# Meta-analysis of randomized trials on access site selection for percutaneous coronary intervention in ST-segment elevation myocardial infarction

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## Abstract

**Introduction:** Superior outcomes with transradial (TRPCI) versus transfemoral coronary intervention (TFPCI) in the setting of acute ST-segment elevation myocardial infarction (STEMI) have been suggested by earlier studies. However, this effect was not evident in randomized controlled trials (RCTs), suggesting a possible allocation bias in observational studies. Since important studies with heterogeneous results regarding mortality have been published recently, we aimed to perform an updated review and meta-analysis on the safety and efficacy of TRPCI compared to TFPCI in the setting of STEMI.
**Material and methods:** Electronic databases were searched for relevant studies from January 1993 to November 2012. Outcome parameters of RCTs were pooled with the DerSimonian-Laird random-effects model.
**Results:** Twelve RCTs involving 5,124 patients were identified. According to the pooled analysis, TRPCI was associated with a significant reduction in major bleeding (odds ratio (OR): 0.52 (95% confidence interval (CI) 0.38–0.71, $p < 0.0001$)). The risk of mortality and major adverse events was significantly lower after TRPCI (OR = 0.58 (95% CI: 0.43–0.79), $p = 0.0005$ and OR = 0.67 (95% CI: 0.52–0.86), $p = 0.002$ respectively).
**Conclusions:** Robust data from randomized clinical studies indicate that TRPCI reduces both ischemic and bleeding complications in STEMI. These findings support the preferential use of radial access for primary PCI.

**Key words:** ST-segment elevation myocardial infarction, transradial, transfemoral, death.

## Introduction

Serious bleeding events are considered major contributors to higher morbidity and mortality in patients undergoing percutaneous coronary intervention (PCI) [1]. Therefore, in the current era of potent antithrombotic regimens, preventing bleeding after PCI remains a major goal. The transradial approach (TRPCI) to coronary interventions has the potential advantage of reducing access site bleeding complications compared to

transfemoral intervention (TFPCI) [2]. However, the exact role of the transradial approach is still debated by the interventional cardiology community [3, 4]. Radialists emphasize the importance of reducing access site bleeding complications together with early ambulation and discharge, which result in better patient comfort [5]. Opponents argue for longer procedural times, higher risk of crossover to femoral puncture, and higher radiation exposure due to the capricious radial anatomy that might compromise timely reperfusion [6].

Numerous studies and meta-analyses have been carried out to compare the safety of the two approaches. As a conclusion, the radial approach was found to reduce major bleeding complications [2, 5]. Furthermore, a prior meta-analysis including the high-risk subset of patients with ST-segment elevation myocardial infarction (STEMI) demonstrated a reduction in ischemic events in the case of TRPCI and a significant mortality benefit [7]. These effects were, however, not consistent in the observational studies and randomized controlled trials (RCTs), i.e. the reduction of neither bleeding nor ischemic events reached the level of significance in RCTs, which may be explained by a possible allocation bias in observational studies (OSs). Lately, meta-analyses including trials with random allocation and focusing on the STEMI subset have reported significant reduction in patient-oriented end-points as well as mortality [8–11]. Recently, large-scale, well-designed studies have been published but their results were not unambiguously positive regarding mortality.

Our objective was to perform an updated review and meta-analysis on the safety and efficacy of TRPCI vs. TFPCI in the setting of STEMI.

## Material and methods

### Search strategy

The analyses were performed according to the PRISMA guideline [12]. Electronic databases were searched for relevant studies between January 1993 and February 2013. Relevant publications were identified from MEDLINE®, SCOPUS®, the Web of Science® with Conference Proceedings, and the Cochrane Central Register of Controlled trials (CENTRAL) using a search strategy that combined text word and MeSH headings. Search keywords included various combinations of the following terms: "transradial", "transfemoral", "radial access", "STEMI", "myocardial", "infarct*". Furthermore, we augmented the search with the reference lists of the relevant studies and reviews, editorials, letters, and also relevant abstracts and presentations from the annual meetings of the American Heart Association, the American College of Cardiology, the European Society of Cardiology and Transcatheter Cardiovascular Therapeutics. No language restriction was used.

### Selection criteria

We selected all randomized trials that evaluated the clinical impact of TRPCI vs. TFPCI in STEMI. The following clinical outcomes with the longest follow-up available were selected: (a) overall mortality (b) major adverse cardiovascular and cerebrovascular events (MACE), including death, recurrent myocardial infarction, emergency percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG), and stroke according to the definitions used in the trials; (c) and major bleeding. A standardized major bleeding definition adapted from the meta-analysis of Jolly *et al.* was used [5]. Briefly, major bleeding was defined as one of the following: fatal bleeding, intracranial hemorrhage, or bleeding associated with a $\geq$ 3 g/dl hemoglobin drop or requiring transfusion or requiring surgery (pseudoaneurysms requiring thrombin injection or ultrasound compression were excluded). For trials where the composite definition was not available, either transfusion rates or proportion of bleeding events associated with a $\geq$ 3 g/dl hemoglobin drop were substituted for major bleeding).

Secondary procedural outcomes were: procedural time (in minutes), door-to-reperfusion time (in minutes), fluoroscopy time (in minutes), volume of contrast agent (ml), length of hospital stay (in days), and access site crossover.

Selection and data abstraction were done independently by two reviewers on pre-specified structure collection forms. Disagreements were resolved by consensus and discussion with a third party.

### Statistical analysis

Statistical analysis was performed using the Open Meta-Analyst software, version 4.16.12, Tufts University, http://tuftscaes.org/open_meta/. Odds ratio (OR) was calculated from the event frequencies and pooled with the DerSimonian-Laird random-effects model. Continuous variables were compared with the inverse-variance method. The choice of random-effects model was made based on the consideration that the true effect of access site choice may vary from study to study influenced by heterogeneity of the included trials. The random-effects model accounts better for inter-study differences. Furthermore, it results in wider confidence intervals and thus provides more conservative and robust results. Heterogeneity was assessed with a $\chi^2$ heterogeneity statistic and an $I^2$ statistic [13]. Sensitivity and subgroup analyses were performed using the following categories:

single center or multicenter trials, trials with patient number over or less than 200, *in extenso* published trials, primary PCI and rescue PCI (studies with > 50% of the patients undergoing PCI were included in this group), cohorts whose use of GP IIb/IIIa inhibitor was below and over 40%. To study the relevance of publication bias, funnel plots were constructed plotting the trial results against their precision. Egger's regression intercept was used to assess the asymmetry of the funnel plots.

## Results

### Search results and study selection

Our search resulted in 904 citations. After the evaluation of abstracts, 33 potentially appropriate studies were found. Finally, 12 studies were selected for data extraction and analysis (Figure 1). These articles included 10 RCTs involving published *in extenso* articles [14–23]. One study [24] was published only as abstract, but this was included in the analysis because of the importance of the so-called "gray" literature and because the data required for our analysis were available either from the abstract or from additional online sources (www.cardiosource.org). The included trials involved 5,124 patients. Detailed characteristics are summarized in Tables I–II.

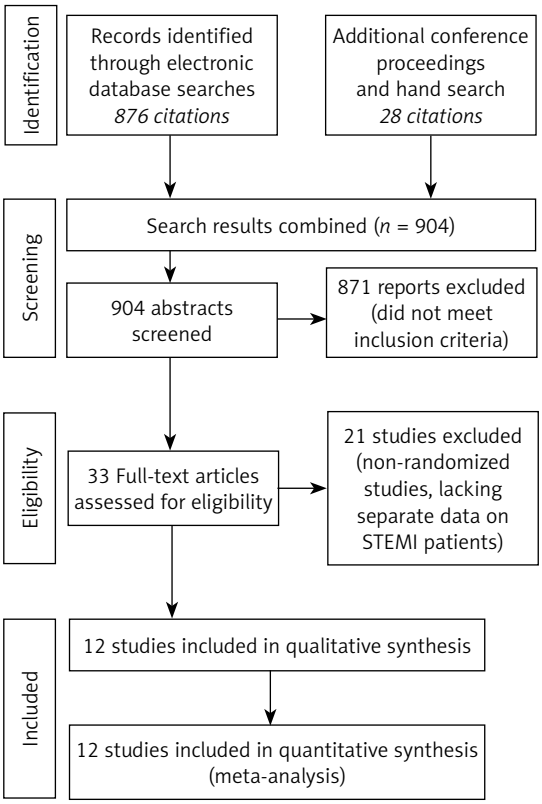


**Figure 1.** Flowchart of trials

### Clinical results

Based on the pooled results of the random-effects model meta-analysis, TRPCI was associated with a 48% odds reduction in major bleeding events compared to TFPCI (OR = 0.52 (95% CI: 0.38–071), $p < 0.0001$) (Figure 2). A 42% odds reduction for mortality and 33% odds reduction for MACE were also observed favoring the transradial approach (OR = 0.58 (95% CI: 0.43–0.79), $p = 0.0005$, and 0.67 (95% CI: 0.52–0.86), $p = 0.002$, respectively). These effects were homogeneous among the included trials (Figures 3 and 4).

Transradial intervention was associated with shorter hospital stay (mean: 6.84 days vs. 8.58 days; mean difference (MD): –1.74 days (95% CI: –2.91, –0.56), $p = 0.004$) but with higher frequency of access site crossover (OR = 3.68 (95% CI: 2.54, 5.32), $p < 0.00001$) and longer time to reperfusion (MD 3.28 min (95% CI: 1.02, 5.54), $p = 0.005$). There were no significant differences in procedural (mean: 47.9 min vs. 46.6 min), fluoroscopy times (mean: 11.0 min vs. 10.3 min) and in the used contrast volume (mean: 169 ml vs. 166 ml). Occurrence of any vascular complication was lower after transradial intervention (OR = 0.50 (95% CI: 0.36, 0.71), $p < 0.0001$). The access site bleeding complications were lower in case of the transradial approach (OR = 0.39 (95% CI: 0.22, 0.69), $p = 0.001$). Stratification and sensitivity analyses showed results similar to those of the comprehensive analysis. Findings were also comparable after pre-specified stratification in studies involving high-risk patients (i.e. studies that included patients with preceding thrombolysis, and with > 45% use of GP IIb/IIIa inhibitors) study size, single or multicenter design or means of publication (Table III). Analyses for publication bias did not show skewed distribution (Figure 5).

## Discussion

The current analysis with the latest available evidence confirms the preferential use of the transradial approach in patients with acute myocardial infarction. The TRPCI reduced the risk of mortality, major adverse cardiac events and bleeding complications compared to the historical standard femoral approach.

Intriguingly, the application of the transradial approach for coronary intervention shows considerable geographical differences, and its adoption is limited by concerns about longer procedural times, higher radiation exposure and more frequent access site crossover [25]. Although numerous data support that these disadvantages are mostly related to the learning curve period and can be easily tackled thereafter, these aspects have questioned the possible benefits of TRPCI in clinical settings where timely reperfusion is crucial [26].

**Table I.** Study characteristics of the included trials

| Study name/ first author (publication year) | Period of study | Design | Number of patients | Screen failure* | Follow-up [month] | Time frame† [h] | MACE | Exclusion criteria | TRA expert |
|---|---|---|---|---|---|---|---|---|---|
| TEMPURA (2003) | 1999.07–2001.02 | Randomized single center | 149 | 64 (30%) | 9 | < 12 | Death, repeat MI, repeat TVR | CSh, aAllen, Graft occlusion | NA |
| RADIAL-AMI (2005) | NA | Randomized multi-center | 50 | NA | 1 | < 12 | Death, repeat MI, repeat TVR | CSh, aAllen, contraindications to GP IIb/IIIa inhibitor use | Yes |
| Vazquez-Rodrigez (2007) | NA | Randomized single center | 439 | NA | 1 | < 12 | Death, severe ischemic complications | NA | NA |
| RADIAMI (2007) | 2005.04–2006.06 | Randomized single center | 100 | 81 (45%) | In hospital | < 12 | Death, repeat MI, repeat TVR, necessity for CABG | Age > 75 years, Killip III–IV, IABP, PM, height < 150 cm, post-CABG | Yes |
| Yan (2008) | 2005.06–2007.06 | Randomized single center | 103 | NA | 1 | < 12 | Death, repeat MI, repeat TVR | Age < 75 years, CSh, non-palpable RA, aAllen, CRF | Yes |
| FARMI (2007) | 2004.01–2005.09 | Randomized single center | 114 | 54 (32.2%) | In hospital | < 12 | Death, ischemic complications | CSh or Killip III–IV, aAllen, contraindications to GP IIb/IIIa inhibitor use, post-CABG | Yes |
| Gan (2009) | NA | Randomized multi-center | 195 | NA | 6 | NA | Death, repeat MI, repeat TVR, necessity for CABG | aAllen | NA |
| Hou (2010) | 2005.08–2008.09 | Randomized single center | 200 | NA | 1 | NA | Death, repeat MI, repeat TVR | CSh, non-palpable RA, aAllen, post-CABG | Yes |
| RIVAL (2011) | 2006.06–2010.11 | Randomized multi-center | 1958 | NA | 1 | NA | Death, MI, and stroke | CSh, aAllen, severe peripheral vascular disease, bilateral mammary CABG | Yes |
| RADIAMI II (2011) | 2006.11–2008.03 | Randomized single center | 108 | 48 (30.8%) | In hospital | < 12 | Death from any cause, repeated MI, need for CABG and need for repeated PCI of IRA | Killip III–IV, IABP, PM, height < 150 cm, post-CABG | Yes |
| RIFLE STEACS (2012) | 2009.01–2011.07 | Randomized multi-center | 1001 | 330 (24.8%) | 1 | NA | Cardiac death, nonfatal MI, TLR, stroke | INR > 2.0 | Yes |
| STEMI-RADIAL (2012) | 2009.10–2012.01 | Randomized multi-center | 707 | 0 | I | < 12 | Death, MI, and stroke | Killip IV, oral anticoagulant, non-palpable artery, aortobifemoral bypass | Yes |

**Number of patients excluded according to exclusion criteria, †intervention from pain onset in hours. PCI – percutaneous coronary intervention, TRI – transradial intervention, TFI – transfemoral intervention, CABG – coronary artery bypass graft surgery, IABP – need for intra-aortic balloon pump, PM – need for pacemaker, CRF – chronic renal failure, MI – myocardial infarction, IRA – infarction-related artery, TLR – target lesion revascularization, TVR – target vessel revascularization, MACE – major adverse cardiovascular events, MVD – multi-vessel disease, CSh – cardiogenic shock, aAllen – abnormal Allen test, RA – radial artery, LM – left main coronary, INR – international normalized ratio, NA – not available, TRA – transradial approach*

**Table II.** Patient and procedural characteristics of the included trials

| Study name/ first author (publication year) | Mean age [year] | Female (%) | Rescue/ primary PCI (%) | GPI use TRI/TFI (%) | Bivalirudin use TRI/TFI (%) | Crossover TRI/TFI (%) | Failed PCI TRI/TFI (%) | Closure device TFI (%) | Culprit artery LAD/Cx/RCA (%) TRI/TFI | | Contrast volume [ml] TRI/TFI | Door to balloon time [min] TRI/TFI | Procedural time [min] TRI/TFI | Fluoroscopic time [min] TRI/TFI | Vascular complications TRI/TFI (%) | Hospital stay [day] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| TEMPURA (2003) | 67 | 18.8 | 0/100 | 0/0 | NA | 0/1.5 | 3.9/2.9 | 0 | 48.1<br>11.7<br>37.7 | 51.4<br>8.3<br>37.5 | 180/186 | NA | 44'/51' | 15.1'/16.1' | 0/2.7 | 5.7/7.4 |
| RADIAL-AMI (2005) | 55 | 12 | 66/34 | 96/92 | NA | 4/0 | 8/4 | 8 | 48<br>8<br>44 | 52<br>4<br>44 | 210/180 | 32'/26' | 49'/47' | 11.3'/7.2' | 9 RA occlusion, pseudoaneurysm 4/4, hematoma 9/20 | NA |
| Vazquez-Rodrigez (2007) | 61 | 15 | NA | NA | NA | NA | 8.5/6.8 | 95.54 | NA | NA | 21'/18' | NA | NA | 0.5/2.3 | 8/9 | |
| RADIAMI (2007) | 59.5 | 32 | 0/100 | 44/42 | NA | 8/2 | 2/4 | NA | 42.9<br>18.4<br>38.8 | 45.8<br>6.2<br>47.9 | 198.7/ 197.7 | 76.9'/64.6' | 98.7'/88.7' | 10.9'/11.2' | 2 RA occlusion, hematoma 10/16 | 6.26/6.75 |
| Yan (2008) | 70.8 | 25.2 | 0/100 | 100/100 | NA | 1.7/0 | 3.5/4.3 | 0 | 38.6<br>49.1<br>12.3 | 41.3<br>50<br>8.7 | NA | 16.2'/15.4' | 44.2'/41.1' | NA | 0.17 RA occlusion, TFI: 8.7 hematoma, 2.2 pseudoaneurysm | 7.2/10.1 |
| FARMI (2007) | 59 | 17.6 | 42.1/50.8<br>5.3/8.8* | NA | NA | 12.3/1.8 | NA | 0 | 50.9<br>14<br>35.1 | 45.6<br>14<br>40.4 | 78/73 | NA | NA | 13'/8' | Hematoma 3.5/19.3 | 7.2/7.5 |
| Gan (2009) | 52.9 | 19.5 | 0/100 | 31.1/34.3 | NA | 1.1/0 | 2.2/11.4 | NA | 52.2<br>16.7<br>31.1 | 54.3<br>18.1<br>27.6 | NA | NA | 29'/27' | NA | NA | 10.6/13.8 |
| Hou (2010) | 65.55 | 29.5 | NA | 28/20 | NA | 4/0 | 4/5 | NA | 48<br>8<br>44 | 50<br>13<br>37 | NA | 16.4'/16.2' | 37.2'/35.7' | 11.8'/11.4' | 1 RA occlusion, hematoma 2/6, pseudoaneurysm 0/2 | 8.6/12.7 |

**Table II.** Continued

| Study name/ first author (publication year) | Mean age [year] | Female (%) | Rescue/ primary PCI (%) | GPI use TRI/TFI (%) | Bivalirudin use TRI/TFI (%) | Crossover TRI/TFI (%) | Failed PCI TRI/TFI (%) | Closure device TFI (%) | Culprit artery LAD/Cx/RCA (%) TRI/TFI | Contrast volume [ml] TRI/TFI | Door to balloon time [min] TRI/TFI | Procedural time [min] TRI/TFI | Fluoroscopic time [min] TRI/TFI | Vascular complications TRI/TFI (%) | Hospital stay [day] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| RIVAL (2011) | 59.49 | 20.9 | 11.9/74.1<br>3.2/3.1 | 34.5/31.1 | 2.2/3.1 | 5.3/1.6 | 4.3/4.2 | NA | NA | 180/180 | NA | 128'/120' | 9.3'/8' | 1.3/3.5 | NA |
| RADIAMI II (2011) | 59.6 | 36.11 | 0/100 | 51/54 | NA | 4.1/1.7 | 0 | 93.2 | 43<br>8<br>49 | 29<br>17<br>53 | 165/162 | 67.4'/57.5'<br>89.6'/76.8' | 7.5'/6.9' | Hematoma 16.3/20.3, pseudoaneurysm 0/3.3 | 4.2/4.4 |
| RIFLE STEACS (2012) | 65 | 26.7 | 7.6/92.4 | 67.4/69.9 | 8/7.2 | 47/14 | 1.4/4.7 | NA | 47<br>17.6<br>33 | 46.7<br>15<br>35.3 | NA | 60'/53' | NA | NA | 5/6 |
| STEMI-RADIAL (2012) | 62 | 23 | 0/100 | 45/45 | NA | 3.7/0.6 | 9/9 | NA | 40<br>47<br>14 | 42<br>47<br>13 | 170/182 | NA | 49'/49' | 7.9'/8' | 0.3/0.8 | NA |

*PCI – percutaneous coronary intervention, GPI – platelet glycoprotein IIb/IIIa inhibitor, TRI – transradial intervention, TFI – transfemoral intervention, RA – radial artery, NA – not available, LAD – left anterior descending coronary artery, Cx – ramus circumflexus, RCA – right coronary artery*

Two prior meta-analyses that pooled data from randomized trials and compared transradial and transfemoral PCI regardless of the clinical setting found that TRPCI was a safer alternative that reduced access site bleeding complications. However, no difference was found either in terms of major ischemic outcomes or in mortality [2, 5]. These works shared a common limitation as they included trials with low risk populations that may explain these latter findings. In addition to this, in the analysis of Agostoni *et al.*, the low number of events and the use of 'access site complication' as an end-point (that incorporated a wide range of events with different clinical relevance) made the results difficult to interpret clinically [2]. In their meta-analysis Jolly *et al.* classified bleeding events as relevant endpoints and reported a significant reduction in bleeding; however, it failed to confirm a significant benefit regarding ischemic events [5]. Lately, in an analysis of 76 studies (15 randomized, 61 observational) involving a total of 761,919 patients Bertrand *et al.* found no significant benefit of mortality or of the composite of death and MI in randomized trials [27].

The above results conflicted with the findings of a pooled analysis including 32,822 patients from three prospective registries in British Columbia, where TRPCI was found to reduce transfusion rates by 50%, which translated into reduced short- and long-term mortality [28]. Of note, the link between transfusion and mortality suggested by this registry data was not further supported by the RIVAL trial. In this, so far the largest acute coronary syndrome trial, significant benefit of the transradial approach was demonstrated among STEMI patients but not among non-STE ACS cases, while the rates of transfusion showed no differences (1.16% vs. 1.51% and 3.46 vs. 3.31, $p = 0.493$ and 0.765, respectively) [29].

The clinical setting with the inherently different bleeding and ischemic risks of patients may have a substantial influence on the benefits of the transradial approach. The feasibility and possible benefits of TRPCI in acute coronary syndromes were very early reported by Japanese authors [14]. Similarly to the positive registry data, our earlier meta-analysis confirmed that besides reducing bleeding, TRPCI was also associated with a lower risk for thrombotic events and mortality in patients with STEMI [7]. The limitation of this latter analysis was that the observed benefit was not significant in the sensitivity analysis that included only randomized, controlled trials. Although the estimates suggested lack of statistical power as an explanation, a selection bias in observational studies influencing access site preference in different patients could not be excluded.

Influence of the clinical setting is further supported by the analysis the "Trans-radial Versus Trans-femoral Percutaneous Coronary Intervention (PCI) Access Site Approach in Patients With Un

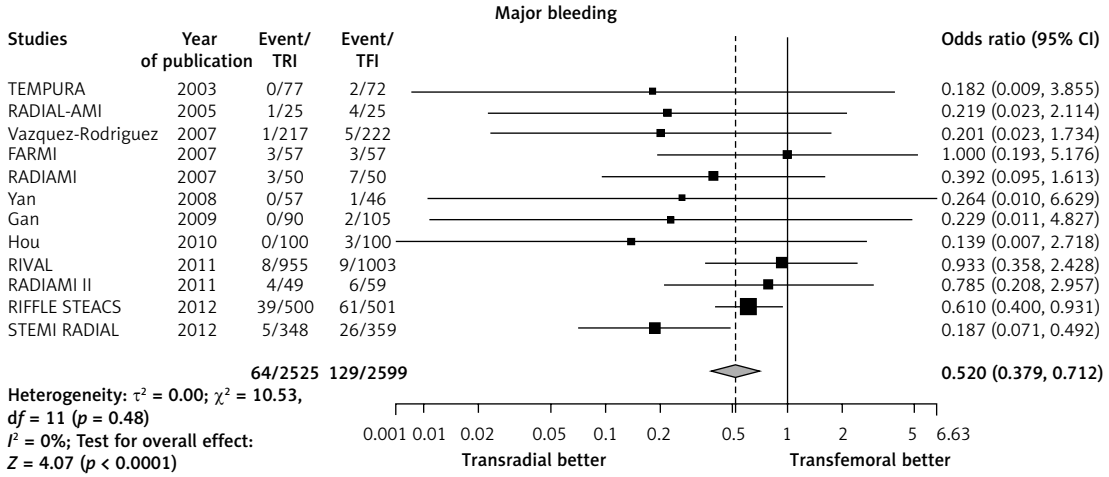


**Figure 2.** Risk of major bleeding

*CI – confidence interval, TRI – transradial intervention, TFI – transfemoral intervention*

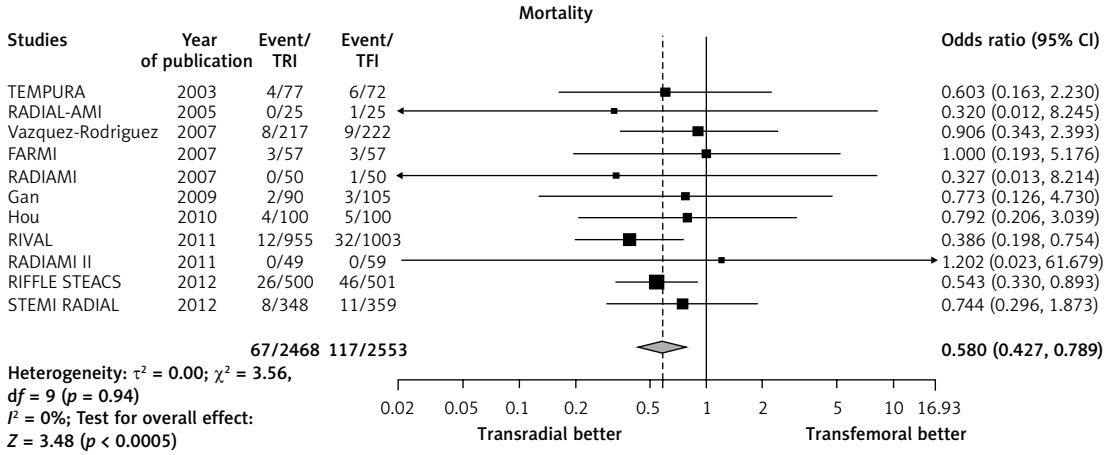


**Figure 3.** Risk of death

*CI – confidence interval, TRI – transradial intervention, TFI – transfemoral intervention*

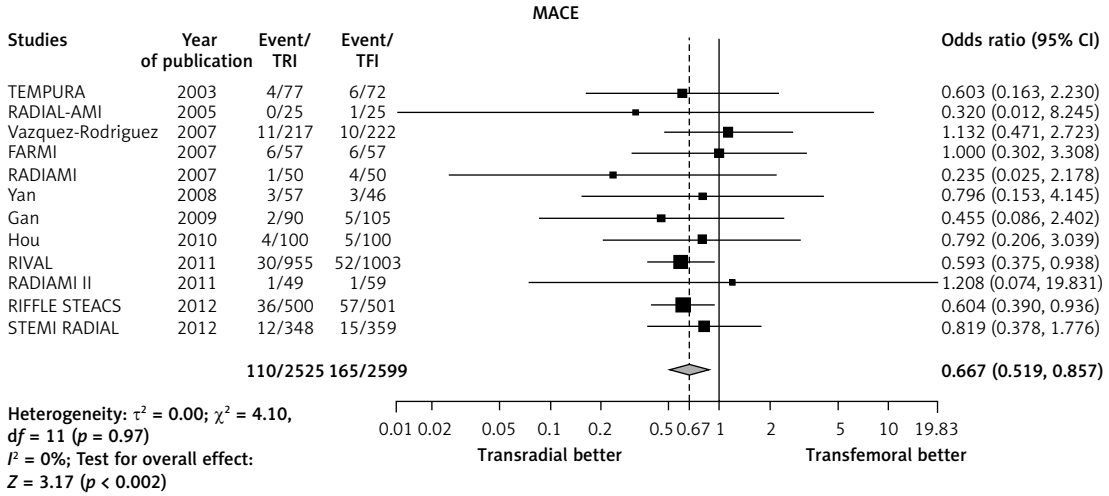


**Figure 4.** Risk of major adverse events (MACE)

*CI – confidence interval, TRI – transradial intervention, TFI – transfemoral intervention*

**Table III.** Sensitivity and subgroup analyses

| Subgroup analysis | | Number of studies (number of patients) | Odds ratio (95% CI) | | |
|---|---|---|---|---|---|
| | | | MACE | Mortality | Major bleeding |
| Overall effect | Fixed effect model | 12 (5124) | 0.66 (0.52, 0.85)*** | 0.57 (0.42, 0.78)*** | 0.49 (0.36, 0.66)*** |
| Publication | *In extenso* | 10 (3978) | 0.62 (0.47, 0.81)*** | 0.53 (0.37, 0.75)*** | 0.59 (0.42, 0.82)** |
| | Abstract or conference | 2 (1146) | 0.94 (0.53, 1.69) | 0.82 (0.42, 1.60) | 0.19 (0.08, 0.46)*** |
| Design | Single center | 7 (1213) | 0.85 (0.51, 1.42) | 0.79 (0.43, 1.45) | 0.43 (0.22, 0.86)* |
| | Multi-center | 5 (3911) | 0.62 (0.46, 0.82)*** | 0.52 (0.36, 0.74)*** | 0.50 (0.36, 0.71)*** |
| Number of patients | < 200 | 7 (819) | 0.65 (0.34, 1.24) | 0.67 (0.29, 1.53) | 0.47 (0.23, 0.94)* |
| | ≥ 200 | 5 (4305) | 0.67 (0.51, 0.88)** | 0.56 (0.41, 0.79)*** | 0.49 (0.35, 0.69)*** |
| Rescue PCI | Yes | 4 (3123) | 0.62 (0.45, 0.83)** | 0.50 (0.34, 0.73)*** | 0.64 (0.45, 0.93)* |
| | No | 6 (1362) | 0.68 (0.39, 1.18) | 0.68 (0.34, 1.35) | 0.29 (0.16, 0.54)*** |
| GP IIb/IIIa use | < 45% | 5 (2602) | 0.58 (0.39, 0.86)** | 0.48 (0.29, 0.81)** | 0.52 (0.26, 1.03)* |
| | ≥ 45% | 5 (1969) | 0.66 (0.46, 0.95)* | 0.58 (0.37, 0.89)** | 0.19 (0.08, 0.46)*** |

*$p < 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$. MACE – major adverse cardiovascular events*

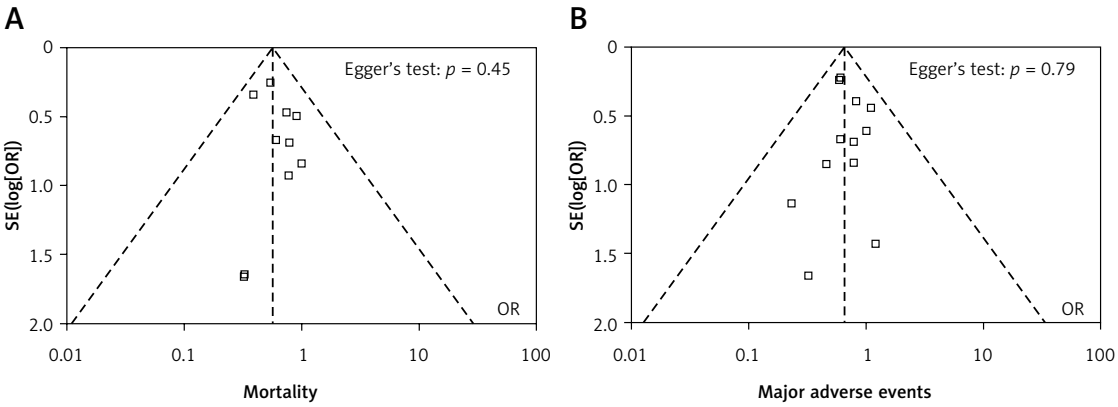


**Figure 5.** Funnel plots for visualizing potential publication bias. **A** – A funnel plot for overall mortality. **B** – The plot for major adverse events. No skewed distribution could be observed

stable Angina or Myocardial Infarction Managed With an Invasive Strategy" (RIVAL) trial, which was a randomized, parallel group, multicenter study involving 7021 patients with acute coronary syndromes. In patients with STEMI, a significant, 40% relative reduction in the primary endpoint was observed, together with a 61% relative decrease in mortality, although the results of the overall trial did not show a significant benefit for TRPCI over TFPCI in the primary endpoint [21, 30]. Meta-analyses including data of the STEMI subgroup of this trial found that the benefit of TRPCI regarding major composite events and mortality became significant [8–11]. However, the main restriction of these analyses is that they were dominated by data from the RIVAL trial representing approximately 60% of the weight attributed to the randomized trials, and sensitivity analyses by the exclusion of the RIVAL data still showed insignificant benefit [8].

Two important multicentre RCTs have been published on this topic. The "Radial Versus Femoral Investigation in ST Elevation Acute Coronary Syndrome" (RIFLE STEACS) trial randomized 1001 patients in four high-volume centers. This study showed a significant reduction in major adverse cardiac events and in 30-day mortality [22]. The STEMI-RADIAL trial of similar design randomized 707 STEMI patients and found an 80% decrease in bleeding events. Intriguingly, the TRPCI did not influence the frequency of MACE or mortality significantly (4.2% vs. 3.5%, $p = 0.7$ and 3.1% vs. 2.3%, $p = 0.4$, respectively) [24].

Based on these results, we aimed to reanalyze the safety and efficacy of TRPCI and found that the up-to-date evidence from randomized trials convincingly supports the current recommendations advising the use of the radial approach in STEMI cases [31].

Our meta-analysis has a number of potential limitations. Study-level meta-analyses are consid-

ered as less conclusive than data from adequately powered clinical trials. Based on the effect estimates from our analysis, a sample size of 2000 in each group would result a 95% power to detect a decrease of 0.02 in mortality with a significance level of 0.05 (two-tailed). Consequently, the trials performed so far were possibly underpowered, which validates the use of meta-analysis in order to achieve greater statistical power and more precise effect estimates. Furthermore, we may anticipate that none of the currently registered trials will substantially change this situation. (MATRIX NCT01433627 (estimated enrollment: 6800, proportion of STEMI cases: unknown), SAFARI-STEMI NCT01398254 (estimated enrollment: 1274, proportion of STEMI cases: 100%)).

Although our findings provide a robust support for TRPCI in STEMI in terms of efficacy, data regarding the occurrence of vascular complications were strikingly inconsistent. We pooled the data according to reported occurrence of any vascular complications and of access site bleeding and found benefit in both measures. However, besides lack of uniform reporting the results of these analyses should be cautiously interpreted as vascular complications have different clinical relevance related to their anatomical situations. This may result in observational, assessment, and referral bias.

An inherent limitation of any meta-analysis is that of publication bias. Therefore we extended our search to non-English and abstract publications. Consequently, the included trials show a wide range in size and origin and many of these were small trials with limited ability to assess clinical outcomes individually. However, subgroup analysis according to the means of publication and trial size showed no meaningful differences while our analysis for publication bias did not demonstrate the presence of this potential confounder. Furthermore, there were differences in medication and in operator experience across the trials. Because the trials in our meta-analysis were randomized, the effect of these limitations should be minimized. Appropriate training in transradial intervention, however, is of high importance and we believe that our findings regarding access site selection are applicable for experienced transradial operators.

Our updated meta-analysis demonstrates that the transradial access reduces mortality, MACE and the rate of bleeding events compared to the transfemoral access. The low heterogeneity of the outcome data also corroborates the robustness of these findings. Hospital stay was also shorter in patients with transradial intervention, but these benefits were accompanied by higher frequency of access site crossover and longer time to reperfusion. Data regarding procedural time parameters and contrast use were heterogeneous but not significantly different. Overall, it seems that possible technical drawbacks do not compromise the clinical efficacy of the transradial intervention. Therefore, transradial PCI should be favored over TFPCI in patients with STEMI.

In conclusion, robust data from randomized clinical studies indicate that TRPCI reduces both ischemic and bleeding complications in STEMI. These findings support the preferential use of radial access for primary PCI.

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