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MANAGEMENT OF ACUTE CORONARY SYNDROMES (R MEHRAN, SECTION EDITOR)

Radial Versus Femoral Access for Percutaneous Coronary Intervention: Implications for Vascular Complications and Bleeding

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Abstract Since its advent over two decades ago, transradial access for cardiac catheterization and percutaneous intervention has evolved into a versatile and evidence-based approach for containing the risks of access-site bleeding and vascular complications without compromising the technical range or success associated with contemporary percutaneous coronary intervention (PCI). Early studies demonstrated reduced rates of vascular complications and access-site bleeding with radial-access catheterization but at the cost of increased access-site crossover and reduced procedural success. Contemporary data demonstrate that while the rates of major bleeding with femoral-access PCI in standard-risk cohorts have declined significantly over time, the transradial approach still retains significant advantages by way of reductions in vascular complications, length of stay, and enhanced patient comfort and patient preference over the femoral approach, while maintaining procedural success. Major adverse cardiovascular events and bleeding are lowest with the transradial approach when procedures are performed at high-volume radial centers, by experienced radial operators, or in the context of ST-segment elevation myocardial infarction. Choice of procedural anticoagulation appears to differentially impact access-site bleeding in transradial versus transfemoral PCI; however, non-access site bleeding remains a significant contributor to major bleeding in both groups. Despite abundant supporting data, adoption of transradial technique as the default strategy in cardiac catheterization in the United States has lagged behind many other countries. However, recent trends suggest that interest and adoption of the technique in the United States is growing at a brisker pace than previously observed.

Keywords Transradial · Transfemoral · Radial access · Percutaneous coronary intervention · Bleeding · Vascular complications

Introduction

Percutaneous coronary intervention (PCI) remains a cornerstone of therapy for ischemic heart disease, encompassing an ever-expanding range of techniques, technologies, and applications. Over 1 million cardiac catheterizations and over 500,000 PCIs are performed annually in the United States alone, with several million more performed in Canada, Europe, Asia, South America, and elsewhere [1]. In the 3.5 decades that have passed since its first successful human application, PCI has continually evolved and presently offers reductions in cardiovascular morbidity and mortality to high-risk patients across the spectrum of disease acuity and complexity. Miniaturization of catheters accompanied improvements in balloon and guidewire technologies and was later followed by the advent of bare-metal coronary stents and then by drug-eluting stents. This convergence of iterative changes and major advances resulted in safer and more durable PCI procedures. Interventional pharmacology similarly evolved from simple heparin-based regimens to more targeted anticoagulants and combinations of oral and parenteral antiplatelet agents aimed at minimizing the risk of ischemia or hemorrhage.

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One of the key aspects of PCI that has remained relatively static in the United States for the past several decades has been the technique and entry point for arterial access. The classic brachial artery cutdown approach pioneered by Sones and Shirey was replaced in the 1970s by the percutaneous femoral access technique of Seldinger and remains, to date, the mainstay of vascular access for PCI employed in the United States [2–5]. In 1989, Campeau [6] published a single-center study with transradial access for diagnostic cardiac catheterization. Four years later, Kiemeneij [7] published his adaptation of the Campeau technique for coronary stent implantation. After an initial period of limited adoption, routine use of the transradial technique has increased over the past decade outside of the United States, likely due to enhanced patient comfort and demonstrated reductions in major access-site bleeding and vascular complications compared with transfemoral PCI. In this article we review in detail the available data as it relates to these issues.

Contemporary Safety Outcomes Following PCI

The evolution of PCI technology and pharmacology noted above has shifted the clinical focus from efficacy to both efficacy and safety (ie, incidence of bleeding and vascular complications). Cited rates of major bleeding and vascular complications vary greatly across studies and over time. A lack of uniform definitions and reporting standards and variability in surveillance techniques further confound accurate estimation of the true incidences of these events. Nevertheless, the association between postprocedural bleeding, vascular complications requiring transfusion, and subsequent morbidity and mortality, has made reducing these complications a critical part of interventional practice.

Mechanisms, Predictors and Clinical Impact of Major Bleeding

In the context of PCI, bleeding can broadly be divided into access site and non-access site–related bleeding. Bleeding after transfemoral PCI in patients without acute coronary syndrome (ACS) is most often vascular access site–related and can span the range from small localized hematomas to potentially catastrophic inguinal, retroperitoneal, and rectus abdominis hemorrhage. Commonly cited predictors of overall bleeding complications after transfemoral PCI include advanced age, ACS presentation, excessive anticoagulation, renal dysfunction, concomitant venous access, longer sheath dwell times, and congestive heart failure [8–11]. Whereas older observational studies have reported periprocedural rates of major or clinically significant bleeding in excess of 10 %, contemporary data would suggest rates well under 5 % [12–15]. Kinnaird et al. [12] found that of the 5.4 % of Thrombolysis in Myocardial Infarction (TIMI) major bleeds and 12.7 % TIMI minor bleeds observed in a large, retrospectively analyzed PCI population, access site bleeds were responsible for 79.3 % and 59.8 % of cases, respectively [11]. Additionally, it was noted that the aggregate rate of major and minor bleeding fell by nearly 50 % over the 10-year period studied. It has been suggested that secular trends in the type, intensity, and duration of anticoagulation as well as reductions in sheath size from 9 Fr to 5–6 Fr have each independently contributed to the observed decline in bleeding over time [11, 12]. Although the absolute rate of bleeding reported in the literature varies from study to study, the association between bleeding complications and adverse outcomes has remained consistent. Major bleeding (access site and non-access site) following PCI is significantly associated with increased short- and long-term risks of myocardial infarction (MI), stroke, stent thrombosis, and mortality [11–14, 16, 17]. In addition, the mortality hazard associated with bleeding seems to persist long after the inciting event has abated, which may reflect the cessation of evidence-based secondary prevention medications among patients who bleed [11–14].

Frequency and Impact of Femoral Access Site Complications

Vascular complications following transfemoral access may occur in concert with or independent of bleeding events. Common vascular complications after transfemoral PCI include groin hematomas, formation of arterial pseudoaneurysms, and arteriovenous fistulae. As with bleeding events, the reported incidence is highly variable, but published estimates range between 1 % and 5 % and are higher among patients undergoing PCI versus diagnostic catheterization [18–20]. Many of the same factors impacting the decline in bleeding events also seem to have impacted vascular complication rates over time. Applegate et al. [20] found that in over 35,000 femoral diagnostic and PCI procedures analyzed retrospectively, vascular complications were infrequent and declined over the 9-year period analyzed. The observed decline in vascular complications trended alongside decreasing arterial sheath size and lower rates of vascular closure device (VCD) failures [20].

The impact of VCD use on femoral complication rates remains controversial. Three separate meta-analyses of studies examining the utility of VCDs came to somewhat contradictory conclusions [21–23]. In a pooled analysis of 16 studies enrolling 5,048 patients, Vaitkus [21] reported an overall reduction in vascular complications with use of VCDs compared with manual compression with differences in outcomes noted between the individual closure devices studied and no difference between VCD and manual compression in the 2,426 PCI patients studied. In a systematic review and meta-analysis including 37,066 patients published the same year, Nikolsky et al. [22] concluded that

the risk of vascular complications was no different between VCD- and manual compression–treated patients. In a third contemporaneous meta-analysis of 30 studies, Koreny et al. [23] found trends toward increased vascular complications with VCD use, which became significant differences when the analysis was limited to trials that employed intention-to-treat approaches. Subsequently, an observational analysis of data from the NCDR (National Cardiovascular Data Registry) CathPCI registry demonstrated an association between the use of closure devices and a reduction in complications in some patient subsets [24]. Similarly, a *post hoc* analysis of the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial showed an association between the combination of bivalirudin and closure devices and the lowest rate of post-PCI bleeding and vascular complications [25]. In summary, randomized trials have failed to show an advantage of closure devices over manual compression, but observational studies suggest a benefit. It bears mention, however, that VCDs have been regarded in many larger analyses as a single class of devices, whereas it is likely that the individual devices differ substantially from one another with respect to mechanism of arteriotomy closure, ease of use, and learning curve, all of which may differentially impact success and complication rates.

Complications Following Transradial PCI: Insights from the Observational Literature

While the safety margin associated with transradial PCI has been widely touted as one of the technique's greatest benefits, it is now recognized that both bleeding and adverse vascular events can occur, albeit with lower frequency than with femoral access. In a recent analysis of 7,804 transradial PCI procedures entered into the NCDR, the transradial approach was associated with a reported vascular complication rate of 0.19 % (vs 0.70 % with femoral approach) and a bleeding complication rate 0.79 % (vs 1.83 % with femoral) [26]. The observed differences in bleeding and vascular complications between the two approaches were even greater in patients less than 75 years of age, female patients, and those undergoing PCI in the context of ACS. The nature of these complications was not reported in this study. Burzotta et al. [27] found a similarly low rate of vascular complications in 10,676 radial procedures performed by trained radial operators at a single high-volume institution. Of the 53 (0.5 %) vascular complications observed, the majority (83 %) were radial-related and the remaining non-radial complications were linked to access-site crossover to the femoral artery [27]. Potential vascular complications after transradial procedures include radial artery perforation/dissection, formation of a pseudoaneurysm or an arteriovenous fistula, forearm hematomas and, rarely, expansion of the hematoma leading to compartment syndrome of the forearm. There are also historical reports of radial artery avulsion and sporadic reports of digital ischemia [28, 29]. The most commonly encountered complication, radial artery occlusion following the procedure, is frequently asymptomatic, usually of little clinical consequence and often not quantified in studies of transradial catheterization; however, it may complicate repeat access through the same radial artery [30]. It should also be noted that in contrast to the previously described radial access complications which mandate early recognition and directed therapies, a significant proportion of radial artery occlusions resolve spontaneously within the first month post-procedure [30, 31]. Evidence-based strategies that reduce the risk for radial artery occlusion include adequate anticoagulation, use of smaller diameter sheaths, and "patent hemostasis" after sheath removal (applying enough pressure over the access site to achieve hemostasis but not occlude antegrade arterial flow) [32]. The incidence of vascular complications after radial procedures decreases significantly with increasing operator experience [33•].

Impact of Patient Acuity and Anticoagulant Choice on Post-PCI Bleeding

As noted previously, intensive or prolonged anticoagulation and ACS or MI presentation have each been linked with increases in post-PCI bleeding complications [8–11]. While individual observational studies and large-scale comparative analyses (detailed below) suggest reduced rates of major and minor complications with the transradial approach, differences in the definition of "major bleeding" across studies and variability in the anticoagulation regimens used pose challenges to the interpretation and broad application of these data. Perhaps the greatest recent paradigm shift in the United States with respect to procedural anticoagulation has been the adoption of bivalirudin-based regimens with attendant reductions in both access site and non-access site bleeding [34, 35]. In the NCDR analysis previously detailed, bivalirudin was used in the small minority (13.76 %) of radial PCI procedures [26]. A limited amount of comparative data exist addressing the interaction of bivalirudin anticoagulation and the choice of radial approach in ACS PCI. In a *post hoc* analysis of the ACUITY trial, Hamon et al. [36] found that the effect of a radial approach on bleeding is diminished in the face of a bivalirudin-based strategy compared with a strategy of heparin/glycoprotein (GP) IIb/IIIa inhibition. Both access-site and non-access site bleeding were reduced with bivalirudin monotherapy, irrespective of access site employed [36]. A *post hoc* analysis of the OASIS-5 (Fifth Organization to Assess Strategies in Acute Ischemic Syndromes) trial similarly evaluated the impact of access site choice in ACS PCI in the face of anticoagulation with subcutaneous fondaparinux versus

enoxaparin. The primary ischemic end point (death, MI, refractory ischaemia at 9 days) was similar in the transradial and transfemoral groups; however, major bleeding was decreased in the transradial group at day 9, irrespective of anticoagulant treatment assignment [37].

Comparative Clinical Data: Transradial Versus Transfemoral PCI

While the early uptake of transradial PCI was predicated on observational series and small randomized comparisons in selected populations, contemporary trials have broadly investigated this approach in a wide range of clinical scenarios, patient acuity, and procedural complexity. As detailed below, the common themes that have emerged from these investigations center on the differentially greater benefit seen with transradial PCI when performed in more medically complex patients and by higher volume operators/centers. Although the technical challenges and learning curve associated with adoption of the technique are issues to be considered, most studies comparing transradial with transfemoral PCI have found tangible clinical benefits, cost savings, and greater patient comfort/preference associated with the radial approach.

Early Comparative Studies and Meta-Analyses

Between 1994 and 2003, several dozen retrospective and randomized comparisons of radial versus femoral catheterization were performed and published. These studies generally had limited sample sizes and were either single-center or limited multicenter studies, with the majority of enrolled patients falling into low-risk/elective categories. Twelve randomized comparisons totaling 3,224 patients, for which complete data and outcomes were available, were selected by Agostoni et al. and analyzed in the context of a systematic overview [38–50]. Approximately one third of patients (1,155) underwent PCI and the balance (2069) underwent diagnostic catheterization. Only two of the 12 studies included patients with ACS or MI. Agostoni et al. [50] found no overall difference in major adverse cardiovascular events (MACE; OR 0.92, 95 % CI, 0.57–1.48; P=0.7) between patients randomized to a radial versus femoral approach. Radial access was associated with a significant reduction in access-site complications (OR 0.20, 95 % CI, 0.09–0.42; P<0.0001), but also with a threefold increase in procedural failure (OR 3.30, 95 % CI, 1.63–6.71; P<0.001) [50]. The authors concluded that even in this early experience the transradial approach served as an effective platform for a wide range of diagnostic and therapeutic procedures, virtually eliminated access-site complications, and was only likely to improve with advances in equipment and operator experience.

An updated meta-analysis inclusive of 23 randomized trials and 7,020 patients was subsequently performed by Jolly et al. building upon the previous observations [38–49, 51–61, 62•]. In this study population, comprised mainly of PCI patients, radial access dramatically reduced major bleeding complications compared with femoral access (0.05 % vs 2.3 %, OR 0.27, 95 % CI, 0.16–0.45, P<0.001). Interestingly, there was also a strong trend in favor of transradial access with respect to reduction in composite MACE (death, MI, stroke; 2.5 % vs 3.8 %, OR 0.71, 95 % CI, 0.49–1.01, P=0.058). Additionally, there was a small numerical reduction in mortality as well as a significant reduction in hospital stay with the transradial approach [62•].

The potential association between radial approach and reduced mortality was also seen in a large, Canadian registry-based analysis of 32,822 PCI patients [63]. Overall, 3.5 % of PCI patients required transfusion with an associated fourfold increase in 30-day and 1-year mortality (OR 4.01, 95 % CI, 3.08–5.22 and OR 3.58, 95 % CI, 2.94–4.36, P<0.001). The use of radial access in 20.5 % of procedures was associated with a nearly 50 % reduction in transfusions compared with a femoral approach (OR 0.59, 95 % CI, 0.48–0.73, P<0.001). Accordingly, utilization of a radial approach was one of only two variables associated with a significant reduction in 1-year mortality (OR 0.83, 95 % CI, 0.71–0.98, P<0.001).

The RIVAL Trial

The aforementioned studies involved small randomized trials or observational studies that are likely hampered by selection bias and/or confounding. To address these limitations, the RIVAL (Radial Versus Femoral Access for Coronary Intervention) trial was performed [33•]. This parallel group, multicenter, randomized trial was nested into the larger CURRENT-OASIS 7 (Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events–Seventh Organization to Assess Strategies in Ischemic Syndromes) trial and randomly assigned 7021 ACS patients with or without ST-segment elevation to early cardiac catheterization via a radial versus femoral approach. Patients were followed for the occurrence of the primary outcome, a composite of death, MI, stroke, or non-coronary artery bypass graft (non-CABG)–related major bleeding at 30 days. The definition of non-CABG–related major bleeding used in the RIVAL trial was the same as was used in the CURRENT trial and included bleeding that: 1) was fatal; 2) resulted in transfusion of two or more units of red blood cells or equivalent whole blood; 3) caused substantial hypotension with the need for inotropes; 4) needed surgical intervention (a requirement for surgical access-site repair constitutes major bleeding only if there has been substantial hypotension or transfusion of at least two units of blood); 5) caused

severely disabling sequelae; or 6) was intracranial and symptomatic or intraocular and led to significant visual loss. The primary outcome occurred with comparable frequency in the radial (3.7 %) and femoral (4.0 %) groups (hazard ratio [HR] 0.92, 95 % CI, 0.72–1.17, P=0.50). In addition, the rate of major bleeding was very low and similar in both groups (0.7 % radial vs 0.9 % femoral, P=0.23) with non-access site bleeding comprising the majority of overall bleeding (approximately two thirds) events. With respect to secondary outcomes, the rate of major vascular complications was significantly lower in the radial arm (1.4 % vs 3.7 %, P<0.0001) and the rate of access-site crossover was significantly higher from radial to femoral (7.6 %) compared with femoral to radial (2.0 %). When other definitions of bleeding were used, the rate of TIMI major bleeding was no different between the arms, but the rate of ACUITY major bleeding was significantly lower in the radial arm. Finally, patients enrolled in the RIVAL trial expressed a strong preference for radial re-access (rather than femoral) for future interventions. Important insights were also gained by examining prespecified subgroups. The primary outcome was significantly reduced in the highest tertile volume radial centers and in patients with ST-segment elevation myocardial infarction (STEMI) compared to non-ST-segment elevation ACS. In addition, 30-day mortality was also lower among STEMI patients randomized to a radial approach. The mechanism of this mortality reduction is unclear since the rate of either ischemic end points (MI, stroke) and major bleeding did not differ between radial and femoral access among STEMI patients.

Radial Approach for STEMI Interventions and Rescue PCI

Insights into potential mechanisms underlying the mortality benefit seen in the STEMI patients enrolled in the RIVAL trial come from recent studies that have focused specifically on patients with STEMI. In the RIFLE STEACS (Radial Versus Femoral Randomized Investigation in ST Elevation Acute Coronary Syndrome) study, 1,001 patients presenting with STEMI for primary PCI at four participating Italian centers were randomized to radial- versus femoral-access PCI [64]. The 30-day occurrence of net adverse clinical events (NACE; composite of cardiac death, MI, target lesion revascularization, stroke, bleeding) was significantly lower with radial-access PCI (13.6 % vs 21 %, P=0.003) as was cardiac death (5.2 % vs 9.2 %, P=0.020). Overall bleeding rates in RIFLE STEACS were substantially higher than that observed in the RIVAL trial and significantly reduced with the use of radial approach (2.6 % vs 6.8 %, P=0.002), a difference that paralleled the difference in 30-day mortality. This suggests that STEMI patients have higher rates of bleeding compared with patients who present without STEMI and that a potential explanation mechanism for the mortality reduction with radial access is the reduction of bleeding in this high-risk group.

A meta-analysis by Joyal et al. [65•] of 10 randomized trials comparing radial and femoral approaches to primary PCI included the STEMI patients from the RIVAL trial for a sample size of 3,347 patients. Transradial primary PCI was associated with a slightly longer procedure time (delta 1.76 min) but lower vascular complications (pooled odds ratio 0.35 (0.24–0.53)), and lower mortality (pooled odds ratio 0.53 [0.33–0.84]). Interestingly, the difference in major bleeding was not statistically different between radial and femoral access.

The majority of patients included in prior studies of radial approach for STEMI were treated with unfractionated heparin (UFH). Whether there is an additional benefit of a radial approach when bivalirudin is used as the anticoagulant is unclear. The HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) trial, which randomized 3,602 STEMI patients undergoing primary PCI to anticoagulation with UFH plus a GP IIb/IIIa inhibitor or bivalirudin with provisional GP inhibitor, showed that the bivalirudin strategy resulted in significantly lower rates of major bleeding as well as 30-day, 1-year, and 3-year mortality [66]. Although the minority of patients in HORIZONS-AMI underwent transradial PCI, a *post hoc* analysis of the trial data found the radial approach to be an independent predictor of reduced non-CABG–related major bleeding, MACE, and NACE at both 30-day and 1-year follow-up [67]. Additional data from a retrospective cohort study of 4534 patients undergoing primary or rescue PCI for STEMI are consistent with these findings, demonstrating an association between radial approach and reductions in bleeding, MI, and death at 30 days [68]. These results in combination with the demonstrated independent association between major bleeding (with or without transfusion need) and mortality create a compelling argument in support of the transradial approach in high-risk patient PCI subsets [9, 11, 12, 69, 70•]. While available data consistently show a mortality difference favoring radial approach in STEMI patients, the mechanism responsible for this effect remains elusive.

Conclusions

The evolution of PCI in terms of both technology and pharmacology has resulted in low rates of ischemic complications; however, bleeding and major vascular complications continue to be issues in high-risk patients. Both randomized trials and observational studies show an association between radial access and a significant reduction in major vascular complications. Most studies also demonstrate a reduction in major bleeding events, particularly

those related to the vascular access site. These benefits appear to be pronounced among experienced radial operators and in patients with STEMI. Multiple studies have consistently shown an association between transradial primary PCI and reduced mortality, but the mechanisms underlying this benefit are unclear. Moreover, the interaction between radial access and antithrombotic strategies that are associated with reduced bleeding has only been studied retrospectively using clinical trial data. Future studies should focus specifically on the role of the radial approach in the setting of either bivalirudin- or fondaparinux-based treatment regimens for ACS and in high-risk patients such as those presenting with STEMI [71].

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