

Analyzing the Outcomes of PCI Access Techniques for STEMI

New information suggests that using radial artery access for primary PCI is not only feasible and safe, but may also save lives.

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The RIVAL trial is the largest randomized clinical study to date comparing radial artery access to femoral artery access for patients undergoing percutaneous coronary intervention (PCI) in the setting of acute coronary syndromes (ACS).¹ This was a negative study in that it did not find lower rates of adverse clinical events or bleeding with radial artery use (as had been expected). Most of the 7,021 patients enrolled presented with non-ST-elevation myocardial infarction, and for these patients, the use of radial access did not provide a benefit.

However, in the subgroup with ST-elevation myocardial infarction (STEMI) treated via radial access, there was a 40% reduction in the primary endpoint—a composite of death, nonlethal MI, stroke, or major bleeding not related to coronary artery bypass graft surgery. There was also a 41% reduction in the risk of death in these patients (hazard ratio [HR], 0.39; 95% CI, 0.2–0.76; $P = .006$). Surprisingly, rates of major bleeding were not reduced in this subgroup. Thus, RIVAL indicates that STEMI patients may derive a mortality advantage with radial access over femoral access, but this advantage cannot be attributed to lower rates of bleeding. Are the RIVAL trial observations about STEMI patients to be believed?

THE PRACTICALITY OF RADIAL PCI DURING STEMI

Following the demonstration by Kiemeneij and colleagues in 1993 that coronary stents could be placed via the radial artery,² a flurry of publications from Asia, Europe, and North America reported successful trans-radial PCI in the setting of ACS.^{3–5} Technical barriers were not insurmountable and were similar to those reported under less acute conditions.⁶ Reduced bleeding and vascular complication rates were seen early, and Mann et al reported in 1998 that the radial approach could be associated with significantly reduced costs of care.³

The challenge of gaining reliable access to the radial artery was of special concern. Although procedure times may be slightly increased, radial access does not require a meaningful extension of door-to-balloon times. The staff at Université de Montreal observed no significant difference in time to revascularization with femoral or radial access.⁷ In fact, door-to-balloon times were numerically (but not statistically) quicker with the radial approach, undoubtedly reflecting the proficiency of these expert radial operators.

Radial arteries are accommodating of vascular sheaths up to 6 or 7 F, but larger sizes are problematic in many patients; thus, the use of large-caliber boutique instru-

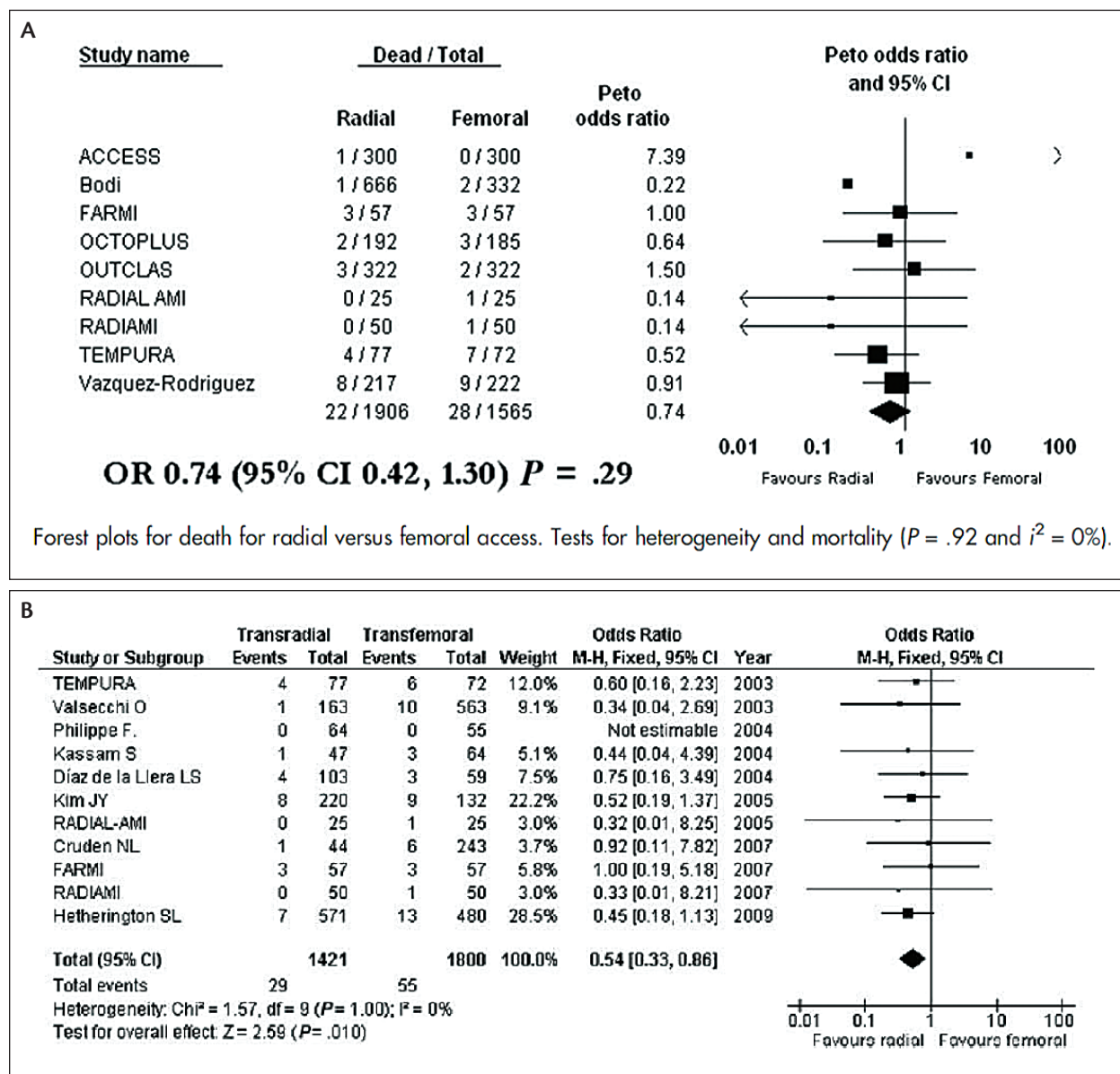


Figure 1. Simultaneous meta-analyses evaluating the impact of radial access on mortality following PCI for STEMI before the RIVAL trial. Meta-analysis from North America (A). Reprinted with permission from Jolly et al.¹⁰ Meta-analysis from Europe (B). Reprinted with permission from Vorobcsuk et al.⁹

ments is problematic. For STEMI patients, a commonly used nonballoon device is an aspiration thrombectomy catheter to remove a clot. Fortunately, simple aspiration catheters are preferable to the mechanical disruption thrombectomy systems,⁸ and aspiration catheters fit snugly through 6-F guide catheters.

OBSERVATIONS ABOUT BLEEDING

Before RIVAL was underway, several small studies had been reported. Ten years ago, Cantor et al conducted

a small but important randomized study.⁵ All patients received glycoprotein IIb/IIIa inhibitor therapy, and two-thirds of patients experienced thrombolytic drug failures and were undergoing rescue PCI. Conceived as a pilot study, this small trial found that radial access took longer than femoral access (by about 6 minutes on average; $P = .04$), but technical and safety measures were otherwise equal in the two groups. Serious bleeding was not observed in either group. They concluded that the radial approach was reasonable in the setting

of STEMI PCI, even among patients undergoing salvage PCI after failed thrombolysis.

By the time RIVAL was completed, observations from nearly a dozen small studies had been published. Two important meta-analyses of these early studies, one from Europe⁹ and one from the RIVAL trial authors in North America,¹⁰ were published almost simultaneously in 2009. However, there was little overlap in the included studies: data from just five studies were common to the two analyses, accounting for approximately 400 of 3,000 patients. Both meta-analyses found that radial access was linked to statistically important reductions in major bleeding. The magnitudes of the reductions were impressive and concordant: the European study found a 70% reduction, the North American study found a 73% reduction.

In 2012, Romagnoli et al published the results of the Radial Versus Femoral Randomized Investigation in ST-Segment Elevation Acute Coronary Syndrome (RIFLE-STEACS) trial.¹¹ This European study of approximately 1,000 patients found that use of radial artery access was associated with an important 62% reduction in bleeding related to vascular access (2.6% vs 6.8%; $P = .002$), consistent with expectations from the preceding meta-analyses. Nonaccess-related bleeds occurred at similar rates following radial or femoral procedures.

After the release of the RIFLE-STEACS findings, two additional meta-analyses were published, one European¹² and one North American.¹³ The European meta-analysis evaluated data from randomized and observational studies and included patients with and without ACS. The United States meta-analysis looked only at data from randomized trials involving patients undergoing primary PCI for STEMI. Both meta-analyses found meaningful reductions in bleeding. For STEMI patients, major bleeding event rates after radial PCI were one-half those observed in femoral cases (1.4% vs 2.9%; OR, 0.51; 95% CI, 0.31–0.85; $P = .01$) in the North American analysis, whereas the European analysis reported a 78% reduction with radial access (OR, 0.22; 95% CI, 0.16–0.29; P value not reported) for all-comers.

Finally, registries of North American practice support the reported bleeding benefits of transradial PCI. Baklanov et al analyzed data from the National Cardiovascular Data Registry (NCDR) CathPCI registry, reporting on a sampling of nearly 300,000 patients treated for STEMI in the United States between 2007 and 2011.¹⁴ Once again, the use of radial access was associated with fewer major bleeds (OR, 0.62; 95% CI, 0.53–0.99; $P = .0455$).

The totality of evidence strongly supports the contention that radial access for STEMI PCI is linked to

important bleeding reductions. So, why did the RIVAL results look different? There are several possible explanations.

RIVAL used a bleeding definition that worked against finding a difference. Varying definitions of bleeding across studies is a substantial concern. The 2012 meta-analysis of bleeding by Bertrand et al provides a glimpse of some of this variation.¹² The earliest patients enrolled in RIVAL were extracted from the CURRENT-OASIS 7 study, a clinical trial assessing the value of an increased dose of clopidogrel following PCI for ACS.¹⁵ The definition for bleeding used in RIVAL conformed to the CURRENT-OASIS 7 definition: major bleeding was fatal, resulted in transfusion of 2 or more units of packed red blood cells, caused serious hypotension requiring inotropic drugs, needed surgical intervention, caused severe disability, and was intracranial or intraocular and caused vision loss.^{1,15} This definition is appropriate for RIVAL because it captures clinical elements of interest, although it does not focus specifically on access-related bleeds. However, a poor definition cannot fully account for the RIVAL findings.

RIVAL was also not powered to make observations about bleeding. At first glance, this would seem impossible, since the study was designed with bleeding in mind. However, major bleeding rates in RIVAL (0.8% for radial, 0.9% for femoral) were not as expected. The pre-RIVAL meta-analysis published by Jolly et al in 2009 found major bleeding rates of approximately 0.5% with radial procedures and 2.5% with femoral procedures for STEMI.¹⁰ In RIVAL, only 32% of bleeds could be attributed to the access site, so just 0.2% of bleeds among radial patients and 0.3% of bleeds among femoral patients could be attributed to the access site. We have no reason to expect significant bleeding reductions with radial use except through reduced access site bleeds. Therefore, RIVAL appears to have been underpowered for access site major bleeding, as pointed out by Rao et al in a recent editorial on this subject.¹⁶

Bleeding was not the right endpoint for RIVAL. Because bleeding can come from anywhere, perhaps an endpoint more specific to the access site would have been preferable. Major vascular access site complications would seem an ideal choice. Major vascular complications were reduced by about two-thirds with radial artery use in RIVAL, and a post-hoc analysis found no major bleeds from access site complications in radial patients but 18 such events in femoral patients.^{1,16}

In summary, the aggregate of data on bleeding linked to primary PCI for STEMI strongly indicates that use of radial artery access substantially lowers bleeding events. RIVAL was an outlier.

TABLE 1. TIME DELAY NEEDED TO OFFSET THE MORTALITY ADVANTAGE OF TRANSRADIAL PCI FOR STEMI*

Analysis Based on Assumed Mortality Reduction			
Population	RR = 0.5	RR = 0.75	RR = 0.88
All patients	83 min	41.8 min	20.9 min
Elderly patients	61.5 min	30.8 min	14.8 min
Analysis Based on Assumed Access Site Crossover Rate			
Population	Crossover rate = 12.8%	Crossover rate = 17.8%	
All patients	81.5 min	79.7 min	
Elderly patients	60 min	58.2 min	

*Adapted from Wimmer et al.²²
Abbreviation: RR, relative risk.

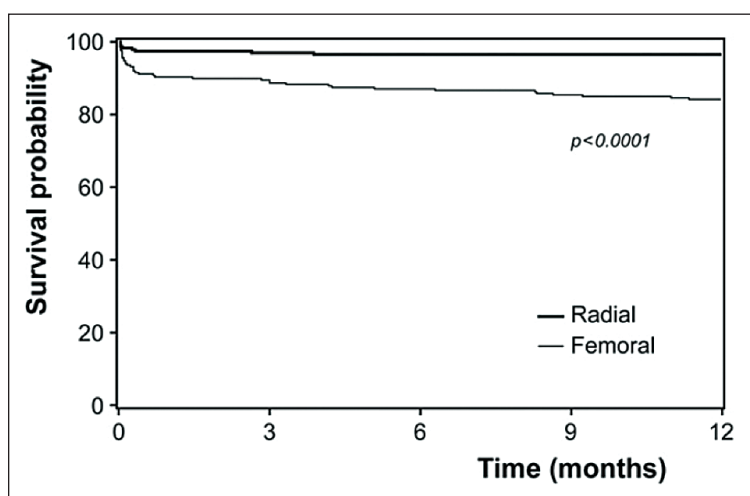


Figure 2. Mortality following PCI for STEMI using the radial (thick line) or femoral approach (thin line). Note the early separation of lines, with continued divergence out to 12 months. Reprinted with permission from Arzamendi et al.⁷

OBSERVATIONS ABOUT MORTALITY

The RIVAL trial indicated an important mortality reduction with the use of radial access.¹ This might not have been initially anticipated because mortality rates are now very low for STEMI patients, especially those enrolled in restrictive clinical trials. The two previously mentioned principal pre-RIVAL meta-analyses^{9,10} did not find important differences in composite clinical measures, but the North American group noted a weak trend toward a mortality advantage with radial access (OR, 0.74; CI, 0.42–1.3; $P = .29$), and the European group reported a meaningful mortality reduction (OR, 0.54; CI, 0.33–0.86; $P = .01$). Both groups found low heterogeneity, indicating a consistent direction of observations across the included studies (Figure 1). A direct association between increased bleeding and increased mortal-

ity after PCI has been established,¹⁷ so less bleeding should mean fewer deaths.

The two previously mentioned post-RIVAL meta-analyses were divided on mortality. The North American study, assessing only randomized trials, found that mortality was cut by nearly half with radial use (2.7% vs 4.7%; OR, 0.55; CI, 0.4–0.76; $P < .001$).¹³ In contrast, the European meta-analysis found a similar mortality reduction (OR, 0.56; CI, 0.45–0.67),¹² but this was driven by data from observational studies; mortality with radial use in the randomized trials they studied was an insignificant 20% lower than mortality with femoral use (OR, 0.8; CI, 0.49–1.23). Baklanov et al's recent NCDR database study¹⁴ also found a propensity-adjusted in-hospital mortality benefit for radial use in a different, much larger observational cohort (OR, 0.76; CI, 0.57–0.99; $P = .046$).

While RIVAL was recruiting patients, Arzamendi et al at Université de Montreal⁷ published provocative observations: they found a propensity-adjusted mortality difference with radial use that was evident during the hospital stay and also noted that survival curves continued to diverge for 12 months after hospital discharge (Figure 2). This implies that radial use is somehow linked to benefits that materialize well after hospital discharge.

If a mortality advantage exists with radial access, perhaps it would be reasonable to look for it in high-risk patient subgroups, such as the elderly and women. Subgroup analyses of radial intervention have found similar or greater vascular risk reductions in these high-bleeding-risk groups.^{17–19} A highly provocative claim has been made by Wimmer and colleagues²⁰ that the

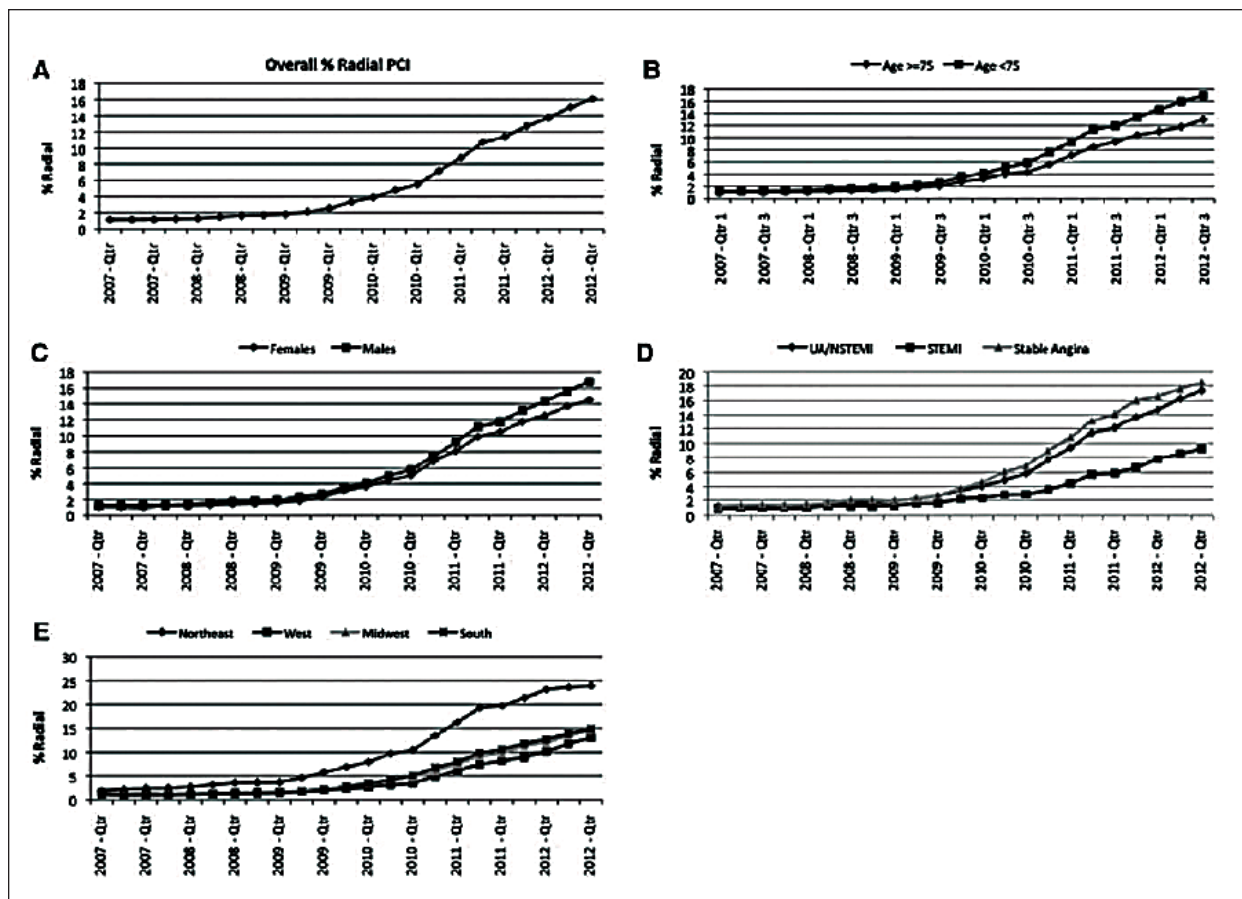


Figure 3. Changes in radial access use for primary PCI in the United States between 2007 and 2012. All patients (A). Patients stratified by age (B). Patients stratified by sex (C). Patients stratified by clinical presentation (D); note that the use in STEMI is < 10%. Patients stratified by region of the United States (E). Reprinted with permission from Feldman et al.¹⁸

mortality benefit with radial use is so powerful, especially for the elderly, that significant delays to revascularization may be tolerated before the benefit is offset. They compiled data from RIVAL and RIFLE-STEACS and modeled the effects of radial access and door-to-balloon time on 30-day mortality. They found that delays in door-to-balloon time of more than 80 minutes would be needed to offset the mortality advantage for patients overall (60 minutes for elderly patients) (Table 1). Although this is highly speculative, it underscores the potential benefit of radial use when there is no delay in treatment.

Does radial artery access really save lives? If so, how does that happen? Again, we have theories but few proven conclusions. Mortality reductions are related to bleeding reductions. This seems self-evident, and the totality of evidence supports this view, but we are left with the nagging RIVAL data: no difference in bleeds, big difference in mortality. Unless RIVAL is an outlier

on this issue too, we must consider other possible mechanisms.

Mortality reductions may be facilitated by fewer restrictions on patient mobility, as laying in a hospital bed for a length of time is dangerous, as prolonged bed rest creates opportunities for aspiration of food or medicines, venous thromboses, and more severe gait instability when patients finally ambulate. Because patients who have had transradial procedures are not required to lie flat afterward, they are more mobile in the first 12 hours after PCI. Perhaps shorter periods of confinement provide an important, if poorly understood, physiologic benefit. Mortality reductions might also be facilitated through quicker hospital discharge. Being a patient in a hospital is also dangerous because they can be hotbeds of infection, they contribute to disorientation at night among elderly patients, and newspaper headlines continue to feature medical errors as common sources of hospital-acquired injury or ill-

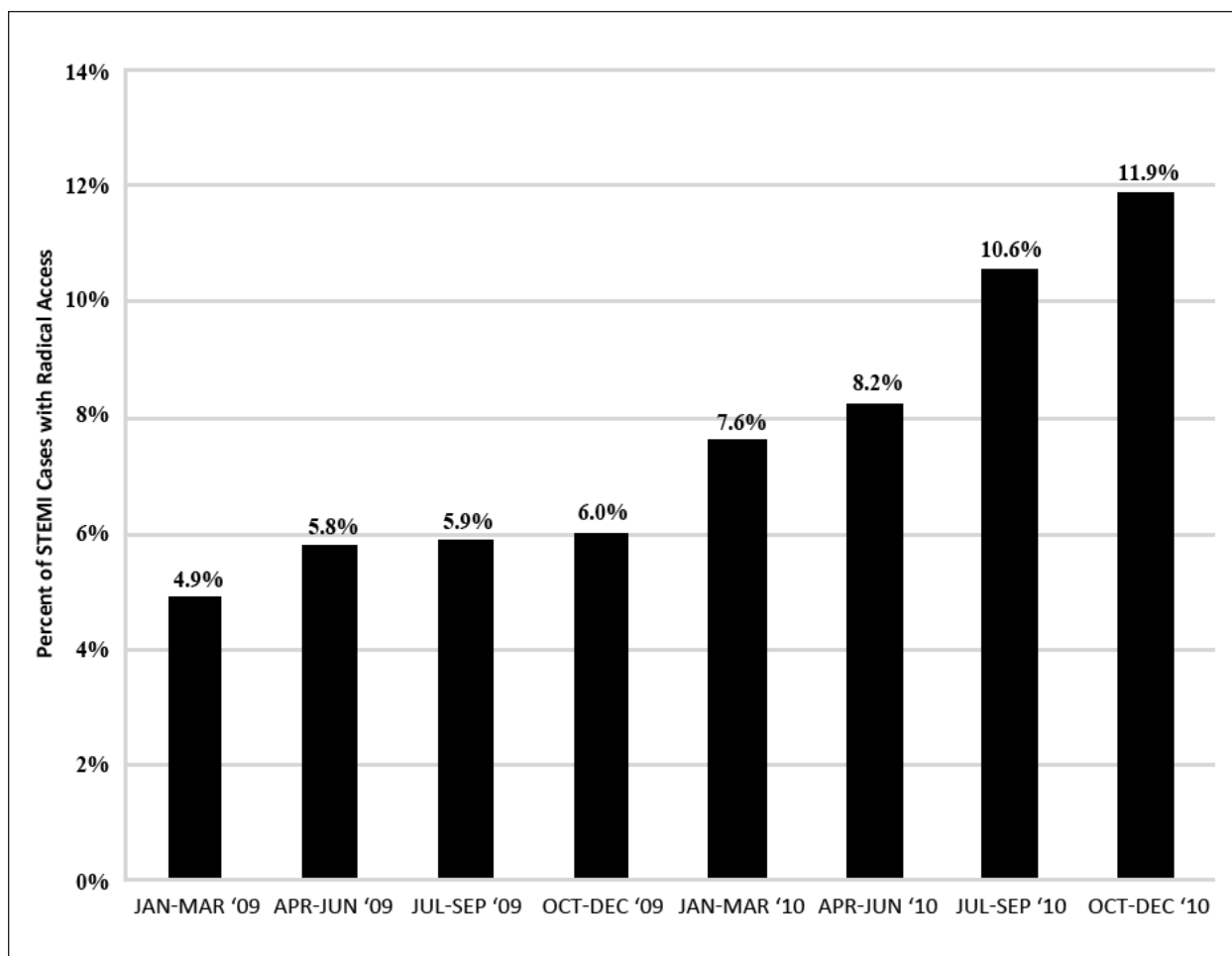


Figure 4. The use of radial artery access for primary PCI in New York State. Although each quarter saw a rise, the percentage use of radial access remained low. Reprinted with permission from Hannan et al.²⁴

ness. Patients treated with radial PCI are eligible for expedited activity, which can shorten the hospital stay. RIVAL and other studies have documented important reductions—up to 1 full day—in intensive care unit stays and overall hospital stays.

The evidence suggests that transradial treatment for STEMI provides a mortality benefit, but the evidence is not concrete, and biologically plausible mechanisms have not been fully established. This question will likely require a properly sized randomized trial powered for mortality in order to be resolved. Baklanov and colleagues have also called for such a trial.¹⁴

REALITIES

Despite the benefits of transradial PCI for STEMI, use of this approach remains low, particularly in the United States. Rao et al²¹ found that approximately 1% of all PCI cases were performed transradially in America

from 2004 to 2007. By the end of 2012, Feldman and colleagues²² noted a meaningful increase to about 16% of all PCI cases reported to the NCDR CathPCI registry. However, radial PCI in STEMI cases was still < 10% (Figure 3). Hannan et al reported quarterly increases in the state of New York over 2 years, but use of radial access was still < 12% of cases going into 2011 (Figure 4).²³ Meanwhile, the use of radial access for all types of PCI is much higher outside the United States.²⁴

As payment reform is underway in the United States, hospitals and operators are increasingly interested in capturing all opportunities to enhance overall quality of care, especially as this pertains to high-reimbursement procedures. In this regard, transradial angiography and intervention is likely to substantially increase in the United States, particularly since it has been recognized as an effective bleeding reduction strategy.²⁵ Interested agencies, such as the Society for

Cardiovascular Angiography and Interventions, are responding to a perceived demand for transradial training by offering regional training programs run by acknowledged radial experts.²⁶ Because radial use varies widely by region, programs will be concentrated in parts of the country where radial access is uncommon.

Finally, there is the issue of cost. Incremental cost increases to conduct transradial PCI are small, but the costs attributable to vascular complications of PCI are huge. A study of Medicare patients found that a vascular complication was the most common complication reported after PCI, occurring in more than 5% of procedures, and the adjusted cost associated with each complication was approximately \$4,000.²⁷ Avoidance of costly complications has become a financial imperative for practices and hospitals.

CONCLUSION

Transradial PCI is possible and practical to treat STEMI. In the hands of proficient operators, time to revascularization is not meaningfully increased, and success rates are similar to those achieved with transfemoral access. Although RIVAL appears to have been an outlier because of much lower rates of bleeding in the femoral-treated group, transradial angioplasty is highly likely to reduce blood loss, and essentially all large-scale reports confirm significant reductions in major vascular access site complications.

Radial artery access may enhance survival directly through blood loss avoidance or indirectly through early ambulation and discharge or other mechanisms. The weight of these benefits is sufficient to consider a reworking of the STEMI care model across the United States, where radial access remains uncommon. Interventional cardiologists should collaborate with hospital administrators to ensure that their patients have access to primary transradial PCI, especially in busy hospital centers that can sustain highly competent radial operators who can prevent treatment delays. ■

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