Bleeding Avoidance Strategies During Percutaneous Coronary Interventions

Mandeep Singh, MD, MPH

ABSTRACT

Bleeding avoidance strategies for percutaneous coronary interventions continue to evolve with the availability of newer antiplatelet and anticoagulation therapies. Advances in interventional practices have altered the balance between ischemic and bleeding complications. With the availability of rapidly-acting platelet adenosine diphosphate–receptor antagonists, the need for routine glycoprotein IIb/IIIa inhibitors has diminished. Recent meta-analyses and trials have advanced our knowledge of vascular access and different anticoagulation regimens. Vascular closure devices have long been used for early ambulation; however, more recent results demonstrating lower bleeding complications from observational registries are encouraging. This review synthesizes this information, taking into account changes in the landscape of interventional practice with respect to current bleeding avoidance strategies. (J Am Coll Cardiol 2015;65:2225–38) © 2015 by the American College of Cardiology Foundation.

Bleeding and vascular complications in patients undergoing percutaneous coronary interventions (PCIs) are associated with significant costs, prolonged hospital stays, and increased short- and long-term morbidity and mortality (1-5). The risk of bleeding is modifiable, and improving bleeding and vascular complication rates provides an opportunity to improve the health care and safety of PCI. In that regard, the Centers for Medicare and Medicaid Services (6) have identified bleeding and hematoma following cardiovascular procedures as quality indicators (7).

Marso et al. (8) used the term “bleeding avoidance strategies” to highlight the importance of bivalirudin and vascular closure devices (VCDs) in reducing bleeding, using data on more than 1.5 million patients undergoing PCI at hospitals participating in the National Cardiovascular Data Registry (NCDR) (8). In high-risk patients, the use of both bivalirudin and VCD was associated with significantly lower bleeding rates. Since the publication of this study, pharmacotherapy and technological advances have shed new light on factors that can further mitigate bleeding risk in patients undergoing PCI.

With this backdrop, this review will report recent advances associated with meaningful reduction in bleeding complications following PCI. It will also review the current data on the status of bivalirudin and VCD. Last, this review will provide the reader with a practical strategy to help individualize a patient’s bleeding risk and deploy interventions to reduce bleeding in high-risk patients.

DEFINITION OF BLEEDING

Bleeding complications have been identified as a crucial endpoint to test the safety and efficacy of new antithrombotic drugs, cardiac devices, or PCI. Reduction in bleeding events is associated with improved survival, and prevention of major bleeding may represent an important step in improving outcomes by balancing the safety and efficacy of pharmacotherapy and devices used during PCI (9).
<table>
<thead>
<tr>
<th>Type 0: No bleeding</th>
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<tbody>
<tr>
<td>Type 1: Bleeding is not actionable</td>
</tr>
<tr>
<td>Type 2: Any overt, actionable sign of hemorrhage</td>
</tr>
<tr>
<td>Type 3:</td>
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<tr>
<td>Type 3a: Overt bleeding plus hemoglobin drop ≤5 g/dl and any transfusion with overt bleeding</td>
</tr>
<tr>
<td>Type 3b: Overt bleeding plus hemoglobin drop ≤5 g/dl and any transfusion with overt bleeding</td>
</tr>
<tr>
<td>Type 3c: Intracranial or intraocular bleed compromising vision</td>
</tr>
<tr>
<td>Type 4: CAGB-related bleeding</td>
</tr>
<tr>
<td>Type 5: Fatal bleeding</td>
</tr>
</tbody>
</table>

**BARC** — Bleeding Academic Research Consortium; **CAGB** — coronary artery bypass graft; **GUSTO** — Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; **NCDR** — National Cardiovascular Data Registry; **TIMI** — Thrombolysis In Myocardial Infarction.
connotation, and do not share a similar temporal decline as access-site bleeds, and their prevalence, predictors, and prognostic importance need to be captured separately (5,14–16).

INCIDENCE AND PREDICTORS OF BLEEDING FOLLOWING PCI

INCIDENCE OF BLEEDING COMPLICATIONS. Varying estimates from several registries’ data reflect heterogeneity in defining significant following PCI. Many centers include hematoma in their bleeding definition, leading to higher bleeding estimates, as compared with more stringent definitions that rely on a significant hemoglobin drop of ≥3 g/dl with or without other major complications (e.g., intraocular or cerebral bleed). For example, data from the Mayo Clinic included hematomas in their definition of bleeding and reported higher rates of major vascular complications (3.5% in the contemporary era between 2000 and 2005), as compared with 2.4% in the NCDR, which included transfusion/lengthened hospital stay and/or hemoglobin drop ≥3 g/dl and access or nonaccess site bleeding (14,17). There is an urgent need to adopt a universal definition for bleeding that will facilitate studying temporal trends and interinstitutional comparisons and that will unify efforts to improve them.

PREDICTORS OF BLEEDING. Doyle et al. (17) found female sex, older age, renal impairment, larger sheath size, higher activated clotting time (ACT), use of glycoprotein (GP) IIb/IIIa inhibitors, VCD use, and longer procedure time to be predictors of higher bleeding among patients undergoing PCI through the femoral route. Two models from the NCDR identified heart failure, peripheral vascular disease, and presentation with ACS as additional variables predicting bleeding (11,18). Identifying predictors associated with higher bleeding rates should prompt health care providers to seek strategies and interventions to lower the risk.

TEMPORAL BLEEDING TRENDS. Risk estimates for bleeding differed among studies, as they used different definitions of bleeding, making interstudy comparisons difficult. Regardless of the definition used, all studies have demonstrated a remarkable decline in access-site bleeding following PCI (17,19–22) (Figure 2). The likely reasons for the decline include, among others: increase in the use of radial access; smaller sheath size for femoral access; bivalirudin use; and judicious utilization of GP IIb/IIIa inhibitors. Nonaccess-site bleeds have not shared similar declines and continue to dominate in patients with ACS (14).

BLEEDING RISK ESTIMATION. The available risk models are sparsely used to predict bleeding and to stratify patients into different risk categories. Individualizing a patient’s bleeding risk may help providers to tailor access and antithrombotic therapy, choose the duration and severity of anticoagulation, and obviate the need for GP IIb/IIIa inhibitors (23). Due to significant overlap in variables predicting bleeding and other major adverse cardiovascular endpoints, bleeding risk models may also help providers predict mortality and other ischemic endpoints (24–26).

Two contemporary bleeding risk models are available. The first model is derived from 3 trials of ACS and comprises 7 easily-obtainable variables (serum creatinine, age, sex, presentation, white blood cell count, cigarette smoking, and randomized treatment). TIMI (Thrombolysis In Myocardial Infarction) major bleeding rates increased by bleeding risk score groups, from 0.4% for those in the lowest-risk group to 5.8% for those in the highest-risk group (Figure 3) (27). The second model is derived from the NCDR database, is contemporary, and can be used even in patients undergoing elective PCI (Figure 4) (11). A patient with a higher bleeding risk can be easily identified with these models (e.g., elderly women presenting with ACS), allowing bleeding avoidance strategies to be preferentially targeted to these patients (28).

PROGNOSTIC IMPLICATIONS OF BLEEDING

Bleeding following PCI is associated with an increased risk of adverse cardiovascular outcomes (17,29–33). Higher risks for mortality, MI, and stent
thrombosis are noted in patients with bleeding, and bleeding avoidance strategies are associated with improvements in survival (8). The increase in risk from bleeding is not limited to the index hospital admission (5); long-term hazard is also noted (6). The underlying mechanisms may include: prothrombotic state; abrupt discontinuation of antiplatelet and anticoagulant therapies; increasing the risk of stent thrombosis; greater prevalence of comorbidities in patients who bleed; anemia; and the effect of blood transfusions to treat bleeding (10,34). Stored blood used for transfusion has: low 2,3-diphosphoglyceric acid activity, thereby increasing the oxygen affinity of hemoglobin and decreasing tissue oxygen delivery (35); decreased red blood cell deformability, leading to increases in osmotic fragility, aggregability, and intracellular viscosity (36); disrupted nitric oxide transport (37); prothrombotic effects; and transfusion-related immunomodulation (38). The association of blood transfusion with poor prognosis should warrant caution toward routine blood transfusions in anemic, but stable patients (39,40), but should not deter clinicians from providing this therapy if severe anemia is associated with signs of ischemia (34).

**ADVANCES IN PHARMACOTHERAPY**

The temporal decline in bleeding complications following PCI has followed an evolutionary change in the type and intensity of anticoagulation and antithrombotic therapy. Very high bleeding complications were observed during the 1990s in trials that mandated the use of GP IIb/IIIa inhibitors concomitant to intensive heparin therapy (41–43). With the use of less intense anticoagulation and with the

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<td>1.0–&lt;1.2</td>
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<tr>
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<td>NSTEMI – Raised biomarkers</td>
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<tr>
<td>STEMI</td>
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<th>Add to score</th>
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<td>Yes</td>
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<tr>
<td>Heparin or Bivalirudin plus a GPI</td>
<td>0</td>
</tr>
<tr>
<td>Bivalirudin monotherapy</td>
<td>0</td>
</tr>
</tbody>
</table>

**FIGURE 3 Bleeding Risk Model**

This simple, easy-to-use model is derived from 3 trials of acute coronary syndrome. For a patient who has a creatinine of 1.3 mg/dL, is 72 years of age, is female, has a white cell count of 11 x 10^9/L, has non-ST-segment elevation myocardial infarction (NSTEMI) without raised biomarkers, and is a nonsmoker, her risk score would be: 4 + 9 + 4 + 5 + 1 + 0 = 19, signifying a 2.7% chance of a non-CABG-related TIMI major bleed within 30 days. If the patient is treated with bivalirudin alone rather than a heparin plus a glycoprotein IIb/IIIa inhibitor, the total score should be reduced by 6 to 13 points, indicating a 1.4% chance of a non-CABG-related TIMI major bleed within 30 days. Reprinted with permission from Mehran et al. (27). PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; other abbreviations as in Figure 1.
advent of dual antiplatelet therapy in the late 1990s, bleeding complications were less commonly observed. Dosing errors still occur and are prevalent in vulnerable populations at high risk for bleeding. In an observational analysis of 30,136 patients from the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines) trial, 42% of patients admitted with non–ST-segment elevation myocardial infarction (STEMI) were administered excessive dosing of unfractionated or low-molecular-weight heparin and GP IIb/IIIa inhibitors (44), which was associated with higher bleeding risk and poor outcomes. This underscores the need for national quality improvement initiatives to reduce dosing errors, thereby yielding improvement in outcomes.

HEPARIN AND ACT. Since the introduction of PCI, intravenous unfractionated heparin has been the cornerstone of antithrombotic therapy. Despite its universal acceptance, there is still controversy regarding the optimal dose and ACT that reflects equipoise between bleeding and ischemic complications. In the ESPRIT (Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy) trial, ischemic endpoints in patients undergoing contemporary PCI with stent placement did not increase with lower ACT levels, at least to a level of 200 s; however, a modest correlation with bleeding was observed at higher ACT levels (45). The current American College of Cardiology/American Heart Association PCI guidelines agree that current dosing of heparin is on the basis of empiricism and experience from randomized trials, and the utility of measured ACT levels in current practice remains uncertain (46). ACT between 200 and 250 s with GP IIb/IIIa inhibitors,
and between 250 and 300 s without, remains standard practice with unfractionated heparin during PCI, and operators are encouraged to keep the ACT on the lower end of the recommended range to lower bleeding complications.

**DUAL ANTIPLATELET THERAPY**

The PLATO (Platelet inhibition and Patient Outcomes) trial demonstrated that ticagrelor (an orally-active agent that binds reversibly to P2Y12), as compared with clopidogrel (irreversible blockade of P2Y12, delayed onset, needs cytochrome P450), was associated with a 16% relative risk reduction with regard to a composite of cardiovascular death, myocardial infarction, and stroke (47). Compared with the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) and TRITON-TIMI 38 (Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction 38) trials (48–50), not only did PLATO demonstrate significant mortality (death from any cause) reduction (4.5% with ticagrelor and 5.9% with clopidogrel), but the bleeding risk did not increase (major bleeding 11.6% vs. 11.2% with clopidogrel) (Figure 5). However, non-CABG bleeding was significantly higher in patients treated with ticagrelor. The newer antiplatelet therapies provide patients with early, reversible, and predictable platelet inhibition, with reduction in ischemic endpoints and, importantly, without increased bleeding complications. Similar results were recently reported with intravenous infusion of cangrelor, an intravenous, fast-acting, reversible, and direct-acting P2Y12 inhibitor. Its antiplatelet effects are immediate and can be maintained with continuous infusion. The plasma half-life of cangrelor is approximately 3 to 5 min, and platelet function is restored within 1 h after cessation of the infusion. The use of cangrelor in patients undergoing PCI was studied in 2 phase 3 trials, the CHAMPION (Cangrelor versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition) PCI and CHAMPION PLATFORM studies (51). Cangrelor was not associated with a significant reduction in the primary efficacy endpoint in either trial, but was associated with reductions in secondary endpoints, including the rate of stent thrombosis, with no excess severe bleeding.

The recent CHAMPION PHOENIX trial, comparing cangrelor with clopidogrel, demonstrated the superiority of cangrelor, both for reducing ischemic events and for not increasing bleeding complications following elective and urgent PCIs (52). Advances in dual antiplatelet therapy have led to early, predictable, and reversible platelet inhibition, obviating the need for routine GP IIb/IIIa inhibition, and thereby reducing bleeding complications.

**BIVALIRUDIN AND PCI.** Bivalirudin is an intravenous direct thrombin inhibitor that is used as an

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**FIGURE 5** Comparison of Dual Antiplatelet Trials

<table>
<thead>
<tr>
<th>Event</th>
<th>CURE Trial Clopidogrel Group</th>
<th>CURE Trial Placebo Group</th>
<th>TRITON-TIMI 38 Prasugrel Group</th>
<th>TRITON-TIMI 38 Clopidogrel Group</th>
<th>RR with Prasugrel (95% CI)</th>
<th>PLATO Ticagrel or Group</th>
<th>PLATO Clopidogrel Group</th>
<th>RR</th>
<th>CHAMPION-PHOENIX Cangrelor Group</th>
<th>CHAMPION-PHOENIX Clopidogrel Group</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>5.7</td>
<td>6.2</td>
<td>0.93 (0.81-1.07)</td>
<td>3.0</td>
<td>3.2</td>
<td>0.95 (0.78-1.16)</td>
<td>4.5</td>
<td>5.9</td>
<td>0.78 (0.69-0.89)</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>CV Death</td>
<td>5.1</td>
<td>5.5</td>
<td>0.93 (0.79-1.08)</td>
<td>2.1</td>
<td>2.4</td>
<td>0.89 (0.70-1.12)</td>
<td>4.0</td>
<td>5.1</td>
<td>0.79 (0.69-0.91)</td>
<td>0.3</td>
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</tr>
<tr>
<td>MI</td>
<td>5.2</td>
<td>6.7</td>
<td>0.77 (0.67-0.89)</td>
<td>7.3</td>
<td>9.5</td>
<td>0.76 (0.67-0.85)</td>
<td>5.8</td>
<td>6.9</td>
<td>0.84 (0.75-0.95)</td>
<td>3.8</td>
<td>4.7</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.2</td>
<td>1.4</td>
<td>0.86 (0.63-1.18)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.02 (0.71-1.45)</td>
<td>1.5</td>
<td>1.3</td>
<td>1.17 (0.91-1.52)</td>
<td>-</td>
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<tr>
<td>Death/MI/</td>
<td>9.3</td>
<td>11.4</td>
<td>0.80 (0.72-0.90)</td>
<td>9.9</td>
<td>12.1</td>
<td>0.81 (0.73-0.90)</td>
<td>9.8</td>
<td>11.7</td>
<td>0.84 (0.77-0.92)</td>
<td>4.7</td>
<td>5.9</td>
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<tr>
<td>Major bleed</td>
<td>3.7</td>
<td>2.7</td>
<td>1.38 (1.13-1.67)</td>
<td>2.5</td>
<td>1.7</td>
<td>1.45 (1.15-1.83)</td>
<td>11.6</td>
<td>11.2</td>
<td>1.04 (0.95-1.13)</td>
<td>0.2</td>
<td>0.1</td>
</tr>
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</table>

Comparison of recent trials with regard to bleeding and ischemic endpoints. With a reduction in ischemic complications, some increase in bleeding events is seen. The CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) trial included patients who had acute coronary syndromes without ST-segment elevation; both PLATO (Study of Platelet Inhibition and Patient Outcomes) and TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction 38) included patients who had acute coronary syndromes with or without ST-segment elevation. Modified with permission from Schomig (106). CHAMPION — Cangrelor versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition; CI — confidence interval; CV — cardiovascular; MI — myocardial infarction; RR — risk ratio.
alternative to heparin in patients undergoing PCI. Trials that compared bivalirudin with heparin found that net adverse cardiovascular events, which included ischemic complications and bleeding endpoints, favored bivalirudin, with superior or noninferior results (9,53–55). The benefit was driven primarily by lower bleeding complications. There are several limitations of the previously-published trials that compared heparin versus bivalirudin monotherapy for PCI. First, the intensity of antiplatelet and anticoagulation therapies was disparate and weighted heavily toward the heparin monotherapy arm (56). This made interpretation of the primary endpoint challenging, with 2 treatment arms expected to have completely opposite effects on the incidence of thrombotic and bleeding complications. For example, in patients treated with heparin monotherapy, differential and routine use of GP IIb/IIIa agents was associated with a higher risk of bleeding complications. Second, even in more recent trials, such as the EUROMAX (European Ambulance Acute Coronary Syndrome Angiography) trial, an international, randomized, open-label study that demonstrated that bivalirudin, initiated during transport for primary PCI in patients with STEMI, was superior to heparin, the dose of heparin (100 IU/kg) and concomitant optional use of GP IIb/IIIa inhibitors (69.1%) was high, leading to increased bleeding complications in the heparin arm (57). Third, ischemic events, specifically acute myocardial infarction or stent thrombosis (especially within the first 24 h), were more frequently noted in patients treated with bivalirudin (58). Despite the consistent, but nonsignificant increase in ischemic events, the concomitant reduction in bleeding events in the bivalirudin-treated patients favored its use as monotherapy. Fourth, upstream use of dual antiplatelet therapy, especially with newer and faster-acting agents, has led to reductions in the routine use of GP IIb/IIIa agents, currently at 28% from 41% (14). This has led to newer trials comparing heparin versus bivalirudin monotherapies, with optional and lower use of GP IIb/IIIa inhibitors. In HEAT-PPCI (How Effective are Antithrombotic Therapies in Primary Percutaneous Coronary Intervention), among 1,829 patients who underwent emergent coronary angiography at a single center, GP IIb/IIIa inhibitor usage was low (13% to 15%) and was equal in the heparin and bivalirudin arms. The primary efficacy outcome at 28 days (all-cause mortality, myocardial infarction, cerebrovascular accidents, unplanned target lesion revascularization) favored heparin (5.7% compared with 8.7% in the bivalirudin group) (59). The primary safety endpoint of major bleeding was similar in the 2 groups. It should be noted that the median ACT value in the HEAT-PPCI trial was lower in the heparin arm (206 s) compared with the bivalirudin arm (246 s) and with other primary PCI trials. In the meta-analyses (58), additional heparin and prolonged duration of bivalirudin did not improve ischemic outcomes, however, in the Swedish Coronary Angiography and Angioplasty Registry, an additional dose of heparin led to improved rates of myocardial infarction (60).

BRIGHT (Bivalirudin in Acute Myocardial Infarction vs Heparin and GPI Plus Heparin Trial), studied bivalirudin in patients undergoing PCI. The trial was performed in 82 centers in China and randomized 2,194 patients into: bivalirudin and provisional GP IIb/IIIa inhibitors (n = 735); heparin and provisional GP IIb/IIIa inhibitors (n = 729); or heparin and routine GP IIb/IIIa inhibitors (n = 730) (61). The net adverse clinical endpoint was lower in the bivalirudin group (65 events, 8.8%) than with either heparin and provisional GP IIb/IIIa inhibitors (96 events, 13.2%) or heparin and routine GP IIb/IIIa inhibitors (124 events, 17.0%). The differences between the groups were almost entirely driven by the differences in the any bleeding category. There were no differences in ischemic events, including stent thrombosis. In the MATRIX (Minimizing Adverse Haemorrhagic Events by TRansradial Access Site and Systemic Implementation of angioX) trial of 7,200 ACS patients undergoing PCI randomized to bivalirudin or unfractionated heparin, Valgimigli (62) did not report significant improvement in risk of cardiac events or cardiac events plus major bleeding after taking bivalirudin, as compared with standard care. However, bivalirudin was shown to significantly lower the risk of bleeding complications, especially near the catheter insertion site, which occurred in 1.7% with bivalirudin versus 2.3% in the standard-care group. Additionally, the bivalirudin group had a significantly lower rate of death, most likely related to the reduction in bleeding complications.

The present data suggest that heparin monotherapy is sufficient for most patients who undergo PCI with radial access. Patients at high risk for ischemic complications or stent thrombosis (bifurcation or long lesions, among others) may be treated with unfractionated heparin with newer P2Y12 antagonists. In contrast, patients with a higher risk for bleeding (older women presenting with ACS and where femoral access is used for the intervention) may benefit from bivalirudin.

**ACCESS AND BLEEDING COMPLICATIONS**

**FEMORAL ARTERY ACCESS.** Access-site bleeding complications predominate, especially in the setting
of elective PCI. It is, therefore, pertinent to advance measures and strategies known to lower bleeding rates from access sites. The femoral artery has traditionally been used for PCI in the United States, and approximately 80% of PCIs are performed through this route (63,64). It also is a preferred route for procedures that require larger catheters. For example, operators still prefer the femoral access route for distal left main, complex bifurcation lesions, and rotational atherectomy with large burrs. Transcatheter aortic valve replacements and other peripheral vascular procedures are also performed through femoral or apical routes due to the need for large catheters.

Few studies have looked into the advantages of using smaller-size sheaths, fluoroscopy, and intravascular ultrasound for femoral artery access (65). The data are derived from a single center (17), but observations from randomized trials and registries are consistent and support the use of a micropuncture needle (FEMORIS [Femoral Micropuncture or Routine Introducer Study]; 21-gauge vs. 18-gauge needle) (66); fluoroscopy or ultrasound (FAUST [Femoral Arterial Access With Ultrasound Trial]) (67) to target the common femoral artery; smaller sheath size; and early sheath removal. On the basis of these observations, operators are encouraged to use fluoroscopy and micropuncture needles with ultrasound guidance, with the goal of performing safe zone arteriotomy (access between the inferior epigastric artery above and the bifurcation of the common femoral artery below).

**Radial Artery Access.** Radial artery access has consistently demonstrated reduction in bleeding and vascular complications following PCI compared with femoral artery access in observational registries and randomized trials (63,68,69). In the randomized trial, RIVAL (Radial Vs Femoral Access for Coronary Intervention), the primary outcome of death, myocardial infarction, stroke, or non-CABG-related bleeding at 30 days occurred in 3.7% in the radial access group, which was not different from the 4.0% observed in patients randomized to femoral access (70). However, if the definition of bleeding was broadened to include large hematomas and pseudoaneurysms, significant differences favoring radial access were observed between the 2 groups. In the recently-published MATRIX trial, 8,404 patients with ACS were randomized to radial (n = 4,197) or femoral (n = 4,207) access for coronary angiography and PCI. Major adverse cardiovascular events were noted in 8.8% of patients with radial access, compared with 10.3% of patients with femoral access. The net adverse clinical events, including bleeding events, favored patients in the radial access group: 410 (9.8%) patients with radial access had net adverse clinical events compared with 486 (11.7%) patients with femoral access. The difference was driven by BARC major bleeding unrelated to CABG surgery (1.6% vs. 2.3%) and all-cause mortality (1.6% vs. 2.2%) (71). The largest observational NCDR also demonstrated that radial access was associated with a significant reduction in bleeding and vascular complications (14,62). The most significant reduction in bleeding rates was observed in patients with STEMI treated via radial access. Patients with STEMI represent the highest risk for both ischemic and bleeding complications. In some randomized trials and meta-analyses, use of the radial approach for access in primary angioplasty resulted in reduced mortality (69,70,72). With heterogeneity in trial inclusion criteria and with the majority of deaths in patients without a major bleed, there is a lack of a distinct, mechanistic link between mortality reduction and radial access that was observed in some studies (34). However, these results underscore the need to use radial access in this subgroup, which is the most prone to bleeding complications following PCI.

In addition to lowering bleeding complications, radial access has cost advantages, promotes early ambulation and discharge, and is preferred by patients (1,70,73). However, despite these advantages, there is a distinct learning curve for proficiency in using radial artery access for cardiac catheterization and PCI. In a pre-specified subgroup analyses from the RIVAL trial, the primary outcome was reduced (hazard ratio: 0.49, 95% confidence interval: 0.28 to 0.87) in high-volume radial centers, defined as the operator’s annual median radial PCI volume >146 (74). Clinical data from 1,298 facilities reporting to the NCDR show that 49% of facilities in the United States performed ≥400 PCIs and 26% performed ≥200 PCIs annually; hence, replicating these results in lower-volume centers may be challenging (75). Procedural learning, however, continues, with further improvement noted in dedicated radial PCI operators who switch from transfemoral angiography (76). In a recent study from the NCDR, higher-risk patients were chosen for transradial PCI with increased operator radial PCI volume (77). Despite this, operator proficiency improved, and the threshold for overcoming the learning curve appeared to be approximately 30 to 50 cases. There is growing published data on the learning curve for transradial PCIs, and despite study differences, 25 to 80 cases are needed for novice operators (78). In summary, volume-outcome relationships are evident in learning transradial PCIs, and available data support higher-volume radial PCI centers to improve PCI outcomes.
RADIAL ARTERY OCCLUSION. Radial artery occlusion is a distinct complication of radial access, and its incidence ranges from 2% to 10% following transradial access (79). To prevent ischemia and reuse the same site for bypass conduit or cardiac catheterization, the Society for Cardiovascular Angiography and Interventions radial committee recently recommended a standardized anticoagulation protocol, using the lowest-profile sheaths, patent hemostasis (80), or radial compression guided by mean artery pressure techniques (81) to reduce its incidence (82). Similar recommendations were made to reduce radiation exposure and to transition to perform primary PCI.

The RADAR (Predictive Value of Allen’s Test Result in Elective Patients Undergoing Coronary Catheterization Through Radial Approach) trial (83) did not find a relationship between functional assessment of dual-artery circulation to the hand by the Allen test and plethysmography and measures of distal ischemia, collaterals between the radial and ulnar arteries, and functionality of the hand following radial access. The Allen test was abnormal in 30% and a D pattern by plethysmography was detected in 40% of 942 screened patients. The investigators suggested the feasibility of transradial access across the spectrum of Allen test results. Further studies are needed to test this proof-of-concept.

VCDs AND BLEEDING COMPLICATIONS. VCDs have been demonstrated to reduce time to ambulation and increase patient comfort (84–86). Recent observational registries and subgroup analyses from randomized trials have noted reductions in the incidence of bleeding complications with VCDs following invasive femoral angiography or PCI; however, there is a lack of randomized trial data to support their use for these indications (87–89). Observational registry data from NCDR and Blue Cross Blue Shield of Michigan demonstrated lower bleeding risk with VCD use (8,90,91). However, meta-analyses and randomized trials comparing bleeding rates following manual compression or from VCD failed to show lower bleeding rates with VCD (84,88,92). To accurately portray the role of VCDs, a high-quality, adequately-powered randomized trial needs to be performed with intention-to-treat and concealment of allocation of manual versus VCD strategy. We also need to account for the learning curve and do post-marketing surveillance to monitor device complications (93,94). Not only is the use of VCDs associated with complications unique to device deployment (loss of limb circulation or severe infection) (95), but also device failure (1.5% to 20%) is associated with significantly higher bleeding complications (96). Gurm et al. (90) noted, in a large observational registry, a reduction in hematoma and pseudoaneurysm, but also a significant increase in retroperitoneal bleeds with the use of VCDs. Their usefulness to reduce bleeding and vascular complications was attenuated in patients with low BMI and in those on GP IIb/IIIa agents (90). In a recent study from the Massachusetts Department of Health, VCD failed in 3.3% of 23,813 procedures (97). VCD failure was associated with excess risk of any (7.7% vs. 2.8%) or major (3.3% vs. 0.8%) vascular complications, as compared with successful VCD deployment, underscoring the need for physicians to be vigilant of predictors of VCD failure (female sex, peripheral vascular disease, and emergency status). These are the same variables that increase the risk of bleeding, and their cautious use or avoidance would be recommended until additional data are accrued.

ADOPTION OF BEST PRACTICES TO LOWER BLEEDING COMPLICATIONS

Recent analyses of a nationally-representative U.S. PCI population suggest that 12.1% of all in-hospital mortality after PCI may be related to bleeding complications, and may therefore be modifiable, and that the number needed to harm (NNH) calculations suggest that the mortality risk associated with bleeding was greatest in patients at the highest bleeding risk (NNH = 21) or with nonaccess-site bleeding (NNH = 16) (5). Likewise, the NNH was lowest in patients age 75 years or older and in patients with STEMI or low glomerular filtration rate. These high-risk subgroups may have the greatest potential for mortality reduction through bleeding avoidance and should be preferentially targeted.

Individualizing and stratifying bleeding risk before coronary angiography and intervention is paramount (Central Illustration). Not only can one tailor the choice of vascular access, but modification of anticoagulation strategies by pre-treatment with dual antiplatelet therapy and use of bivalirudin to lower access- and nonaccess-site bleeds in patients deemed to be higher risk will likely lower their bleeding complications. Excessive bleeding is also associated with acute kidney injury and ischemic complications; thus, preventing bleeding complications will translate into overall improvement in PCI outcomes (98). Recognition and mitigation of bleeding risk following PCI is a recognized health care priority. Despite consistent observations from contemporary registry data documenting reductions in vascular and bleeding complications, there is still a paucity of systematic efforts to lower bleeding in these patients.
Marso et al. (8) used the available risk model to categorize patients in a large population undergoing PCI into different tertiles of bleeding risk. In that study, the use of VCD and bivalirudin lowered bleeding rates, especially among patients at the greatest risk for bleeding. The strategies that lowered bleeding risk were used less commonly in the subgroup with the highest bleeding risk (risk-treatment paradox). In another study, incorporation of individualized risk estimates in the consent form led to reversal of this paradox through rational increase in the use of bivalirudin (23). At the Mayo Clinic, pretreatment with dual antiplatelet agents has reduced the need for GP Iib/IIa agents, and a concomitant increase in the adoption of radial access for PCI has resulted in reduction of bleeding and vascular complications (unpublished data). Reduction of bleeding complications with the use of bivalirudin needs to be put in perspective. Recent data from HEAT-PPCI and now from the BRIGHT and MATRIX trials comparing bivalirudin versus heparin has rekindled the debate on anticoagulation during PCI. It has encouraged the use of heparin monotherapy with pre-loading of dual antiplatelet therapy. Bivalirudin has demonstrated lowered bleeding and may be advantageous in patients with a high likelihood of bleeding. Unlike HEAT-PPCI, the BRIGHT and MATRIX trials reported lower bleeding; hence, there is a need to revisit the value proposition of bivalirudin. For example, older patients, women, those with renal dysfunction, and those presenting with ACS are subgroups that will benefit preferentially from bleeding avoidance strategies, including radial access and bivalirudin. More studies need to be performed to lower the acute thrombotic risk with bivalirudin, and readers are encouraged to read the recent meta-analysis on this topic (58). If ischemic complications in the first 24 h following bivalirudin administration can be lowered, short- and long-term prognoses seem excellent (99). In the Swedish Coronary Angiography and Angioplasty Registry, an additional bolus dose of unfractionated heparin was associated with a lower rate of death or definite target lesion thrombosis at 30 days in patients undergoing primary PCI with bivalirudin as the anticoagulant (60). The BRIGHT trial demonstrated the usefulness of prolonged bivalirudin infusion in lowering ischemic events among patients with acute myocardial infarction undergoing emergent PCI (61).

The recent observational data on the use of VCD to lower bleeding rates following PCI is encouraging (87,89,90). However, the results of meta-analyses of randomized trials are not concordant. At present, the use of VCD to lower bleeding and vascular complications cannot be recommended, and there is a need for an adequately-powered randomized trial.

The use of the radial artery for access has increased, albeit at a slower pace in North America. Most trials, including the recent MATRIX trial, and registry data support the use of the radial artery to lower access-site bleeding complications. Substantial expertise is needed to perform PCI through the radial approach, and the best outcomes have only been reported at high-volume centers. The prognostic link between bleeding and survival prompts consideration of radial artery access as a default strategy in most patients, but especially in patients who are at high bleeding risk (older patients presenting with ACS), who will derive the most benefit from this
change (100). In a large study from the British Cardiovascular Intervention Society database, a 35% reduction in 30-day mortality with radial artery access for PCI was seen across various risk categories, but was most evident in patients at the highest baseline bleeding risk (4). Current efforts to train interventional fellows and consultants will certainly increase adoption of this technique, but at the same time, the role and safety of femoral access should not be undermined. Readers are encouraged to review the meta-analysis comparing radial and femoral access for coronary angiography and interventions (70,101). Femoral access is still needed for larger sheath sizes, complex left main interventions, rotational atherectomy with large burrs, transaortic valve replacement (TAVR), intra-aortic balloon pump and other assist devices, and abdominal and lower-extremity angiography and interventions. High rates of bleeding complications are noted in patients undergoing TAVR. A recent study demonstrated a reduction in major bleeding rates with the adoption of heparin doses according to the ACT value. Major bleeding was higher in patients treated with a weight-based dosing strategy (33.5% vs. 7.5%, p < 0.001). Multivariate adjustment favored the use of ACT-based dosing of heparin, with a significantly lower incidence of 30-day major bleeding (102). Recently, the use of the radial crossover technique, with a salutary effect on bleeding, has been described for tortuous contralateral femoral arteries in patients undergoing TAVR (103). The data on angiograms and PCI in patients with prior bypass surgery also favor the transfemoral route (104). More data are needed to support the routine use of fluoroscopy, micropuncture needle with ultrasound assistance, smaller sheath size, early sheath removal, and use of the right dose of anticoagulation agents that will likely lower bleeding and vascular complication rates from femoral access.

We eagerly await the results of SAFARI-STEMI (Femoral Versus Radial Access for Primary PCI; NCT01398254) (105).

SUMMARY AND CONCLUSIONS

New iterations of catheters, closure devices, and anticoagulation doses and regimens have lowered bleeding rates following PCI; however, bleeding still accounts for significant morbidity and mortality. Tools to estimate an individual’s bleeding risk need to be routinely used. The bleeding risk is modifiable; therefore, interventionalists are encouraged to adopt the safest and best practices to lower the bleeding rates. Operators need to choose the right anticoagulation agent and administer the right dose. Switching to radial access for PCI will be a paradigm shift for operators who have previously used femoral access. It has a learning curve, and only high-volume operators will be able to demonstrate lower bleeding rates and improved outcomes. Proficiency in femoral access is still required. Adoption of best practices to lower bleeding rates will certainly improve quality of care and downstream outcomes of PCI.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Mandeep Singh, Division of Cardiovascular Diseases, Department of Internal Medicine, Mayo Clinic, 200 First Street Southwest, Rochester, Minnesota 55905. E-mail: singh.mandeep@mayo.edu.

REFERENCES

11. Rao SV, McCoy LA, Spertus JA, et al. An updated bleeding model to predict the risk of

20. Bovill EG, Terrin ML, Stump DC, et al. Hemor-


22. Subherwal S, Peterson ED, Dai D, et al. Temporal trends in and factors associated with bleeding complications among patients undergo-


23. Verheugt FW, Steinshul SR, Hamon M, et al. Incidence, prognostic impact, and influence of antithrombotic therapy on access and nonaccess site bleeding in percutaneous coronary interven-


24. Vavalle JP, Clare R, Chiswell K, et al. Prog-

nostic significance of bleeding location and severity among patients with acute coronary syn-


25. Doyle BJ, Ting HH, Bell MR, et al. Major femoral bleeding complications after percuta-

neous coronary intervention: incidence, pre-

dictors, and impact on long-term survival among 17,901 patients treated at the Mayo Clinic from 1994 to 2005. J Am Coll Cardiol Intv 2008;1:

202-9.


ical risk algorithm from the National Cardiovas-

cular Data Registry. Circ Cardiovasc Inter 2009;2:

222-9.

27. Ahmed B, Piper WD, Malenka D, et al. Signifi-

antly improved vascular complications among women undergoing percutaneous coronary inter-


28. Applegate RJ, Sacrity MT, Kitcher MA, et al. Trends in vascular complications after diag-

nostic cardiac catheterization and percutaneous coronary intervention via the femoral artery, 1998 to 2007. J Am Coll Cardiol Intv 2008;1:

317-26.


34. Singh M, Lennon RJ, Holmes DR Jr., et al. Correlates of procedural complications and a simple integer risk score for percutaneous coro-

nary intervention. J Am Coll Cardiol 2002;40:

387-93.

35. Mehran R, Pocock S, Nikolsky E, et al. Impact of bleeding on mortality after percutaneous coronary intervention results from a patient-level pooled analysis of the REPLACE-2 (randomized evaluation of PCI linking angiolysis to a major bleeding) clinical event. ACUTY (acute catheterization and urgent inter-

vention triage strategy), and HORIZONS-AMI (harmonizing outcomes with revascularization and stents in acute myocardial infarction) trials. J Am Coll Cardiol Intv 2011;4:654-64.

36. Daugherty SL, Thompson LE, Kim S, et al. Patterns of use and comparative effectiveness of bleeding avoidance strategies in men and women following percutaneous coronary interventions: an observational study from the National Cardiovas-

cular Data Registry. J Am Coll Cardiol 2013;61:

2070-8.

37. Kissin RD, Stabile E, Mintz GS, et al. Inci-

dence, predictors, and prognostic implications of bleeding and blood transfusion following percu-


1364-9.


procedural bleeding and 1-year outcome after percutaneous coronary interventions: appropri-

ateness of including bleeding as a component of a quadrule end point. J Am Coll Cardiol 2008;51:

690-7.


42. EPISTENT Investigators. Randomized placebo-

controlled and balloon-angioplasty-controlled trial to assess safety of coronary stenting with use of platelet glycopro-

tein Iib/IIa receptor in high-risk coronary angio-


43. EPISTENT Investigators. Randomized placebo-


ation in Percutaneous Transluminal Coronary An-

gioplasty to Improve Long-Term Outcome with Abciximab GP Iib/IIa blockade. Evaluation of Platelet Iib/IIa Inhibitor for Stent. J Am Coll Car-


45. Alexander KP, Chen AV, Roe MT, et al., for the CRUSADE Investigators. Excess dosing of anti-


46. Tolleson TR, O’Shea JC, Bittle JA, et al. Rela-

tionship between heparin anticoagulation and clinical outcomes in coronary stent intervention: observations from the ESPRIT trial. J Am Coll Cardiol 2003;41:386-93.


48. Wallentin L, Becker RC, Budaj A, et al., PLATO Investigators. Ticagrelor versus clopidogrel in pa-


49. Mehta SR, Yusuf S, Peterson RJ, et al., Clopi-

dogrel in Unstable angina to prevent Recurrent Events trial (CURE) Investigators. Effects of pre-


50. Mehta SR, Yusuf S, Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) Study Investigators. The Clopidogrel in Unstable angina
to prevent Recurrent Events (CURE) trial program, rationale, design and baseline characteristics including a meta-analysis of the effects of thienopyridines in vascular disease. Eur Heart J 2000;21:2033–41.


Bleeding Complications Following PCI

Singh

**KEY WORDS** anticoagulants, platelet aggregation inhibitors, thrombosis, vascular closure devices