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Transradial Versus Transfemoral Percutaneous Coronary Intervention in Acute Coronary Syndromes

Re-Evaluation of the Current Body of Evidence

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Recent literature has argued the superiority of radial access compared with femoral access for percutaneous coronary intervention (PCI) in acute coronary syndrome (ACS). Three particular trials—RIVAL (Radial Versus Femoral Access for Coronary Intervention), RIFLE-STEACS (Radial Versus Femoral Randomized Investigation in ST-Elevation Acute Coronary Syndrome), and STEMI-RADIAL (ST Elevation Myocardial Infarction Treated by Radial or Femoral Approach–Randomized Multicenter Study Comparing Radial Versus Femoral Approach in Primary PCI)—demonstrated lower rates of bleeding and vascular complications with the transradial approach. Bleeding is a major independent predictor of negative long-term outcomes including death, predisposes patients to transfusions, and attenuates the ability to administer cardioprotective post-procedural anticoagulation. These trials, however, employed suboptimal antithrombotic practices. Namely, the dose of heparin and percent of patients on glycoprotein IIb/IIIa inhibitors were unnecessarily high, and a paucity of patients were on bivalirudin, which decreases bleeding and improves outcomes compared with heparin and glycoprotein IIb/IIIa inhibitors. The use of larger gauge catheters in femoral access patients predisposed them to major bleeding and its subsequent complications. In addition, these trials were carried forth in high-volume transradial centers, further limiting the ability to generalize the findings to most PCI centers. These are important considerations especially for high-risk and ACS patients, in whom the negative implications of major bleeding are even greater. Without an optimized design, the applications of the trial findings are uncertain. Ultimately, a trial comparing femoral versus radial access in patients on bivalirudin, potent oral antiplatelet medication, and without adjunctive glycoprotein IIb/IIIa inhibitors is needed to assess outcomes based on access site alone. (J Am Coll Cardiol Intv 2013;6:1149–52) © 2013 by the American College of Cardiology Foundation

The benefits of early invasive treatment with percutaneous coronary intervention (PCI) in patients presenting with acute coronary syndrome (ACS) are well accepted (1,2). However, recent literature has challenged the common practice of attaining access via the femoral artery, arguing the superiority of radial access in terms of bleeding and mortality, and calling for a paradigm shift in the approach of interventionalists (3–9). Though the published evidence favoring radial access is compelling, there exist fundamental limitations in the methodology of these studies. Namely, the administration of antithrombotic agents was either excessive, inappropriate, or both. Here, we offer insight into and special consideration to these trials with reconsideration of the femoral approach.

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Trials Comparing Radial and Femoral Access in Acute Coronary Syndrome

The RIVAL trial. The RIVAL (Radial Versus Femoral Access for Coronary Intervention) trial was initiated as a substudy of the CURRENT-OASIS 7 (Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events/Optimal Antiplatelet Strategy for Interventions) trial (which investigated standard vs. high-dose aspirin and clopidogrel in ACS patients for early invasive intervention),

with additional patients independently enrolled (Table 1) (3). Ultimately, 7,021 patients with ACS (unstable angina, non–ST-segment elevation myocardial infarction, and ST-segment elevation myocardial infarction [STEMI]) and planned PCI were randomized to either radial or femoral access (n = 3,507 and 3,514, respectively) (3). The primary outcome, defined as the composite of death, MI, stroke, and non-coronary artery bypass grafting–related major bleeding at 30 days, was not significantly different between the radial versus femoral approach (3.7% vs. 4.0%, p = 0.50) (3).

In the subgroup of STEMI patients, the radial access arm met primary outcome criteria (3.1% vs. 5.2%, p = 0.026) and was associated with significantly lower mortality (1.3% vs. 3.2%, p = 0.006) (3). Interestingly, bleeding was not significantly different (p = 0.87) (3). Notably, a majority of patients were a subgroup of the negative CURRENT-OASIS 7 trial, an important consideration because subgroup analyses of negative studies are not generally considered statistically appropriate (10).

Abbreviations and Acronyms

ACS = acute coronary syndrome

PCI = percutaneous coronary intervention

STEMI = ST-segment elevation myocardial infarction

TFI = transfemoral intervention

TRI = transradial intervention

The RIFLE-STEACS trial. The RIFLE-STEACS (Radial Versus Femoral Randomized Investigation in ST-Elevation Acute Coronary Syndrome) trial randomized 1,001 STEMI patients to PCI with radial or femoral access (n = 500 and 501, respectively). The primary outcome—composite of cardiac death, stroke, MI, target lesion revascularization, or bleeding at 30 days—was significantly lower in the radial group (13.6% vs. 21.0%, p = 0.003) (4). Major adverse cardiac events were also lower (7.2% vs. 11.4%, p = 0.029) owing mainly to differences in cardiac death (5.2% vs. 9.2%, p = 0.020) (4). Non-coronary artery bypass grafting–related major bleeding was reduced with the radial approach (7.8% vs. 12.2%, p = 0.026), driven by a 62% reduction in access-site bleeding (2.6% vs. 6.8%, p = 0.002) (4).

The STEMI-RADIAL trial. In the STEMI-RADIAL (ST Elevation Myocardial Infarction Treated by Radial or Femoral Approach–Randomized Multicenter Study Comparing Radial Versus Femoral Approach in Primary PCI) trial, patients with STEMI undergoing primary PCI were randomized to radial or femoral access (n = 348 and 359, respectively). The primary outcome of bleeding or access-site complications was measured at 30 days. Radial access was associated with 80% less bleeding and access-site complications compared with femoral access (1.4% vs. 7.2%, p = 0.0001) (5). The composite rate of adverse events was also significantly lower in the radial group (4.6% vs. 11.0%, p = 0.0028) (5). However, there was no difference in major adverse cardiac events (3.5% vs. 4.2%, p = 0.7) or mortality (2.3% vs. 3.1%, p = 0.64) between the 2 groups (5).

Table 1. Summary of Clinical Trials Comparing TRI and TFI

	Trial		
	RIVAL (N = 7,021)	**RIFLE-STEACS (N = 1,001)**	**STEMI-RADIAL (N = 707)**
Patients, TRI/TFI	3,507/3,514	500/501	348/359
Type of patients	ACS patients: STEMI 27.9% NSTEMI 27.1% UA 45%	STEMI patients	STEMI patients
Heparin, IU/kg	*/*	70/71	103/105
GP IIb/IIIa inhibitors	25.3%/24.0%	67.4%/69.9%	45%/45%
Bivalirudin	2.2%/3.1%	8.0%/7.2%	*/*
Catheter, ≤6-F	91.8%/87.0%	90.8%/81.4%	100%/99.8%
Major bleeding	0.8%/0.9% (p = 0.87)	7.8%/12.2% (p = 0.026)	1.4%/11.0% (p = 0.0001)
MACE	2.7%/4.6% (p = 0.031)	7.2%/11.4% (p = 0.029)	3.5%/4.2% (p = 0.7)
Mortality	1.3%/3.2% (p = 0.006)	5.2%/9.2% (p = 0.02)	2.3%/3.1% (p = 0.64)

Values are n/n or %/% TRI/TFI, except as indicated. *Data not provided.

ACS = acute coronary syndrome; GP = glycoprotein; MACE = major adverse cardiac events; NSTEMI = non–ST-segment elevation myocardial infarction; RIFLE-STEACS = Radial Versus Femoral Randomized Investigation in ST-Elevation Acute Coronary Syndrome trial; RIVAL = Radial Versus Femoral Access for Coronary Intervention; STEMI = ST-segment elevation myocardial infarction; STEMI-RADIAL = ST Elevation Myocardial Infarction Treated by Radial or Femoral Approach–Randomized Multicenter Study Comparing Radial Versus Femoral Approach in Primary PCI trial; TFI = transfemoral intervention; TRI = transradial intervention; UA = unstable angina.

Anticoagulation: The Forgotten Variable

Antithrombotic dose. In the United States, as many as 32% of patients receive antithrombotic doses in excess of guidelines (11). In patients with STEMI being referred for primary PCI, the American College of Cardiology Foundation/American Heart Association guideline recommends a 50- to 70-IU/kg bolus to achieve an activated clotting time of 200 to 250 s when use of glycoprotein IIb/IIIa receptor antagonists are planned and a 70- to 100-U/kg bolus to achieve an activated clotting time of 250 to 300 s (as measured by the HemoTec device [Medtronic, Parker, Colorado]) when no glycoprotein IIb/IIIa inhibitor use is planned (12). Heparin doses in excess of this have not been associated with improved pre-procedural patency or post-procedural outcomes, but have been associated with greater bleeding (13). The average dose of pre-procedural heparin was 71 IU/kg in the RIFLE-STEACS trial and, more egregiously, 104 IU/kg in STEMI-RADIAL, doses higher than current guideline recommendations when glycoprotein IIb/IIIa inhibitors are used because low-dose heparin is equally effective (4,5,12,13).

Antithrombotic drug. The ACUITY (Acute Catheterization and Urgent Intervention Triage strategy) trial demonstrated

significantly less bleeding with the direct thrombin inhibitor bivalirudin compared with heparin and glycoprotein IIb/IIIa inhibitors at 30 days (3.0% vs. 5.7%, $p < 0.001$) in patients with ACS undergoing an invasive strategy (14). The HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) trial, which compared STEMI patients randomized to heparin plus glycoprotein IIb/IIIa inhibitors or bivalirudin, reported a 34% reduction in mortality in patients treated with bivalirudin ($p = 0.047$), driven by a reduction in major bleeding of 40% ($p < 0.001$) that was similarly seen in a subsequent large meta-analysis (15,16). In both the radial and femoral arms, a paucity of patients received bivalirudin (RIVAL: 2.2% and 3.1%, respectively; RIFLE-STEACS: 8.0% and 7.2%, respectively) despite the evidence showing that bivalirudin attenuates bleeding events by one-half without additional ischemic complications (3,4,14,15). The importance of this cannot be ignored; bleeding independently predicts ischemic complications, transfusion, and death (17,18).

Presumably, the differences in bleeding and mortality relate in part to the aggressive use of glycoprotein IIb/IIIa inhibitors—approximately one-third in the RIVAL trial, nearly half in the STEMI-RADIAL trial, and over two-thirds in the RIFLE STEACS trial—predisposing to bleeding and vascular complications in the large-caliber femoral artery in which larger sheaths were used.

Implications and Considerations: High-Risk Patients, Procedural Characteristics, and Operator Experience

Lower doses of heparin, decreased use of potent parenteral antiplatelet agents, and increased use of bivalirudin could ultimately reduce bleeding and need for transfusions. This would permit continuation, not only of post-procedural oral antiplatelet drugs, but also of other cardioprotective agents, lessening the risk for subsequent cardiac compromise (a main determinant of mortality in the femoral access approach). These considerations are particularly relevant in high-risk ACS patients, in whom the larger femoral artery may be necessary anyway for device insertion such as an intra-aortic balloon pump.

Procedural characteristics are also affected by the choice of access site. Door-to-balloon and fluoroscopy times tend to be less with the femoral approach, and choice of sheath size is less restrictive (3–5). Outcomes with vascular closure devices have evolved over time, but recent meta-analyses have noted they may safely reduce femoral bleeding, further reducing the gap in bleeding and mortality outcomes between access sites (19).

Finally, the prospective randomized trials supporting the radial approach were all done at high-volume radial access centers. Indeed, the RIVAL study demonstrated no difference in the lower 2 tertiles of operator experience (3). This is an important consideration in the United States, where <7% of PCI procedures are accessed radially (11,20).

Conclusions

At first glance, current studies support the benefits of radial access PCI in ACS. These conclusions, however, are drawn from patients on suboptimal antithrombotic regimens as well as liberal use of potent parenteral antiplatelet agents. Thus, the influence of access site alone on outcomes cannot be accurately measured. Ultimately, a trial comparing femoral versus radial access in patients treated with bivalirudin or appropriate doses of heparin, novel $P2Y_{12}$ receptor inhibitors such as prasugrel or ticagrelor and without adjunctive glycoprotein IIb/IIIa inhibitors, is needed to assess outcomes on the basis of access site alone. The ongoing SAFARI-STEMI (the Safety and Efficacy of Femoral Access Versus Radial for Primary Percutaneous Coronary Intervention in ST-Elevation Myocardial Infarction) trial (NCT01398254) will help shed light into this particular topic. Until further data emerge, femoral access with optimal pharmacotherapy should be considered a safe, viable and time-tested option for PCI access in ACS.

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Key Words: bleeding ■ transfemoral intervention ■ transradial intervention ■ vascular access.