

Mechanisms by Which Transradial Approach May Reduce Mortality in ST-Segment–Elevation Myocardial Infarction

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Radial access for central arterial catheterization was first described in 1948, but it was not until 1989 that Lucien Campeau published his experience of 100 successful coronary angiograms via the radial route.¹ In 1993, the transradial approach for coronary angiography took a significant step forward when Kiemeneij and Laarman described the use of radial access for successful percutaneous coronary intervention (PCI).¹ Since that time the use of the transradial approach for PCI has become increasingly popular, mainly because of improved patient comfort and observed reductions in periprocedural bleeding and vascular complications.² Current use of transradial intervention (TRI) in the United States is 16%.³ Although still underused, TRI is becoming increasingly popular in the United States with a 13-fold increase during the past 6 years.³ Currently, TRI is considered not only an effective alternative to transfemoral intervention (TFI) but also in some instances the preferred approach. This may be particularly true in the setting of primary PCI because some studies have shown an association between TRI and reduced mortality when compared with the transfemoral approach. Although this association remains controversial, the purpose of this review is to propose and discuss the mechanisms for a potential reduction in mortality.

TRI Associated With Reduced Major Adverse Cardiac Events and Mortality in ST-Segment–Elevation Myocardial Infarction

The most important outcome measured in any cardiovascular study is the effect the intervention of interest has on mortality. Major adverse cardiac events (MACE), which is most commonly a composite of death, myocardial infarction (MI), or revascularization, is also an outcome of interest. Current data suggest that TRI when compared with TFI may be associated with a reduction in MACE and mortality in patients with ST-segment–elevation MI (STEMI).

In a post hoc analysis of Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI), 30-day MACE was significantly lower in patients who underwent TRI when compared with those who underwent TFI (2.0% versus 5.6%; odds ratio [OR], 0.35; 95% confidence interval [CI], 0.13–0.95; $P=0.02$).⁴ This reduction in MACE with TRI continued out to 1 year (6.0%

versus 12.4%; OR, 0.47; 95% CI, 0.26–0.83; $P<0.01$) and was driven by a reduction in reinfarction and revascularization rates. Patients who underwent TRI also had lower 30-day rates of death or reinfarction (1.0% versus 4.3%; $P=0.02$) and 1-year rates of death or reinfarction (4.0% versus 7.8%; $P=0.05$). The benefit of TRI was independent of the type of anticoagulation regimen used.

The largest trial comparing radial with femoral approach for cardiac catheterization or PCI was the radial versus femoral access for coronary angiography and intervention in patients with acute coronary syndromes (RIVAL) trial, which randomized ≥ 7000 patients with acute coronary syndrome.⁵ The primary outcome of the RIVAL trial was the combination of MACE and non-coronary artery bypass grafting (CABG) major bleeding with MACE as a secondary outcome. When compared with TFI, patients with STEMI who underwent TRI had a reduction in the primary outcome (3.1% versus 5.2%; $P=0.026$) and a reduction in MACE (2.7% versus 4.6%; $P=0.031$). Interestingly, patients with STEMI, but not patients with non–ST-segment elevation–acute coronary syndrome, had a reduction in mortality with TRI (1.3% versus 3.2%; $P=0.006$).⁵ This reduction in MACE and mortality with TRI was also seen in the RIFLE-ST-Elevation Acute Coronary Syndrome (STEACS) study, which randomized 1001 patients undergoing primary PCI for STEMI to radial or femoral access.⁶ The 30-day incidence of MACE in the TRI group was 9.3% when compared with 11.4% in patients who underwent TFI ($P=0.029$), and the incidence of cardiac death was 43% lower in patients who underwent TRI (5.2% versus 9.2%, $P=0.020$).⁶

A meta-analysis by Mamas et al⁷ corroborates the above findings. The meta-analysis included 9 randomized trials that compared outcomes between TRI and TFI in patients with STEMI. Of the 2997 patients included in the study, 1460 underwent TRI and 1517 underwent TFI. When compared with TFI, transradial PCI was associated with a reduction in MACE (OR, 0.62; 95% CI, 0.43–0.90; $P=0.012$) and mortality (OR, 0.53; 95% CI, 0.33–0.84; $P=0.008$).⁷ Of note, this meta-analysis did not include results from RIFLE-STEACS, which had not been published at the time of the study. The results of this meta-analysis, with the addition of the RIFLE-STEACS study, are summarized in Figure 1. Although not

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definitive, there is evidence that TRI in the highest risk patients (those presenting with STEMI) is associated with a reduction in MACE and mortality when compared with transfemoral PCI. Although several theories abound, the cause for this reduction in mortality with TRI remains unclear.

Proposed Mechanisms for Reduced Mortality Bleeding Reduction

Does TRI Decrease Bleeding?

Patients with STEMI undergoing primary or rescue PCI are at increased risk for bleeding partly because of aggressive treatment with antithrombin and antiplatelet therapy. In addition, patients undergoing primary PCI for STEMI have a significant proportion of bleeding events that are related to the arterial access site.² Periprocedural bleeding is not benign because data have shown an association between bleeding complications and morbidity and mortality.^{17–21} For example, using the National Cardiovascular Data Registry CathPCI Registry, Rao et al²² demonstrated a >30% increase in 30-day mortality in patients with PCI-related bleeding. When compared with TFI, TRI has consistently been shown to reduce access site bleeding (Figure 2), major vascular complications, and blood transfusions.

In registry data published by De Carlo et al,²⁸ case-matched comparison with TFI using propensity analysis showed that TRI in patients with STEMI or non-ST-segment elevation-acute coronary syndrome was associated with a significant reduction in overall bleeding (8.7% versus 29.2%; $P<0.0001$) and TIMI major bleeding (0.2% versus 4.6%; $P=0.0003$). Additional studies published from the European Registry on Patients With ST-Elevation Myocardial Infarction Transferred for Mechanical Reperfusion With a Special Focus on Early Administration of Abciximab (EUROTRANSFER) registry and the National Cardiovascular Data Registry database also show a reduction in bleeding with TRI in patients with STEMI.²⁹ In the National Cardiovascular Data Registry database, TRI was associated with a 40% reduction in bleeding when compared with TFI (OR, 0.62; 95% CI, 0.53–0.72; $P<0.0001$).³⁰

The reduction in bleeding with TRI has also been observed in randomized trials. In the test for myocardial infarction by prospective uniconter randomization for access sites (TEMPURA) trial, Saito et al⁹ randomized 149 patients with STEMI to TRI or TFI. Severe bleeding, defined as cerebral bleeding or bleeding requiring blood transfusion and surgical repair, was 0% in the TRI group and 3% in the TFI group.

In the more contemporary RIVAL trial, patients with STEMI randomized to TRI did not have decreased study-defined non-CABG-related major bleeding when compared with patients randomized to TFI (0.8% versus 0.9%; $P=0.87$).⁵ RIVAL major bleeding was defined as (1) fatal, (2) resulting in transfusion of ≥ 2 units of packed red blood cells, (3) intracranial, (4) needing surgical intervention, (5) causing hypotension with the need for inotropy, (6) severely disabling, or (7) leading to a drop in hemoglobin of ≥ 5 g/dL. Overall, there was a decrease in Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY)-defined major bleeding in patients who underwent TRI when compared with those who underwent TFI (1.9% versus 4.5%; $P<0.0001$), but there was no

difference in the rate of blood transfusion. Of note, however, ACUITY bleeding and blood transfusion rates were not specifically defined for patients with STEMI.⁵

The RIFLE-STEACS study compared bleeding outcomes in 1001 patients with STEMI randomized to either TRI or TFI.⁶ In RIFLE-STEACS, postprocedural bleeding was defined using the Bleeding Academic Research Consortium (BARC) definition, with a significant bleed defined as BARC ≥ 2 . BARC ≥ 2 bleeding includes bleeding that is (1) fatal, (2) cerebral, (3) intracranial or retroperitoneal, (4) causing tamponade, (5) decreasing hemoglobin by ≥ 3 g/dL, (6) requiring blood transfusion, or (7) requiring surgical repair. In addition, it is required that the bleeding lead to unplanned diagnostic examinations, prolonged hospitalization, and lifesaving drug discontinuation. Using this definition, patients who were randomized to TRI had a significant reduction in bleeding (7.8% versus 12.2%; $P=0.026$), driven by a 60% reduction in access site bleeding.⁶ There was also a reduced blood transfusion rate in patients receiving TRI when compared with those receiving TFI (1.0% versus 3.2%; $P=0.025$). There was no difference in non-access site bleeding, which accounted for >50% of the major bleeding complications.

In both RIVAL and RIFLE-STEACS, the predominant anticoagulation strategy consisted of heparin with provisional glycoprotein IIb/IIIa inhibitor (GPI). A post hoc analysis of the HORIZONS-AMI trial showed that the reduced bleeding observed with TRI is still apparent, despite contemporary anticoagulation with bivalirudin.⁴ In HORIZONS-AMI, the 30-day incidence of non-CABG-related major bleeding was 3.5% for patients who received TRI when compared with 7.6% for patients who received TFI (OR, 0.45; 95% CI, 0.21–0.95; $P=0.03$). The incidence of non-CABG-related major bleeding was lowest in the patients who received TRI with bivalirudin (2.9%) followed by patients who received TRI with heparin and a GPI (4.1%). The highest incidence of non-CABG-related major bleeding was observed in patients who received TFI with heparin and a GPI (9.7%).

In summary, TRI has consistently been shown to decrease access site bleeding complications in patients with STEMI, but a reduction in major bleeding varies by study and how major bleeding is defined (Table 1). A reduction in blood transfusion has been variable across studies but is decreased in the largest, contemporary, randomized trial comparing TRI to TFI in patients with STEMI. This reduction in bleeding is independent of the anticoagulation regimen.

Is This Reduction in Bleeding Responsible for the Mortality Benefit?

Regardless of the cause, bleeding, including access site bleeding, is a strong predictor of increased mortality.^{17,21,33,34} When Doyle et al³⁴ examined the effect that major femoral bleeding had on patients treated with PCI at the Mayo Clinic, they discovered that patients with a major femoral bleed had a markedly increased 30-day mortality rate. After adjustment for baseline patient and procedural characteristics, the excess 30-day mortality hazard ratio for patients who experienced a major femoral bleed was 9.96 (95% CI, 6.94–14.3; $P<0.001$).

If the above is true, then a study that randomizes patients with high yet similar bleeding risk to radial versus femoral PCI

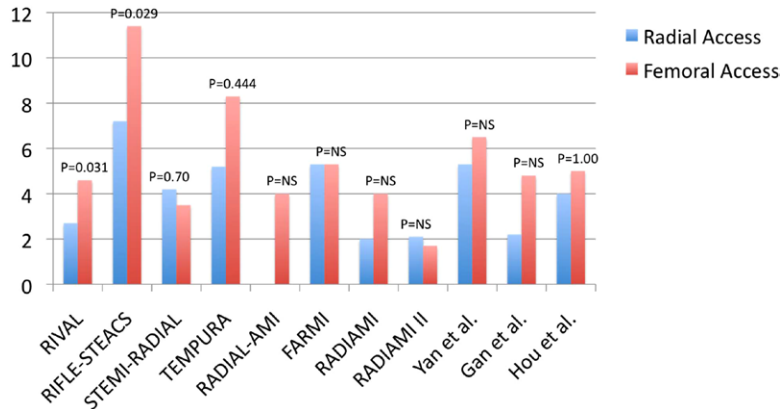


Figure 1. Percentage of major adverse cardiac events in radial vs femoral percutaneous coronary intervention for STEMI.^{5,6,8-16} FARMi indicates Five French Arterial Access With Reopro in Myocardial Infarction; NS, not significant; RADIAL-AMI, Radial Versus Femoral Access for Emergent Percutaneous Coronary Intervention With Adjunct Glycoprotein IIb/IIIa Inhibition in Acute Myocardial Infarction; RADIAMI, Radial Versus Femoral Approach for Percutaneous Coronary Interventions in Patients With Acute Myocardial Infarction; RADIAMI II, Radial Versus Femoral Approach With StarClose Clip Placement for Primary Percutaneous Coronary Intervention in Patients With ST-Segment–Elevation Myocardial Infarction; RIFLE-STEACS, Radial Versus Femoral Randomized Investigation in ST-Segment–Elevation Myocardial Infarction Treated by Radial or Femoral Approach in a Multicenter Randomized Clinical Trial; and TEMPURA, Test for Myocardial Infarction by Prospective Unicenter Randomization for Access Sites.

should demonstrate reduced mortality with TRI. Initially, several small randomized trials demonstrated a reduction in major bleeding in patients with STEMI who received radial versus transfemoral PCI, but these trials failed to show a statistically significant difference in mortality.⁷ The lack of expected mortality benefit with TRI was felt to be secondary to the small size of these trials, each of which consisted of 200 or fewer patients (Table 2).⁷ In 2011, the need for a large, randomized study was met by publication of the RIVAL trial, which randomized 7021 patients with ACS (1958 with STEMI) to transradial or transfemoral PCI. As discussed previously, patients with STEMI undergoing TRI experienced a marked reduction in mortality when compared with patients with STEMI undergoing TFI.⁵ Interestingly, this occurred without a difference in study defined non-CABG-related major bleeding.⁵ Given the plethora of data showing that TRI in patients with STEMI reduces bleeding, this

is most likely related to specific characteristics of the RIVAL study design rather than equivalent bleeding rates between the 2 PCI approaches. These characteristics include a conservative definition of bleeding, a low overall event rate (<1% bleeding as defined by the trial), and lack of power to detect a difference in a subgroup. Evidence of this is a post hoc analysis using ACUTY-defined major bleeding, which was lower in the patients who underwent TRI (1.9% versus 4.5%; $P < 0.0001$).⁵ In addition, the incidence of large access site hematoma was significantly lower in the patients undergoing TRI (1.2% versus 3.0%; $P \leq 0.0001$). Although the definition of major bleeding may vary between trials, there is likely a threshold above which bleeding may be causally linked to increased mortality. By setting a high threshold for what qualifies as major bleeding, the RIVAL trial may have masked the vital role that reduced bleeding plays in survival of patients undergoing radial PCI.

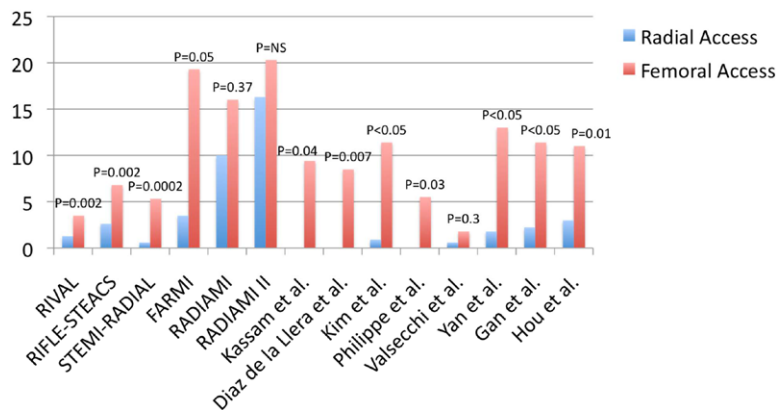


Figure 2. Percentage of access site bleeding in radial vs femoral percutaneous coronary intervention for STEMI.^{5,6,8,11-16,23-27} FARMi indicates Five French Arterial Access With Reopro in Myocardial Infarction; NS, not significant; RADIAMI, Radial Versus Femoral Approach for Percutaneous Coronary Interventions in Patients With Acute Myocardial Infarction; RADIAMI II, Radial Versus Femoral Approach With StarClose Clip Placement for Primary Percutaneous Coronary Intervention in Patients With ST-Segment–Elevation Myocardial Infarction; RIFLE-STEACS, Radial Versus Femoral Randomized Investigation in ST-Segment–Elevation Acute Coronary Syndrome; RIVAL, Radial Versus Femoral Access for Coronary Intervention; and STEMI-RADIAL, ST-Segment–Elevation Myocardial Infarction Treated by Radial or Femoral Approach in a Multicenter Randomized Clinical Trial.

Table 1. Percentage of Major Bleeding in Radial Versus Femoral Percutaneous Coronary Intervention for STEMI

Study	Radial (%)	Femoral (%)	P Value
RIVAL ^{5*}	8/955 (0.8)	9/1003 (0.9)	0.87
RIFLE-STEACS ⁶	39/500 (7.8)	61/501 (12.2)	0.399
HORIZONS-AMI ⁴	7/200 (3.5)	237/3134 (7.6)	0.03
STEMI-RADIAL ⁸	5/348 (1.4)	26/359 (7.2)	0.0001
TEMPURA ⁹	0/77 (0)	2/72 (2.8)	0.141
FARMI ¹¹	3/57 (5.3)	3/57 (5.3)	NS
RADIAL-AMI ¹⁰	0/25 (0)	0/25 (0)	NS
RADIAMI ¹²	3/50 (6)	7/50 (14)	0.18
RADIAMI II ¹³	4/49 (8.2)	6/59 (10.2)	NS
Kassam et al ²³	3/47 (6.4)	12/64 (18.8)	0.06
Diaz de la Llera et al ²⁴	0/103 (0)	2/59 (3.4)	0.131
Kim et al ²⁵	2/220 (0.9)	7/132 (5.3)	<0.05
Cruden et al ³¹	0/44 (0)	2/243 (0.8)	NS
Hetherington et al ³²	0/571 (0)	2/480 (0.4)	NS
Philippe et al ²⁶	0/64 (0)	9/55 (16.4)	0.03
Valsecchi et al ²⁷	0/163 (0)	7/563 (1.2)	0.04
Yan et al ¹⁴	0/57 (0)	1/46 (2.2)	NS
Gan et al ¹⁵	0/90 (0)	2/105 (1.9)	NS
Hou et al ¹⁶	0/100 (0)	3/100 (3.0)	NS
Total	74/3720 (2)	398/7107 (5.6)	

FARMI indicates Five French Arterial Access With Reopro in Myocardial Infarction; HORIZONS-AMI, Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction; NS, not significant; RADIAL-AMI, Radial Versus Femoral Access for Emergent Percutaneous Coronary Intervention With Adjunct Glycoprotein IIb/IIIa Inhibition in Acute Myocardial Infarction; RADIAMI, Radial Versus Femoral Approach for Percutaneous Coronary Interventions in Patients With Acute Myocardial Infarction; RADIAMI II, Radial Versus Femoral Approach With StarClose Clip Placement for Primary Percutaneous Coronary Intervention in Patients With ST-Segment–Elevation Myocardial Infarction; RIFLE-STEACS, Radial Versus Femoral Randomized Investigation in ST-Segment–Elevation Acute Coronary Syndrome; RIVAL, Radial Versus Femoral Access for Coronary Intervention; STEMI-RADIAL, ST-Segment–Elevation Myocardial Infarction Treated by Radial or Femoral Approach in a Multicenter Randomized Clinical Trial; and TEMPURA, Test for Myocardial Infarction by Prospective Unicenter Randomization for Access Sites.

*Includes patients with only STEMI.

In the RIFLE-STEACS study, postprocedure bleeding was not defined as major or minor but as present or not present based on the BARC definition.⁶ Using this definition, TRI was associated with significantly less postprocedural bleeding and reduced mortality, which is consistent with previously published studies associating BARC bleeding and mortality.^{35,36} In addition, the RIFLE investigators examined access site and non-access site bleeding; importantly, radial access significantly decreased access site bleeding (as would be expected) and had no effect on non-access site bleeding. This served as an internal control to support the effect of the randomized intervention (access site) on the outcome of bleeding.

In summary, there is a strong association between bleeding and mortality, and as outlined above, TRI markedly reduces periprocedural bleeding in patients with STEMI. Given this, the most plausible explanation for a potential improvement in mortality with TRI is a reduction in bleeding events.

Table 2. Percentage of Mortality in Radial Versus Femoral Percutaneous Coronary Intervention for STEMI

Study	Radial (%)	Femoral (%)	P Value
RIVAL ^{5*}	12/955 (1.3)	32/1003 (3.2)	0.006
RIFLE-STEACS ^{6†}	26/500 (5.2)	46/501 (9.2)	0.020
HORIZONS-AMI ⁴	7/200 (3.5)	126/3134 (4)	0.69
STEMI-RADIAL ⁸	8/348 (2.3)	11/359 (3.1)	0.64
TEMPURA ⁹	4/77 (5.2)	6/72 (8.3)	0.444
FARMI ¹¹	3/57 (5.3)	3/57 (5.3)	NS
RADIAL-AMI ¹⁰	0/25 (0)	1/25 (4)	NS
RADIAMI ¹²	0/50 (0)	1/50 (2)	NS
RADIAMI II ¹³	0/49 (0)	0/59 (0)	NS
Kassam et al ²³	1/47 (2.1)	3/64 (4.7)	0.6
Diaz de la Llera et al ²⁴	4/103 (3.9)	3/59 (5.1)	0.513
Kim et al ²⁵	8/220 (3.6)	9/132 (6.8)	NS
Cruden et al ³¹	1/44 (2.3)	6/243 (2.5)	NS
Hetherington et al ³²	7/571 (1.2)	13/480 (2.7)	0.111
Philippe et al ²⁶	0/64 (0)	0/55 (0)	NS
Valsecchi et al ²⁷	1/163 (0.6)	10/563 (1.8)	0.3
Yan et al ¹⁴	3/57 (5.3)	3/46 (6.5)	NS
Gan et al ¹⁵	2/90 (2.2)	3/105 (2.9)	NS
Hou et al ¹⁶	4/100 (4)	5/100 (5)	NS
Total	91/3720 (2.4)	281/7107 (4)	

FARMI indicates Five French Arterial Access With Reopro in Myocardial Infarction; HORIZONS-AMI, Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction; NS, not significant; RADIAL-AMI, Radial Versus Femoral Access for Emergent Percutaneous Coronary Intervention With Adjunct Glycoprotein IIb/IIIa Inhibition in Acute Myocardial Infarction; RADIAMI, Radial Versus Femoral Approach for Percutaneous Coronary Interventions in Patients With Acute Myocardial Infarction; RADIAMI II, Radial Versus Femoral Approach With StarClose Clip Placement for Primary Percutaneous Coronary Intervention in Patients With ST-Segment–Elevation Myocardial Infarction; RIFLE-STEACS, Radial Versus Femoral Randomized Investigation in ST-Segment–Elevation Acute Coronary Syndrome; RIVAL, Radial Versus Femoral Access for Coronary Intervention; STEMI-RADIAL, ST-Segment–Elevation Myocardial Infarction Treated by Radial or Femoral Approach in a Multicenter Randomized Clinical Trial; and TEMPURA, Test for Myocardial Infarction by Prospective Unicenter Randomization for Access Sites.

*Includes patients with only STEMI.

†Only cardiac death reported.

Is a Decrease in Bleeding or Blood Transfusion More Important?

Many bleeding events do not result in blood transfusion, and some blood transfusions are administered inappropriately. Thus, it is important to consider bleeding and blood transfusion as separate end points. Independent of bleeding, receipt of blood transfusion is a predictor of mortality.^{17,37,38} The increase in mortality with blood transfusion is thought to be secondary to several factors, including the impaired ability of transfused red blood cells to deliver oxygen and decreased red blood cells deformability, which leads to increased viscosity and a proclivity for small vessel thrombosis.^{39,40} In addition, because transfused red blood cells are deficient in nitric oxide (NO) and release excessive amounts of ADP, they increase platelet activation.⁴¹

Yatskar et al³³ noted that in patients undergoing PCI, access site hematoma resulting in blood transfusion was independently

associated with in-hospital mortality (OR, 3.59; 95% CI, 1.66–7.77) and 1-year death (hazard ratio, 1.65; 95% CI, 1.01–2.70; $P=0.048$). Similar findings were observed in the Mortality benefit Of Reduced Transfusion after PCI via the Arm or Leg (M.O.R.T.A.L.) study, which compared transfusion rates and mortality in patients undergoing TRI versus TFI.⁴² In this study, patients who received a blood transfusion had a significant increase in 30-day (OR, 4.01; 95% CI, 3.08–5.22) and 1-year (OR, 3.58; 95% CI, 2.94–4.36) mortality, with a 6.78% absolute increase risk of death at 1 year.⁴² Radial PCI was associated with a reduction in blood transfusions by 50% and a reduction in 30-day (OR, 0.71; 95% CI, 0.61–0.82; $P<0.001$) and 1-year (OR, 0.83; 95% CI, 0.71–0.98; $P<0.001$) mortality.⁴²

In the RIFLE-STEACS study, patients who underwent TRI for STEMI experienced a 3-fold decrease in the rate of blood transfusion when compared with patients who received TFI, and as previously discussed a 43% reduction in cardiac death.⁶ The RIVAL study reported no difference in transfusion rates between radial and femoral PCI, but the transfusion rates were not specifically reported for the patients with STEMI.⁵

Overall, there is clear evidence that bleeding is associated with mortality and the risk of mortality with blood transfusion is additive. These data support a hypothesis that the combined reduction in bleeding and blood transfusions may explain the mortality benefit seen with transradial primary PCI; however, the mortality benefit is more robust than would be expected with a reduction in these events. The remainder of this review will focus on other factors that may be contributing to this observed mortality benefit.

More Potent Antiplatelet Therapy With Less Bleeding

It is clear that the addition of an intravenous GPI to an oral P2Y₁₂ inhibitor provides more potent platelet inhibition. Although studies have shown reduced ischemic events with GPI therapy, the increased major bleeding that occurs with the use of these agents has in most part negated the benefit. TRI for primary PCI potentially allows the benefit of GPI therapy, while avoiding the consequence of increased bleeding.

This reduction in bleeding was demonstrated in a study by De Carlo et al²⁸ involving 531 consecutive patients undergoing urgent transradial PCI. All patients received unfractionated heparin (60–70 IU/kg bolus) or enoxaparin (1 mg/kg subcutaneously), 300 to 600 mg of plavix, and either abciximab or tirofiban. When compared with case-matched patients undergoing transfemoral PCI, patients undergoing TRI had reduced access site bleeding (29.2% versus 10.0%; $P<0.0001$), reduced transfusion rate (7.7% versus 0.8%; $P=0.01$), and reduced TIMI major/minor bleeding (13.1% versus 2.3%; $P=0.002$). Although there was a significant difference in the death rate between patients undergoing TRI versus TFI (4.7% versus 10.0%; $P=0.02$), this was not significantly different after propensity matching (7.7% versus 10.0%; $P>0.2$).

Siudak et al²⁹ reported similar outcomes when evaluating data on 1650 patients with STEMI in the EUROTRANSFER registry. In patients who received abciximab, there was a significant reduction in access site bleeding with TRI when compared with TFI (1.2% versus 9.4%; $P<0.001$). However, in contrast to the findings by De Carlo et al,²⁸ there was no

reported difference in TIMI major bleeding or blood transfusion rate.

Unfortunately, neither of the above studies compared TRI with a GPI versus TRI without a GPI. This was done in a post hoc analysis of the HORIZONS-AMI trial. In HORIZONS-AMI, the addition of GPI therapy did not reduce MACE or death/reinfarction in patients undergoing TRI, with the rates being equal among patients undergoing TRI regardless of the antiplatelet/anticoagulation strategy. Also, although TRI compared with TFI reduced major bleeding with GPI therapy (4.1% versus 9.7%), the incidence of major bleeding was even lower in patients undergoing TRI who received bivalirudin (2.9%).⁴ This is most likely secondary to an increase in non-access site bleeding caused by GPI therapy, events that would not be directly affected by access site selection.

Therefore, although it is likely that bleeding complications associated with GPI therapy can be attenuated by TRI, they are not eliminated. Whether this attenuation in bleeding is strong enough to unmask a mortality benefit from potent platelet inhibition with GPI therapy is uncertain.

Simplified Approach With Radial PCI

The relatively small caliber of the radial artery compared with the femoral artery limits the sheath size in TRI, with 6 French considered by most to be the maximum size that can be safely inserted. Although sheathless TRI with 7 French catheters has been reported, to date this has not been standard practice. This anatomic limitation on sheath size has potential to alter procedural techniques, leading to a minimalist approach. Patients with complex anatomy (left main trunk, bifurcation, severe calcification, etc) who might otherwise receive simultaneous stenting and atherectomy with TFI are deferred to simpler techniques with TRI. Simplified procedures are less prone to procedural complications and thus have the potential for improved mortality. A major limitation to the currently available data is that, although patient anatomy is sometimes reported (LMT and bifurcation lesions were equal between TRI and TFI in RIFLE-STEACS), techniques for intervention are often not. HORIZONS-AMI did report that patients who received TRI were more likely to undergo direct stenting, which has been associated with decreased periprocedural MI.^{4,43} Although a single study, it supports the idea that TRI involves alteration to procedural techniques that goes beyond access site. How this affects mortality is uncertain.

More Experienced Operators/Centers Performing Radial PCI

In RIVAL and RIFLE-STEACS, radial and femoral PCI was performed by experienced operators. The average annual volume for operators in the RIVAL trial was 300 PCI per year, with 40% being radial. Operators in the RIFLE-STEACS study performed ≥ 150 PCI per year with $\geq 50\%$ being radial.^{5,6} Subgroup analyses in the RIVAL study showed no difference in the primary outcome between radial versus femoral PCI when the results were stratified based on operator radial PCI volume. There was, however, a decrease in the primary outcome with radial PCI when the results were stratified by center radial PCI volume (hazard ratio, 0.49; 95% CI, 0.28–0.87; $P=0.015$).⁵ In addition, in the highest volume radial PCI

centers, there was a strong trend toward a reduction in mortality with radial versus femoral PCI. Thus, center radial PCI experience seems to be more important than operator radial PCI experience, which suggests that there is something unique about these high-volume radial centers that leads to improved outcomes. It is plausible that centers with the highest radial PCI volume have measures in place to improve overall PCI quality. Centers that have adopted radial PCI as a means to decrease vascular and bleeding complications may have also adopted advanced protocols to improve periprocedural care and reduce complications of PCI. This in turn could contribute to a reduction in mortality.

Conclusions

Transradial PCI has become increasingly popular because of improved patient comfort and a reduction in vascular complications and access site bleeding. In patients with STEMI, TRI may also be associated with a reduction in mortality. Several theories for this reduction in mortality have been proposed, and all may contribute, but it seems that the most likely explanation is a reduction in bleeding and blood transfusions. Although there is no reduction in what is generally considered more dangerous non-access site bleeding, numerous studies have demonstrated that mortality is strongly related to bleeding of any source.

Future Directions

Although 2 randomized trials have demonstrated that TRI for primary PCI in STEMI is associated with a reduction in mortality, further randomized trials are needed to confirm these findings. Specifically, these trials should focus on the benefit of transradial PCI in the setting of contemporary anticoagulation and antiplatelet regimens. In both RIVAL and RIFLE-STEACS, most patients received heparin±GPI; however, current practice in the United States is to use bivalirudin in the setting of STEMI. As mentioned above, post hoc analysis of HORIZONS-AMI showed that although major bleeding was reduced in patients with STEMI who received bivalirudin, major bleeding was lowest in patients who received bivalirudin plus TRI.⁴ This further reduction in major bleeding was not associated with lower MACE or mortality although this was a post hoc analysis and should be investigated in randomized fashion.

It is also worth investigating factors that contribute to a reduction in mortality with TRI in high-volume radial PCI centers when compared with low-volume centers. As discussed previously, the RIVAL study showed that the mortality benefit of TRI was based on center as opposed to operator experience. The reason for this is unclear but may be related to pre- and postprocedural care and reduced iatrogenesis.

Disclosures

Dr Rao receives modest consulting fees from The Medicines Company and Terumo Medical.

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KEY WORDS: catheter-based coronary interventions, stents ■ hemorrhage ■ mortality ■ myocardial infarction

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