

Femoral Access Is Still a Contender

An examination of the data on bleeding complications shows that the femoral access route remains a reasonable choice during PCI.

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The appropriate choice and management of arterial access during percutaneous coronary intervention (PCI) cannot be overemphasized because it remains the most common cause of complications during PCI.¹ Its importance is evident in the fact that a debate over the preferred strategy, mainly femoral versus radial, can be found at every national meeting. However, there is room for discussion on the strength of the available evidence supporting the choice of arterial access as a bleeding-avoidance strategy—in part because of the heterogeneity of the data within studied populations, variable definitions of major bleeding, and disparities among results from observational versus randomized controlled data comparing various approaches and techniques. In this article, we provide data supporting a continued need for transfemoral access (TFA) during PCI and attempt to put the data surrounding this debate into perspective.

In the next section, we first address the remaining resistance to universal acceptance of transradial access (TRA). Legitimate procedural concerns related to TRA exist, which include operator and patient radiation exposure, procedural times and success rates, contrast volume, guide catheter support, equipment delivery during complex coronary interventions, and catheterization lab quality metrics, such as door-to-balloon times for acute myocardial infarction. Some of these issues can be resolved with increased operator experience with TRA; however, TFA remains the most widely used approach to arterial access for PCI worldwide—and for a respectable reason.

LIMITATIONS OF TRA

The major downside to TRA is its size and unpredictable course to the ascending aorta. The radial artery is anywhere between three to four times smaller in diameter than the femoral artery, which limits the deliverability

of certain equipment necessary for completing complex interventions or devices requiring large-bore access, particularly left ventricular assist devices. This can pose a challenge during acute myocardial infarction, especially for patients in cardiogenic shock. The unpredictable course to the ascending aorta can ultimately lead to increased procedural times and procedural failure, forcing crossover to TFA.

Consider the significantly increased rates of crossover (7.6% vs 2%; $P < .001$) from TRA to TFA in the RIVAL (Radial Versus Femoral Access for Coronary Intervention in Patients With Acute Coronary Syndromes) trial. In this instance, radial artery spasm proved to be the culprit in the majority of cases, and spasm often follows excessive catheter manipulation and/or exchanges when attempting to negotiate a brachial loop, recurrent radial artery, tortuous subclavian, or aorta. Even high-volume radial operators found radial loops (13%), subclavian tortuosity (7%), and inadequate guide catheter support (7%) to be causes for TRA crossover.¹ Furthermore, cardiogenic shock was an independent predictor of TRA PCI failure, with an 11-fold increase in the odds of failure.

The size of the radial artery also lends itself to occlusion after sheath removal. Although typically asymptomatic because of the palmar arch, radial artery occlusion is not a rare complication (occurring in 1%–10% of cases)² and is likely underreported. The long-term outcomes of such patients are not well documented in the literature and are not collected systematically in the National Cardiovascular Data Registry database. That said, advances in equipment and techniques (such as hydrophilic sheaths), universal “radial” diagnostic catheters to limit exchanges and reduce spasm, smaller guide catheters, and the sheathless guiding catheter technique have improved radial success to complete procedures in what otherwise may necessitate TFA “bailout.”

Despite the potential limitations, we as clinicians should adapt and choose the best approach to ensure patient safety and produce the best outcomes. This, of course, raises the question of whether the choice of arterial access during PCI should more strongly be considered as a best practice outcomes measure. To answer this, we need to review the strength of the available evidence. The vast majority of published literature on this topic comes via observational studies and/or registry-based data. Much of the challenge in comparing access site benefit in this manner is that an operator's choice for TRA versus TFA is often based on the anatomic limitations of the patient and limitations related to PCI, such as acuteness of the patient's presentation, catheter size (in the case of complex PCI), the operator's expertise with a particular access site, and a multitude of other factors. An operator's clinical decision bias for arterial access choice should not be underestimated. Given the heterogeneity and potential bias of populations selected in observational studies, data derived from randomized controlled trials (RCTs) are preferred. Particular emphasis should be placed on those outcomes considered most deleterious to patients, namely vascular complications associated with major bleeding and subsequent major adverse cardiovascular events (MACE).

We should note that there has yet to be a large, multicenter RCT providing compelling evidence for superiority of TRA for all included populations with regard to a reduction in MACE that is attributable to a decrease in major bleeding. Before the recently published MATRIX (Minimizing Adverse Hemorrhagic Events by Transradial Access Site and Systemic Implementation of Angiox) trial,³ the RIVAL trial⁴ failed to show a reduction in the composite primary endpoint of death, myocardial infarction, stroke, or noncoronary artery bypass graft major bleeding at 30 days. Likewise, no difference was observed with rates of protocol-defined major or minor bleeding between radial and femoral groups. Although we will later put the results of MATRIX into perspective, it is worth spending a moment to discuss the RIVAL trial, as it provided a strong take-home message: When it comes to bleeding and vascular access site complications, volume and operator experience matters—a point that will be echoed in the MATRIX trial.

RIVAL TRIAL

Enrollment centers in the RIVAL trial required expertise for operators in both radial and femoral access, translating into three significant findings. The first finding was that there were low rates of major bleeding in both the radial and femoral groups, with lower overall rates of access site complications in the TRA cohort when com-

pared with previous studies. The second finding was that there was a reduced MACE rate among high-volume radial operators (1.3% vs 2.7%; hazard ratio [HR], 0.5; 95% confidence interval [CI], 0.27–0.92; $P = .03$) with a trend toward reduction in major bleeding events compared with non-high-volume operators, suggesting that the benefits of radial access might be linked to operator proficiency and experience. Finally, patients presenting with ST-segment elevation myocardial infarction (STEMI), who are at greatest risk of bleeding, may derive benefit from TRA over TFA for the primary outcome.

We should remember that when an RCT has a negative overall endpoint, yet significant differences are found among the subgroups, this is considered hypothesis generating and requires additional studies to confirm the results. Such was the case with the STEMI prespecified subgroup analysis in RIVAL, in which a 40% reduction in the primary endpoint was seen in the TRA group (3.1% vs 5.2%; HR, 0.6; 95% CI, 0.38–0.94; $P = .03$). It is worth noting that despite these findings in the STEMI population, no difference was seen in the primary endpoint in the non-ST-segment elevation acute coronary syndromes group (3.8% for TRA vs 3.5 for TFA; HR, 1.11; 95% CI, 0.83–1.48; $P = .49$). The positive STEMI subgroup analysis in RIVAL was followed by two RCTs and subsequent meta-analyses to identify a population who may benefit from TRA. Although both RCTs showed reductions in protocol-defined major bleeding, they were inconsistent in regard to a reduction in MACE.^{5,6} Important limitations of these trials include high rates of major bleeding, marked glycoprotein IIb/IIIa inhibitor use (nearly 70%), low use of bivalirudin, high unfractionated heparin dosing, and twice as many 7-F or larger sheaths placed in the TFA group as compared with the TRA group.

One confounder of the differences between femoral versus radial is the type and dosing of anticoagulation. This differential in anticoagulation may also have an impact on the different bleeding rates for TRA versus TFA.

Although the meta-analyses^{7,8} showed a reduction in MACE and major bleeding, a word of caution is necessary regarding the interpretation of these data. The RCTs included are limited by significant clinical heterogeneity in their definitions of major bleeding, even though there is minimal statistical heterogeneity. Study-level data and per-protocol definitions can add further heterogeneity for major bleeding outcomes, as they often include non-bleeding-related vascular access site complications, single-unit blood transfusions, or minor hemoglobin drops (< 3 g/dL) without overt sources as criteria for major bleeding events. Such events are clinically relevant, but they are less likely to produce serious long-term adverse events. This may offer a reason as to why the results of

TABLE 1. PER-STUDY/PROTOCOL MAJOR BLEEDING IN STEMI PATIENTS UNDERGOING PCI WITH TRA VS TFA

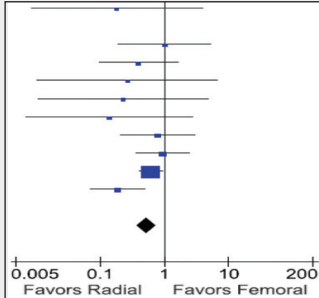
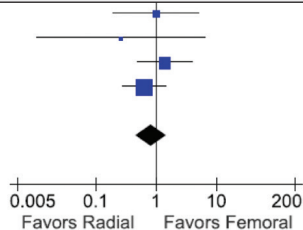
Study or Subgroup	Radial Events	Total	Femoral Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year	Odds Ratio M-H, Random, 95% CI
TEMPURA	0	77	2	72	1.2%	0.18 (0.01–3.85)	2002	
RADIAL-AMI	0	25	0	25	–	Not estimable	2004	
FARMI	3	57	3	57	4.1%	1 (0.19–5.18)	2007	
RADIAMI	3	50	7	50	5.6%	0.39 (0.1–1.61)	2007	
Yan et al	0	57	1	46	1.1%	0.26 (0.01–6.63)	2008	
Gan et al	0	90	2	105	1.2%	0.23 (0.01–4.83)	2009	
Hoe et al	0	100	3	100	1.3%	0.14 (0.01–2.72)	2010	
RADIAMI II	4	49	6	59	6.3%	0.79 (0.21–2.96)	2011	
RIVAL		955	9	1,003	12%	0.93 (0.36–2.43)	2011	
RIFLE-STEACS		500	61	501	55.6%	0.61 (0.4–0.93)	2012	
STEMI-RADIAL		348	26	359	11.7%	0.19 (0.07–0.49)	2014	
Total (95% CI)		2,308		2,377	100%	0.54 (0.38–0.75)		
Total events	62		120					
Heterogeneity: Tau ² = 0.01; Chi ² = 9.14, df = 9 (P = .42); I ² = 2%								
Test for overall effect: Z = 3.65 (P = .0003)								

TABLE 2. TIMI MAJOR BLEEDING IN PATIENTS UNDERGOING PCI WITH TRA VS TFA

Study or Subgroup	Radial Events	Total	Femoral Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year	Odds Ratio M-H, Random, 95% CI
FARMI	3	57	3	57	13.5%	1 (0.19–5.18)	2007	
Yan et al	0	57	1	46	3.5%	0.26 (0.01–6.63)	2008	
RIVAL	8	955	6	1,003	32.3%	1.4 (0.49–4.06)	2011	
RIFLE-STEACS	9	500	14	501	50.8%	0.64 (0.27–1.49)	2012	
Total (95% CI)		1,569		1,607	100%	0.85 (0.46–1.55)		
Total events	20		24					
Heterogeneity: Tau ² = 0.00; Chi ² = 1.84, df = 3 (P = .61); I ² = 0%								
Test for overall effect: Z = 0.54 (P = .59)								

Although TRA is growing nationally, we believe that it is shortsighted to consider it a superior approach, as there are still many valid reasons to prefer a TFA strategy in selected patients.

major bleeding and mortality do not seem to run parallel in these trials. Tables 1 and 2 compare the risk of major bleeding in RCTs of STEMI patients for TRA versus TFA (Table 1) and among studies that provided data on thrombolysis in myocardial infarction (TIMI) major bleeding (Table 2). Although a significant reduction in major bleeding exists when assessing protocol-defined major bleeding, the difference was no longer significant when assessing TIMI major bleeding, albeit with a smaller number of trials available for inclusion.

MATRIX TRIAL

The much-anticipated MATRIX trial was presented at this year's American College of Cardiology scientific sessions and is now the largest adequately powered RCT to address the hypothesis that the choice of arterial access when treating acute coronary syndromes provides a reduction in MACE and bleeding-related complications. Although touted as an overwhelming win for TRA, to the point of suggesting a change in guidelines and practices, the 15% relative reduction in MACE (coprimary endpoint defined as all-cause death, myocardial infarction, or stroke; 8.8% radial vs 10.3% femoral; HR, 0.85; 95% CI, 0.74–0.99; $P = .031$) did not meet the prespecified significance level of 0.025. The individual composites of MACE were also not very different, with the exception of all-cause mortality, which marginally made statistical significance ($P = .045$).

TRA did reduce the second coprimary net adverse clinical events endpoint of death, myocardial infarction, stroke, or Bleeding Academic Research Consortium (BARC) major bleeding by 17% (HR, 0.83; 95% CI, 0.73–0.96; $P = .009$). Unfortunately, the expectation that a reduction in bleeding translates into a reduction in MACE is not clearly realized. Consider the fact that in MATRIX, BARC bleeding was driven by a reduction in the composite of type 3 bleeds, the majority being type 3a (overt bleeding plus a hemoglobin drop of < 5 g/dL or any transfusion with overt bleeding), which are arguably the least likely to produce short- or long-term morbidity. Furthermore, the proportion of BARC type 5 (fatal) bleeding was nearly identical (0.2% vs

0.3%) between the groups, and no differences were seen in either major or minor TIMI or Global Use of Strategies to Open Occluded Arteries bleeding. It is more than a stretch to conclude that TRA reduced bleeding to a degree that affected MACE.

CONCLUSION

It is worth noting that RCT data on this topic are generated from high-volume PCI centers and operators (for the TRA approach, in particular), so to generalize these results across the board may overstep the conclusion boundaries. Similar to RIVAL, the efficacy endpoint in MATRIX showed a benefit in centers with a high proportion (80%–98%) of TRA PCIs (HR, 0.64; 95% CI, 0.51–0.81). Furthermore, outcomes at high-volume centers were superior, and overall major bleeding event rates were low, suggesting that both access choices can be safely performed when in the hands of a confident operator. Specifically, when using available bleeding-avoidance strategies, the femoral technique can be safely performed with a low risk of vascular or major bleeding complications. The available data are not strong enough to dictate an operator's choice of vascular access. Although TRA is growing nationally, we believe that it is shortsighted to consider it a superior approach, as there are still many valid reasons to prefer a TFA strategy in selected patients. ■

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