Transfemoral access (TFA) through the percutaneous Seldinger technique is currently considered the gold standard access site in most catheterization laboratories worldwide. Although several methodological refinements for puncture technique and sheath management have been identified in the literature, access site complications remain frequent in clinical practice when the TFA site is used to deliver treatment, especially in patients with acute coronary syndrome (ACS). The femoral artery, being a relatively deep and terminal vessel, may present rare ischemic complications but frequent bleeding and vascular complications (3%–7%), especially in the myocardial infarction setting.

The most common vascular access site complications at the femoral level are hematomas accompanied by significant blood loss, arterial pseudoaneurysm, and arteriovenous fistulas requiring surgery. Consequently, hospitalization duration, costs, and periprocedural morbidity are increased. The incidence of these complications ranges from 2% to 4% for noncomplex percutaneous coronary intervention (PCI) to 10% to 14% for more complex PCI. This consistent observation across studies may be explained by the complex interplay between several factors, including the high-risk patient profiles, the emergent nature of intervention, and the need for bigger sheath sizes in this population.

Moreover, potent antithrombotic drugs, frequently employed in combination, are now widely used in association with angioplasty in patients with ACS, which may also have a major impact on the occurrence of local complications. Bleeding has been consistently associated with worse outcomes in patients undergoing coronary angioplasty in registries. At present, the burden of bleeding complications after primary PCI is similar to those of ischemic complications, not only in terms of in-hospital morbidity, but also in mid- and long-term survival rates.

Recently, two distinct pharmacological agents, fondaparinux and bivalirudin, were able to reduce hemorrhagic events and concomitantly lowered cardiac mortality in randomized trials of patients affected by myocardial infarction. This finding was not explained by the effect of treatment on ischemic endpoints such as myocardial infarction, stroke, or recurrent angina. Therefore, a new paradigm has emerged whereby bleeding prevention itself may improve survival in patients with acute myocardial infarction undergoing invasive coronary management. In this context, transradial access (TRA) for coronary interventions was progressively established as a cornerstone bleeding avoidance strategy.

TRA FOR DIAGNOSIS AND TREATMENT

After Campeau’s successful coronary angiography by TRA, this technique has increasingly been employed as an alternative access site to TRA for diagnostic and intervention procedures. Although technically more demanding, transradial intervention offers the advantage of minimal clinically relevant and access site vascular complications, allowing for early patient mobilization and discharge. Yet, in the emergent setting of acute myocardial infarction, in which a timely procedure is of paramount importance and the coronary anatomy is unknown, TRA intervention is rarely employed.
The scientific literature has begun to investigate the safety and feasibility of TRA by initially comparing it with the current standard of care. A systematic review of the literature, including all comparative trials up to 2008, compared TRA and TFA both in diagnostic and interventional procedures. This pooled analysis involved 13 studies and 4,458 patients who had been randomized to TRA versus TFA. This analysis showed a remarkable and highly significant 73% reduction of major bleeding complications in the TRA arm. Interestingly, this dramatic reduction of major bleeding complications was associated with a trend toward fewer deaths, myocardial infarctions, or strokes (odds ratio [OR], 0.71; 95% confidence interval [CI], 0.4–1.01; \( P = .06 \)) compared to the TFA group.

**TRA INTERVENTION IN STEMI**

The first study exploring the safety and feasibility of primary PCI via TRA dates back to 1998. In this seminal experience, Ochiai et al reported on a series of 33 patients with ST-segment elevation myocardial infarction (STEMI) who underwent successful primary PCI via TRA. Until that time, TFA was considered to be the only feasible access site, especially in the acute setting. Therefore, a “taboo” was broken, and afterward, randomized studies took place. Due to the limited number of patients enrolled and a lack of confidence that this new access site route may positively affect hard endpoints, no significant breakthrough was made among the worldwide interventional audience.

In the past few years, the idea of TRA for primary PCI had an incredible momentum, both in the scientific arena and in clinical practice, which was largely driven by the increased awareness across the medical community that bleeding may result in worse short- and long-term outcomes. One of the most important references comes from the MORTAL registry, which retrospectively analyzed 38,872 patients who had undergone PCI either via TRA (7,972 patients) or TFA (30,900 patients). Chase et al showed in this study that the need for blood transfusion (as an indirect indicator of major bleeding) was halved (1.4% vs 2.8%) by TRA, and 1-year mortality decreased accordingly from 3.9% to 2.8%. Blood transfusion was independently associated with a fourfold increase in 30-day mortality (95% CI, 3.08–5.22). Of note, approximately two-thirds of the study population were ACS patients who were treated on an urgent basis.

Next, the PREVAIL study was published, in which Pristipino et al prospectively studied bleeding and vascular complications in 1,052 patients who had undergone coronary procedures either via TRA or TFA. In the subgroup of ACS/STEMI patients, both the composite of bleeding (3.2% vs 6.9%) and ischemic complications, including death (1.1% vs 4.9%), favored TRA.

A systematic review of the literature involving 2,808 STEMI patients, who were largely recruited via nonrandomized comparisons, showed that TRA intervention was associated with a significant (nearly 50%) decrease in overall mortality. Mortality in the 516 patients in whom access sites were randomly allocated was also approaching 40% lower in the TRA group, but this difference failed to reach statistical significance.

These observational findings finally led to the pivotal RIVAL trial, which recruited 7,021 patients who were enrolled from 158 hospitals in 32 countries. Of these patients, 3,507 were randomly assigned to TRA and 3,514 to TFA. The primary outcome, which was a composite of death, myocardial infarction, stroke, or non-coronary artery bypass graft-related major bleeding at 30 days, occurred in 128 (3.7%) of 3,507 patients in the TRA group compared with 139 (4%) of 3,514 in the TFA group (hazard ratio [HR], 0.92; 95% CI, 0.72–1.17; \( P = .5 \)). Of the six prespecified subgroups, there was a significant interaction within the primary outcome, with benefit in favor of TRA in the highest tertile volume radial centers (HR, 0.49; 95% CI, 0.28–0.87; \( P = .015 \)) and in patients with STEMI (HR, 0.6; 95% CI, 0.38–0.94; \( P = .026 \)).

Interestingly, in the 1,958 STEMI study patients, not only was a 41% significant reduction of the composite ischemic endpoint noted, but also a 61% reduction of mortality alone in the TRA arm was reported, suggesting that this patient population may benefit more from a dedicated strategy to minimize bleeding. An alternative hypothesis that merits further investigation is that only centers with high TRA PCI volume were confident in randomizing STEMI patients in the study; therefore, STEMI patients in the study may simply identify operators who are particularly experienced with TRA PCI.

Given the wide confidence interval (0.38–0.94) for the primary outcome of the RIVAL study, the certainty that the reduction of the combined endpoint was not a chance finding is not sufficiently robust enough to provide a firm indication in the guidelines. However, it certainly justifies dedicated future trials, especially in STEMI patients. On the other hand, it is worth noting that a significant correlation with respect to the composite ischemic endpoint of death, myocardial infarction, or stroke has been also reported with respect to the indication of the procedure. Patients with non-STEMI ACS showed a trend toward higher ischemic events (HR, 1.25; 95% CI, 0.91–1.71; \( P = .18 \)) when treated via TRA compared to those treated via TFA, and this was despite major vascular and bleeding complications that remained consistently lower in the TRA arm. This worrisome finding merits further investigation and calls for studies addressing whether a gradient in benefit may exist in TRA treatment of patients with various degrees of coronary
disease (patients with non-STEMI ACS are older, are more frequently women, and present with more extensive coronary artery disease) or that operator expertise is the main driver for this puzzling observation.

A recent meta-analysis of patients with STEMI undergoing PCI by Mamas et al. analyzed all existing randomized controlled studies that compared the impact of access site selection on mortality, major adverse cardiac events, major bleeding, and access site complications. It included nine randomized studies consisting of 2,977 patients with STEMI undergoing PCI. An odds ratio of 0.53 (95% CI, 0.33–0.84; \( P = .006 \)) for mortality in favor of the TRA group (48% reduction in the risk of mortality in this group) was reported. In a sensitivity analysis, after removing the largest study (RIVAL) from the dataset, the reduction in mortality failed to reach statistical significance, even if it was viewed on a relative basis, and there was a benefit in mortality reduction favoring the radial approach of similar magnitude (ie, whether the difference between the two study groups was statistically significant). There was a significant difference in major adverse cardiac events and in access site complications that favored the TRA group, whereas the analysis of major bleeding events showed no significant difference between the two groups (OR, 0.63; 95% CI, 0.35–1.12; \( P = .12 \)).

The most recently updated meta-analysis of randomized controlled trials comparing the radial and femoral approach in primary PCI for STEMI was published by Joyal et al. The data were pooled using random effects models. Ten randomized controlled trials involving 3,347 patients met the inclusion criteria. The inclusion criteria were a randomized study design, a patient population with documented STEMI undergoing primary PCI, a control group undergoing femoral access, and the type of clinical outcome (death, major bleeding, vascular complications, or hematoma), and procedure time. The radial approach was associated with improved survival (OR, 0.53; 95% CI, 0.33–0.84) and reduced vascular complications/hematoma (OR, 0.35, 95% CI 0.24–0.53). A nonsignificant trend was found toward reduced major bleeding with the radial approach (OR, 0.63; 95% CI, 0.35–1.12). The procedural time with the radial approach was longer by < 2 minutes (mean difference, 1.76 minutes; 95% CI, 0.59–2.92).

However, it is of note that none of these studies was powered to assess whether the use of the radial instead of the femoral route may translate into an improved short- to medium-term outcome.

An observational region-wide study directly compared the medium-term outcomes, as well as the safety profile, of TRA versus TFA intervention in patients with STEMI undergoing primary PCI. Between January 1, 2003, and June 30, 2009, 12,407 patients underwent PCI for STEMI in Emilia-Romagna, Italy. Of these patients, 8,000 (median follow-up, 1,204 days) underwent TFA and 3,068 (median follow-up, 605 days) were primarily treated with TRA intervention. However, the number of TRA interventions greatly increased over time (Figure 1).

The adjusted outcomes based on a propensity score analysis of the entire population showed a 30% mortality reduction (HR, 1.309; 95% CI, 1.07; 1.602; \( P = .0089 \)) at 2 years in favor of TRA intervention (Figure 2), reflecting an early significant mortality benefit within 30 days after treatment (HR, 1.38; 95% CI, 1.016–1.876; \( P = .0395 \)). In subgroup analysis, the mortality benefit at 2 years favoring TRA appeared largely consistent across several analyzed covariates.

The relatively slow rate of TRA adoption over time in the previously cited regional STEMI registry suggests that the transition from TFA to TRA is a long-term process in
this challenging patient population. Although 10 of the 12 regional sites launched a transradial intervention (TRI) program in 2004 and 2005, several hundreds of PCI cases performed during a 3-year time frame were deemed necessary to make TRA intervention the more prevalent access site in the acute setting of STEMI treatment. Similarly, the crossover from TRA to TFA peaked at approximately 8% in 2006 and subsequently declined to a much more acceptable 3% rate, despite a progressive TRI increase over time.

This study, in keeping with recent evidence, suggests that the risks of transitioning to TRA over TFA in STEMI patients (provided the process is undertaken in a stepwise approach as part of a global TRI program) may be largely outweighed by a lower mortality rate. In addition, based on a substantial reduction in hospitalization, as well as in access site bleeding and vascular complications, the widespread adoption of TRI may dramatically affect the economical burden of ACS in western countries.

A clear limit of available studies comparing TFA and TRA is that they have been conducted in the absence of a contemporary pharmacological environment, including the most recent achievements in terms of adjunctive treatment during PCI. By significantly reducing the rate of access site complications, this emerging set of new antithrombotic therapies replacing unfractionated heparin may drastically reduce the benefit of TRA over TFA in terms of access site complications. Thus, the contemporary benefit of TRA versus TFA in the context of the emerging antithrombotic therapies, especially bivalirudin, needs to be established.

In the HORIZONS AMI trial, 3,602 STEMI patients undergoing primary PCI were randomized to receive either bivalirudin monotherapy with a provisional glycoprotein (GP) IIb/IIIa inhibitor or unfractionated heparin plus a routine GP IIb/IIIa inhibitor. At 30 days, bivalirudin monotherapy demonstrated statistical superiority over unfractionated heparin plus a GP IIb/IIIa inhibitor for the two primary endpoints of net adverse clinical outcomes (9.2% vs 12.1%; \( P = .006 \)) and major bleeding (4.9% vs 8.3%; \( P = .0001 \)), and no significant differences in the secondary endpoint of major adverse cardiovascular events (5.4% vs 5.5%; \( P = .95 \)).

Treatment with bivalirudin rather than heparin plus a GP IIb/IIIa inhibitor also resulted in significantly lower 30-day rates of cardiac mortality (1.8% vs 2.9%; risk ratio, 0.62; 95% CI, 0.4–0.95; \( P = .03 \)) and all-cause mortality (2.1% vs 3.1%; risk ratio, 0.66; 95% CI, 0.44–1; \( P = .047 \)), with nonsignificantly different rates of reinfarction, target vessel revascularization, and stroke. Of note, in HORIZON AMI, the use of TRA was extremely limited: 200 TRA primary PCIs versus 3,134 TFA primary PCIs. Given this limitation, a recent substudy compared the two different approaches. TRA compared to TFA access was associated with significantly lower 30-day rates of composite death or reinfarction (1% vs 4.3%; OR, 0.23; 95% CI, 0.06–0.94; \( P = .02 \)), non–CABG-related major bleeding (3.5% vs 7.6%; OR, 0.45; 95% CI, 0.21–0.95; \( P = .03 \)), major adverse cardiac events (MACE) (2% vs 5.6%; OR, 0.35; 95% CI, 0.13–0.95; \( P = .02 \)), and net adverse clinical events (NACE) (5% vs 11.6%; OR, 0.42; 95% CI, 0.22–0.78; \( P < .01 \)). At 1 year, the TRA group still had significantly reduced rates of death or reinfarction (4% vs 7.8%; OR, 0.51; 95% CI, 0.25–1.02; \( P = .05 \)), non–CABG-related major bleeding (3.5% vs 8.1%; OR, 0.42; 95% CI, 0.2–0.89; \( P = .02 \)), MACE (6% vs 12.4%; OR, 0.47; 95% CI, 0.26–0.83; \( P < .01 \)), and NACE (8.5% vs 17.8%; OR, 0.45; 95% CI, 0.28–0.74; \( P < .001 \)). By multivariable analysis, TRA was an independent predictor of freedom from MACE and NACE at 30 days and 1 year.

Recently, in the RIFLE-STEACS study, 1,001 patients with STEMI were randomized to TRA versus TFA. This important study showed an impressive reduction of overall mortality in the TRA group (5.2 vs 9.2; \( P = .02 \)), which came along with a reduction in bleeding complications, whereas the rates of myocardial infarction, stroke, or reintervention in the target vessel did not differ between the two study groups. Yet, in this study, the use of bivalirudin was minimal (approximately 7%), and roughly 70% of patients received unfractionated heparin in conjunction with GP IIb/IIIa inhibitors.

The results of the ongoing MATRIX study will provide a paramount contribution in the comparison between TRA versus TFA intervention and bivalirudin monotherapy versus unfractionated heparin plus provisional use (at the discretion of the treating physician) of GP IIb/IIIa inhibition in ACS patients as intended for an invasive management strategy (Figure 3).

**CONCLUSION**

The significance of bleeding complications after primary PCI is now understood, as they affect mid- and long-term mortality, and are considered to be as important as ischemic complications. Therefore, TRA, in association with
new pharmacological agents, represents a paramount strategy in reducing bleeding and improving survival rates. Moreover, TRA nearly eliminates access site complications and reduces hospitalization duration, costs, and perioperative morbidity, even in the emergent setting. On the other hand, the transition from TFA to TRA for primary PCI is a long-term process, requiring several hundreds of PCI cases performed over years into a global TRI program.

The dramatic mortality reduction associated with TRA has been shown in registries and meta-analyses, leading to the pivotal RIVAL trial, which, at least in part, frustrated these expectations. However, in the STEMI study patients, TRA showed an impressive 61% reduction in mortality alone in the TRA arm. This result calls for dedicated future trials, especially in STEMI patients.

A clear limit within the available studies comparing TFA and TRA is that they have been conducted in the absence of a contemporary pharmacological environment. Thus, the benefit of TRA versus TFA in the context of the emerging antithrombotic therapies remains to be established. The ongoing MATRIX study will attempt to overcome this limitation by comparing TRA versus TFA, as well as bivalirudin versus unfractionated heparin plus provisional use of GP IIb/IIIa inhibitor in ACS patients.

Simone Biscaglia, MD, is with the Institute of Cardiology, University Hospital of Ferrara, in Ferrara, Italy. He has disclosed that he has no financial interests related to this article.

Marco Valgimigli, MD, PhD, FESC, is with the University of Ferrara Cardiovascular Institute, Arcispedale S. Anna Hospital in Ferrara, Italy. He has disclosed that he received an honorarium as a public speaker from the following companies: Terumo, The Medicines Company, Medtronic, Iroko, Merck, Abbott, Lilly, Astra Zeneca, Cordis, CID, and Bayer. Dr. Valgimigli may be reached at +39 0532-202143; vlgmrc@unife.it.