artery access, and modified antithrombotic regimen may reduce bleeding during PCI as well as improve patient outcomes.
[Rev Cardiovasc Med. *2007;8(suppl 3):S18-S26*]

Key words: Cardiovascular disease • Percutaneous coronary intervention • Bleeding complications • Blood transfusion

Percutaneous coronary intervention (PCI) is a fundamental part of the treatment of coronary artery disease. Over time, ischemic outcomes after PCI, such as death and myocardial infarction (MI), have steadily decreased despite treatment of patients at higher risk of complications or ischemic outcomes.[1] In addition, the routine use of PCI as the initial therapy for patients with stable anginal symptoms has been called into question.[2] Therefore, in the modern era of PCI, the appropriate approach for patients who are stable is one of "first, do no harm." In this context, the safety of diagnostic or therapeutic procedures has taken on new significance. For PCI, safety includes a minimization of periprocedural ischemic events as well as bleeding complications. The

issue of bleeding complications has become a clinical and research priority and is now considered an essential part of evaluating new antithrombotic and antiplatelet drugs that are being developed for use in the cardiac catheterization laboratory. This review will highlight bleeding issues related to PCI with emphasis on the evaluation of bleeding complications, association between bleeding and adverse outcomes, and strategies to reduce periprocedural bleeding complications.

Reported bleeding rates are highly dependent on the definition used.

Bleeding: Definitions, Incidence, and Risk Factors

A challenge that has recently come to light relates to capturing the incidence of PCI-related bleeding in both clinical trials and registries. Reported bleeding rates are highly dependent on the definition used.[3] A liberal definition of bleeding that includes clinical events (eg, blood transfusion, hypotension, hematomas) and laboratory parameters (eg, decrease in hemoglobin) will result in capturing a large proportion of complications and result in a high incidence of bleeding, whereas, a conservative definition will have the opposite effect. Table 1 provides a sample of bleeding definitions that have been used previously in PCI clinical trials.[4-12]

Two commonly used definitions in trials of acute coronary syndromes (ACS) are the Thrombolysis in Myocardial Infarction (TIMI) and Global Use of Strategies to Open Occluded Arteries (GUSTO) scales (Table 2). The TIMI scale classifies bleeding severity as minimal, minor, or major based on decreases in hemoglobin or hematocrit values, corrected for the effects of blood transfusion.[13] In contrast, the GUSTO scale relies solely on clinical events and separates bleeding severity into classifications of mild, moderate, or severe.[14] Some studies use definitions that combine elements of both scales, whereas others use both scales to capture bleeding events occurring during the course of the same study.

Blood transfusion also plays an important role in the assessment of bleeding. The TIMI scale incorporates the effect of transfusion on changes in hemoglobin level, whereas, according to the GUSTO scale, moderate bleeding is defined by the occurrence of transfusion. Ample clinical data suggest, however, that transfusion does not always occur in the setting of a clinical bleeding event.[15,16] Moscucci and colleagues found that up to 64% of blood transfusions were given inappropriately when published transfusion guidelines were used as the benchmark.[15,17] Because transfusion may reflect a bias on the part of the physician rather than indicate a true bleeding event, reliance solely on incidence of transfusion to capture bleeding events in retrospective databases can be problematic. Despite this limitation, transfusion may be helpful as a marker of a clinical event that was judged severe enough to warrant intervention.

Lack of standards for assessing bleeding severity, often within the same study, leads to variation in the reported incidence of bleeding among patients undergoing PCI. For example, in the Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events II (REPLACE-2) study,[9] bleeding events were evaluated using the REPLACE-2 definition and the TIMI definition. When the REPLACE-2 definition was used, the strategy of bivalirudin with provisional glycoprotein (GP) IIb/IIIa inhibitor was associated with significantly less bleeding than the strategy of heparin with planned GP IIb/IIIa inhibitor. In contrast, when the TIMI bleeding definition was applied, there was no significant difference in bleeding between the 2 arms. Another factor influencing the incidence of bleeding is the origin of the data—clinical trials versus registries. Bleeding rates tend to be higher in registries, which include a broad sampling of patients, compared with clinical trials, which are often less representative of patients seen in clinical practice.[18] Finally, the evolution in interventional pharmacotherapy and devices also affects bleeding rates—catheters have decreased in size, the number of unfractionated heparin doses used during PCI have decreased due to recognition of the risk of overanticoagulation,[5,8] and newer agents that reduce bleeding risk, such as bivalirudin, are being increasingly adopted into clinical practice.

Although evaluating the incidence of PCI-related bleeding with accuracy is challenging because of the factors discussed above, data from clinical trials and registries offer some insight. In the Evaluation of 7E3 for the Prevention of Ischemic Complications (EPIC) trial comparing abciximab (bolus only or bolus and infusion) plus unfractionated heparin versus unfractionated heparin alone in patients undergoing balloon angioplasty, the rates of TIMI major bleeding were 7% for heparin alone,

The evolution in interventional pharmacotherapy and devices also affects bleeding rates.

Table 1
"Major" or "Severe" Bleeding Definitions Used in Percutaneous Coronary Intervention Trials and Registries

Trial	Regimens Studied	Bleeding Definition
EPIC[4]	Abciximab bolus vs abciximab bolus + infusion vs placebo	TIMI*
EPILOG[5]	Abciximab + standard-dose heparin vs abciximab + low-dose heparin vs heparin	TIMI*
RESTORE[6]	Tirofiban + heparin vs heparin	TIMI* and RESTORE "Major bleeding" • Decrease in hemoglobin > 5 g/dL • Transfusion > 2 units PRBCs or whole blood • Associated with surgery • Intracranial bleeding • Retroperitoneal bleeding
ESPRIT[7,8]	Eptifibatide + heparin vs heparin	TIMI* and GUSTO*
REPLACE-2[9]	Bivalirudin + provisional GP IIb/IIIa inhibitor vs heparin + planned GP IIb/IIIa inhibitor	REPLACE-2 "Major bleeding" • Intracranial, intraocular, or retroperitoneal hemorrhage • Clinically overt blood loss resulting in a decrease in hemoglobin > 3 g/dL • Any decrease in hemoglobin > 4 g/dL • Transfusion of ≥ 2 units PRBCs or whole blood
ACUITY[10]	Bivalirudin + provisional GP IIb/IIIa inhibitor vs bivalirudin + planned GP IIb/IIIa inhibitor vs heparin + planned GP IIb/IIIa inhibitor	ACUITY "Major bleeding" • Intracranial or intraocular bleeding • Hemorrhage at the access site requiring intervention • Hematoma with a diameter of ≥ 5 cm • Reduction in hemoglobin ≥ 4 g/dL without an overt bleeding source or ≥ 3 g/dL with such a source • Reoperation for bleeding • Transfusion of a blood product
Bivalirudin Angioplasty Study[11]	Bivalirudin vs heparin	"Major hemorrhage" • Overt bleeding with a decrease in hemoglobin of ≥ 3 g/dL • Need for transfusion • Intracranial hemorrhage • Retroperitoneal bleeding
STEEPLE[12]	Enoxaparin 0.5 mg/kg IV vs enoxaparin 0.75 mg/kg IV vs heparin	STEEPLE "Major bleeding" • Bleeding resulting in death • Retroperitoneal or intraocular bleeding • Bleeding leading to hemodynamic compromise requiring intervention • Bleeding requiring surgical or endoscopic intervention • Clinically overt bleeding with transfusion of ≥ 1 unit PRBCs or whole blood • Clinically overt bleeding with a decrease in hemoglobin ≥ 3 g/dL

ACUITY, Acute Catheterization and Urgent Intervention Triage Strategy Trial; EPIC, Evaluation of 7E3 for the Prevention of Ischemic Complications trial; EPILOG, Evaluation of Percutaneous Transluminal Coronary Angioplasty to Improve Long-term Outcome with Abciximab Glycoprotein IIb/IIIa Blockade trial; ESPRIT, European Study of the Prevention of Reocclusion After Initial Thrombolysis trial; GUSTO, Global Strategies for Opening Occluded Coronary Arteries trial; IV, intravenous; PRBCs, packed red blood cells; REPLACE-2, Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events II; RESTORE, Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis Trial; STEEPLE, Safety and Efficacy of Enoxaparin in Percutaneous Coronary Intervention Patients, an International Randomized Evaluation trial; TIMI, Thrombolysis In Myocardial Infarction.
*See Table 2 for definition.

11% for abciximab bolus plus heparin, and 14% for abciximab bolus and infusion plus heparin.[4] Heparin doses used in the EPIC trial were not reduced when abciximab was added. The strategy of reducing the heparin dose in the presence of GP IIb/IIIa inhibitors was tested in the Evaluation of Percutaneous Transluminal Coronary Angioplasty to Improve Long-term Outcome with Abciximab Glycoprotein IIb/IIIa Blockade (EPILOG)

Table 2
TIMI and GUSTO Bleeding Classifications

TIMI Bleeding Classification[13]	
Major	Intracranial hemorrhage or ≥ 5 g/dL decrease in the hemoglobin concentration or ≥ 15% absolute decrease in the hematocrit
Minor	Observed blood loss: ≥ 3 g/dL decrease in the hemoglobin concentration or ≥ 10% decrease in the hematocrit No observed blood loss: ≥ 4 g/dL decrease in the hemoglobin concentration or ≥ 12% decrease in the hematocrit
Minimal	Any clinically overt sign of hemorrhage (including imaging) that is associated with a < 3 g/dL decrease in the hemoglobin concentration or < 9% decrease in the hematocrit
GUSTO Bleeding Classification[14]	
Severe or life-threatening	Either intracranial hemorrhage or bleeding that causes hemodynamic compromise and requires intervention
Moderate	Bleeding that requires blood transfusion but does not result in hemodynamic compromise
Mild	Bleeding that does not meet criteria for either severe or moderate bleeding

*All TIMI definitions take into account blood transfusions, so that hemoglobin and hematocrit values are adjusted by 1 g/dL or 3%, respectively, for each unit of blood transfused. Therefore, the true change in hemoglobin or hematocrit if there has been an intervening transfusion between 2 blood measurements is calculated as follows: Δ Hemoglobin = [baseline Hgb − post-transfusion Hgb] + [number of transfused units]; Δ Hematocrit = [baseline Hct − post-transfusion Hct] + [number of transfused units × 3]. GUSTO, Global Strategies for Opening Occluded Coronary Arteries trial; Hct, hematocrit; Hgb, hemoglobin; TIMI, Thrombolysis In Myocardial Infarction trial. Reprinted with permission from Rao SV et al.[3]

trial.[5] The EPILOG trial randomized patients undergoing PCI to abciximab plus standard-dose heparin, abciximab plus reduced-dose heparin, or heparin alone; the rates of TIMI major bleeding were 3.5%, 2.0%, and 3.1%, respectively. Notably, the rate of bleeding in the heparin alone arm of the EPILOG trial was less than half the bleeding rate seen in the heparin alone arm of the EPIC trial, suggesting that either procedural techniques or catheter design had evolved to reduce the risk of bleeding.

Two more contemporary trials of PCI are the European Study of the Prevention of Reocclusion After Initial Thrombolysis (ESPRIT) and REPLACE-2 trials, both of which used different bleeding definitions. In the ESPRIT trial, patients undergoing elective PCI were randomized to unfractionated heparin alone or the combination of unfractionated heparin plus eptifibatide.[7] Bleeding was assessed using the TIMI scale and the rate of TIMI major bleeding in the heparin alone arm was 0.4%, whereas the rate of TIMI major bleeding in the combination therapy arm was 1.0% ($P = .027$). A post-hoc analysis of ESPRIT found that decreasing the heparin dose could reduce the risk of bleeding with combined heparin plus eptifibatide therapy. The REPLACE-2 trial randomized over 6000 patients, undergoing either elective or urgent PCI, to a strategy of bivalirudin plus provisional GP IIb/IIIa inhibitor (given for procedural complications) or unfractionated heparin plus planned GP IIb/IIIa inhibitor.[9] The definition used in this study (see Table 1 for definition) captured more bleeding events. Accordingly, the rate of protocol-defined major bleeding was 4.1% in the heparin plus GP IIb/IIIa inhibitor arm and 2.4% in the bivalirudin alone arm ($P < .001$).

Although the data provide a perspective on bleeding incidence in the context of clinical trials, registry data can be helpful in delineating the incidence in a "real-world" population. Kinnaird and colleagues described the incidence of TIMI major and minor bleeding in 10,974 consecutive patients undergoing PCI at 3 hospitals.[19] In this unselected cohort, the incidence of TIMI major bleeding was 5.4%, the incidence of TIMI minor bleeding was 12.7%, and the rate of blood transfusion was 5.4%. Most bleeding events were related to the vascular access site. Data from 6656 patients enrolled in the multicenter National Heart, Lung, and Blood Institute (NHLBI) Dynamic Registry show that the overall incidence of access-site hematoma requiring blood transfusion was 1.8%.[20] One of most serious complications of vascular access is retroperitoneal hematoma, which is rare, but can be potentially life-threatening. Data suggest that this complication occurs in approximately 0.74% of patients undergoing PCI.[21]

The marked differences between clinical trial and registry data suggest that the risk of bleeding among patients undergoing PCI in clinical practice is higher than that seen in clinical trials. Clearly, some patients are at higher risk for bleeding than others. Certain risk factors have been described in virtually every bleeding study performed. Age, female gender, and decreased renal function have consistently been shown to be independent predictors of bleeding.[10,22,23] Recently, analysis from the Acute Catheterization and Urgent

Intervention Triage Strategy Trial (ACUITY) population of patients with ACS undergoing a rapid invasive risk strategy has described some novel bleeding risk factors.[10] In this analysis, markers of high ischemic risk such as diabetes mellitus and elevated cardiac markers, as well as signs of general chronic illness such as baseline anemia, were also associated with bleeding. These data suggest that a risk profile can be constructed before the PCI procedure to identify patients for whom a bleeding reduction strategy should be employed.

Bleeding, Transfusion, and Outcomes

If ischemic outcomes after PCI (MI, stroke, urgent revascularization) are avoided, is there a level of bleeding risk that might be acceptable or even inevitable? The evolution of PCI over the last 2 decades has resulted in the paradox of higher-risk patients undergoing the procedure and a lower incidence of ischemic outcomes.[24] Thus, PCI is now performed in patients who are at high risk for MI, stroke, and urgent revascularization; yet, the risk for these complications is the lowest that it has ever been. In contrast, bleeding still occurs with relative frequency. Several studies have outlined the association between PCI-related bleeding complications (variously defined) and short- and long-term death, MI, and stroke.

Using pooled data from 4 large randomized controlled trials of patients (N = 26,452) with ACS, Rao and colleagues examined the relationship between in-hospital GUSTO bleeding and 30-day and 6-month mortality.[25] Among patients who experienced periprocedural bleeding, there was a stepwise increase in the risk of both short- and intermediate-term mortality. The adjusted hazard ratio [HR] for 30-day mortality was 1.3 for mild bleeding (95% confidence interval [CI], 0.9-1.8), 3.7 for moderate bleeding (95% CI, 2.8-4.9), and 16.5 for severe bleeding (95% CI, 12.0-22.8). The adjusted HR for 6-month mortality was 1.1 for mild bleeding (95% CI, 0.9-1.4), 2.6 for moderate bleeding (95% CI, 2.1-3.3), and 10.5 for severe bleeding (95% CI, 8.0-13.7). Similarly, patients with ACS undergoing a rapid invasive strategy in the ACUITY trial who developed in-hospital ACUITY-defined major bleeding experienced an increased risk for 30-day mortality (adjusted odds ratio [OR] 7.55; 95% CI, 4.68-12.18).[10]

Registry data also corroborate the increased risk associated with bleeding. The study by Kinnaird and colleagues showed a stepwise increase in the incidence of in-hospital death, MI, repeat intervention, and major adverse cardiac events as TIMI bleeding severity worsened.[19] After adjustment, TIMI major bleeding and transfusion were independently associated with an increased risk for in-hospital death; transfusion of more than 2 units of blood was independently associated with an increased risk for 1-year mortality. Data from the NHLBI Dynamic Registries show that access-site hematoma requiring transfusion is independently associated with an increased risk for both in-hospital mortality (adjusted HR 3.59; 95% CI, 1.66-7.77) and 1-year mortality (adjusted HR 1.65; 95% CI, 1.01-2.70).[20]

Conventional wisdom suggests that if bleeding is associated with increased mortality and morbidity, the use of blood transfusion would mitigate the risk. However, clinical data suggest the opposite effect—the use of blood transfusion is associated with an *increased* risk for both mortality and morbidity. In addition to the data from the Kinnaird study above, an analysis from the REPLACE-2 trial of patients undergoing either elective or urgent PCI showed that blood transfusion was associated with a marked increased risk for 1-year mortality (adjusted OR 4.26; 95% CI, 2.25-8.08).[26] The clinical data, therefore, suggest that transfusion does not mitigate the risk for bleeding, and when used indiscriminately may increase mortality. The mechanisms underlying this association are unclear but likely relate to the inability of packed red blood cells to improve tissue oxygenation. Unlike native hemoglobin, the hemoglobin in stored blood is depleted of 2,3-diphosphoglycerate, which shifts the oxyhemoglobin dissociation curve to the left; therefore, stored blood does not readily release oxygen.[17] In addition, stored blood is depleted of nitric oxide, which is essential to oxygen exchange,[27] and blood transfusion has been shown to be associated with increases in markers of inflammation.[28]

Of note, results from the previously described studies do not show a causal relationship between bleeding and mortality or morbidity. Although it may be true that severe or major bleeding may directly result in death through exsanguination or intracranial hemorrhage, or cause myocardial ischemia through sudden and profound ischemia, it is less obvious why milder degrees of bleeding, such as hematomas, would be associated with adverse outcomes. There is no reason to suspect causality between milder degrees of bleeding and death. Instead, the association may be explained by the actions taken by caregivers when a patient experiences a bleeding event. Specifically, the initial reaction is to stop or reverse antithrombin and antiplatelet therapy, which may be appropriate in the setting of hemorrhage. After the bleeding event has resolved, these agents still may not

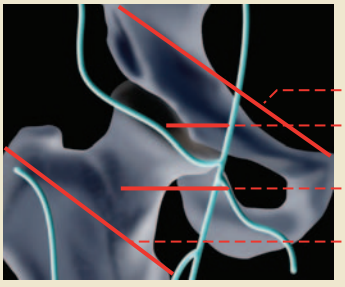
be restarted, which may explain the association between bleeding and stent thrombosis seen in the ACUITY trial.[10] This is supported by data from the Prospective Registry Evaluating Myocardial Infarction: Events and Recovery (PREMIER) that shows significantly lower odds of aspirin and clopidogrel prescription at discharge and at 6 months after discharge among patients with ACS who develop bleeding while hospitalized.[29]

Strategies to Reduce Bleeding Risk

As the data summarized above show, PCI-related bleeding and transfusion is common and is associated with increased risk for mortality. Therefore, reduction in bleeding risk is a desirable goal for PCI practice and can potentially improve survival and increase patient comfort. Two strategies that can be employed to reduce bleeding risk during PCI are careful femoral arterial access (or alternative vascular access such as radial artery access), modification of the antithrombotic regimen, or both.

Because most hemorrhagic complications in the PCI population are related to vascular access, focusing on appropriate techniques during arteriotomy is important. Using the femoral approach, the site of catheter or sheath entry is the common femoral artery. In most patients, the common femoral artery bifurcates below the middle third of the femoral head. Simple fluoroscopy can be used to identify the middle third of the femoral head before obtaining vascular access (Figure 1).[30] Then the midpoint of the femoral head can be marked using a hemostat, and the skin incision can be made 1 to 2 cm inferior to the hemostat to achieve arteriotomy into the common femoral artery in most cases. Sherev and colleagues examined 1570 left heart catheterization procedures performed via the femoral approach and found that arteriotomy location in the common femoral artery above the bifurcation but below the inferior border of the inferior epigastric artery was associated with the lowest rate of access-site complications (including retroperitoneal hematoma) compared with higher or lower arteriotomies.[31] In addition to high or low arterial punctures, the use of arteriotomy closure devices is associated with increases in vascular complications.[32] Therefore, with the femoral approach, using femoral head fluoroscopy to increase the chances of appropriate arteriotomy and avoiding routine use of closure devices can reduce the risk for bleeding.

Figure 1. *Radiographic landmarks during femoral arteriography and their position relative to the bifurcation of the femoral artery. Inguinal crease identified by the use of radio-opaque marker at the time of arteriography. Reprinted with permission from Garrett PD et al.*[30]



Radiographic Landmark	Location Relative to Femoral Artery Bifurcation	
	Superior	Inferior
Inguinal ligament	100%	0%
Middle femoral head	99%	1%
Inferior femoral head	80%	20%
Inguinal crease	22%	78%

Another strategy is to avoid the femoral arteriotomy altogether by performing PCI via the radial artery approach. PCI using 6-French guiding catheters (and 7-French or 8-French catheters in selected patients) can be performed safely and effectively via the radial artery[33] and dedicated radial artery access kits, diagnostic catheters, and interventional equipment are now available. Kiemeneij and colleagues conducted a randomized trial in which 900 patients undergoing balloon angioplasty were randomly assigned to radial, brachial, or femoral access.[34] Although vascular access was successfully obtained more often in the patients assigned to the femoral or brachial approaches, the incidence of procedure success did not differ among the groups. The radial approach had the lowest incidence of vascular complications (0%), compared with the brachial (2.3%) or femoral (2.0%) groups. Mann and colleagues performed a randomized trial of radial versus femoral access in 142 patients with ACS undergoing coronary stenting.[35] The rate of procedure success was identical in both arms (96%), but the rate of bleeding complications was lower in the radial access group (0% vs 4%; $P < .01$), as was the length of hospital stay (1.4 days vs 2.3 days; $P < .01$), and total hospital charges ($20,476 vs $23,389; $P < .01$). A meta-analysis of 12 randomized trials showed that the transradial approach was associated with an 80% decrease in vascular access complications, although the procedure failure rate was 3 times higher than the femoral approach.[36] These data from randomized trials have been corroborated by data from observational studies.[37-41] Risks of the transradial approach include the inability to obtain radial access, which occurs in approximately 0.5% to 4.0% of patients[35,40]; longer procedure times and operator radiation exposure[42]; radial

artery occlusion in 2% to 5% of patients[43]; and potentially increased risk for stroke because of catheter exchanges in the ascending aorta.[44]

Besides vascular access techniques, the choice of pharmacological agents and careful dosing also play a role in bleeding reduction. The mainstay of antithrombin therapy during PCI is unfractionated heparin.[45] Although there is little relationship between activated clotting time (ACT) and ischemic outcomes, there appears to be a relationship between higher ACT values and bleeding complications when unfractionated heparin is the antithrombin agent.[46] If GP IIb/IIIa inhibitors are not used, then heparin dosing to achieve ACT values between 250 seconds and 300 seconds is recommended. However, if GP IIb/IIIa inhibitors are used, then the heparin dose should be lowered to achieve ACT values between 200 seconds and 250 seconds.[45] Studies show that elderly and female patients are more likely to be overdosed with unfractionated heparin, low-molecular-weight heparin, and GP IIb/IIIa inhibitors, which are associated with increased bleeding rates.[47,48] For patients with chronic kidney disease, dosage adjustment of agents that are renally cleared, such as enoxaparin and eptifibatide, is necessary. These data strongly suggest that careful dosing can significantly lower bleeding risk among patients undergoing PCI and receiving heparin and GP IIb/IIIa inhibitors.

Reducing bleeding risk has been the focus of several large randomized trials that have studied the newer antithrombin agents in the setting of PCI. Bivalirudin is a direct thrombin inhibitor that has a half-life of 25 minutes, carries no risk of heparin-induced thrombocytopenia, and has an anticoagulant effect that is reflected by an increase in the ACT. The REPLACE-2 trial studied the role of bivalirudin in over 6000 patients undergoing elective or urgent PCI.[9] Patients were randomized in a double-blind, double-dummy fashion to receive either unfractionated heparin with planned GP IIb/IIIa inhibitor or bivalirudin with provisional use of GP IIb/IIIa inhibitors, given for procedural complications. The primary endpoint was a composite of 30-day death, MI, urgent target vessel revascularization, or major bleeding (see Table 1 for definition). At 30 days, the incidence of the primary endpoint was 10.0% for patients assigned to heparin plus GP IIb/IIIa inhibitors and 9.2% for patients assigned to bivalirudin ($P = .32$), which met the criteria for noninferiority. The incidence of death, MI, and urgent target vessel revascularization was not significantly different between the 2 arms, but the incidence of major bleeding was significantly lower for patients receiving bivalirudin (2.4% vs 4.1%; $P < .001$). The ACUITY trial was conducted to determine whether the benefit of bivalirudin would extend to patients with ACS.[49] The ACUITY trial randomized over 13,800 patients to 1 of 3 treatment arms: heparin (unfractionated heparin or low-molecular-weight heparin) plus GP IIb/IIIa inhibitor (arm A), bivalirudin plus GP IIb/IIIa inhibitor (arm B), or bivalirudin alone (arm C).[50] There was a second randomization among the GP IIb/IIIa inhibitor arms in which the GP IIb/IIIa inhibitor could be given either at the time of randomization or during PCI. Invasive risk stratification had to be performed within 72 hours of randomization; the median time from administration of trial medication to cardiac catheterization was 3.5 to 4.0 hours for all 3 treatment arms. At 30 days, the incidence of the primary composite endpoint of death, MI, urgent target vessel revascularization, and ACUITY-defined major bleeding (see Table 1 for definition), also known as the "net clinical composite endpoint," was 11.7% in arm A, 11.8% in arm B, and 10.1% in arm C ($P < .001$). This was driven by a significantly lower rate of major bleeding among the bivalirudin-treated patients (5.7% arm A, 5.3% arm B, 3.0% arm C; $P < .001$). Of the overall ACUITY trial population, 56% underwent PCI during hospitalization.[50] Although the trial was not specifically powered to examine outcomes in this subgroup, the findings paralleled those of the overall trial with a significantly lower rate of major bleeding among patients treated with bivalirudin, as well as a trend toward improved net clinical composite endpoint in arm C. Together, the results of the REPLACE-2 and ACUITY trials show in low-risk and high-risk patients undergoing PCI that bleeding reduction can be achieved with bivalirudin alone compared with a strategy that employs GP IIb/IIIa inhibitors.

Another agent, enoxaparin, has also been studied in the context of bleeding reduction during PCI. Although enoxaparin is usually administered subcutaneously for the treatment of non–ST-segment elevation ACS, an intravenous regimen, assessed in smaller nonrandomized studies, was associated with low rates of bleeding complications.[51-53] The Safety and Efficacy of Enoxaparin in Percutaneous Coronary Intervention Patients, an International Randomized Evaluation (STEEPLE) trial randomized 3528 patients undergoing elective PCI to receive intravenous enoxaparin 0.5 mg/kg, intravenous enoxaparin 0.75 mg/kg, or unfractionated heparin, administered just before the start of the PCI procedure.[12] The primary endpoint was the occurrence of STEEPLE-defined major or minor bleeding not related

to coronary artery bypass surgery at 48 hours (see Table 1 for definition). When compared with the heparin arm, the primary endpoint was significantly lower in the enoxaparin 0.5 mg/kg arm (5.9% vs 8.5%; P = .01) and trended lower in the enoxaparin 0.75 mg/kg arm (6.5% vs 8.5%; P = .051). The rate of nonfatal MI during the first 30 days was lowest in the enoxaparin 0.5 mg/kg arm compared with the enoxaparin 0.75 mg/kg and heparin arms (4.7% vs 6.1% vs 5.2%, respectively). However, the rate of death was highest in the enoxaparin 0.5 mg/kg arm (1.0% vs 0.2% vs 0.4%, respectively) prompting early termination of enrollment into that treatment arm. These data are difficult to put into a clinical context because although the rate of bleeding and MI was lowest in the enoxaparin 0.5 mg/kg arm, the rate of death was the highest at this dose level. This may be a statistical anomaly or it may be related to the dose itself. Regardless, results from the STEEPLE trial provide some support for a reduction in PCI-related bleeding complications with intravenous administration of enoxaparin.

Conclusions

PCI is now widely used for the treatment of coronary artery disease. Developments in device technology and pharmacotherapy have reduced periprocedural ischemic complications; however, the risk for bleeding and blood transfusion still remains. Determining the incidence of PCI-related bleeding is difficult because of multiple definitions being used to assess bleeding complications, different antithrombotic agents used in studies, and differing incidence between clinical trials and real-world registries. Despite the lack of standardized definitions, the available observational data suggest that all degrees of bleeding are associated with increased morbidity and mortality. Studies also indicate that blood transfusion does not correct the risk associated with bleeding and is itself independently associated with increased mortality. Therefore, bleeding reduction is an important goal for interventionalist cardiologists. Strategies to reduce bleeding risk include careful attention to vascular access, use of transradial PCI, appropriate dosing of unfractionated and low-molecular-weight heparin as well as GP IIb/IIIa inhibitors, and use of newer antithrombin agents such as bivalirudin. Because ischemic complications are relatively rare in the modern era of PCI, reducing the risk of bleeding has the potential to improve PCI-related outcomes even further. ■

References

1. Prasad A, Rihal CS, Lennon RJ, et al. Trends in outcomes after percutaneous coronary intervention for chronic total occlusions: a 25-year experience from the Mayo Clinic. *J Am Coll Cardiol*. 2007;49:1611-1618.
2. Boden WE, O'Rourke RA, Teo KK, et al. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med*. 2007;356:1503-1516.
3. Rao SV, O'Grady K, Pieper KS, et al. A comparison of the clinical impact of bleeding measured by two different classifications among patients with acute coronary syndromes. *J Am Coll Cardiol*. 2006;47:809-816.
4. The EPIC Investigators. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. *N Engl J Med*. 1994;330:956-961.
5. The EPILOG Investigators. Platelet glycoprotein IIb/IIIa receptor blockade and low-dose heparin during percutaneous coronary revascularization. *N Engl J Med*. 1997;336:1689-1696.
6. The RESTORE Investigators. Effects of platelet glycoprotein IIb/IIIa blockade with tirofiban on adverse cardiac events in patients with unstable angina or acute myocardial infarction undergoing coronary angioplasty: Randomized Efficacy Study of Tirofiban for Outcomes and REstenosis. *Circulation*. 1997;96:1445-1453.
7. The ESPRIT Investigators. Novel dosing regimen of eptifibatide in planned coronary stent implantation (ESPRIT): a randomised, placebo-controlled trial. *Lancet*. 2000;356:2037-2044.
8. Tolleson TR, O'Shea JC, Bittl JA, et al. Relationship between heparin anticoagulation and clinical outcomes in coronary stent intervention: observations from the ESPRIT trial. *J Am Coll Cardiol*. 2003;41:386-393.
9. Lincoff AM, Bittl JA, Harrington RA, et al. Bivalirudin and provisional glycoprotein IIb/IIIa blockade compared with heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary intervention: REPLACE-2 randomized trial. *JAMA*. 2003;289:853-863.
10. Manoukian SV, Feit F, Mehran R, et al. Impact of major bleeding on 30-day mortality and clinical outcomes in patients with acute coronary syndromes: an analysis from the ACUITY Trial. *J Am Coll Cardiol*. 2007;49:1362-1368.
11. Bittl JA, Chaitman BR, Feit F, et al. Bivalirudin versus heparin during coronary angioplasty for unstable or postinfarction angina: Final report reanalysis of the bivalirudin angioplasty study. *Am Heart J*. 2001;142:952-959.
12. Montalescot G, White HD, Gallo R, et al. Enoxaparin versus unfractionated heparin in elective percutaneous coronary intervention. *N Engl J Med*. 2006;355:1006-1017.
13. 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;76:142-154.
14. The GUSTO investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med*. 1993;329:673-682.
15. Moscucci M, Ricciardi M, Eagle KA, et al. Frequency, predictors, and appropriateness of blood transfusion after percutaneous coronary interventions. *Am J Cardiol*. 1998;81:702-707.
16. Rao SV, Eikelboom JA, Granger CB, et al. Bleeding and blood transfusion issues in patients with non-ST-segment elevation acute coronary syndromes. *Eur Heart J*. 2007;28:1193-1204.
17. Welch HG, Meehan KR, Goodnough LT. Prudent strategies for elective red blood cell transfusion. *Ann Intern Med*. 1992;116:393-402.
18. Lee PY, Alexander KP, Hammill BG, et al. Representation of elderly persons and women in published randomized trials of acute coronary syndromes. *JAMA*. 2001;286:708-713.
19. 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;92:930-935.
20. Yatskar L, Selzer F, Feit F, et al. Access site hematoma requiring blood transfusion predicts mortality in patients undergoing percutaneous coronary intervention: data from the National Heart, Lung, and Blood Institute Dynamic Registry. *Catheter Cardiovasc Interv*. 2007;69:961-966.
21. Farouque HM, Tremmel JA, Raissi SF, et al. Risk factors for the development of retroperitoneal hematoma after percutaneous coronary intervention in the era of glycoprotein IIb/IIIa inhibitors and vascular closure devices. *J Am Coll Cardiol*. 2005;45:363-368.
22. Moscucci M, Fox KA, Cannon CP, et al. Predictors of major bleeding in acute coronary syndromes: the Global Registry of Acute Coronary Events (GRACE). *Eur Heart J*. 2003;24:1815-1823.
23. Rao SV, Jollis JG, Harrington RA, et al. Relationship of blood transfusion and clinical outcomes in patients with acute coronary syndromes. *JAMA*. 2004;292:1555-1562.
24. Holmes DR Jr., Kereiakes DJ, Laskey WK, et al. Thrombosis and drug-eluting stents: an objective appraisal. *J Am Coll Cardiol*. 2007;50:109-118.

25. Rao SV, O'Grady K, Pieper KS, et al. Impact of bleeding severity on clinical outcomes among patients with acute coronary syndromes. *Am J Cardiol*. 2005;96:1200-1206.
26. Voeltz MD, Lincoff AM, Feit F, Manoukian SV. Major bleeding and transfusions are associated with increased mortality in elderly patients undergoing percutaneous coronary intervention. *Circulation*. 2005;112(17):II-613.
27. McMahon TJ, Moon RE, Luschinger BP, et al. Nitric oxide in the human respiratory cycle. *Nat Med*. 2002;8:711-717.
28. Fransen E, Maessen J, Dentener M, et al. Impact of blood transfusions on inflammatory mediator release in patients undergoing cardiac surgery. *Chest*. 1999;116:1233-1239.
29. Wang TY, Xia L, Alexander KP, et al. Trends in antiplatelet therapy use after discharge among acute myocardial infarction patients with in-hospital bleeding [abstract]. Presented at AHA Scientific Forum on Quality of Care and Outcomes Research 2007; May 9-11, 2007: Washington, DC.
30. Garrett PD, Eckart RE, Bauch TD, et al. Fluoroscopic localization of the femoral head as a landmark for common femoral artery cannulation. *Catheter Cardiovasc Interv*. 2005;65:205-207.
31. Sherev DA, Shaw RE, Brent BN. Angiographic predictors of femoral access site complications: implication for planned percutaneous coronary intervention. *Catheter Cardiovasc Interv*. 2005; 65:196-202.
32. Koreny M, Riedmuller E, Nikfardjam M, et al. Arterial puncture closing devices compared with standard manual compression after cardiac catheterization: systematic review and meta-analysis. *JAMA*. 2004;291:350-357.
33. Saito S, Ikei H, Hosokawa G, Tanaka S. Influence of the ratio between radial artery inner diameter and sheath outer diameter on radial artery flow after transradial coronary intervention. *Catheter Cardiovasc Interv*. 1999;46:173-178.
34. Kiemeneij F, Laarman GJ, Odekerken D, et al. A randomized comparison of percutaneous transluminal coronary angioplasty by the radial, brachial and femoral approaches: the access study. *J Am Coll Cardiol*. 1997;29:1269-1275.
35. Mann T, Cubeddu G, Bowen J, et al. Stenting in acute coronary syndromes: a comparison of radial versus femoral access sites. *J Am Coll Cardiol*. 1998;32:572-576.
36. Agostoni P, Biondi-Zoccai GG, de Benedictis ML, et al. Radial versus femoral approach for percutaneous coronary diagnostic and interventional procedures: systematic overview and meta-analysis of randomized trials. *J Am Coll Cardiol*. 2004;44:349-356.
37. Jaffe R, Hong T, Sharieff W, et al. Comparison of radial versus femoral approach for percutaneous coronary interventions in octogenarians. *Catheter Cardiovasc Interv*. 2007;69:815-820.
38. Cruden NL, Teh CH, Starkey IR, et al. Reduced vascular complications and length of stay with transradial rescue angioplasty for acute myocardial infarction. *Catheter Cardiovasc Interv*. 2007. June 11; Epub ahead of print.
39. Cantor WJ, Mahaffey KW, Huang Z, et al. Bleeding complications in patients with acute coronary syndrome undergoing early invasive management can be reduced with radial access, smaller sheath sizes, and timely sheath removal. *Catheter Cardiovasc Interv*. 2007;69:73-83.
40. Louvard Y, Lefevre T, Allain A, et al. Coronary angiography through the radial or the femoral approach: The CARAFE study. *Catheter Cardiovasc Interv*. 2001;52:181-187.
41. Mann T, Cowper PA, Peterson ED, et al. Transradial coronary stenting: comparison with femoral access closed with an arterial suture device. *Catheter Cardiovasc Interv*. 2000;49:150-156.
42. Lange HW, von Boetticher H. Randomized comparison of operator radiation exposure during coronary angiography and intervention by radial or femoral approach. *Catheter Cardiovasc Interv*. 2006;67:12-16.
43. Stella PR, Kiemeneij F, Laarman GJ, et al. Incidence and outcome of radial artery occlusion following transradial artery coronary angioplasty. *Cathet Cardiovasc Diagn*. 1997;40:156-158.
44. Lund C, Nes RB, Ugelstad TP, et al. Cerebral emboli during left heart catheterization may cause acute brain injury. *Eur Heart J*. 2005;26:1269-1275.
45. Smith SC Jr., Feldman TE, Hirshfeld JW Jr., et al. ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention). *J Am Coll Cardiol*. 2006;47:e1-121.
46. Brener SJ, Moliterno DJ, Lincoff AM, et al. Relationship between activated clotting time and ischemic or hemorrhagic complications: analysis of 4 recent randomized clinical trials of percutaneous coronary intervention. *Circulation*. 2004;110:994-998.
47. Alexander KP, Chen AY, Roe MT, et al. Excess dosing of antiplatelet and antithrombin agents in the treatment of non-ST-segment elevation acute coronary syndromes. *JAMA*. 2005;294: 3108-3116.
48. Alexander KP, Chen AY, Newby LK, et al. Sex differences in major bleeding with glycoprotein IIb/IIIa inhibitors: results from the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines) initiative. *Circulation*. 2006;114: 1380-1387.
49. Stone GW, McLaurin BT, Cox DA, et al. Bivalirudin for patients with acute coronary syndromes. *N Engl J Med*. 2006;355:2203-2216.
50. Stone GW, White HD, Ohman EM, et al. Bivalirudin in patients with acute coronary syndromes undergoing percutaneous coronary intervention: a subgroup analysis from the Acute Catheterization and Urgent Intervention Triage strategy (ACUITY) trial. *Lancet*. 2007;369: 907-919.
51. Kereiakes DJ, Grines C, Fry E, et al. Enoxaparin and abciximab adjunctive pharmacotherapy during percutaneous coronary intervention. *J Invasive Cardiol*. 2001;13:272-278.
52. Rabah MM, Premmereur J, Graham M, et al. Usefulness of intravenous enoxaparin for percutaneous coronary intervention in stable angina pectoris. *Am J Cardiol*. 1999;84:1391-1395.
53. Bhatt DL, Lee BI, Casterella PJ, et al. Safety of concomitant therapy with eptifibatide and enoxaparin in patients undergoing percutaneous coronary intervention: results of the Coronary Revascularization Using Integrilin and Single bolus Enoxaparin Study. *J Am Coll Cardiol*. 2003;41:20-25.

Main Points

- Advances in pharmacotherapy and devices have decreased the risk of ischemic outcomes for patients undergoing percutaneous coronary intervention (PCI).
- Bleeding complications are a major clinical concern for patients undergoing PCI.
- Determining the incidence of and risk factors for bleeding is complicated by the multiple systems used to classify bleeding severity and report bleeding events.
- The reported incidence of bleeding events is influenced by whether the data comes from clinical trials or registries.
- Registry data suggest that risk of bleeding among patients undergoing PCI is higher in clinical practice than the incidence observed in clinical trials.
- The possible association between PCI-related bleeding complications and myocardial infarction, stroke, or death is also of concern.
- Reduction in bleeding risk may potentially improve survival and increase comfort for patients undergoing PCI.
- Careful vascular access, alternative radial artery access, and modified antithrombotic regimen may reduce bleeding during PCI and improve patient outcomes.