Primary percutaneous coronary intervention (PCI) has been shown to be more effective than thrombolytic therapy for treating ST-segment elevation myocardial infarction (STEMI). In terms of death, reinfarction, and stroke, bleeding remains just as frequent, if not more so with primary PCI, with bleeding complications now exceeding the prevalence of ischemic complications in contemporary acute coronary syndromes (ACS) and PCI populations. A causal relationship between major bleeding in patients with ACS and/or PCI and increased mortality and morbidity has recently been demonstrated in several publications and meta-analyses. Bleeding in the setting of coronary angioplasty is driven by pharmacological and nonpharmacological factors. Therefore, a combination of strategies designed to address both of these (without increasing ischemic complications) may synergize to lower bleeding risk and, consequently, may be advantageous in terms of outcomes.

**BLEEDING COMPLICATIONS IN ACS**

Initial studies reported that major bleeding is associated with an odds ratio of 3.5 for in-hospital and 1-year mortality. This hazard at 1 year was greater than that associated with in-hospital ischemic complications and reinfarction. Hemorrhagic complications and transfusions have been identified as independent predictors of adverse outcomes and significantly influence combined efficacy and safety endpoints, as demonstrated in the recent OASIS-5 (Organization for the Assessment of Strategies for Ischemic Syndromes) and ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trials. A recent meta-analysis of the impact of bleeding on outcomes in patients with ACS reported an 11% increase in the absolute risk of death associated with major bleeding (95% confidence interval [CI], 8%–14%), which corresponds to one life that is saved for every nine major bleeds avoided. Prevalence estimates of procedure-related bleeding varies between the available studies and might be due to a combination of differences in study populations and the criteria used to define bleeding events, with many grouping both access site and remote (eg, intracranial) bleeding events together. This has led to some ambiguity regarding the importance of access-related bleeding.

Hence, recognizing bleeding risk early in patients with ACS, especially those scheduled to undergo PCI, is of critical importance in selecting pharmacologic and nonpharmacologic strategies to optimize outcomes, as has been recently outlined in guidelines.

**MECHANISM FOR INCREASED MORTALITY**

Although the underlying mechanisms of increased mortality of patients with major bleeding remain unclear, increased myocardial ischemia has been proposed to be a final common pathway. Gastrointestinal bleeding or retroperitoneal bleeding, secondary to femoral artery instrumentation, causes a rapid loss of circulating volume and, consequently, hypotension and reduced tissue perfusion. Local bleeding and femoral site hematoma formation is also thought to lead to systemic activation of prothrombotic pathways and may influence clinicians to cease antiplatelet medications: both increase the risk of stent thrombosis and subsequent myocardial ischemia and reinfarction.

The initiation of blood transfusion in response to such major bleeding is necessary to restore circulating volume and oxygen-carrying capacity, but blood transfusion itself is a strong predictor of the length of the in-hospital stay after PCI and is associated with increased mortality. Although this association is real, a causal link has not been established, and instead, transfusion status may only identify patients at increased overall risk. However, there is evidence that stored blood has less effective oxygen-carrying capacity; that structural changes in the red blood cells impair their ability to navigate the microcirculation.
causing stagnation and worsening local ischemia; and that they are also depleted in nitric oxide, which is normally released along with oxygen so that local vasodilatation may occur in the regions of maximal oxygen extraction. These hypotheses will need specifically designed studies to evaluate their individual contributions to the increased mortality observed with procedural bleeding before any steps to modify them can be taken.

**MANIPULATION OF PHARMACOLOGICAL FACTORS TO REDUCE BLEEDING RISK**

The increasing use of periprocedural full anticoagulation, commonly with heparin or low-molecular-weight heparins and the combination of antiplatelet agents such as aspirin, clopidogrel, and platelet glycoprotein IIb/IIIa inhibitors, has proven beneficial in preventing ischemic complications of myocardial infarction and stent thrombosis. However, this has come at the cost of increasing bleeding complications.

The advent of direct thrombin inhibitors, such as bivalirudin and anti-Xa inhibitors such as fondaparinux, has served to restore this imbalance. In the OASIS-5 trial, which compared fondaparinux and low-molecular-weight heparins in patients presenting with ACS, a reduced incidence of major bleeding and improved long-term morbidity and mortality was observed. In the ACUITY trial, bivalirudin monotherapy compared to a heparin plus glycoprotein IIb/IIIa inhibitor significantly reduced access site–related bleeding complications with femoral but not radial artery access, although nonaccess site–related bleeding was reduced by bivalirudin monotherapy in all patients. It is postulated that the short half-life of bivalirudin, which allows rapid recovery of normal hemostasis after the infusion is discontinued, along with avoidance of glycoprotein IIb/IIIa inhibitors, both contributed to the reduction in hemorrhagic complications with femoral artery access. Data from the HORIZONS AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) study of patients with STEMI undergoing primary PCI have confirmed that reduced bleeding was associated with lower all-cause 30-day mortality in patients treated with bivalirudin. A combined analysis of the REPLACE-2, ACUITY, and HORIZONS AMI trials looking at the effect of antithrombotic therapy on organ bleeding (nonaccess site–related bleeding) has recently been conducted. In this pooled analysis, organ bleeding associated with PCI was not uncommon, representing up to one-third of all bleeding events, and bivalirudin instead of a heparin plus glycoprotein IIb/IIIa inhibitor not only diminishes access site bleeding but also significantly decreases organ bleeding by over 50% (oral communication, September 2009).

**MANIPULATION OF NONPHARMACOLOGICAL FACTORS TO REDUCE BLEEDING RISK**

The choice of vascular access site for PCI is one of the most important factors in determining bleeding risk. Access site complications and bleeding are a leading cause of procedural morbidity and possibly mortality, particularly in the setting of primary PCI for acute STEMI in which the most aggressive pharmacotherapy to inhibit platelet aggregation and to protect against early stent thrombosis is employed, often including the use of platelet glycoprotein IIb/IIIa inhibitors.

Femoral bleeding complications, which are influenced by anatomical variations, obesity, and puncture technique, include hematomas, arteriovenous fistulas, arterial pseudoaneurysms, and retroperitoneal hemorrhage. These were traditionally viewed as relatively benign; however, it is now recognized that major femoral bleeding complications, such as major hematoma formation, external bleeding, and retroperitoneal bleeding, are associated with decreased long-term survival. This association persisted after correction for multiple predictors of PCI-related mortality, with a 30-day adjusted hazard ratio of 9.96 (95% CI, 6.94–14.3; P = .001). Thus, major femoral bleeding should not be dismissed as a trivial complication of PCI.

In addition, in patients for whom femoral artery access is used, the sheath is often removed several hours after the procedure to allow coagulation recovery after discontinuation of intravenous (but not oral) antithrombotic therapy, a situation that may increase the bleeding risk. Alternatively, femoral sheaths can be removed immediately in conjunction with the use of vascular closure devices. Unfortunately, vascular closure devices have not been found to reduce the rate of hemorrhagic or vascular complications in meta-analyses of randomized trials.

The single most effective way for the operator to reduce major bleeding is to use radial rather than femoral access. A systematic review of randomized trials revealed an odds ratio of 0.20 (95% CI, 0.09–0.42; P = .0001) for access site complications after radial rather than femoral PCI. Selection bias could certainly account for the finding of decreased mortality, because it seems likely that the most complex cases requiring large devices and hemodynamic support would have been performed via the femoral route. However, it is possible that decreased bleeding complications (and transfusion requirements) could also have contributed, at least in part, to the finding of lower mortality among patients treated via the radial artery.

Recently, the MORTAL (Mortality Benefit of Reduced Transfusion After PCI via the Arm or Leg) study retrospec-
tively examined the association between access site, transfusion, and outcomes in over 32,000 patients who underwent PCI in British Columbia from 1999 to 2005. The main finding was that by reducing vascular access site complications, the use of the radial access site was associated with a 50% reduction in the transfusion rate and a relative reduction in 30-day and 1-year mortality rates of 29% and 17%, respectively ($P < 0.001$), which corresponds to around 1% absolute risk reduction at 1 year. Therefore, the number needed to treat via the radial approach was 100 patients to save one life.

The MORTAL data are consistent with the recently reported RIVIERA (Registry on Intravenous Anticoagulation in the Elective and Primary Real World of Angioplasty), a large, prospective international registry, which also reported that by limiting the bleeding risk and transfusion requirement, the use of radial access is associated with a reduction in PCI-related mortality.

There is emerging evidence that in the primary PCI setting, the transradial approach is safe. A large single-center study assessing the safety of transradial primary PCI experienced no major bleeding complications in 163 patients with STEMI treated via the radial approach. In addition, a recent larger study demonstrated similar findings with complications occurring only in radial procedures that crossed over into the femoral group because of access site difficulties. However, nonrandomized data should be treated with a degree of caution, because many other factors would have contributed to the reasons a particular route is selected.

**NONBLEEDING-RELATED ADVANTAGES OF THE TRANSRADIAL APPROACH IN STEMI**

In the context of primary PCI for STEMI, several investigators have reported that the length of hospital stay after the procedure has been shorter for patients treated via a radial approach. This has a number of important implications with regard to patient comfort, the cost of each patient admission, and increased bed turnover. A recent study reported that patients treated with transradial primary PCI needed a hospital stay of 1 day less than those treated by the transfemoral route. Although this may be accounted for by early mobilization in the radial group, it could easily reflect a degree of selection bias against femoral access, which may have been used in the more complex cases.

**PERCEIVED LIMITATIONS OF THE TRANSRADIAL APPROACH**

Despite the current evidence, the radial access route is still not widely utilized, although uptake of the technique varies between countries. This slow adoption is in part due to the need for a specific skill set and navigation of a significant learning curve, but also because there are a number of perceived limitations with the technique, such as the risk of radial artery spasm, arterial puncture failure, or vascular anomalies with consequent failure to reach the ascending aorta. However, in the context of the emergent setting of primary PCI for acute STEMI, small studies have shown lower vascular complication rates but also similar procedural success when using the radial artery for access. Hence, with appropriate training, success rates comparable to those of the femoral approach may be achieved, even in complex cases and high-risk groups that would benefit most from the reduced rates of hemorrhagic and vascular complications.

With the need to achieve rapid reperfusion in acute STEMI to improve outcomes, many believe that adopting a transradial approach may have an impact on needle-to-balloon times given the perceived potential for greater access site problems. However, a recent study demonstrated equivalent reperfusion times, with a median of 17 minutes for both approaches. Reduced procedural times are also important for minimizing the use of radiographic contrast, a particular priority in the acute MI setting, because these patients are at higher risk of contrast-related complications such as nephropathy and acute pulmonary edema. Higher volumes of contrast used during primary PCI have also been associated with increased mortality. Studies have shown that the volume of contrast used during primary PCI via the transradial approach is similar to the volume used in the transfemoral approach.
CONCLUSION

The evidence base now clearly demonstrates use of the radial artery access site to be associated with fewer major bleeding events and transfusions than the femoral approach, having the added benefits of being superficial, easily compressible, and not an end artery. In addition, it allows for increased patient comfort, reduced nursing staff workload, and makes outpatient treatment feasible in the elective setting. Ongoing randomized trials, in particular the sub study of the CURRENT (Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events) OASIS-7 trial, will confirm or refute the positive impact of radial access on patient outcomes. There is also growing evidence for its use in high-risk subgroups such as ACS and STEMI.

However, it is important to remember that the choice of access site is only one facet of improving patient outcomes, and substantial gains are also to be made with optimizing periprocedural pharmaceutical strategies to maintain antithrombotic efficacy while limiting both access site and remote bleeding risk (Figure 1). Therefore, it could be envisioned that given time, radial artery access along with direct thrombin inhibition may actually become the new gold standard for PCI in patients with high-risk features.

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