



## ORIGINAL ARTICLE

# Influence of access site selection on PCI-related adverse events in patients with STEMI: meta-analysis of randomised controlled trials

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## See Editorial, p 269

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## ABSTRACT

**Objective** A meta-analysis of all randomised controlled studies that compare outcomes of transradial versus the transfemoral route to better define best practice in patients with ST elevation myocardial infarction (STEMI).

**Design** A Medline and Embase search was conducted using the search terms 'transradial,' 'radial,' 'STEMI,' 'myocardial' and 'infarction'.

**Setting** Randomised controlled studies that compare outcomes of transradial versus the transfemoral route.

**Patients** A total of nine studies were identified that consisted of 2977 patients with STEMI.

**Interventions** Studies that compare outcomes of transradial versus the transfemoral route.

**Main outcome measures** The primary clinical outcomes of interest were (1) mortality; (2) major adverse cardiac events (MACE); (3) major bleeding and (4) access site complications.

**Results** Transradial PCI was associated with a reduction in mortality (OR 0.53, 95% CI 0.33 to 0.84;  $p=0.008$ ), MACE (OR 0.62, 95% CI 0.43 to 0.90;  $p=0.012$ ), major bleeding events (OR 0.63, 95% CI 0.35–1.12;  $p=0.12$ ) and access site complications (OR 0.30, 95% CI 0.19 to 0.48;  $p<0.0001$ ) compared with procedures performed through the femoral route.

**Conclusions** This meta-analysis demonstrates a significant reduction in mortality, MACE and major access site complications associated with the transradial access site in STEMI. The meta-analysis supports the preferential use of radial access for STEMI PCI.

## INTRODUCTION

Peri-procedural bleeding complications following percutaneous coronary intervention (PCI) are common and occur in up to 5% of cases performed in patients presenting with acute coronary syndromes (ACS).<sup>1,2</sup> This procedure-related bleeding is independently associated with adverse events including 30-day mortality, reinfarction and stroke (cerebrovascular accident).<sup>2–6</sup> Indeed, major bleeding was a more powerful predictor of mortality than peri-procedural myocardial infarction (MI) after PCI in the REPLACE-2 trial.<sup>7</sup> Clinical trials evaluating new pharmacological strategies have focused on reducing this bleeding risk,<sup>2,8–10</sup> although the benefits are often relatively modest. A significant proportion of major bleeding is related to the access site<sup>11</sup> and the transradial approach

has been shown to reduce access site bleeding complications<sup>5</sup> and the requirement for blood transfusion<sup>12,13</sup> in observational and randomised controlled trials. More recently, promising trends in mortality reduction have been found in observational studies.<sup>12,14</sup>

Patients with ST elevation myocardial infarction (STEMI) undergoing PCI are at the highest risk for the development of such bleeding complications. Data from the National Heart, Lung and Blood Institute Dynamic Registry have documented an independent fourfold increase in in-hospital mortality in patients presenting with STEMI compared with those with non-STEMI as well as greater access site bleeding complications requiring blood transfusion (3.3% vs 2.1%).<sup>15</sup> As STEMI represents the highest bleeding risk in the spectrum of ACS, these data have led some interventionists to recommend that radial access is employed as the primary access site in patients with STEMI as this cohort represents the highest bleeding risk in the spectrum of ACS.<sup>16</sup> In contrast, this view is contested by other commentators, who argue that the enthusiasm for the transradial approach in patients with STEMI is not sufficiently justified by the evidence to support such a move towards its use.<sup>17</sup>

Although a previous meta-analysis of outcomes in patients with STEMI related to access site suggested benefits related to the use of radial access, many of the enrolled studies had a suboptimal (and often non-randomised) design.<sup>18</sup> Recent publication of the RIVAL study<sup>19</sup> has provided substantial new data derived from subgroup analysis on access site-mediated outcomes in patients with STEMI. When added to previous randomised trials the combined data may provide the current best available information on the influence of access site selection on outcome for patients with STEMI and may provide further insight into the controversy surrounding optimal access site choice for STEMI PCI. We, therefore, performed a meta-analysis in patients with STEMI undergoing PCI, analysing all randomised controlled studies that compared the impact of access site selection on mortality, major adverse cardiac events (MACE), major bleeding and access site complications to better define best practice in this high-risk group.

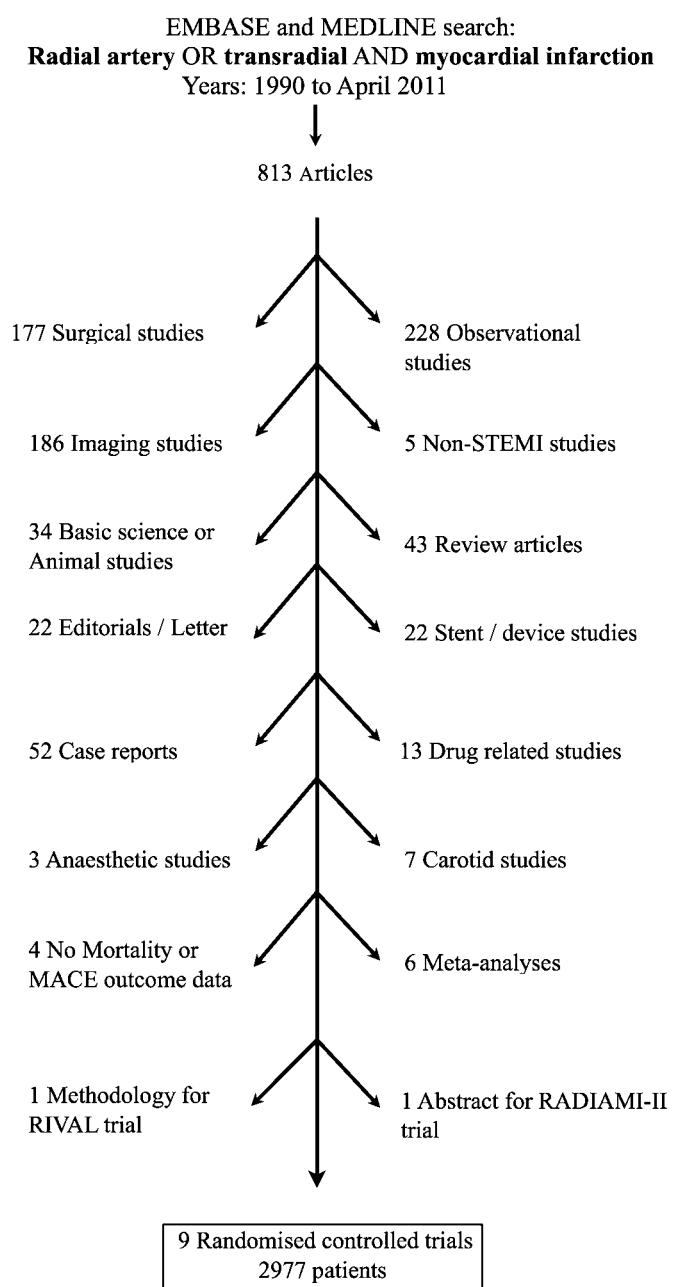
## METHODS

This study was performed according to guidelines for preferred reporting for systematic reviews and

meta-analyses (PRISMA).<sup>20</sup> A Medline and Embase search (1990 to September 2011) was performed using the search terms 'transradial', 'radial', 'STEMI', 'myocardial' and 'infarction'. References and review articles were further scrutinised to ensure that all relevant studies were identified (figure 1). Only randomised controlled studies comparing outcomes after PCI in patients with STEMI between the radial versus the femoral access site were included in our analysis. STEMI within these studies comprised of primary PCI, rescue PCI and facilitated PCI. The primary clinical outcomes of interest, evaluated at the longest available follow-up, were (1) mortality; (2) MACE (according to study definitions); (3) major bleeding (according to study definition) and (4) access site complications.

### Statistical analysis

All trials included in this meta-analysis were prospective, randomised controlled trials and publication level data were used for



**Figure 1** Search strategy for the studies.

the analysis. For individual trials, the  $\chi^2$  heterogeneity test was used to calculate the significance, OR and 95% CIs for the differences in outcome between radial and femoral access in patients with STEMI. The treatment received was clearly shown for all trials and analysis was performed on the basis of the intention to treat. We used the Cochran Q test to assess heterogeneity across trials. Also, we calculated the  $I^2$  statistic to measure the consistency between trials with values of 25%, 50% and 75% defining the cut-off points for identifying low, moderate and high degrees of heterogeneity respectively.<sup>21</sup> Treatment effects from individual trials were pooled using the random-effects DerSimonian and Laird model. The likelihood of publication or 'small-study' bias was assessed graphically by generating a funnel plot for the primary end point of MACE and by means of Egger's test. Exploratory meta-regression analyses were performed to assess the interaction of covariates, including proportion of primary PCI cases in each study, year of publication and percentage crossover rates on the OR for mortality of transradial versus transfemoral PCI in the setting of STEMI. A random-effects model of regression using the method of moments estimator was used for the meta-regression analysis. Data were analysed using Comprehensive Meta-analysis (version 2.0, Engelwood, New Jersey, USA).

### RESULTS

A total of nine studies, dating from 2003 to 2011, were identified that fulfilled the search criteria: RIVAL,<sup>19</sup> TEMPURA,<sup>22</sup> RADIAL-AMI,<sup>23</sup> FARMI,<sup>24</sup> Yan *et al*,<sup>25</sup> RADIAMI<sup>26</sup> Gan *et al*,<sup>27</sup> Hou *et al*,<sup>28</sup> RADIAMI II,<sup>29</sup> consisting of 2977 patients with STEMI. A summary of the studies included in this analysis including patient numbers, exclusion criteria, antiplatelet/anticoagulant protocols and operator experience in transradial PCI is presented in table 1. Baseline characteristics were evenly distributed between the two treatment groups in all trials. An overview of the defined end points is presented in table 2 and outcomes are presented in table 3.

The mortality end point was reached in 28/1460 individuals in the radial group and 54/1517 in the femoral group. Meta-analysis of these data demonstrated an OR of 0.53 (95% CI 0.33–0.84;  $p=0.006$ ) for mortality in favour of the radial group (figure 2A). There appeared to be no heterogeneity among studies ( $Q=2.39$ ;  $p=0.94$ ,  $I^2=0$ ). A funnel plot of studies included in the meta-analysis of mortality data to assess for publication bias is presented in figure 2B. Studies were symmetrically distributed, indicating the absence of publication bias, confirmed by means of a negative Egger's test ( $p=0.20$ ).

Even after removal of the largest study, RIVAL from the dataset and repeating the meta-analysis a similar magnitude in reduction of mortality was seen, although this was not statistically significant (OR 0.71, 95% CI 0.37–1.37,  $p=0.31$ ). Furthermore, exploratory meta-regression analyses disclosed no statistically significant association between either proportion of patients who were primary PCI cases in each study ( $p=0.76$ ), year of publication ( $p=0.38$ ) or percentage crossover rates ( $p=0.46$ ) and mortality OR outcomes.

A total of 47/1461 MACE occurred in the radial group and 77/1508 in the femoral group. Figure 3 illustrates the Forrest plot after meta-analysis of MACE (OR 0.62, 95% CI 0.43 to 0.90;  $p=0.012$ ). Similarly no heterogeneity between studies was documented ( $Q=2.13$ ;  $p=0.98$ ,  $I^2=0$ ).

Analysis of major bleeding events as defined by the individual studies themselves showed 18/1435 events in the radial group and 33/1492 events in the femoral group (OR 0.63, 95% CI

**Table 1** Summary of the studies included in meta-analysis

Studies (year)	Number	Single centre/multi centre	Exclusion criteria	STEMI cohort	Anticoagulant/antiplatelet protocol	Operator radial experience for participation in study
TEMPURA (2003)	149	Single centre	Thrombolysis, cardiogenic shock with weak radial pulse, abnormal Allen's test, occluded SVG grafts, culprit artery considered not suitable for PCI because of extreme tortuosity and/or calcification proximally or vessel size <2.5 mm in diameter by visual estimate	Primary PCI 100%	5000/6000 units of heparin given for female/male patients, respectively. Oral administration of aspirin of 162 mg or more and ticlopidine of 200 mg daily were started as soon as possible after stent implantation and continued for more than 4 weeks	Not available
RADIAL-AMI (2005)	50	Multicentre	Cardiogenic shock, abnormal Allen's test result, or contraindication to GP IIb/IIIa inhibitor	Primary PCI 34% Rescue PCI 66%	Heparin (target activated clotting time, 200–300 s), aspirin (325 mg before the procedure) and clopidogrel (300 mg loading dose, 75 mg daily for a minimum of 28 days after the procedure). Abciximab (a bolus of 0.25 mg/kg before or during procedure followed by an infusion of 0.125 microg/kg/min (maximum of 10 µg/min)) for 12 h after PCI	Required to have performed minimum of 100 transradial PCI procedures before study
FARMI (2007)	114	Single centre	History of CABG, cardiogenic shock, atrioventricular block and contraindication to abciximab or an abnormal Allen's test	Primary PCI 50.9% Rescue PCI 42.1% Facilitated PCI 7%	IV bolus heparin (unfractionated heparin 50 IU/kg or low molecular weight heparin (enoxaparin) 30 mg IV and 1 mg/kg subcutaneously) and a bolus of aspirin (250 mg IV). During PCI abciximab given (0.25 mg/kg bolus followed by 0.125 micrograms/kg/min infusion during 12 h). Clopidogrel (300 mg), followed by 75 mg daily for 1 year, plus 75–300 mg/day oral aspirin	Required to have undertaken more than 100 previous successful transradial coronary procedures
Yan <i>et al</i> (2008)	103	Single centre	Cardiogenic shock, non-palpable radial artery, abnormal Allen's test and chronic renal failure	Primary PCI 100%	All patients loaded with clopidogrel 600 mg and aspirin 300 mg after the diagnosis of AMI established. Tirofiban administered with 10 µg/kg bolus IV for 3 min followed by 0.15 micrograms/kg/min infusion for 24 h. During PCI, patients received a bolus of heparin (70 U/kg) then received another 2000–5000 U heparin every hour during the procedure. After PCI, patients given clopidogrel 75 mg/day for 1 year, aspirin 100–200 mg/day for life and subcutaneous fragmin 5000 U twice daily for at least 5–7 days	No formal entry requirements but the operators were interventional cardiologists who had performed over 500 cases of transradial PCI
RADIAMI (2009)	100	Single centre	Age >75 years, Killip class III or IV, intra-aortic balloon pump placement before the angiogram, height <150 cm, history of CABG, if the infarction may be due to occluded bypass graft	Primary PCI 100%	All patients received heparin (70 U/kg), and GP IIb/IIIa receptor blockers were administered during the PCI. Heparin administration was continued after the intervention only in the presence of clinical indications	No formal entry requirements but operators performed at least 50–100 transradial PCI cases previously
Gan <i>et al</i> (2009)	195	Multicentre	Abnormal Allen's test	Primary PCI 100%	All patients loaded with 300 mg aspirin and 300 mg clopidogrel as soon as they were diagnosed as having an AMI. Heparin administered at 100 IU/kg. GP IIb/IIIa inhibitors were administered according to the operator's discretion	Not available
Hou <i>et al</i> (2010)	200	Single centre	Cardiogenic shock, history of coronary bypass graft, Abnormal Allen's test and non-palpable radial artery	Primary PCI 100%	All patients received aspirin (300 mg) and clopidogrel (300 mg) once diagnosis of AMI was made. Fragmin 5000 U s/c was used and GP IIb/IIIa inhibitors were administered according to the operator's discretion	At least 200 transradial PCI cases previously

Continued

**Table 1** Continued

Studies (year)	Number	Single centre/multi centre	Exclusion criteria	STEMI cohort	Anticoagulant/antiplatelet protocol	Operator radial experience for participation in study
RIVAL (2011)	1958	Multicentre	Cardiogenic shock, severe peripheral vascular disease precluding a femoral approach, or previous coronary bypass surgery with use of more than one internal mammary artery	Primary PCI 74% Rescue PCI 12% Facilitated PCI 3% Other 11%	Antithrombotic regimen (including GP IIb/IIIa inhibitors) used for PCI was at the discretion of the treating doctor	At least 50 radial procedures for coronary angiography or PCI within the previous year
RADIAMI II (2011)	108	Single centre	Killip class III or IV, use of an intra-aortic balloon pump or temporary right ventricular pacing, patient's height <150 cm, history of CABG, age >75 years	Primary PCI	Heparin was used in all cases and administered in doses to achieve ACT of 350–450 s during procedures performed without the use of abciximab and 250–350 s when abciximab was used. Use of abciximab was at the operator's discretion	No formal entry requirements but senior operators with 17–20 years of experience in performing PCI via TFA and several years' experience in performing PCI via TRA, took part in the study

ACT, activated clotting time; AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; GP, glycoprotein; STEMI, ST elevation myocardial infarction; SVG, saphenous vein grafts; TFA, transfemoral approach; TRA, transradial approach.

0.35–1.12;  $p=0.12$ ; figure 4A. No heterogeneity between studies was detected;  $Q=3.82$ ,  $p=0.80$ ,  $I^2=0$ ). After removal of the largest study, RIVAL from the dataset and repeating the meta-analysis an even greater magnitude in reduction of major bleeding (OR 0.50, 95% CI 0.24–1.04,  $p=0.062$ ) was found.

Finally, access site complications were meta-analysed with a significant reduction in access site complications seen in the radial group (OR 0.30, 95% CI 0.19 to 0.48;  $p<0.0001$ ; figure 4B), which remained significantly reduced even if RIVAL was removed from the analysis (OR 0.25, 95% CI 0.13 to 0.50;  $p<0.0001$ ).

## DISCUSSION

Radial access was reintroduced into clinical practice just over 20 years ago and used for PCI shortly after. Over this time period extensive data have accumulated confirming that the technique is preferred by patients, reduces procedural costs, may protect against renal complications such as contrast-induced nephropathy<sup>30</sup> and access site complication rates. Technical and procedural innovations have progressively improved the applicability of the technique. In this meta-analysis of nine randomised studies consisting of 2977 patients we demonstrate that adoption of the transradial route for PCI in patients with STEMI is associated with a 48% reduction in the risk of mortality in comparison with procedures performed through the femoral route. This is in agreement with a previous meta-analysis of pooled randomised and prospective and retrospective observational studies including 12 studies and 3324 patients with STEMI,<sup>18</sup> which also demonstrated a 46% reduction in mortality.

Observational studies such as the MORTAL study (Mortality benefit Of Reduced Transfusion after PCI via the Arm or Leg) in which over 32 000 PCI procedures were analysed have similarly demonstrated that PCI performed through the transradial route is independently associated with a reduction in mortality in comparison with procedures performed through the femoral route.<sup>12</sup> Similarly, in a large retrospective observational study involving 1051 patients admitted with STEMI, in-hospital mortality in the femoral group was approximately double that recorded in the radial group.<sup>31</sup> When data were analysed by the actual site of access, significantly greater major access site complications were recorded in the femoral group than in the radial group (1.9% vs 0%,  $p=0.001$ ). Other retrospective studies have also demonstrated both a decrease in mortality and a reduction in major bleeding complications in patients with

STEMI undergoing PCI through the transradial route in comparison with the femoral access site.<sup>32</sup>

Both large randomised controlled studies and numerous elective and ACS registries have demonstrated that major bleeding and transfusion after PCI are associated with increased in-hospital and 1-year mortality.<sup>2–6</sup> For example, in the MORTAL study, blood transfusion was independently associated with fourfold increase in 30-day mortality (95% CI 3.08 to 5.22).<sup>12</sup> Furthermore, previous studies with treatments that reduce the risk of bleeding but retain efficacy similar to that of standard treatment have shown reductions in mortality in ACS,<sup>9, 10, 33</sup> thereby suggesting a causative link between major bleeding and death. In the MORTAL study, transradial access reduced blood transfusions by 50% with an associated mortality benefit.<sup>12</sup>

In our meta-analysis we have also demonstrated that the decrease in mortality was associated with a parallel reduction in major access site complications (OR 0.30, 95% CI 0.19 to 0.48;  $p<0.0001$ ) and trend towards a reduction in major bleeding (OR 0.63, 95% CI 0.35–1.12;  $p=0.12$ ). Other studies have similarly shown a reduction in both bleeding and access site complications associated with the transradial route. For example, analysis of over 500 000 PCI procedures in the US national cardiovascular data registry showed a 58% reduction in bleeding (OR 0.42, 95% CI 0.31 to 0.56) with an approximately 3.5-fold decrease in vascular complications.<sup>4</sup> Similarly, in a meta-analysis of 23 randomised studies, the transradial route was associated with a 73% reduction of major bleeding compared with the femoral route.<sup>13</sup> When these data were combined with the recent RIVAL study, analysis of 10 967 patients showed that major bleeding remained significantly reduced in those patients undergoing PCI through the transradial route (OR 0.51 95% CI 0.33 to 0.79;  $p=0.002$ ).

Our meta-analysis demonstrated a trend towards a reduction in major bleeding (OR 0.63, 95% CI 0.35–1.12;  $p=0.12$ ), although risk of major bleeding even if performed through the transradial route in the setting of STEMI still remain significant. The reasons for this are several fold. The use of transradial access does not eliminate all bleeding after PCI. Major bleeding complications comprise both access site and non-access site complications. Adoption of the transradial route would only be expected to reduce bleeding complications from the access site. In a post hoc analysis of the REPLACE-2, ACUITY and HORIZONS AMI trial involving 17 393 patients, 61.4% of all recorded bleeds were not related to the access site,<sup>11</sup> hence the transradial approach would only be expected to affect the incidence of

**Table 2** Summary of study definitions

Studies (Year)	Major bleeding definition	Minor bleeding definition	Access site complications	Primary end point
TEMPURA (2003)	Bleeding requiring blood transfusion and/or surgical repair or cerebral bleeding	Not defined	Not defined	MACE: TLR, repeat AMI or death
RADIAL-AMI (2005)	Intracranial or retroperitoneal bleeding, a drop in haemoglobin level >5 g/dl or haematocrit >15%, whole blood or packed red cell transfusions	Not defined	Haematoma >5 cm, pseudoaneurysm, arteriovenous fistula, access site rebleeding after initial haemostasis	Primary efficacy end point: reperfusion time. Primary safety end point: major bleeding
FARMI (2007)	TIMI major bleeding involving a haemoglobin drop of >5 g/dl or intracranial haemorrhage or cardiac tamponade	TIMI minor bleeding: haemoglobin drop >3 g/dl but <5 g/dl, with bleeding from a known site or spontaneous gross haematuria, haemoptysis or haematemesis	False aneurysm, haematoma (defined as local induration of >4 cm diameter) and ecchymosis (defined as cutaneous bruise or induration of <4 cm)	Peripheral vascular complication rates and PCI efficiency and tolerance of the procedure
Yan <i>et al</i> (2008)	Haemoglobin loss of at least 2 mmol/l, the administration of a blood transfusion, vascular repair, or prolonged hospitalisation	Haematoma formation not requiring specific treatment	Haematoma, pseudoaneurysm and arterial occlusion	Vascular access site complications including minor bleeding (haematoma), major bleeding, pseudoaneurysm and artery occlusion. MACE defined as death, recurrent AMI and repeat target vascular revascularisation
RADIAMI (2009)	Fatal bleeding, bleeding requiring blood transfusion, operation or resulting in a drop of haemoglobin count of >3 g/dl as well as any intracranial haemorrhage	All bleeding complications that did not fulfil criterion for major bleeding complications defined as minor	Not defined	Primary end point not defined
Gan <i>et al</i> (2009)	Not defined, although data presented for major bleeding	Not defined	Not defined, although data presented for presence of and type of vascular access site complications	Major adverse cardiac events, including death, CABG, myocardial infarction and target lesion revascularisation
Hou <i>et al</i> (2010)	Haemoglobin loss of ≥2 mmol/l or administration of blood transfusions	Haematoma formation not requiring specific treatment	Not defined	MACE defined as death, recurrent myocardial infarction, or target vessel revascularisation
RIVAL (2011)	Fatal bleeding, transfusion of two or more units of red blood cells or equivalent whole blood, bleeding causing substantial hypotension with the need for inotropes, surgical intervention (only if there has been substantial hypotension or transfusion of at least two units of blood), bleeding causing severely disabling sequelae, intracranial bleeding and symptomatic or intraocular leading to significant visual loss	Bleeding events that did not meet the criteria for a major bleed and required transfusion of one unit of blood or modification of the drug regimen (ie, cessation of antiplatelet or antithrombotic treatment)	Pseudoaneurysm needing closure, large haematoma (as judged by investigator), arteriovenous fistula, or an ischaemic limb needing surgery	Primary end point composite of death, AMI, stroke, or non-CABG-related major bleeding at 30 days
RADIAMI II (2011)	Fatal bleeding, bleeding requiring blood transfusion, operation or resulting in a drop of haemoglobin count of >3 g/dl or any intracranial haemorrhage	Bleeding events that did not meet the criteria for a major bleed	Not defined	Serious cardiac events including repeat cardiac revascularisation in the infarct-related artery, new CABG, new MI occurrence and death from any cause

AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; MACE, major adverse cardiac event; TIMI, thrombolysis in myocardial infarction; TLR, target lesion revascularisation.

38.6% of these major bleeds. Similarly, in the RIVAL study, only 30% of all major bleeds not related to coronary artery bypass grafting (non-CABG) were related to the access site.<sup>19</sup>

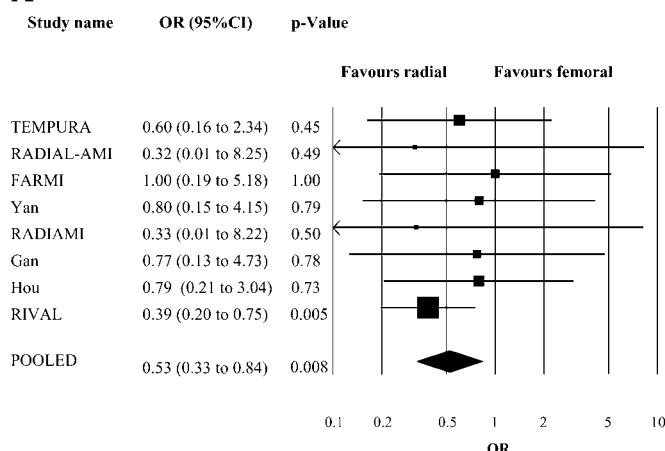
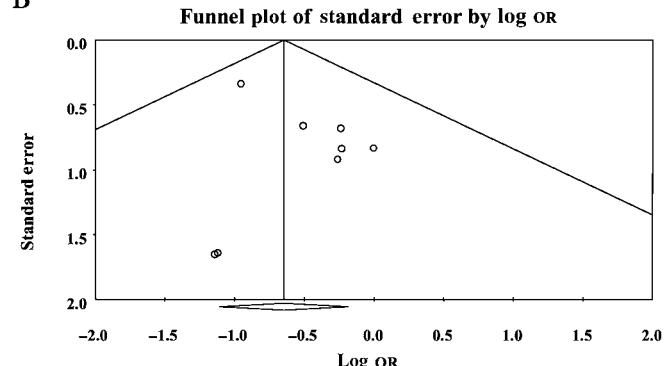
The prognostic implications of non-access site-related bleeds are greater than those of access site-related bleeds, hence an intervention that reduces only the latter will have a smaller effect on mortality outcomes than an intervention influencing non-access site-related bleeding rates. For example, analysis of REPLACE-2, ACUITY and HORIZONS AMI studies showed that access site bleeds were independently associated with a 1.82 increase in 1-year mortality (95% CI 1.17 to 2.83;  $p=0.008$ ), whereas non-access site complications were associated with a 3.94-fold increase in 1-year mortality (95% CI 3.07 to 5.15;

$p<0.0001$ ).<sup>11</sup> These data suggest that PCI patients will benefit from the adoption of safest access site practice (use of the transradial approach) in combination with an antithrombotic regimen optimised to preserve anti-ischaemic efficacy but minimise systemic bleeding.

The mechanism by which radial access reduces mortality and MACE in patients with STEMI may be related to the prevention of both bleeding and access site complications. Large access site bleeds can lead to haemodynamic instability and blood transfusion with an associated range of deleterious consequences. Although these events are relatively infrequent, associated cardiovascular adverse events are common in these patients. Some access site complications will not result in substantial

**Table 3** Summary of outcomes of studies

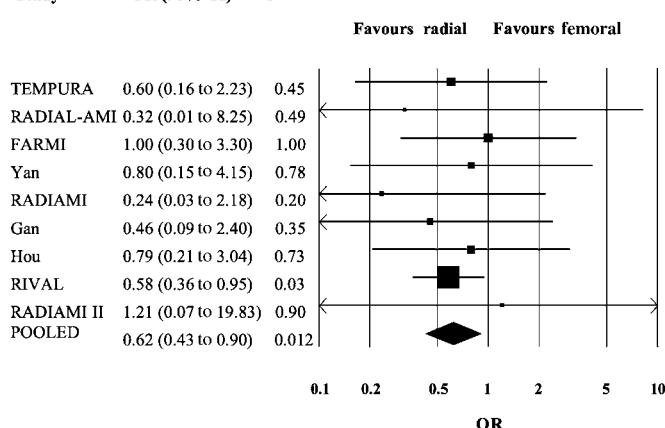
Studies (Year)	Mortality (%)		MACE (%)		Major bleeding		Access site complications		Other outcomes
	Radial	Femoral	Radial	Femoral	Radial	Femoral	Radial	Femoral	
TEMPURA (2003)	4/77 (5.2%) (NS)	6/72 (8.3%)	4/77 (17.8%) (NS)	6/72 (8.3%)	0/77 (0%) (NS)	2/72 (3.0%)	Not available		Procedure time shorter in radial group (mean 44 vs 51 min; p<0.05). Cost of admission, length of stay and crossover not significantly different between 2 arms.
RADIAL-AMI (2005)	0/25 (0%) (NS)	1/25 (4.0%)	0/25 (0%) (NS)	1/25 (4.0%)	0/25 (0%) (NS)	0/25 (0%)	2/25 (8%) (NS)	5/25 (20%)	No differences in quality of life measures using SF-36 acute survey. Radial crossover rate 4%, femoral 1% (NS)
FARMII (2007)	3/57 (5.3%) (NS)	3/57 (5.3%) (NS)	3/57 (5.3%) (NS)	3/57 (5.3%) (NS)	3/57 (5.3%)	8/57 (14%) (p=0.014)	20/57 (35.1%)		Crossover 12.3% radial vs 1.8% femoral (p=0.03). Fluoroscopy duration mean 13 vs 8 min in radial and femoral respectively (p<0.01)
Yan et al (2008)	3/57 (5.3%) (NS)	3/46 (6.5%)	3/57 (5.3%) (NS)	3/46 (6.5%)	0/57 (0%) (NS)	1/46 (2.2%)	1/57 (1.8%) (p<0.01)	6/46 (13.1%)	Hospital stay shorter in radial group (p<0.01; mean 7 vs 10 days). Time to reperfusion, procedural time and procedural success similar in both groups.
RADIAMI (2009)	0/50 (0%) (NS)	1/50 (2%)	3/50 (6%) (NS)	4/50 (8%)	3/50 (6%) (NS)	7/50 (14%)	Not available		Mean door to balloon time longer in radial group (64.6 vs 76.9 min; p=0.02)
Gan et al (2009)	2/90 (2.2%) (NS)	3/105 (2.9%)	2/90 (2.2%) (NS)	5/105 (4.8%)	0/90 (0%) (NS)	2/105 (1.9%)	2/90 (2.2%) p<0.05	12/105 (11.4%)	Mean procedure time longer in radial arm (mean 29 vs 27 min p<0.05)
Hou et al (2010)	4/100 (4%) (NS)	5/100 (5%)	4/100 (4%) (NS)	5/100 (5%)	0/100 (0%)	3/100 (3%)	Not available		Puncture time, procedural time, reperfusion time and fluoroscopy time all similar in both groups.
RIVAL (2011)	12/955 (1.3%) p=0.0006	32/1003 (3.2%)	26/955 (2.7%) p=0.03	46/1003 (4.6%)	8/955 (0.8%) (NS)	9/1003 (0.9%)	12/955 (1.3%) p=0.002	35/1003 (3.5%)	Access site crossover 5.3 vs 1.6% in radial and femoral groups respectively (p<0.0001)
RADIAMI II (2011)	0/49	0/59 (0%)	1/49 (2.1%)	1/59 (1.7%)	4/49 (8.2%)	6/59 (10.2%)	Not available		Procedure time similar but door to balloon time 64.6 vs 76.9 min (means; p<0.05)

**A****B**

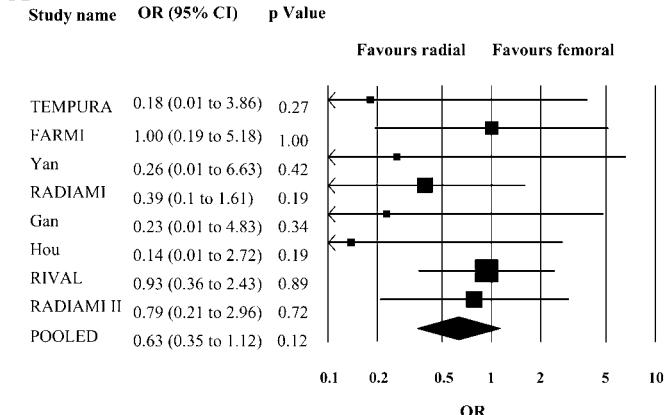
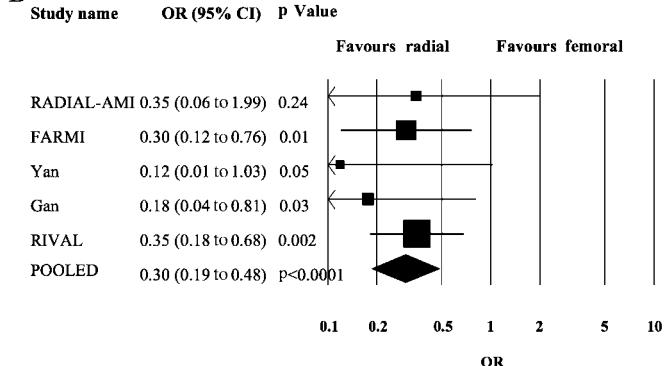
**Figure 2** (A) Forest plot comparing mortality outcomes in the radial versus the femoral access site in randomised PCI trials in STEMI patients. Odds ratios (OR) and 95% confidence intervals (CI) are presented for individual studies and pooled data. (B) Funnel plot of studies for mortality data.

blood loss but still require intervention with consequent activation of systemic inflammation and coagulation and compromised antiplatelet regimens. This results in a disproportionate risk of cardiovascular events even though the initial insult is not haemodynamically significant.

**Study**      **OR (95% CI)**      **p Value**



**Figure 3** Forest plot comparing major adverse cardiac events outcomes in the radial versus the femoral access site in randomised PCI trials in patients with ST elevation myocardial infarction. ORs and 95% CIs are presented for individual studies and pooled data.

**A****B**

**Figure 4** (A) Forrest plot comparing major bleeding outcomes in the radial versus the femoral access site in randomised PCI trials in patients with ST elevation myocardial infarction (STEMI). ORs and 95% CIs are presented for individual studies and pooled data. (B) Forrest plot comparing access site complication outcomes in the radial versus the femoral access site in randomised PCI trials in patients with STEMI. ORs and 95% CIs are presented for individual studies and pooled data.

All of the studies contained in our meta-analysis were intention to treat and were associated with significant crossover rates of between 1.8% and 12%. For example, in the largest study used in this analysis, the RIVAL study, the crossover rate was 7.6% and when access site major bleeds were analysed in the radial group, the location of these access site bleeds were found to be in the femoral access site only mainly due to crossover.<sup>19</sup>

The definition of major bleeding used in individual studies may in itself influence the reported outcomes. For example, in the RIVAL study,<sup>19</sup> while non-CABG related major bleeding as defined by the study (see table 2) showed a trend towards a reduction, although it was not statistically significant (OR 0.73, 95% CI 0.43 to 1.23; p=0.9), use of the ACUITY major bleeding criterion was associated with a statistically significant reduction in major bleeding in the radial arm of study compared with the femoral arm (OR 0.43 95% CI 0.32 to 0.57; p<0.0001). Furthermore, differing definitions of major bleeding will have different effects on outcome—for example, in pooled analysis of PURSUIT and PARAGON randomised controlled trials involving 15 454 patients a stronger association between the GUSTO definition of major bleeding and 30-day death or MI (OR 5.57 95% CI 4.33 to 7.17) than between TIMI major bleeding definition and 30-day death or MI was seen (OR 1.45, 95% CI 1.23 to 1.70).<sup>34</sup>

There is some evidence that operator and unit expertise plays a role in the relationship between radial access and the prevention of MACE. In RIVAL, the high-volume radial units had reduced MACE in all patients with ACS, not just those with STEMI. This suggests that adopting a high-volume radial programme will bring additional benefits to a wide range of patients. It is important to recognise that the radial approach is associated with an important learning curve. Before embarking on a transradial STEMI programme operators and institutions must develop their skills in less challenging patient populations. Studies included in this analysis had relatively modest requirements for transradial operator experience for participation—for example, several of the studies only required operators to have performed from 50 to 100 transradial procedures in total,<sup>19 23 24 26</sup> even though data have suggested that the learning curve for transradial procedures begins to plateau at around 1000 cases.

Our meta-analysis has a number of potential limitations. First, an inherent limitation of any meta-analysis is that of publication bias; studies that show a neutral outcome in mortality are less likely to be published than those that show a positive outcome and thus tend to bias any meta-analysis of published data towards a more positive outcome. However, our analysis for publication bias did not demonstrate the presence of this potential confounder. Second, the RIVAL study contributed 66% of all the patients analysed as part of this meta-analysis, hence it is possible that the larger RIVAL dataset may ‘drive’ the outcome of the pooled meta-analysis. To assess for this potential confounder, we repeated our analyses without the inclusion of the RIVAL dataset and found similar magnitudes of the end points, including mortality (47% reduction with inclusion of RIVAL, 39% reduction without), major bleeding (37% with inclusion of RIVAL, 50% reduction without) and access site complications (70% with inclusion of RIVAL, 75% reduction without). Finally, although all the studies analysed included only patients with STEMI, these comprised patients presenting for primary PCI, rescue PCI and facilitated PCI, hence it is unclear whether individual analyses of these subgroups might have yielded different outcomes. However, exploratory meta-regression analysis of the largest subgroup of the STEMI cohort (primary PCI) did not show a statistically significant association between either the proportion of patients who were primary PCI cases in each study and the magnitude of outcomes.

In conclusion, in this meta-analysis of 9 studies including 2977 STEMI patients we have observed a significant reduction in mortality, major access site complications and a trend towards a reduction in major bleeding events. Primary PCI represents the ‘gold standard’ of care in the management of STEMI and these patients are at the highest risk for bleeding complications and mortality. It is therefore not surprising that reducing access site-related bleeding complications has the potential to favourably affect mortality rates. Our meta-analysis must be considered to be hypothesis generating since no single adequately powered randomised controlled study has compared the influence of arterial access site selection on clinical outcomes in primary PCI patients. There is an urgent need for such a trial in view of the potential for radial access to reduce mortality and MACE. Until such a trial is available, our meta-analysis provides the best available data and supports the use of radial access for primary PCI reinforcing the view of earlier editorialists.<sup>35</sup>

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