

Radial Versus Femoral Access

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Perspective: Radial Access Is Preferred

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In the world of cardiovascular medicine, debates are as common as unanswered questions—medical therapy versus percutaneous coronary intervention (PCI), drug-eluting stents versus bare-metal stents, Red Sox versus Yankees...and the list goes on. The increasing adoption of transradial PCI over the past few years has led to the inevitable “radial versus femoral” deliberations. In the United States, the predominant approach to PCI is via the femoral artery (1), and the radial approach is used as a “bailout” for many operators when they are not able to access the coronary arteries from either the right or left groin. This “femoral first” paradigm has been solidly in place since the invention of PCI, and there seemed little reason to question it until now. Rather than fall into the trap of arguing for one approach to the exclusion of the other, a more appropriate question is: Do we have enough evidence to change the paradigm to a radial first, femoral as bailout approach? Importantly, the concept is not radial instead of femoral, but rather radial as default. A sea change in the interventional culture to radial first should only occur if the radial approach is a priori safer than the femoral approach (i.e., the safest strategy should be the default) and at least as efficacious. Does the available evidence support this sea change?

Bleeding and Vascular Complications and Associated Outcomes

Risks related to PCI include ischemic events like periprocedural myocardial infarction (MI), stent thrombosis, and stroke, as well as vascular complications including bleeding. The risk of these events occurring after PCI are dependent on underlying patient characteristics, the antithrombotic therapy that is used, the integrity of the arteriotomy, and the method of post-procedure hemostasis. In general, the risks are higher as the clinical risk increases, that is, the risk is lowest among patients undergoing elective procedures for stable angina, higher among patients with non-ST-segment elevation acute coronary syndrome (ACS), and highest among patients with ST-segment elevation myocardial infarction (STEMI). Among patients undergoing PCI, 30% to 70% of the bleeding complications that occur are related to the vascular access site (2).

Across the spectrum of clinical risk, post-procedural bleeding and vascular complications have traditionally been regarded as minor events; however, multiple studies have shown a strong association between these events and subsequent morbidity and mortality (3). This is especially true in patients with ACS. In a study of over 26,000 patients with non-ST-segment elevation ACS, there was a stepwise increase in the risk of 30-day mortality, 30-day death or MI, and 6-month mortality as bleeding severity worsened (4). This association was present for both procedure- and non-procedure-related bleeding events. Other outcomes such as stroke (5) and stent thrombosis (6) also appear to be significantly higher among patients who develop bleeding complications. Blood transfusion, which has been used liberally in patients with ACS, is also associated with increased mortality among patients with ACS (7) and those undergoing PCI (3). In terms of nonclinical outcomes, studies of ACS and PCI patients show an association between bleeding and vascular complications and length of stay and costs (8). A study of over 335,000 Medicare patients undergoing PCI showed that the most commonly recorded complication was a vascular complication, occurring in 5.47% of patients (more common than emergency bypass surgery, stroke, or renal failure combined) (9). After adjustment, each vascular complication was associated with >\$4,000 incremental cost; given how commonly PCI is performed, this suggests that over \$70 million of U.S. taxpayer money is going to pay for vascular complications that are potentially preventable.

Radial Approach and Complex PCI

In contemporary clinical practice, transradial PCI is associated with rates of procedure success similar to transfemoral PCI (1). The radial artery readily accommodates 6-F sheaths, and sheathless 7-F techniques have recently been described (10,11). Thus, there is no limitation to performing complex PCI successfully via the radial approach. High-risk subsets such as unprotected left main coronary artery (12) and chronic total occlusions (13) can all be readily addressed through radial access.

However, effectiveness alone is not enough to change the paradigm to radial first because complex PCI can also be performed via femoral access. There should be some advantages of transradial PCI over transfemoral PCI before it can be recommended as the default approach.

Radial Approach and Bleeding and Vascular Complications

Compared with the femoral artery, the radial artery is more superficial, smaller in caliber, lacks any important adjacent structure or potential spaces (such as the retroperitoneal space), and is easily compressible. Observational and smaller randomized trials have found a significant reduction in the rate of major bleeding and major vascular access site complications with radial compared with femoral access in patients undergoing PCI (1,14), even when femoral vascular closure devices are used (15). The largest and most contemporary trial to compare radial and femoral access was the RIVAL (Radial Vs femoral access for coronary intervention) trial (14), which randomized 7,021 ACS patients undergoing coronary angiography or intervention to either radial or femoral access. The primary endpoint was a composite of death, MI, stroke, or major bleeding (defined according to the CURRENT–OASIS 7 [Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events–Seventh Organization to Assess Strategies in Ischemic Syndromes 7] trial) at 30 days. Secondary endpoints included 30-day death, MI, or stroke, and 30-day non-coronary artery bypass graft (CABG)-related major bleeding. In addition, major vascular access site complications, access site crossover, and patient preference were measured. There was no significant difference between the 2 arms with respect to the primary outcome (radial 3.7% vs. femoral 4.0%, $p = 0.50$) or the secondary outcomes of death, MI, or stroke (3.2% vs. 3.2%, $p = 0.90$) or non-CABG-related major bleeding (0.7% vs. 0.9%, $p = 0.23$). Do these results indicate that radial access is no better than femoral access and thus the status quo of femoral first, radial as bailout should be maintained?

Let us delve deeper into the RIVAL trial results. As mentioned, the definition of non-CABG-related major bleeding used in RIVAL was the same as was used in the CURRENT–OASIS 7 trial and is very relevant to an ACS population: bleeding that was fatal, intracranial, or intra-ocular leading to significant vision loss; required ≥ 2 U of blood transfusion; led to hypotension requiring inotropes; led to a hemoglobin decrease of ≥ 5 g/dl; or required surgical intervention. However, the definition does not distinguish between access-site and non-access-site bleeding. Moreover, the rates of bleeding were significantly lower than in prior ACS studies, and only 32% of the bleeding events were related to the vascular access site. Therefore, only 0.2% and 0.3% of the bleeding events in the radial and femoral groups, respectively, could be attributed to the access site. This likely reflects the expertise of the investigators in obtaining arterial access regardless of the site. Given these low event rates, the trial was underpowered to detect a difference in non-CABG-related major bleeding. By contrast, major vascular access site complications, an outcome sensitive to the randomized treatment, were significantly lower among patients assigned to the radial

approach (1.4% vs. 3.7%, $p < 0.0001$). Moreover, in a post hoc analysis that assessed the actual location of access site major bleeding, there were no access site major bleeds in the radial group compared with 18 in the femoral group. Combined with other radial versus femoral trials, the aggregate effect of the radial approach is a 65% reduction in major vascular access site complications, a 49% reduction in non-CABG-related major bleeding, and a 35% reduction in the need for transfusion compared with the femoral approach (14). Given the strong relationship between radial access and reduced vascular complications, the American College of Cardiology Foundation/American Heart Association/Society for Cardiovascular Angiography and Interventions PCI practice guidelines now give a strong recommendation to radial approach (16), and the European Association of Percutaneous Cardiovascular Interventions group has recently taken the position that it should be the default access site for PCI (17).

Radial Approach and Nonbleeding Outcomes

Other outcomes worth discussion when comparing radial and femoral approaches include patient preference, results in certain patient groups, access site crossover, and costs. In randomized trials, patients overwhelmingly prefer radial access to femoral access (14,18). In the RIVAL trial, 90% of patients assigned to radial access preferred it for their next procedure compared with only 49% of patients assigned to femoral who preferred femoral access for a subsequent procedure ($p < 0.0001$). This is likely due to the early ambulation and marked reduction in vascular complications seen with the radial approach. With respect to specific clinical scenarios, patients with STEMI undergoing primary or rescue PCI are at particularly high risk for bleeding. A pharmacological strategy, such as bivalirudin, that is associated with reduced bleeding risk is associated with a reduction in mortality (19). Recently, the RIFLE-STEACS (Radial versus Femoral Randomized Investigation in ST-Elevation Acute Coronary Syndrome) trial was presented (20). This study randomized 1,001 patients undergoing primary PCI at 4 experienced radial centers to radial or femoral access. Compared with femoral access, patients assigned to radial access experienced a significantly lower rate of Bleeding Academic Research Consortium Type ≥ 2 bleeding (12.2% vs. 7.8%, $p = 0.026$) and significantly lower 30-day cardiac mortality (9.2% vs. 5.2%, $p = 0.020$). These data are supported by a meta-analysis of randomized trials comparing radial and femoral access for PCI in STEMI patients that demonstrated an association between transradial primary PCI and reduced mortality, with a slight increase in procedure time compared with femoral approach (mean increase 1.76 min) (21).

In the RIFLE-STEACS trial, the rate of access site crossover overall was 6.1%, with 5.6% of patients assigned to femoral access crossing over to radial access and 6.8% of patients assigned to radial access crossing over to femoral

access. The outcome of access site crossover is of interest because of the potential for interpreting the rates as an indictment of one approach or the other. The body of evidence shows that the rates of access site crossover from radial to femoral are higher than from femoral to radial (22). In the RIVAL trial, the rates of crossover from initial radial access assignment to femoral and vice versa were 7.6% and 2.0%, respectively. However, in exploratory analyses where outcomes were analyzed according to the access site used to complete the procedure, the rates of non-CABG-related major bleeding were 47% lower with radial access compared with femoral access (0.6% vs. 1.0%, $p = 0.025$). Thus, when transradial PCI can be accomplished successfully, there is a distinct safety advantage over transfemoral PCI. Figure 1 displays a proposed initial arterial access algorithm for patients undergoing PCI. It should be noted that procedures performed with hemodynamic support devices (e.g., intra-aortic balloon counterpulsation, Impella [Abiomed, Danvers, Massachusetts], or TandemHeart [Cardiac Assist, Pittsburgh, Pennsylvania]) require concomitant femoral arterial access. Similarly, exceedingly rare complications that require treatment with a large covered stent, for example, coronary perforation, will also require bailout femoral arterial access in order to use large-bore guiding catheters that can accommodate the device.

Another advantage of radial access is its association with lower hospital costs. Safley et al. (23) examined procedural and post-procedural costs among 61,509 femoral and radial procedures from 2004 to 2009 in a large administrative database and found that, whereas radial procedures were associated with \$17 higher procedural costs, post-procedure costs were \$478 to \$917 lower for radial procedures. These savings were driven by reduced length of stay among patients undergoing transradial PCI. Coupled with studies showing a strong patient preference for radial access, the data support a significant benefit of transradial procedures on outcomes other than clinical endpoints.

Does the Evidence Support a Radial First, Femoral as Bailout Approach?

Deciding between 2 therapeutic strategies involves weighing the risks and benefits of each. However, the decision between radial and femoral access for PCI does not involve the choice of one at the exclusion of the other. Although the default vascular access for PCI has traditionally been via the femoral artery, the bulk of evidence calls for a re-evaluation of this dogma. PCI-related bleeding and vascular complications are associated with increased morbidity, mortality, and costs. The evidence consistently shows that, compared with the

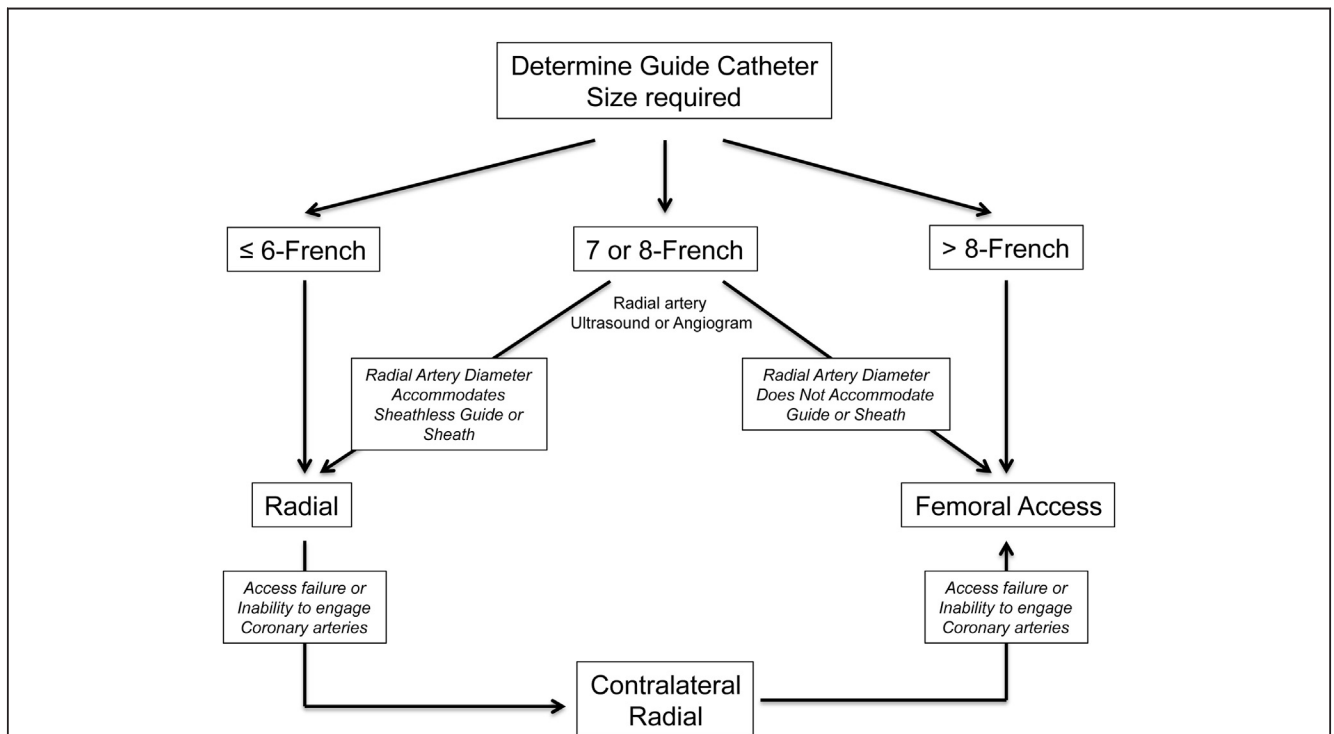


Figure 1 Proposed Algorithm for Arterial Access in Patients Undergoing PCI

Procedures performed with hemodynamic support devices require concomitant femoral arterial access. Procedural complications that require treatment with a covered stent, for example, coronary perforation, will require bailout femoral arterial access in order to use large-bore guiding catheters that can accommodate the device. PCI = percutaneous coronary intervention.

femoral approach, the radial approach is safer, preferred by patients, associated with reduced mortality in primary PCI, and is associated with lower hospital costs. Therefore, in the modern era of PCI, radial access is preferred, and femoral access should be used as a bailout strategy.

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Perspective: Femoral Access Is Preferred Don't Throw the Femoral Out With the Bathwater

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In the current radial–femoral debate, the rush to transradial access (TRA), much delayed in the United States, though long embraced in the rest of the world, may result in a loss of perspective on the benefits of femoral access. An increasing minority of laboratories and individual operators are exposing patients to a long learning curve; additional procedure time, radiation, and morbidity; and in some cases, decreased quality of diagnostic angiograms as well as interventions. We believe that femoral remains the preferred technique in a variety of settings, with as yet an incomplete evidence base for the overall superiority of the radial approach.

After Seldinger (1) introduced his percutaneous arterial access technique, the introduction of catheters was vastly simplified, and the complications associated with cutdowns were dramatically reduced. Nevertheless, the initial cardiac and coronary catheterizations were done through the arm, via open brachial access, and the 2 methods competed for primacy through the 1970s. Eventually, the brachial approach for routine cardiac catheterization was largely abandoned, and there are lessons that are applicable to TRA: the speed, simplicity, and flexibility provided by

percutaneous femoral catheterization were compelling. Some of the intrinsic limitations of the brachial approach apply to TRA as well, in particular the 50% to 70% smaller size of the radial artery than the typical femoral.

But, the generic issues of arm access are worth emphasizing, and these apply equally to radial as well as brachial access. First, access to the coronary arteries, usually trivial via transfemoral access (TFA), requires 3 distinct steps: 1) arterial access; 2) negotiating the catheter to the ascending aorta; and 3) intubating the coronary arteries. We maintain that each of these steps is more difficult, more time consuming, and more likely to fail or be inadequate with TRA. Ample evidence comes from the RIVAL (Radial Vs femoral access for coronary intervention) trial of 7,021 patients randomized to TRA versus TFA (2); access failure occurred in 7% of radial cases versus 0.9% of femoral when there was protocol adherence. Second, once coronary access is secured, the quality of the procedure is more likely to be compromised by inadequate support or visualization. Although, with proper training and experience, many if not most of these issues can be surmounted, there is a far greater learning curve (3) with TRA, and as is always the case with learning curves, a significant percentage of practitioners may never reach the plateau required for results comparable to what they would achieve much more easily via the femoral route. Further, we do not believe the learning curve issue will be resolved as long as we continue to have substantial numbers of low-volume operators as well as trainees. Third, the flexibility in terms of catheter sizes and procedures inherent in access to a large vessel cannot be achieved via TRA, no matter the operator's skill and experience. Fourth, the longer time and greater radiation (both for the patient and the operator) inherent in radial access (4) when performed by all but the most experienced and highest-volume operators are important points in favor of the femoral approach. We concede a fifth point, that closure is generally simpler, cheaper, and potentially safer via the radial route, but even on this issue, there are some potential concerns, in particular the loss of arterial patency in a significant percentage of radials.

Access

Most operators using traditional landmarks can access the femoral artery with great facility and speed; failure to access a patent femoral artery is uncommon. Use of comprehensive fluoroscopic or ultrasound guidance can optimize puncture below the inguinal ligament and above the femoral bifurcation without significant compromise in time to sheath placement. Much of the debate regarding complications of femoral versus radial access compares radial access to traditional landmark-guided femoral access only—we maintain that if micropuncture and adjunctive fluoroscopy or ultrasound were used effectively in these studies, the complication differences would be minimal, though this hypothesis has not been adequately tested (5). Regardless, radial access

is an art form that, even in the most skilled of hands, has a higher failure rate and longer access time than femoral. As a result, even though the most compelling evidence base clearly demonstrates the superiority of TRA only in the setting of ST-segment elevation myocardial infarction (2), many radial operators still prefer the femoral approach in order to minimize door-to-balloon times.

Negotiating to the Ascending Aorta

In typical patients, the iliac system provides little if any impediment to access the aorta. Even in patients with significant vascular disease, access can usually be achieved. By contrast, traversing the arm requires skill in overcoming obstacles that are rare in the iliac—spasm; intrinsically small vessel size; blind alleys such as accessory radial branches, severe tortuosity, and complete loops; entry into small side branches that can result in perforation and compartment syndrome; and any number of other hazards that may be found even in patients without vascular disease per se. Further along, tortuous subclavians, including the lusoria anomaly, can make access difficult and sometimes impossible, or even when achieved, impair torquability to such an extent that the procedure cannot be completed. In general, deploying in the ascending rather than descending aorta, although readily achievable in most cases, requires additional effort usually not required in the femoral approach. How often is each of these factors responsible for failure to reach the ascending aorta? Data from a subset of 3,190 patients in the RIVAL trial included failure of TRA due to radial spasm in 5.0%, radial artery loop in 1.3%, and subclavian tortuosity in 1.9%. By contrast, iliac tortuosity accounted for failure in only 0.6% of patients, as did peripheral vascular disease in the femoral cohort. The results did not describe failure to enter the radial artery, but initial entry can be time consuming and adds significantly to the failure rate. Finally, manipulating under the vertebral artery in the subclavian and under the common carotid artery adds embolic hazards, either from plaque and atheroma disruption or clot forming on guidewires and catheters. Emboli by transcranial Doppler are substantially more frequent via the radial than the femoral route (6). In a recent randomized comparison of TRA versus TFA for diagnostic catheterization in patients with aortic stenosis, diffusion-weighted magnetic resonance imaging showed a nonsignificant trend toward higher cerebral infarction rates in patients undergoing TRA (17.5% vs. 11.7%, $p = 0.31$) in a study that was underpowered (7).

Coronary Intubation

Somewhat surprisingly, pre-formed catheters that spring readily into the coronary arteries via the femoral route are used in the majority of radial cases as well (8), despite limitations that make them potentially inferior in terms of access and backup when deployed transradially. Although catheters have been designed

specifically for radial use, the “one-type-fits-all” catheter has been an elusive goal since the early days of the Sones brachial approach. The need for such a catheter is minimal via the femoral route because removal of one catheter and placement of another is usually trivial. However, via the radial, repeat negotiation of the catheter from the radial to the ascending aorta is undesirable for the reasons already described. Thus, an exchange technique is usually used for subsequent catheters, a somewhat tedious process that includes additional risk of spasm and, more importantly, embolization, especially when wire exposure under the cranial vessels is prolonged. Although many of the problems of coronary intubation can be addressed by access via the left radial, 90% of operators use the right (8); the latter is associated with decreased torquability and substantial loss of mechanical backup force (9), in particular for left coronary interventions.

Quality

The limitations imposed by the smaller size of the radial artery incline users to smaller diagnostic and interventional catheters. Although using power injectors and more sensitive x-ray equipment can improve coronary visualization, the combination of smaller catheters and more difficulty in selective cannulation results in poorer quality imaging in some cases, particular in less experienced hands. Maneuvers, such as taking a deep breath, that improve angiographic quality by displacing the diaphragm from the field and slowing contrast transit time, can dislodge TRA coronary catheters.

Time and Radiation

Although conceding that both of these parameters are substantially influenced by operator learning curves, both procedure time and radiation are generally greater via the radial approach (10). Even in the RIVAL trial, fluoroscopy times were statistically significantly longer with radials.

We concede that vascular complications and bleeding are more frequent with TFA, although analysis of the latter is confounded by variable definitions and by inconsistent findings of various subgroup analyses (11,12). We believe the rate of TFA complications is significantly dependent on the less than optimal access techniques used by many femoral operators. With improved access and better anticoagulation regimens, arguably in combination with vascular closure devices, data suggest a continuing decrease in femoral access site complications (13), including bleeding. And although bleeding is independently associated with adverse outcomes, only a minority of major bleeds are directly related to the femoral access site (14). In addition, some admittedly uncommon complications of radial access virtually never occur with femoral access: arm compartment syndrome and inability to extract the catheter or avulsion of the radial. Studies of the stroke issue as previously discussed have been underpowered and thus are inconclusive, but the results to date remain

concerning for excess stroke risk with TRA. We would add that the loss of radial artery patency in up to 12% of cases at 24 h (15) is not a “victimless crime” (though several techniques to preserve radial flow improve this, in particular the patent hemostasis technique). The need to preserve the radial artery is a subtle but important issue: for subsequent catheterizations, possibly for providing radial artery grafts, and perhaps for patients who will someday require dialysis. Although patients prefer the early ambulation and limited immobility associated with radial access, some experience severe pain during catheter manipulation, in particular when there is spasm of the radial and brachial arteries. Finally, the theoretical advantage of early ambulation with TRA can be addressed with vascular closure devices, admittedly at greater cost and some additional risk.

Those arguing in favor of TRA usually cite the effects of experience and optimal techniques as substantial mitigating factors for its limitations, an argument that has been used in behalf of both the radial (16) and femoral approaches (as we have in this paper). Thus, although the RIVAL trial failed to show overall superiority of TRA for the primary outcome, the highest tercile of TRA experience did favor radial (2). It should be noted that even in this subgroup, the crossover rate had a hazard ratio of 1.9 ($p = 0.007$) favoring the femoral approach. And the majority of catheterizers do not meet the criteria for the highest tercile experience of the RIVAL trial: in a meta-analysis of 2,460 patients by Jolly et al. (17), those not deemed “experts” had a 3.5-fold higher rate of inability to cross with wire, balloon, or stent via the radial approach. Not measured by such studies is the flexibility inherent in femoral access, including the ability to place intra-aortic balloon pumps as well as devices >20 -F, whereas even 8-F may be a challenge via the radial artery.

In the real world, we have watched our colleagues, even those who are highly experienced, occasionally struggle with access, angiography, and interventions because of limitations of the radial approach. For those of us who have converted to radial (Z.G.T.) and choose to do the occasional femoral case, it is like rediscovering an old friend—simple access to both the artery and the coronaries, excellent backup support for interventions, and flexibility in choosing devices—these all seem like rediscovered pleasures in the catheterization laboratory. We think that in the rush to embrace radials, we should remember the advantages of the femoral approach, continue to utilize it in a significant percentage of patients, and not throw out a reliable and well-established technique with the proverbial bathwater.

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Commentary: The Ongoing Debate Between “Femorlists” and “Radialists” Should There Be a Default Strategy?

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As more complex invasive procedures are performed in patients with increasing comorbidities, there is a compelling need to develop approaches to make these procedures safer (for patient and operator), more efficient, and more comfortable. Improvements in equipment, modifications in adjunctive therapies, and enhanced imaging have improved outcomes and have reduced complications associated with the invasive nature of coronary diagnostic and therapeutic procedures. Arguably, the adoption of transradial access (TRA) has been 1 of the principal advancements in this quest.

In this issue of the *Journal*, 2 perspectives illuminate the controversy surrounding the preferred access site for coronary imaging and intervention. Dr. Rao elegantly proposes that TRA has matured to the point where it should be the default strategy for diagnostic cardiac catheterization and percutaneous coronary intervention (PCI). In a counterperspective, Drs. Turi and Wong argue as convincingly that there are still many reasons why transfemoral access (TFA) should not be discarded in the rush to adopt a still incompletely tested paradigm.

Although we find both viewpoints compelling, the present commentary will clarify some of the essential elements of the 2 approaches, without repeating the arguments already made.

The TRA Learning Curve

A learning curve refers to the ability of operators to gain proficiency as they repeatedly perform a certain task. As none of us is born knowing how to perform diagnostic and therapeutic cardiac catheterization, it is obvious that such a curve would exist for both TFA and TRA. As long as it is reasonable in length and predictable in its apogee, the existence of a learning curve should not be an argument against TRA. On the contrary, if TRA is indeed superior to TFA, we should intensify the exposure of trainees and certified operators to TRA and render everyone competent as soon as possible. Ball et al. (1) recently studied this issue in a rigorous fashion among 28 operators performing the first 1,628 PCI procedures by TRA at their institutions. PCI failure was inversely related with volume ($p = 0.003$), and there was a 32% decrease in failure rates for every additional 50 procedures performed. Optimistically, they concluded that a case volume of at least 50 PCIs is required to achieve proficiency similar to that of experienced operators (>300 cases). However, even when

proficient, TRA operators use significantly more radiation and contrast than TFA operators. Failure to access the coronary arteries remains unpredictable, even in the most experienced hands (2). Before the very large RIVAL (A Trial of Trans-radial Versus Trans-femoral Percutaneous Coronary Intervention [PCI] Access Site Approach in Patients With Unstable Angina or Myocardial Infarction Managed With an Invasive Strategy) trial, 23 randomized clinical trials had been performed comparing the 2 access strategies, encompassing >7,000 patients. Meta-analysis of these moderate-size trials suggested that compared with femoral access, radial access reduces the composite of death, myocardial infarction (MI), or stroke (hazard ratio [HR]: 0.71; 95% confidence interval [CI]: 0.49 to 1.01) and major bleeding (according to trial definition) (HR: 0.27; 95% CI: 0.16 to 0.45), although at the cost of a marginally higher rate of failure to complete the PCI procedure (HR: 1.31; 95% CI: 0.87 to 1.96) (3).

As is not uncommon, the results of this meta-analysis were “overturned” by RIVAL (6), a dedicated large-scale randomized trial performed in 7,021 patients with acute coronary syndromes undergoing angiography (with PCI in 66%) enrolled from 158 hospitals in 32 countries. The RIVAL trial demonstrated nonsignificant differences between TRA and TFA in the 30-day rates of composite death, MI, or stroke (3.2% in both groups, $p = 0.90$); non-coronary artery bypass graft–related major bleeding (0.7% vs. 0.9%, $p = 0.73$); or transfusions (1.1% vs. 1.3%, $p = 0.51$). There was also no significant interaction by operator TRA volume and a randomized arm on the outcomes of composite ischemic plus bleeding events (although a borderline significant interaction unadjusted for the number of comparisons was present between outcome and center volume). Moreover, despite the fact that RIVAL enrolled experienced radial operators (median 300 PCI procedures per year; 40% TRA), crossover from TRA to TFA was required in 7% of patients, most commonly for radial artery spasm, radial artery loop, and subclavian tortuosity. In contrast, crossover from TFA to TRA was required in only 0.9% of patients ($p < 0.0001$). Thus, at least based on the most contemporary evidence-based definitive trial, there would not seem to be an overwhelming societal need to train all operators in TRA (to the exclusion of TFA), although the door remains open as to whether improved outcomes might be obtained at the most experienced centers (and, intuitively, by the most experienced operators).

The reasons why RIVAL did not achieve its goal of showing superiority of TRA over TFA deserve a deeper look and hinges on the relationship between bleeding, vascular complications, and mortality.

Bleeding and Vascular Access Complications

The relationship between (major) bleeding complications and subsequent death in patients undergoing PCI has been demonstrated in numerous studies, particularly in the

setting of acute coronary syndromes (5). Importantly, many of the risk factors that predispose patients to bleeding also increase their risk of ischemic events, placing the treating physician in a difficult predicament (6). Although vascular access complications can occur during both diagnostic and interventional procedures, major bleeding occurs predominantly with the latter. However, at least one-half of these bleeding episodes are related to systemic anticoagulation and occur remotely from the access site; thus, they cannot be modified by changing the vascular access site (7). After PCI in ST-segment elevation myocardial infarction (STEMI), the proportion of access-site bleeding may be closer to 50% of all episodes, whereas in elective PCI, two-thirds of hemorrhagic complications occur remotely from the vascular access site. In a recent analysis from the National Cardiovascular Data Registry, greater use of bivalirudin and vascular closure devices (VCDs) was associated with a marked reduction in the incidence of major bleeding and vascular access complications (10). In this study of >1.5 million procedures, the rate of major bleeding was 2%. VCDs, bivalirudin, or both were used in 24%, 23%, and 18%, respectively, of the cohort. Bleeding was noted in 2.8% of those in whom manual compression was used after heparin-supported PCI, and in 2.1%, 1.6%, and 0.9% when VCD, bivalirudin, or both were used; this is, an impressive 70% reduction in risk with the combination of pharmacological and mechanical bleeding avoidance strategies. When patients were characterized by the National Cardiovascular Data Registry bleeding risk model, those at the highest risk had a 65% risk reduction when VCDs and bivalirudin were used (from 6.1% with manual compression and heparin to 2.3%). Although these data do not stem from randomized clinical data, the associations remained valid after propensity matching and provide a credible snapshot of clinical practice in the United States. Finally, the association between major bleeding and death is far greater for nonaccess site bleeds than for access site bleeds (9,10). Indeed, in the ABOARD (Angioplasty to Blunt the Rise of Troponin in Acute Coronary Syndromes Randomized for an Immediate or Delayed Intervention) trial (11), despite nearly universal use (85%) of TRA, major bleeding still occurred in 5.4% of patients (80% nonaccess site) and was associated with increased mortality at 1 month (26.3% vs. 0.6% in those without major bleeding, $p < 0.001$).

Back to RIVAL. Among the >7,000 patients enrolled in this trial, there were only 18 cases (0.2%) of major bleeding related to the access site (12 in the TFA group and 6 in the TRA group, the latter because of a switch to TFA after failure of TRA) (4). Not surprisingly, therefore, by intention-to-treat, the rates of Thrombolysis In Myocardial Infarction (TIMI) major bleeding were similar between the 2 groups, although there were significantly more vascular access complications (large hematoma, pseudoaneurysm requiring closure, arteriovenous fistula, or other vascular surgery related to the access site) in the

TFA group. However, VCDs were used in only 26% of patients in the TFA group, and bivalirudin was used as the procedural anticoagulant in <3% of patients.

Moreover, it is important to discern which types of bleeding actually influence late mortality. Using 3 large contemporary trial databases in which patients with stable ischemic heart disease, non–ST-segment myocardial infarction (NSTEMI), and STEMI were enrolled, Mehran et al. (9) showed that although numerous definitions of major bleeding were strongly associated with subsequent mortality, isolated large hematomas—the predominant difference between TRA and TFA—does not affect mortality (9). In this study, TIMI major bleeding was associated with a nearly 5-fold increase in mortality, and even transfusion without major bleeding carried a nearly 3-fold higher risk of death. Using the same studies, Verheugt et al. (7) showed that 61% of all TIMI major bleeding episodes after TFA were not related to access site and that bivalirudin reduced the incidence of these events by ~40%, both at the access site and systemically. Remarkably, however, the impact of non–access-site bleeding on subsequent 1-year mortality was significantly more pronounced than that of access-site bleeding (HR: 3.94 vs. 1.82, respectively), possibly reflecting the magnitude of blood loss. Similarly, in the STEEPLE (Safety and Efficacy of Intravenous Enoxaparin in Elective Percutaneous Coronary Intervention: An International Randomised Evaluation) trial, large hematomas did not affect either 30-day outcomes or 1-year mortality (12). Finally, examining the results at a single high-volume institution, Applegate et al. (13) showed that vascular access complications did not affect the rates of 30-day or 1-year MI or death, unless they were associated with major bleeding.

Is TRA Particularly Beneficial in STEMI?

One of the more intriguing observations from recent trials comparing TRA with TFA was the suggestion that mortality can be reduced in STEMI patients treated with primary PCI when TRA is used. In the recently published RIFLE STEACS (Radial Versus Femoral Randomized Investigation in ST Elevation Acute Coronary Syndrome) study, 1,001 patients with STEMI were randomly assigned to TRA or TFA (14). There were no differences in total ischemic time, use of glycoprotein IIb/IIIa inhibitors (69%), thrombus aspiration (41%), or final TIMI flow grade 2 to 3 (96%) between the groups. Yet, the incidence of death was markedly lower in the TRA group (5.2% vs. 9.2%, $p = 0.02$). Access-site bleeding was 62% lower in the TRA arm (2.6% vs. 6.8%, $p = 0.002$), and there were no differences in non–access-site bleeding (5.2% and 5.4%, respectively). Consistent with these data, a subgroup analysis from RIVAL (although methodologically unsound because it was derived from a trial which did not meet its primary endpoint) found a significant interaction between

clinical presentation and access site, such that there was a benefit for TRA compared with TFA in STEMI patients and a neutral effect in NSTEMI (p for interaction = 0.025, unadjusted for multiple subgroups) with respect to the composite outcome of death, MI, stroke, or major bleeding. It is important to note, however, that in both of these trials, the absolute reduction in major bleeding with TRA was smaller than the overall reduction in death or major adverse cardiovascular events (!), suggesting that the play of chance was involved in these observations. We completely support the recent recommendations in the position paper of the European Association of Percutaneous Cardiovascular Interventions and Working Groups on Acute Cardiac Care and Thrombosis of the European Society of Cardiology that implementation of TRA in STEMI should be reserved as the last step of a carefully monitored program of transition from TFA, after all-comer PCI and complex PCI have been performed via this access route (15).

Summary

The data and concepts discussed in the 2 perspectives and in our commentary lead us to the following observations and recommendations:

1. There is little doubt that major bleeding after diagnostic and interventional procedures is strongly and independently associated with adverse outcomes via a host of putative mechanisms. Prevention of these complications is an essential goal for practitioners and an important target for quality improvement projects.
2. The majority of prognostically significant bleeding episodes do not arise from the access site and thus cannot be modified by the route of vascular access. It is thus unlikely that a major survival advantage would be realized by choosing TRA rather than TFA (or vice versa). Other bleeding avoidance strategies, such as the use of bivalirudin (for PCI with both radial and femoral vascular access), avoidance of potent antiplatelet agents in patients in whom the risk of bleeding is likely to be greater than the anti-ischemic benefit, and possibly the use of VCDs if TFA is selected (acknowledging that a contemporary randomized trial is needed to validate recent favorable findings for these devices), are more likely to improve outcome.
3. Undoubtedly, TRA results in faster time to ambulation and, in most cases, less discomfort at the access site; also, many patients prefer TRA to TFA. TRA is also clearly preferred for morbidly obese patients and for most patients with severe peripheral vascular disease. However, TRA is more likely to be associated with greater radiation exposure (especially to the operator), may result in radial artery occlusion and other complications, and is associated with crossover to TFA not infrequently, which may affect door-to-

balloon times in STEMI. TFA is also more adaptable to large sheaths and devices (as well as hemodynamic support device use and venous access), provides superior guide support in many patients, and is the easier route from which to cannulate saphenous vein bypass graft conduits. Thus, both the TRA and the TFA are important for the expert interventionalist to master. Interventional fellowship programs should provide training in both approaches.

- High-volume operators (>150 PCI/year) should maintain proficiency in both TRA and TFA and select the optimal route of vascular access according to the patient's indication for procedure, the likelihood of requiring large sheaths or anticipated difficulty with guide support, the presence of obesity and peripheral vascular disease, and the complexity of PCI. Lower-volume operators should concentrate on 1 access route predominantly (either TRA or TFA) and optimize their performance with that approach in the context of a rigorous quality assurance program.

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