Meta-Analysis of Transradial vs Transfemoral Access for Percutaneous Coronary Intervention in Patients With ST Elevation Myocardial Infarction

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Transradial access (TRA) has emerged as an alternative to transfemoral access (TFA) for percutaneous coronary intervention (PCI) in ST elevation myocardial infarction (STEMI) patients. However, the rate of TRA adoption has been much slower in the acute coronary syndrome (ACS) patient population. This meta-analysis was conducted to assess clinical outcomes of TRA compared with TFA in STEMI patients undergoing PCI. A manual search of PubMed, EMBASE, Cochrane library database, Cumulative Index to Nursing and Allied Health Literature (CINAHL), ClinicalTrials.gov, and recent major scientific conference sessions from inception to October 15th, 2019 was performed. Primary outcomes in our analysis were all-cause mortality and trial-defined major bleeding. Secondary outcomes included vascular complications, myocardial infarction, stroke, procedure, and fluoroscopy time. 17 randomized controlled trials (RCTs) (N = 12,018) met inclusion criteria. TRA was associated with lower all-cause mortality (risk ratio [RR]: 0.71, 95% confidence interval [CI]: 0.57 to 0.88), major bleeding (RR: 0.59, 95%CI: 0.45 to 0.77), and vascular complications (RR: 0.42, 95% CI: 0.32 to 0.56) compared with TFA. There was no difference in the incidence of myocardial infarction (MI), stroke, or procedure duration between the 2 groups. The difference in all-cause mortality between TRA and TFA was statistically nonsignificant when major bleeding was held constant. In conclusion, TRA was associated with lower risk of all-cause mortality, major bleeding, and vascular complications compared with TFA in STEMI patients undergoing PCI. © 2020 Elsevier Inc. All rights reserved. (Am J Cardiol 2021;141:23−30)

Percutaneous coronary intervention (PCI) remains the standard of care for treatment of ST-elevation myocardial infarction (STEMI).1 Procedural advances and tailoring of antithrombotic regimens have improved outcomes post PCI in STEMI patients at the expense of increased risk of periprocedural bleeding complications that vary from 0.9% to 9% in STEMI.2 Efforts to minimize these risks were developed including alternative strategies of arterial access such as the transradial access (TRA). However, the utilization of TRA has been limited by the perception of higher procedural failure and longer procedural duration that can be detrimental, especially in STEMI patients where immediate reperfusion is essential. Earlier randomized controlled trials (RCTs) that compared TRA with transfemoral access (TFA) were inadequately powered to detect meaningful reductions in hard outcomes such as mortality.3−16 Previously published meta-analysis have shown that TRA reduced the risk of all-cause mortality, major bleeding, and major adverse cardiovascular events (MACE).17,18 However, results from the recently conducted Safety and Efficacy of Femoral Access versus Radial Access in ST-Elevation Myocardial Infarction (SAFARI-STEMI) trial showed no difference in 30-day all-cause mortality and major bleeding between the two approaches.19 Given these conflicting findings, we performed an updated meta-analysis of RCTs to compare the efficacy and safety of TRA versus TFA in STEMI patients undergoing PCI.

Methods

The systematic review and meta-analysis was performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines.20 The initial search strategy was developed by 2 authors (AJ and RD). A systematic search, without language restriction was...
performed in PubMed, EMBASE, Cochrane Library database, Cumulative Index to Nursing and Allied Health Literature (CINAHL) and ClinicalTrials.gov from inception to October 15th, 2019 for studies comparing TRA versus TFA in STEMI. Conference proceedings of American College of Cardiology, American Heart Association, European Society of Cardiology, and Transcatheter Cardiovascular Therapeutics from 2016 to October 2019 were also searched. The reference lists of original studies, conference abstracts, and relevant review articles were further reviewed. We used varied combinations of the following keywords in our search strategy: Radial access, transradial access, femoral access, transfemoral access, ST elevation myocardial infarction, STEMI, acute myocardial infarction, acute coronary syndrome, percutaneous coronary intervention, coronary intervention, randomized controlled trial, randomized trial, and clinical trial. The search strategy was verified and independently validated by an experienced librarian. Additional details of the search terms and strategy are provided in Supplementary Table 1.

We included studies that met the following eligibility criteria: (1) Randomized controlled trials, (2) evaluating the efficacy and safety of TRA versus TFA, (3) PCI (primary or rescue) in STEMI.

Two investigators (AJ and RD) independently performed the literature search, screened studies for eligibility and extracted data using a standardized data collection form. Any differences in the included studies and collected data were resolved through consensus among the authors.

We extracted the following prespecified clinical outcomes from individual trials: (1) All-cause mortality (cardiovascular and noncardiovascular causes), (2) trial-defined major bleeding, (3) vascular complications, (4) myocardial infarction (MI), (5) stroke, (6) procedure duration, and (7) fluoroscopy time. Trial specific definitions were used for major bleeding, Supplementary Table 2. The primary study outcomes were all-cause mortality and major bleeding. Secondary outcomes included stroke, MI, vascular complications, procedure, and fluoroscopy time.

The meta-analysis was performed using R version 3.4.0 (The R Project for Statistical Computing, Vienna, Austria) with the metafor package and Review Manager (RevMan), Version 5.3. (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Due to heterogeneity in the methodologies of the included studies, the risk ratios [RRs] and 95% confidence intervals (CI) were calculated using random effects Mantel-Haenszel method for dichotomous variables. Heterogeneity was assessed using Higgins’ and Thompson’s I² statistic, with I² values of <25%, 25% to 75%, and >75% corresponding to low, moderate, and high levels of heterogeneity, respectively. Since the duration of follow-up was variable among the included studies, we performed a subgroup analysis for primary outcomes based on the duration of follow-up (in-hospital vs 30-day or longer). Meta regression using random effects was performed to measure the influence of baseline characteristics on all-cause mortality and major bleeding. Sensitivity analysis was performed using fixed effects model and study exclusion method. Publication bias was visually estimated by constructing funnel plots. A 2-tailed p <0.05 was considered statistically significant for all analyses. The risk of bias among the included RCTs was assessed using Cochrane risk of bias assessment tool, Supplementary Table 3.

Results

A total of 990 articles were identified through database search. After excluding duplicates and studies that did not meet inclusion criteria, a total of 17 RCTs comparing TRA and TFA in STEMI-PCI were selected for the quantitative analysis (Figure 1).

This meta-analysis included 17 RCTs with 12,018 patients, of which 5,958 underwent PCI using TRA and 6,060 using TFA in STEMI. Mean/median age of study population ranged from 52 to 71.4 years, and 76.6% were males, Table 1. The prevalence of diabetes mellitus (DM) and hypertension were 24.5% and 47.5% respectively with 17.4% patients having a previous history of MI. The proportion of rescue PCI ranged from 0% to 100%, Supplementary Table 4. The use of glycoprotein IIb/IIIa inhibitors was 50.4% in TRA and 50.3% in TFA. Cross over rate in TRA group was 5.7%, and 1.6% in the TFA group. Follow-up duration varied among included trials. Post-hospitalization follow-up was unavailable in 5 trials whereas 8 trials reported outcomes at 30 days.

All-cause mortality was reported in 16 trials. Radial access was associated with lower risk of all-cause mortality compared with femoral access (RR: 0.71, 95%CI: 0.57 to 0.88), Figure 2A. Test of heterogeneity was low (I² = 0%). Data on major bleeding were available in 16 trials. Trial-defined major bleeding was significantly lower with TRA compared with TFA (RR: 0.59, 95%CI: 0.45 to 0.77), Figure 2B. Test of heterogeneity was low (I² = 0%).

Data on vascular complications were reported in 13 trials. Vascular complications were significantly lower with TRA compared with TFA (RR: 0.42, 95%CI: 0.32 to 0.56),
Table 1: Baseline characteristics of study population in the included RCTs

<table>
<thead>
<tr>
<th>Study</th>
<th>Study period</th>
<th>Single/ Multi</th>
<th>Patient population</th>
<th>Mean age (years)</th>
<th>DM (%)</th>
<th>Hypertension (%)</th>
<th>Smoking (%)</th>
<th>Prior (%)</th>
<th>Follow up (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>STEMI-RADIAL, 2012</td>
<td>10/2009-02/2012</td>
<td>Multi</td>
<td>348</td>
<td>63.7</td>
<td>77</td>
<td>21</td>
<td>61</td>
<td>40</td>
<td>30</td>
</tr>
<tr>
<td>Wang, 2012</td>
<td>07/2008-12/2010</td>
<td>Single</td>
<td>60</td>
<td>62.1</td>
<td>85</td>
<td>30</td>
<td>71</td>
<td>14</td>
<td>30</td>
</tr>
<tr>
<td>Gan, 2009</td>
<td>06/2004-07/2017</td>
<td>Multi</td>
<td>90</td>
<td>63.6</td>
<td>81</td>
<td>18</td>
<td>39</td>
<td>18</td>
<td>30</td>
</tr>
<tr>
<td>Li, 2007</td>
<td>06/2004-07/2006</td>
<td>Single</td>
<td>25</td>
<td>60</td>
<td>84</td>
<td>18</td>
<td>39</td>
<td>18</td>
<td>30</td>
</tr>
</tbody>
</table>

DM = diabetes mellitus; IQR = interquartile range; MI = myocardial infarction; RCT = randomized controlled trial; TFA = transfemoral access; TRA = transradial access.

Discussion

In this meta-analysis of 17 RCTs evaluating 12,018 patients randomized to TRA versus TFA for PCI in STEMI, TRA was associated with a 29% lower risk of all-cause mortality, 58% lower risk of vascular complications and 41% lower risk of trial-defined major bleeding. There was no difference in stroke, MI, or procedure duration between the 2 access sites. Meta-regression demonstrated that the difference in all-cause mortality between TRA and TFA became statistically nonsignificant when major bleeding was held constant which is a novel finding not previously reported in previous studies.

Since its first use in 1989, TRA has garnered widespread use in clinical practice due to lower risk of vascular and
bleeding complications compared with the traditional TFA to become the most used access site in PCI. However, the rate of TRA adoption has been much slower in the ACS patient population. Some concerns such as procedural failure and longer reperfusion time associated with TRA are based on confounded data from earlier observational studies derived from less experienced operators and have contributed to physician apprehension in selection of this technique. An analysis of the National Cardiovascular Disease Registry (NCDR) demonstrated that TRA was associated with a modest increase in door-to-balloon time compared with TFA, however this was off-set by the lower risk-adjusted mortality rate driven by lower rates of major bleeding with TRA. Another analysis of the NCDR among 692,433 patients undergoing PCI for STEMI found that a greater use of TRA across operators was associated with reduced bleeding and an increasing use of TRA across institutions was associated with a decrease in in-hospital mortality. In our analysis, mortality benefit observed among patients randomized to TRA was mainly driven by lower risk of bleeding and vascular complications. Such benefit has been consistently demonstrated in previous meta-analyses as well. However, when compared with the other previous meta-analyses, we found that the weighted bleeding rate of 2.2% with TRA was lower than 3.8% observed with TFA. For every 1000 patients receiving TRA PCI for STEMI, the bleeding events were fewer by at least 16. Moreover, the difference in all-cause mortality between TRA and TFA was no longer statistically significant when major bleeding was held constant. STEMI patients represent the highest risk population in the spectrum of ACS that are subjected to aggressive pharmacological treatments with ischemic benefits, albeit with higher vascular and bleeding complications. This also means that they are likely to derive the largest benefit from reduction of such bleeding and vascular complications. As it is well reported, bleeding from both access and nonaccess sites has been directly correlated with short-term and long-term mortality, with nearly 12% of in-hospital deaths reported in NCDR CathPCI registry attributed to periprocedural bleeding complications. As such TRA can effectively minimize access site bleeding complications without any direct effect on nonaccess site bleeding. Even a modest reduction of such bleeding can accommodate additional doses of antithrombics providing an overall net benefit of ischemic outcomes. It is also worth noting that similar magnitude of benefit in terms of bleeding complications has been observed with TRA even in high risk STEMI population (cardiogenic shock, hemodynamic instability, or failed antithrombotic therapy) enrolled in the RIFLE-STEACS.

Figure 2. Forest plot showing primary outcomes between TRA and TFA. (A) All-cause mortality, (B) Trial-defined major bleeding. M-H = Mantel-Haenszel.
(Radial Versus Femoral Randomized Investigation in ST-Elevation Acute Coronary Syndrome) trial. Similar results were later reproduced in real world patient registries as well. Paradoxically, TRA is less frequently utilized in such high-risk groups.

One of the many reasons for limited utilization of TRA among the U.S. operators included longer fluoroscopy and procedure times that were attributed to the steep learning curve including challenges in obtaining radial access. Our results demonstrate a modest increase in fluoroscopy time with TFA but no difference in total procedure time. TRA has also been shown to shorten the time to ambulation, improve patient satisfaction, comfort and substantially lower healthcare costs. Nevertheless, TRA is highly operator dependent, with a strong direct correlation between operator volume and procedural outcomes. To minimize the learning curve and enhance performance metrics, certain volume requirements have been previously laid down by SCAI (Society for Cardiovascular Angiography and Interventions) transradial working group. Other measures include gradual operator escalation through complex cases with ultimate plan for use in STEMI setting and increased use of hydrophilic transradial sheaths to help facilitate the rapid dispersion of radial-first strategy. Once TRA technique is mastered, and patients with high-bleeding risk are selected, the benefits will likely be greatest.

Some potential limitations of our meta-analysis are worth mentioning while interpreting the results. First, the use of intention to treat protocol in the included RCTs likely affected the interpretation of bleeding events due to high crossover rates, often favoring TFA. Second, TRA is highly operator dependent; hence results might have been influenced by underlying confounders that cannot be accounted. Third, the proportion of patients undergoing rescue PCI varied widely across the trials and may have potentially confounded the bleeding rates. Fourth, the definition of major bleeding varied widely among the included RCTs. Fifth, only 4 out of the 17 trials provided follow-up data beyond 30 days, thus the findings of our analysis may not be applicable over a longer follow-up period. Sixth, all the included RCTs except, RIFLE-STEACS excluded patients with cardiogenic shock, hence these results cannot be extrapolated to this high-risk population. Seventh major proportion of study population were male and less than 70 years of age. Finally, an inherent limitation of any meta-analysis is publication bias.

In conclusion, in STEMI patients undergoing PCI, TRA was associated with lower risk of all-cause mortality driven by lower bleeding complications compared with TFA. The difference in all-cause mortality between TRA and TFA was no longer statistically significant when major bleeding was held constant.

Disclosures
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Contributorship Statement

Aravdeep Jhand, Varunsiri Atti and Poonam Velagapudi were involved in planning, conduct, and reporting the described work.

Rest of the authors were involved in reviewing the manuscript and providing critical feedback.

Ethics Committee Approval

The study is exempted from IRB approval as it involves study level data from previous publications.

Reporting Patient and Public Involvement in Research

No patients were involved for this research.

Declaration of Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.11.016.


