

# OPEN ACCESS

**Citation:** Senguttuvan NB, Reddy PMK, Shankar P, Abdulkader RS, Yallanki HP, Kumar A, et al. (2022) Trans-radial approach versus trans-femoral approach in patients with acute coronary syndrome undergoing percutaneous coronary intervention: An updated meta-analysis of randomized controlled trials. PLoS ONE 17(4): e0266709. https://doi.org/10.1371/journal.pone.0266709

Editor: Giuseppe Andò, University of Messina, ITALY

Received: November 23, 2021

Accepted: March 25, 2022

Published: April 28, 2022

**Copyright:** © 2022 Senguttuvan et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

**Data Availability Statement:** All relevant data are within the paper and its Supporting information files.

**Funding:** This study was funded by Terumo India Pvt Ltd.

**Competing interests:** The authors have declared that no competing interests exist.

RESEARCH ARTICLE

Trans-radial approach versus trans-femoral approach in patients with acute coronary syndrome undergoing percutaneous coronary intervention: An updated metaanalysis of randomized controlled trials

Nagendra Boopathy Senguttuvan<sup>1,2\*</sup>, Pothireddy M. K. Reddy<sup>3</sup>, PunatiHari Shankar<sup>3</sup>, Rizwan Suliankatchi Abdulkader<sup>4</sup>, Hanumath Prasad Yallanki<sup>3</sup>, Ashish Kumar<sup>5</sup>, Monil Majmundar<sup>5,6</sup>, Vadivelu Ramalingam<sup>7</sup>, Ravindran Rajendran<sup>8</sup>, Kesavamoorthy Bhoopalan<sup>9</sup>, Dhamodharan Kaliyamoorthy<sup>10</sup>, Muralidharan T. R.<sup>1</sup>, Ankur Kalra<sup>5,11</sup>, Ramamoorthi Jayaraj<sup>12</sup>, Sivasubramanian Ramakrishnan<sup>13</sup>, Ramesh Daggubati<sup>14</sup>, Sadagopan Thanikachalam<sup>1</sup>, Ashok Seth<sup>15</sup>, Vinay Kumar Bahl<sup>14,16</sup>

1 Department of Cardiology, Sri Ramachandra Institute of Higher Education and Research (SRIHER), Chennai, Tamil Nadu, India, 2 Adjunct Faculty, Department of Engineering and design, Indian Institute of Technology-Madras, Chennai, India, 3 Department of Medicine, Sri Ramachandra Institute of Higher Education and Research (SRIHER), Chennai, Tamil Nadu, India, 4 Scientist-D, ICMR-National Institute of Epidemiology, Chennai, India, 5 Section of Cardiovascular Research, Heart, Vascular, and Thoracic Department, Cleveland Clinic Akron General, Akron, Ohio, 6 Department of Internal Medicine, New York Medical College, Metropolitan Hospital, New York, New York, United States of America, 7 Department of Cardiology, Velammal Medical College and Hospital, Madurai, India, 8 Department of Cardiology, Apollo Hospitals, Trichy, India, 9 Department of Cardiology, Meenakshi Hospital, Thanjavur, India, 10 Department of Cardiology, Apollo Hospitals, Chennai, India, 11 Department of Cardiovascular Medicine, Heart, Vascular, and Thoracic Institute, Cleveland Clinic, Cleveland, Ohio, 12 UNAA, Darwin, Australia, 13 Department of Cardiology, All India Institute of Medical Sciences, New Delhi, India, 14 Department of Cardiology, Fortis Escorts Heart Institute, New Delhi, India, 16 Department of Cardiology, Max- Super-speciality Hospitals, New Delhi, India

\* drsnboopathy@gmail.com

# Abstract

# Introduction

Trans-radial approach (TRA) is recommended over trans-femoral approach (TFA) in patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI). We intended to study the effect of access on all-cause mortality.

# Methods and results

We searched PubMed and EMBASE for randomized studies on patients with ACS undergoing PCI. The primary outcome was all-cause mortality at 30-days. The secondary outcomes included in-hospital mortality, major adverse cardiac or cerebrovascular event (MACE) as defined by the study, net adverse clinical event (NACE), non-fatal myocardial infarction, non-fatal stroke, stent thrombosis, study-defined major bleeding, and minor bleeding, vascular complications, hematoma, pseudoaneurysm, non-access site bleeding, need for transfusion, access site cross-over, contrast volume, procedure duration, and hospital stay duration. We studied 20,122 ACS patients, including 10,037 and 10,085 patients undergoing trans-radial and trans-femoral approaches, respectively. We found mortality benefit in patients with ACS for the trans-radial approach [(1.7% vs. 2.3%; RR: 0.75; 95% CI: 0.62–0.91; P = 0.004; I2 = 0%). Out of 10,465 patients with STEMI, 5,189 patients had TRA and 5,276 had TFA procedures. A similar benefit was observed in patients with STEMI alone [(2.3% vs. 3.3%; RR: 0.71; 95% CI: 0.56–0.90; P = 0.004; I2 = 0%). We observed reduced MACE, NACE, major bleeding, vascular complications, and pseudoaneurysms. No difference in re-infarction, stroke, and serious bleeding requiring blood transfusions were noted. We noticed a small decrease in contrast volume(mI) {mean difference (95% CI): -4.6 [-8.5 to -0.7]}, small but significantly increase in procedural time {mean difference (95% CI) 1.2 [0.1 to 2.3]}and fluoroscopy time {mean difference (95% CI) 0.8 [0.3 to 1.4] min} in the trans-radial group.

## Conclusion

TRA has significantly reduced 30-day all-cause mortality among patients undergoing PCI for ACS. TRA should be the preferred vascular access in patients with ACS.

## Introduction

Cardiovascular diseases are one of the leading causes of morbidity and mortality affecting millions of people worldwide [1]. Management of acute coronary syndrome (ACS) has evolved over a period of time to reach its current position. Percutaneous coronary intervention (PCI) is an established treatment of patients with ACS. PCI using trans-femoral approach (TFA) was embraced initially, and was replaced by the trans-radial approach (TRA). Many randomized studies comparing trans-radial and trans-femoral approaches in patients with coronary artery disease are available. Major scientific societies recommend trans-radial procedures in patients with ACS [2, 3]. In contrast to prior studies, a recently published study showed no difference in outcomes according to the access (4). None of the included randomized studies were powered for all-cause mortality events. Hence, we aimed to do an updated systematic review and metanalysis to understand the safety and efficacy of TRA Vs TFA in patients with the ACS undergoing PCI.

#### Methods

#### Search strategy

We searched PubMed and Embase for all studies on patients with ACS [unstable angina, non-ST elevation myocardial infarction (NSTEMI) and STE myocardial infarction (ST elevation MI)] undergoing PCI (Since inception to April 2021) published in the English language. Also, we looked for cross-references in the screened studies, review articles, and prior similar metaanalysis along with conference proceedings to identify studies that can be potentially included. Our complete search strategy is described in the S1 File.

#### Study registration and ethical clearance

Our study protocol is registered with PROSPERO, International prospective register of systematic reviews (CRD42020185367). As it is a meta-analysis of already published studies whose data is available online, Institute ethical committee clearance was not obtained.

#### Study eligibility

Only randomized studies on patients with ACS or STEMI undergoing PCI comparing TRA with TFA in the English literature were eligible.

#### Eligibility assessment, data extraction, and validity assessment

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was followed in the execution of this systematic review and meta-analysis. Studies identified through the databases were incorporated into a single database file using Rayyan. Screening of the studies was performed using the title and abstracts after eliminating the duplicates by two independent authors (PR and PS). The full text of the screened articles was methodically assessed later for their eligibility for inclusion into the final data extraction and qualitative data synthesis. Validity assessment for individual studies was performed by two independent authors (PR&PS) using Risk of bias assessment was done using the Cochrane risk-of-bias tool for randomized trials version 2 (RoB 2). We obtained baseline characteristics of patients, procedural details, and clinical outcomes from the included studies. Data were extracted individually by two independent physicians (PR and PS). Any disagreement between the authors in the process of title and abstract screening, full-text screening, data extraction, and validity assessment was resolved by a third author (NS).

#### Outcomes

The primary outcome of our study was all-cause mortality at 30 days. The secondary outcomes included in-hospital mortality, major adverse cardio-vascular events (MACE) (composite of death, MI, or stroke) as defined by the study, net adverse clinical event (NACE) (composite of death, MI, stroke, or major bleeding), non-fatal myocardial infarction, non-fatal stroke, stent thrombosis, study-defined major bleeding, and minor bleeding, vascular complication, hematoma, pseudoaneurysm, access site bleeding, non-access site bleeding, need for transfusion, access site cross-over, contrast volume, procedure duration, study defined acute kidney injury, mean difference in creatinine, and hospital stay duration. When an outcome is reported only by a single study, it was not included in the final analysis.

#### Statistical analysis

Data extracted from the studies were noted into a Microsoft Excel sheet which was later imported into Review Manager Version 5.3 (The Nordic Cochrane Center, The Cochrane Collaboration Copenhagen, Denmark) and R version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria) for analysis. **Random effect model was used in our meta-analysis**. We executed a random effects meta-analysis using the Mantel-Haenszel method of pooling risk ratios (RR) with 95% confidence interval (CI) for all outcomes. We computed between-study heterogeneity by using the Higgins I<sup>2</sup> statistic. We defined low and high heterogeneity as I<sup>2</sup><25% and >75% respectively. Publication bias for the primary outcome was assessed visually by the asymmetry in funnel plots. We performed a sensitivity analysis using fixed effect model. We intended to do subgroup analysis based on age (age<60/>60), sex, concurrent anticoagulation status, chronic kidney diseases (eGFR<60), Anemia (Hb<9/>/>9), and diabetes mellitus whenever the data of the same is available in more than two studies. We performed a leave-one-out sensitivity analysis to remove the effect of one study at a time on our results. We also did an analysis restricting to high-quality studies, and studies that included patients with STEMI alone. We calculated the anticipated power of the meta-analysis for major outcomes using information from previous literature and compared them with actual power attained at a 5% significance level. Several candidate covariates (mean age, % of females, % with diabetes, % with hypertension, % of smokers, and % of patients receiving GpIIb/IIIa inhibitors) were examined for association with treatment effect for all-cause mortality in ACS and STEMI patients, separately. A mixed-effects DerSimonian-Laird meta-regression was performed (based on predetermined criteria) to determine factors that significantly affected the treatment effect. Significant covariates were visualized using a bubble plot plotting treatment effect across categories of the covariate. A p-value of <0.05 was considered to be statistically significant. All Analyses were performed utilizing Review Manager version 5.3 (The Nordic Cochrane Center, The Cochrane Collaboration Copenhagen, Denmark) and R version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria).

### Results

Our search strategy resulted in 1,339 studies. After exclusion of duplicates, and inclusion of articles from references, we ended up screening 702 studies for screening. After excluding 645 which were not fulfilling the inclusion criteria, we included 57 articles for full-text screening. We excluded 37 articles due to various reasons as elucidated (Fig 1 & S1 Table in S1 File) that resulted in 20 manuscripts for final quantitative data synthesis with two of those being sub-group analysis published separately.

#### Characteristics of included studies including risk-of bias assessment

We included 18 studies for our final analyses [4-21]. Nine of them are single-center studies. Twelve of them were exclusively done in patients with STEMI. Though Jolly et al [13] and



Fig 1. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) chart. Electronic search from databases and study selection.

https://doi.org/10.1371/journal.pone.0266709.g001

Valgimigli et al [19] have conducted their study in patients with ACS, they have reported their outcomes in patients with STEMI separately leading to a total of 14 studies with clinical outcomes for patients with STEMI. Risk of-bias for the primary outcome as assessed by RoB-2 showed a low risk for 5 studies, some concerns for 9 studies, and a high risk for 4 studies (S2 Table in S1 File).

We studied 21,296 patients from 18 studies in our systematic review with 10,616 patients in the trans-radial arm and 10,680 patients in the trans-femoral arm. Baseline characteristics of the patient population in the included studies are shown in Table 1. Four of the included studies were having a large patient population (>500 patients) which contributed to the majority of the patient population in our meta-analysis [4, 5, 17, 19]. Trials differed in the use of antic-oagulation with unfractionated heparin, low molecular weight heparin and bivalirudin, and usage of vascular-closure devices (Table 1).

#### **Clinical outcomes**

The primary outcome of the study being 30-day mortality in patients with ACS was available in 10 studies only. Out of 20,122 patients with 10,037 patients in the trans-radial arm and 10,085 patients in the trans-femoral arm, we observed 30-day mortality in 174 and 232 patients, respectively underscoring the mortality benefit with the trans-radial approach [(1.7% vs. 2.3%; RR: 0.75; 95% CI: 0.62–0.91; P = 0.004; I<sup>2</sup> = 0%); Fig 2a]. A funnel plot observation showed no publication bias (S1 Fig in S1 File). A sensitivity analysis using a fixed-effect model revealed the same results (S3 Table in S1 File). A leave-one study at a time analysis showed a similar result favoring trans-radial procedure. When we restricted our analysis to high-quality RCTs with low-risk bias, we found similar results [(1.7% vs.2.2%; RR: 0.76; 95% CI: 0.62–0.93; P = 0.007; I<sup>2</sup> = 0%) Fig 2b]. There was no significant difference in the primary outcome when subgroup analysis was done based on the use of bivalirudin as the predominant anticoagulant. (S2 Fig in S1 File) Similarly, subgroup analysis based on clinical presentation i, e., NSTEMI Vs STEMI showed no effect on the primary outcome (S3 Fig in S1 File).

We performed a separate analysis for studies with clinical outcomes for patients with STEMI. Out of 14 studies with a patient population of 11,027, only 9 studies with a total population of 10,465 patients reported 30- day mortality. We observed 120 events in the trans-radial arm and 172 events in the trans-femoral arm that resulted in a significant mortality benefit with trans-radial procedures as compared with trans-femoral procedures in patients with STEMI [(2.3% vs. 3.3%; RR: 0.71; 95% CI: 0.56–0.90; P = 0.004; I<sup>2</sup> = 0%) Fig 3a]. When we restricted our analysis to studies with low-risk bias, we found a similar result with reduced 30-day mortality in trans-radial arm [(2.2% vs. 3.1%; RR: 0.70; 95% CI: 0.50–0.99; P = 0.04; I<sup>2</sup> = 43%); Fig 3b].

In patients with ACS, we found reduced MACE with trans-radial procedures [(5.8% versus 6.7%; RR: 0.87; 95% CI: 0.78–0.97; P = 0.009; I<sup>2</sup> = 0%; S4 Fig in S1 File]. However, when we restricted our analysis to high quality studies only, we observed no difference between the two arms [5.9% Vs 6.7%; RR: 0.89; 95% CI: 0.76–1.03; P = 0.11; I<sup>2</sup> = 24%; S5 Fig in S1 File]. When we performed sub-group analysis on patients with STEMI only, we found reduced MACE with trans-radial procedures [(4.8% versus 5.6%; RR: 0.82; 95% CI: 0.68–1.00; P = 0.05; I<sup>2</sup> = 14%); S6 Fig in S1 File]. However, we observed no difference in MACE when restricted to high quality studies with STEMI patients alone [(4.8% VS 5.6%; RR: 0.83; 95% CI: 0.64–1.07; P = 0.15; I<sup>2</sup> = 47%) S7 Fig in S1 File].

#### Power of the meta-analysis for various outcomes and meta-regression

For the primary outcome, all-cause mortality at 30 days in patients with ACS, both anticipated and actual power was very high (>90%) regardless of the quality of studies (S8A-S8D Fig in <u>S1</u>

| CHARACTERISTICS                                | GAN et al 2009   | HOU et al 2010   | TEMPURA<br>(SAITO et al)  | MATRIX<br>(VALGIMIGLI et al)  | YAN et al 2008   | WANG et al 2012   |
|--|--|--|---|---|--|---|
| Trial design                                   | RCT; <u>MC</u><br>June 2004- July 2007   | RCT; SC<br>Aug 2005- Sept 2008   | RCT; SC<br>July 1999- Feb 2001  | RCT; <u>MC</u><br>Oct-11-2011- Nov-7-2014   | RCT; <u>MC</u><br>June 2005- June 2007   | RCT; SC<br>July 2008- Dec 2010  |
| Population                                     | STEMI; 195 PTS   | ACUTE MI; 200 PTS  | STEMI; 149 PTS  | ACS; TR- 4197; TF-4207  | STEMI; TR- 57, TF-46   | STEMI; TR- 60, TF- 59   |
| Age  | 53.6±12.5/52.3±11.9  | 64.9±8.4/66.2±7.7  | 66±12/67±10   | 65.6(11.8)/65.9(11.8)   | 70.3±7.5/71.4±8.4  | 59.8±12.4/60.2±11.4   |
| Mean guiding catheter<br>per patient (mean) sd | 1  | ı  | $1.1\pm0.4/1.1\pm0.3$   |   |  |   |
| Inclusion criteria                             | Typical chest pain<br>>30min and <12<br>houres; nitrate losing<br>efficacy, with ST<br>segment elevation<br>>0.1mV in the limb<br>leads or >0.2mV in 2<br>or more adjacent<br>chest leads. | Patients with AMI  | <b>Pa</b> tients with<br>AMI-STEMI within<br>12 hr from onset   | Patients with high-risk<br>unstable angina, NSTE-ACS,<br>or STEMI undergoing invasive<br>approach   | Chest pain for more than 30 minutes<br>without response to nitroglycerine,<br>ST elevation > 1mm in 2 or more<br>contiguous leads. | Typical Clinical<br>presentation, ST<br>elevation of over<br>0.2mm, Received<br>Intravenous<br>thrombolysis within 6<br>hours from symptom<br>onset in non-PCI<br>hospital within 12<br>hours after Intravenous<br>thrombolysis.  |
| Exclusion criteria                             | Negative Allen's test  | Femoral approach due<br>to Cardiogenic shock,<br>History of CABG<br>Negative Allen test<br>Non palpable radial<br>artery | Radial artery pulse was<br>too weak for<br>successful radial artery<br>puncture. If the culprit<br>vessel was the previous<br>coronary bypass graft<br>and if the operator for<br>that particular patient<br>did not consider that<br>both TRI and TFI<br>would be equally<br>feasible. | Stable or silent coronary artery<br>disease; LMWH in the<br>previous 6 h; glycoprotein IIb/<br>IIIa inhibitors in the previous 30<br>d; any PCI in the previous 30<br>d; contraindications to<br>angiography, including but<br>not limited to severe<br>peripheral vascular disease | Cardiogenic shock, Non-palpable<br>radial artery, Negative Allen test,<br>Chronic renal failure                                    | Contraindications of<br>thrombolysis, History<br>of CABG, Cardiogenic<br>shock, Known<br>difficulties with<br>Femoral or radial<br>approach, Pathologic<br>Allen's test Pre-<br>procedural<br>implantation of<br>transient pacemaker or<br>IABP, Chronic renal<br>insufficiency with<br>potential necessity of<br>using radial artery as<br>native fistula,<br>Hemodialysis patients<br>with AV fistula Patient<br>refusal. |
| Minimum expertise<br>required yes/No           |  | > 200 cases of TRI   |   | >75 transradial coronary<br>procedures within previous<br>year  | Those who performed >500 cases of TRI.   | Those who performed<br>>500 cases of TRI.   |
| Primary outcome of<br>the study                | 1  |  | MACE during the<br>initial hospitalization<br>period and the<br>9-month follow-up<br>period.  | MACE: death, nonfatal MI,<br>and stroke; NACE: non–<br>CABGrelated major bleeding,<br>BARC type 3 or 5 or MACE  |  | 1   |

Table 1. Characteristics of included studies.

(Continued)

| Anticoagulant used                                     | 1   |  |                                       | Before Cathlab- UFH- 1239<br>VS 1236 Bivalirudin- 4 VS 2<br>LMWH- 684(16.3%) VS 738<br>(17.5%) In-Cathlab- UFH-<br>2094(49.9%) VS 1916(45.5%)<br>Bivalirudin- 1683(40.1%) VS<br>1712(40.7%) LMWH- NA  |   |  |
|--|---|--|---------------------------------------|---|---|--|
| Vascular closure<br>device                             | 1   | I  | I                                     | 1   | 1   | 1  |
| GpIIb/IIIa inhibitor                                   | 28(31.1%) VS 36<br>(34.3%)  | 28 (28%) VS 20 (20%)   | Not Approved for Use<br>In Japan then | Before Cath Lab—8(0.2%) VS<br>7(0.2%) In-Cath Lab-574<br>(13.7%) VS 520(12.4%)  | 1   | 33(55%) VS 30 (58%)  |
| Chronic kidney<br>disease (as defined by<br>the study) |   |  |                                       | Renal failure and dialysis <b>TR-</b><br>46+4 (1.2%) <b>TF-63 (1.5%</b> )   |   | GIVEN LAB VALUES<br>(micromol/L); SCr<br>before PCL- TR- 83<br>±14.9 TF- 76.1±27.1<br>SCr 72 hours after PCI-<br>TR- 93.7±20.2 TF- 86.1<br>±19.3           |
| CHARACTERISTICS  | RIVAL<br>(JOLLY et al 2011)   | ETRIBY et al 2017  | MANN et al 1998                       | RADIAL-AMI<br>(CANTOR et al)  | OCEAN RACE<br>(KOLTOWSKI et al)   | LI et al 2007  |
| Trial design   | RCT; MC<br>June-6-2006-Nov-3-<br>2010   | RCT; SC<br>Dec-13- Dec '15   | RCT; SC<br>April-July 97              | RCT; MC   | RCT; SC OPEN LABEL<br>Sept 2010- Oct 2012   | RCT; SC<br>June 2004- June 2006  |
| Population   | ACS- TR-3507, TF-<br>3514   | ACS-100 PTS  | ACS; 142 PTS                          | STEMI, 50 PTS   | STEMI, TR-52, TF-51   | AMI; TR-184, TF-186  |
| AGE  | 62±12/62±12   | 55.18±8.1/55.94±8.76   | 63/62                                 | 52(48,60)(MEDIAN)/<br>58(49,72)   | 61(49.7-72.2)/62.8(50.2-75.4)   | 56.5±10.9/55.4±12.8  |
| Mean guiding catheter<br>per patient (mean) sd         |   |  |                                       |   |   |  |
| Inclusion criteria                                     | Patients with ACS,<br>with or without ST-<br>segment elevation,<br>and planned invasive<br>approach   | Recent onset acute<br>coronary syndrome<br>(whether (UA)/<br>(NSTEMI)(STEMI))<br>undergoing<br>revascularization via<br>PCI. |                                       | All patients with STEMI for<br>primary and rescue PCI,<br>patients could be enrolled<br>within 12 hours of symptom<br>onset and within 12 hours of<br>thrombolysis, respectively.   | Patients with STEMI, symptoms<br>between 20min and 24 h of symptom<br>onset, undergoing PCI   | Patients admitted as<br>Acute MI(AMI)  |
| Exclusion criteria                                     | Cardiogenic shock,<br>severe peripheral<br>vascular disease<br>precluding a femoral<br>approach, or<br>previous CABG with<br>use of >1 internal<br>mammary artery | Cardiogenic shock or<br>resuscitated from<br>cardiac arrest, history<br>of CABG or chronic<br>kidney disease.                |                                       | Patients in cardiogenic shock,<br>abnormal Allen's test result, or<br>had contraindications to GP<br>IIb/IIIa inhibitor use (active<br>bleeding, major surgery/<br>biopsy/significant trauma in<br>the past 6 weeks, SBP<br>>200mmHg or DBP>110 mm<br>Hg, INR >2, recent<br>noncompressible vascular<br>puncture, central nervous<br>system structural damage or<br>stroke/ transient ischemic<br>attack within the last 6<br>months, baseline platelet count<br><100000 cells/AL). | INR > 1.4<br>Thrombocytopenia < 100 × 103<br>Previous CABG Known vascular<br>access difficulties or complications<br>Active bleeding Gastric or duodenal<br>peptic ulcer Current or planned<br>dialysis Severe liver failure<br>(MELD > 10 points) Uncontrolled<br>hypertension (> 160/100 mm Hg)<br>Cardiogenic shock Low compliance<br>to long-term follow-up | Negative Allen test<br>Aorto-arteritis<br>Cardiogenic shock<br>Non-palpable radial<br>artery Severe tortousity<br>of radial arteries Body<br>height <150cm |

Table 1. (Continued)

| Minimum expertise<br>required yes/no                   | >50 transradial<br>coronary procedures<br>within previous year                |                                   |                                      | All operators in this study had<br>performed >100. transradial<br>PCI procedures before the<br>study.  | Procedures were performed by<br>independent radial operators who<br>carry out at least 200 PCIs per year<br>using a radial approach, and<br>operators who were in training<br>(< 200 PCI per year). | ,                                   |
|--|---|-----------------------------------|--------------------------------------|--|---|-------------------------------------|
| Primary outcome  | NACE: Death, MI,<br>stroke, or non-<br>CABG-related major<br>bleeding         |                                   |                                      | The primary efficacy end point<br>of the trials was reperfusion<br>time (time from local<br>anesthesia infiltration to the<br>first balloon inflation). The<br>primary safety end points of<br>the trial were major bleeding<br>(intracranial or retroperitoneal<br>bleeding, a drop in<br>hemoglobin level >5 g/dL or<br>hematocrit>15%, or whole<br>blood or packed red cell<br>transfusions) and access site<br>complications (hematoma >5<br>cm, pseudoaneurysm,<br>arteriovenous fistula, access<br>site rebleeding after initial<br>hemostasis) during the initial<br>hospitalization. | The primary endpoints were major<br>bleeding by the REPLACE-2 scale<br>and minor bleeding by the EASY<br>scale (TR arm) or the FEMORAL<br>scale (TF arm).   |                                     |
| Anti-coagulation used                                  | UFH- 1168(33.3%)<br>VS 1110(31.6%)<br>Bivalirudin- 76<br>(2.2%) VS 109 (3.1%) |                                   |                                      |  |   | UFH                                 |
| Vascular closure<br>device                             | 1   |                                   | 1                                    | 0 VS 2(8%)   | I   | 1                                   |
| GP IIb/IIIa inhibitor                                  | 887 (25.3%) VS 844<br>(24%)   | 2 (4%) VS 9 (18%)                 | 10(15%) VS 8(10%)                    | 24(95%) VS 23(92%)   | 31 (59.2%) VS 34 (66.7%)  | 1                                   |
| Chronic kidney<br>disease (as defined by<br>the study) |   |                                   |                                      |  | TR-6 (12%) TF- 9 (18.4%)  |                                     |
| CHARACTERISTICS  | FARMI-<br>(BRASSELET et al)   | RADIAMI-<br>(CHODOR<br>et al2009) | RADIAMI-II<br>(CHODOR et al<br>2011) | SAFARI STEMI<br>(LE MAY et al 2020)  | RIFLE- STEACS<br>(ROMAGNOLI et al)  | STEMI RADIAL<br>(BERNAT et al)      |
| Trial Design And<br>Centre                             | RCT; <u>MC</u><br>Jan 2004-Sept 05  | RCT; SC<br>April 2005- June 2006  | RCT; SC<br>Nov 2006- March<br>2008   | RCT; <u>MC</u><br>July 2011- Dec 2018  | RCT; <u>MC</u><br>Jan 2009- July 2011   | RCT; <u>MC</u><br>Oct 2009-Feb 2012 |
| Population   | STEMI; 114 PTS  | STEMI 100 PTS                     | STEMI; 108 PTS                       | STEMI; 2292 PTS  | STEMI; 1001 PTS   | STEMI; 707 PTS                      |
| Age  | 60±12/58±13   | 59.9±9.4/59.1±9.0                 | 62.1±9.3/57.6±10.3                   | 61.6±12.3/62.0±12.1  | 65(56–75)/ 65(55–77)  | 60±12/58±13                         |
| Mean guiding catheter<br>per patient (mean) sd         | 1.24±0.68/ 1.11±0.42  |                                   |                                      |  |   |                                     |
|  |   |                                   |                                      |  |   | (Continued)                         |

Table 1. (Continued)

| Table 1. (Continued)                                   |   |   |  |  |   |  |
|--|---|---|--|--|---|--|
| Inclusion criteria                                     | Acute coronary<br>syndrome with ST<br>segment elevation<br>associated with<br>sustained chest pain,<br>undergoing PCI   | Age between 18 and<br>75 years; Presence of<br>M1- ST elevation<br>defined as retrosternal<br>pain lasting longer<br>than 20 minutes, but<br>not longer than 12<br>hours,   | ACS with ST segment<br>elevation associated<br>with retrosternal pain<br>lasting between 20<br>min and 12 h,<br>undergoing PCI   | Patients with STEMI who were<br>referred for primary PCI<br>within 12 hours after symptom<br>onset   | Patients suspected of having STEMI<br>planned for early revascularization<br>strategy, within 24 h of symptom<br>onset  | Patients with STEMI,<br>within 12 h of symptom<br>onset, undergoing PCI  |
| Exclusion criteria                                     | Haemodynamic<br>instability (ie, Killip<br>state .2 or<br>cardiogenic shock),<br>the need for an intra-<br>aortic balloon pump<br>or temporary<br>or temporary<br>pacemaker, a history<br>of a coronary artery<br>bypass graft (CABG)<br>or intolerance to<br>abciximab | Age over 75 years;<br>Killip class III or IV;<br>Necessity of an intra-<br>aortic balloon<br>pumping placement<br>before the CA;<br>Necessity of an<br>endocavitary<br>stimulating electrode<br>placement before the<br>CA; Height < 150 cm;<br>history of coronary<br>artery by pass grafting<br>(CABG), if the<br>infarction may be due<br>to a closed venous or<br>arterial bypass graft | Killip class III or IV.<br>Necessity to use an<br>intra-aortic<br>counterpulsation<br>balloon or temporary<br>right ventricular<br>pacing, with the<br>decision made before<br>decision made before<br>coronary<br>arteriography (CA).<br>Patient's height < 150<br>cm. History of<br>cm. History of<br>coronary artery bypass<br>grafting (CABG). | Patients who had received<br>fibrinolytic therapy, had been<br>prescribed oral anticoagulant<br>therapy,<br>orhadundergoneprevious<br>coronary arterybypass graft<br>(CABG) surgery. | Contraindication to radial or femoral<br>vascular access (abnormal result on<br>Allen test, severe peripheral vascular<br>disease), recent stroke (within 4 wk),<br>oral anticoagulation, or other severe<br>bleeding diathesis | Cardiogenic shock,<br>prior aortobifemoral<br>bypass, absence of<br>bilateral radial or<br>femoral artery pulses,<br>negative result on Allen<br>test or Barbeau test type<br>D curve, oral<br>anticoagulation |
| Minimum expertise<br>required yes/No                   |   | Many years'<br>experience of heart<br>catheterization with<br>TFA (300–400 PCI<br>per year), who had<br>performed at least 50–<br>100 interventions<br>using TRA  | Three physicians with<br>17–20 years of<br>experience in<br>performing PCI via<br>TFA and several years<br>experience in<br>performing PCI via<br>TRA, took part in the<br>study.  | Operators typically performed<br>more than 250 PCI procedures<br>annually.   | >150 PCIs/y with adequate expertise<br>in both approaches, minimal<br>proficiency criteria of >50%<br>transradial coronary procedures per<br>year   | >200 PCIs/y in high-<br>volume radial centers<br>(>80% cases/y)  |
| Primary Outcome  |   |   |  | All-cause 30-day mortality   | NACE: Cardiac death, MI, stroke,<br>TLR, and non–CABG-related per<br>protocol bleeding  | Major bleeding and<br>vascular access-site<br>complications<br>requiring intervention  |
| Anticoagulation Used                                   |   |   |  | UFH- 135(11.9%) VS 88(7.6%)<br><u>BIVA</u> LIRUDIN- 1001 (88.1%)<br>VS 1068 (92.4%)  | UFH- DOSE <u>BIVALIRUDIN</u> - 40<br>(8%) VS 36 (7.2%)  | LMWH- 6(1.7%) VS 0<br>UFH- DOSE GIVEN<br>(NOT THE<br>POPULATION)   |
| Vascular Closure<br>Device Used                        |   |   |  | 63(5.5%) VS 789 (68.3%)  | 1   | 4(1.1%) VS 136(38%)  |
| Gp IIb/IIIa inhibitor                                  |   | 22(44%) VS 21(42%)<br>Abciximab   | 25 (51%) VS 32(54%)<br>Abcixmab  | 69(6.1%) VS 68(5.9%)   | 337 (67.4%) VS 350(69.9%)   | 155(45%) VS 162 (45%)  |
| Chronic kidney<br>disease (as defined by<br>the study) |   |   |  | eGFR at baseline (mL/min)<br>TR- 101.7 TF- 103.8   |   |  |
| Abbreviations: TR- Tra                                 | uns-radial; TF-Transfemo  | oral; UFH- unfractionated   | l heparin; LMWH- Low r   | nolecular weight heparin; ACS- A   | cute coronary syndrome; STEMI- ST el  | levation myocardial  |

infarction.



**Fig 2.** Comparison of Trans-radial approach (TRA) versus Trans-femoral approach (TFA) in patients with acute coronary syndrome showing that TRA is associated with reduced risk of all-cause mortality at 30 days (2.A) in all studies and in studies with low-risk bias (2.B). (B). ACS = Acute coronary syndrome; M-H = Mantel-Haenszel; CI- = confidence interval.

https://doi.org/10.1371/journal.pone.0266709.g002

File). For MACE at 30 days, the actual power was much higher (>95%) compared to the anticipated power of <45%, regardless of the quality of studies (S8E-S8H Fig in S1 File). In patients with STEMI, a similar pattern was observed with >99% power for all-cause mortality at 30 days, regardless of the quality of studies included (S8I-S8K Fig in S1 File) For MACE among STEMI, the actual power for all included studies (80.3%) and only high-quality studies (70.2%) were much lower than the anticipated power of 94.6%(S8L-S8N Fig in S1 File).

For ACS, the subgroup analysis did not reveal any significant covariates. Meta-regression carried out with mean age, % of females, % with diabetes, and % receiving GpIIb/IIIa inhibitors also did not reveal any significant covariates (S4 Table in S1 File) in patients with ACS. For patients with STEMI, % of patients receiving GpIIb/IIIa inhibitors was significantly associated with treatment effect in both subgroup and meta-regression analyses. In trials where  $\geq$ 25% of patients received GpIIb/IIIa inhibitors, all-cause mortality was 46% lower in the TR group but in trials where <25% received the inhibitors, there was no difference between the TRA and TFA groups (S5 Table and S9 Fig in S1 File).

### Other clinical outcomes

We found significantly decreased study-defined major bleeding(0.9% versus 1.5%; RR: 0.61; 95% CI: 0.47–0.79; P = 0.0002; I<sup>2</sup> = 0%), BARC class 3–5 bleeding(1.6% vs 2.3%; RR: 0.68; 95% CI: 0.52–0.90; P = 0.007; I<sup>2</sup> = 0%), minor bleeding(1.6% versus 2.0%; RR: 0.77; 95% CI: 0.62–0.94; P = 0.01; I<sup>2</sup> = 0%), vascular site complications(1.3% vs 3.7%; RR: 0.36; 95% CI: 0.26–0.50; P<0.00001; I<sup>2</sup> = 0%), hematoma(1.5% vs 4.3%; RR: 0.38; 95% CI: 0.29–0.50; P<0.00001; I<sup>2</sup> = 0%), and pseudoaneurysms(0.2% vs 0.7%; RR: 0.39; 95% CI: 0.20–0.77; P = 0.007; I<sup>2</sup> = 0%) in the trans-radial arm [Fig 4A–4D & S10 and S11 Figs in S1 File]. We noticed increased NACE in trans-femoral arm mostly due to the effect of study-defined major bleeding [7% versus



**Fig 3.** Comparison of Trans-radial approach (TRA) versus Trans-femoral approach (TFA) in patients with STEMI showing that TRA is associated with reduced risk of all-cause mortality at 30 days (3.A) in all studies and in studies with low-risk bias (3.B) (B). STEMI = ST elevation myocardial infarction; M-H = Mantel-Haenszel; CI- = confidence interval.

https://doi.org/10.1371/journal.pone.0266709.g003

| $\frac{\log    \log t_{1} }{\log t_{2} } = \frac{\log t_{1}}{\log t$  |  | TRANS RAD  | DIAL 1   | RANS FEMO   | RAL   |   | Risk Ratio   |  | Risk Ratio          |                       | Church or Cultureup   | TRANS  | RADIAL   | TRANS FE   | MORAL  | Moinht I  | Risk Ratio   | Ris                                     | k Ratio           |     |
|--|--|--|--|---|---|---|--|--|---------------------|-----------------------|---|--|--|--|--|---|--|---|-------------------|-----|
| All and a set of a  | or Subgroup  | Events   | 249  | 26  | 269   | 7 6%  | Random, 95% CI   | M-H  | 1, Kandom, 95% CI   |                       | Bernat 2014   | LYGIN  | 1 34   | 3 3  | 359  | 1.9%  | 0.34 (0.04.3.29)   | men, roa                                |                   |     |
| Sector 10 2 2 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0  | elet 2007  | 3  | 67   | 3   | 57  | 2.8%  | 1.00 (0.21 4.75)   | - 11 I I -   |                     |                       | Gan 2009  |  | 2 9  | 1 12   | 105  | 4.6%  | 0.19 (0.04, 0.85)  | 1 - 1 - 1 - 1 - 1 - 1 - 1 - 1 - 1 - 1 - |                   |     |
| 2000 3 0 0 7 0 0 4 7 0 0 4 7 0 0 4 7 0 0 4 7 0 0 4 7 0 0 4 7 0 0 4 7 0 0 4 7 0 0 4 7 0 0 0 7 0 0 2 7 0 7 0 0 0 0 0 0 0 0 0   | 2005   | 0  | 25   | 0   | 25  |   | Not estimable  |  |                     |                       | Mehta NSTEMI 2012   | 3  | 7 255  | 96   | 2511   | 70.1%   | 0.38 (0.26, 0.55)  | -                                       |                   |     |
| Applied a general description of the second description of the seco  | r 2009   | 3  | 50   | 7   | 50  | 4.1%  | 0.43 [0.12, 1.56]  |  |                     |                       | Mehta STEMI 2012  | 1  | 2 95   | 5 35   | 1003   | 23.4%   | 0.36 (0.19, 0.69)  |   |                   |     |
| $\frac{10}{101} \frac{1}{102} 1$   | or 2011  | 4  | 49   | 6   | 59  | 4.7%  | 0.80 (0.24, 2.68)  |  |                     |                       |   |  |  |  |  |   |  |   |                   |     |
| $\frac{1}{1000} \frac{1}{100} 1$   | 010  | 0  | 100  | 3   | 100   | 0.8%  | 0.14 [0.01, 2.73]  |  |                     |                       | Total (95% CI)  |  | 394  | 5  | 3978   | 100.0%  | 0.36 [0.26, 0.50]  | •                                       |                   |     |
| $\frac{1}{100} \frac{1}{100} \frac{1}$   | 011  | 24   | 3507   | 33  | 3514 :  | ;4.9%   | 0.73 [0.43, 1.23]  |  |                     |                       | Total events  | 5  | 2  | 146  |  |   |  |   |                   |     |
| Carding on 2 Car  | /SKI 2014  | 3  | 1100   | 20  | 5/  | 2.2%  | 1.34 [0.23, 7.71]  | 1 ale a 21 a   |                     |                       | Heterogeneity: Tau <sup>2</sup>   | = 0.00; Ch   | i <sup>2</sup> = 0.75,   | If = 3 (P = 0.8  | 6); I <sup>2</sup> = 0%  |   |  | 0.01 01                                 | 1 1               |     |
|  | enoli 2012   | 12   | 500  | 14  | 501   | 0.0%  | 0.64 (0.28, 1.24)  |  |                     |                       | Test for overall effect   | t: Z = 6.33  | (P < 0.000   | 01)  |  |   |  | Eavours levnerimenta                    | I Favours Icont   |     |
| <figure></figure>  | 2003   | ő  | 77   | 2   | 72  | 0.7%  | 0.19 (0.01, 3.83) *  |  |                     |                       |   |  |  |  |  |   |  | r arours texperimenta                   | d i aroaro feorie |     |
| by 0 by 0 to 27 to 28 by 0.5%  | igli 2015  | 26   | 4197   | 37  | 4207  | 17.3%   | 0.70 [0.43, 1.16]  |  |                     |                       |   |  |  |  |  |   |  |   |                   |     |
| <sup>90</sup> 0 67 1 40 07% 027 01,044<br><sup>91</sup> 1022 1022 1022 1022 1022 1022 1025 10 50 10 41<br><sup>91</sup> 2022 1020 0 801 [0.47, 0.7]<br><b>91</b> 2022 1020 0 801 [0.47, 0.7]<br><b>94</b> 1022 1022 1020 0 801 [0.47, 0.7]<br><b>95</b> 0.0022 1022 1020 0 801 [0.47, 0.7]<br><b>95</b> 0.0022 1022 1020 0 801 [0.47, 0.7]<br><b>95</b> 0.002 102 100 0 801 [0.22, 0.40]<br><sup>100</sup> 0 17 116 226 0 0020 1 100 [0.600 0 902 0 118]<br><b>95</b> 0.002 102 100 0 80 102 100 [0.600 0 100 0 900 0 23] 077 04% 0 0210 (0.41, 0.7]<br><sup>100</sup> 0 17 116 226 0 0020 1 100 0 900 0 230 077, 145 0 0280 0.40, 0.22]<br><sup>100</sup> 0 17 116 226 0 0020 1 100 0 900 0 230 077, 145 0 0280 0.40, 0.22]<br><sup>100</sup> 0 17 116 226 0 0020 1 100 0 900 0 230 077, 145 0 0280 0.40, 0.22]<br><sup>100</sup> 0 17 116 226 0 0020 1 100 0 900 0 230 077, 145 0 0280 0.40, 0.22]<br><sup>100</sup> 0 17 116 226 0 0020 1 100 0 900 0 230 077, 145 0 0280 0.41, 0.22]<br><sup>100</sup> 0 17 110 316 0 256 0 032107, 141<br><sup>100</sup> 0 17 110 316 0 256 0 032107, 141<br><sup>100</sup> 0 17 110 316 0 256 0 032107, 141<br><sup>100</sup> 0 17 110 316 0 256 0 032107, 141<br><sup>100</sup> 0 17 110 316 0 256 0 032107, 141<br><sup>100</sup> 0 17 110 316 0 256 0 032107, 141<br><sup>100</sup> 0 17 110 316 0 256 0 032107, 141<br><sup>100</sup> 0 17 110 316 0 256 0 032107, 141<br><sup>100</sup> 0 17 110 316 0 256 0 032107, 141<br><sup>100</sup> 0 17 110 316 0 256 0 032107, 141<br><sup>100</sup> 0 17 110 316 0 256 0 032107, 141<br><sup>100</sup> 0 17 10 316 0 256 0 032107, 141<br><sup>100</sup> 0 17 10 316 0 256 0 032107, 141<br><sup>100</sup> 0 17 10 316 0 256 0 032107, 141<br><sup>100</sup> 0 17 10 316 0 256 0 032107, 141<br><sup>100</sup> 0 17 10 316 0 256 0 032107, 141<br><sup>100</sup> 0 17 10 316 0 256 0 032107, 141<br><sup>100</sup> 0 17 10 316 0 256 0 032107, 141<br><sup>100</sup> 0 17 10 316 0 10 0 08 0 023107, 141<br><sup>100</sup> 0 17 10 000 0 10 0 0 0 0 0 0 0 0 0 0 0   | 012  | 0  | 60   | 3   | 59  | 0.8%  | 0.14 [0.01, 2.66] 4  |  |                     |                       |   |  |  |  |  |   |  |   |                   |     |
| $\frac{95 (2)}{100}  \frac{1027}{100}  \frac{102}{100}  \frac{102}{100$  | 08   | 0  | 57   | 1   | 46  | 0.7%  | 0.27 [0.01, 6.48]  |  |                     |                       | 1 E Homate  | ama  |  |  |  |   |  |   |                   |     |
| $\frac{1}{1000} \frac{1}{1000} \frac{1}{100} \frac{1}{1$   | NEW CIL  |  | 10227  |   | 10262 4   | 00.02   | 0 64 10 47 0 701   |  |                     |                       | 4.L Heman   | Jilla  |  |  |  |   |  |   |                   |     |
| $\frac{1}{Partial dett. 2 = 2 B d triangle detter dett$   | 35% CI)  | 00   | 10221  | 157   | 10202 1   | 50.0%   | 0.01 [0.47, 0.79]  |  | •                   |                       |   | FRANS RAD  | AL TRA   | IS FEMORAL   |  | Risk Rat  | lio  | Risk Ratio                              |                   |     |
| $\frac{Our min}{16 \text{ more transformed}} = \frac{Our min}{16  more transfor$   | ogeneity: Tau <sup>2</sup>   | = 0.00: Ch <sup>2</sup> =  | 10.71 dt   | = 12 (P = 0.5   | 55): I <sup>2</sup> = 04                                      | 6   |  |  |                     |                       | Study or Subgroup   | Events   | 249  | 10 269   | 2.6%   | 0.11.10   | 02.0461  | M-H, Kandom, 95% CI                     |                   |     |
| $\frac{1}{10000} \frac{1}{10000} \frac{1}{10000} \frac{1}{10000} \frac{1}{10000} \frac{1}{100000} \frac{1}{100000} \frac{1}{1000000} \frac{1}{10000000000000000000000000000000000$   | or overall effect  | : Z = 3.74 (P =  | = 0.0002)  |   |   |   | c  | 3.01 0.1   | 1 10                | 0 100                 | Brasselet 2007  | 2  | 57   | 11 57  | 3.5%   | 0.18 10   | 04 0.781   |   |                   |     |
| BARC 3-5 bleeding<br>TRANS RADAL TARKS FEMORAL Rest: The Main rest: Trans RADAL rest: Rest RATE<br>radia rest:   |  |  |  |   |   |   |  | Favours (experim   | nemaij Pavouis (com | aoij                  | Cantor 2005   | 2  | 25   | 7 25   | 3.4%   | 0.29 [0.  | 07, 1.24]  |   |                   |     |
| $\frac{12 \text{ Mir} \text{ C} 9 \text{ C} \text{ Set} \text{ Set} \text{ Real}}{1139 2 \text{ C} 2 \text{ Real} \text{ Tetal} \text{ Weight MAL Readom, 59 \times C} \\ \frac{12 \text{ Mir} \text{ Real}  R$   | BARC   | 3-5 hl   | ihaa   | nσ  |   |   |  |  |                     |                       | Chodor 2009   | 5  | 50   | 8 50   | 6.7%   | 0.63 [0.  | 22, 1.78]  |   |                   |     |
| $\frac{\text{TRANS RADUL}}{\text{Sphere}} \underbrace{\text{Trans read}}_{\text{Sphere}} \underbrace{\text{Trans read}} \underbrace{\text{Trans read}} \underbrace{\text{Trans read}} \underbrace{\text{Trans read}} \text{$ | DAILC  | 2-2 DIG  | eeui   | 116   |   |   |  |  |                     |                       | Chodor 2011   | 8  | 49   | 12 59  | 11.3%  | 0.80 [0.  | 36, 1.81]  |   |                   |     |
| $\frac{f \ Subgrow}{f \ Subgrow} \frac{F \ Subgrow}{f \ Subgrow} $   |  | TRANS RA   | ADIAL  | TRANS FEM   | IORAL   |   | Risk Ratio   |  | Risk Ratio          |                       | Ethioy 2017   | 2  | 50   | 8 50   | 3.3%   | 0.25 [0.  | 06, 1.12]  |   |                   |     |
| $\frac{2020}{12015} \underbrace{19}{1138} \underbrace{17}{116} \underbrace{188}{27} \underbrace{178}{1158} \underbrace{228}{258} \underbrace{0.72}{1204,123} \underbrace{0.49,123}{0.6016,0.001} \underbrace{0.610,0.01}{0.610,0.01} $   | or Subgroup  | Events   | Total  | Events  | Total   | Weight N  | i-H, Random, 95% (   | <u>ci</u>  | M-H, Random, 95%    | CI                    | Jolly 2010  | 42   | 3507   | 106 3514   | 58.9%  | 0.40 (0.  | 28 0.571   | -                                       |                   |     |
| $ \begin{array}{cccccccccccccccccccccccccccccccccccc$  | ay 2020  | 19   | 1136   | 27  | 1156  | 22.6%   | 0.72 [0.40, 1.2]   | 8]   |                     |                       | Li 2007   | 2  | 184  | 7 186  | 3.0%   | 0.29 [0.  | 06, 1.37]  |   |                   |     |
| $\frac{995 (C)}{900 (S)} = 533 \frac{123}{933} \frac{533}{100,0\%} \frac{100,0\%}{10.4} 100,0$  | nigli 2015   | 64   | 4197   | 95  | 4207  | 77.4%   | 0.68 (0.49, 0.9)   | 2]   | -                   |                       | Mann 1998   | 0  | 65   | 3 77   | 0.9%   | 0.17 [0.  | 01, 3.21]  | -                                       |                   |     |
| $\frac{1}{1000} = \frac{1}{1000} = \frac{1}{1000} = 0.08(t; t = 0.05)} + \frac{1}{1000} =$   | (95% Ch  |  | 5333   |   | 5363  | 100.0%  | 0.68 (0.52, 0.9)   | 01   | •                   |                       | Wang 2012   | 1  | 60   | 6 59   | 1.7%   | 0.16 (0.  | 02, 1.32   |   |                   |     |
| $\frac{1}{10000} \frac{1}{10000} \frac{1}{100000} \frac{1}{10000000000000000000000000000000000$  | events   | 83   | 0000   | 122   | 0000  | 1001010   | 0100 [0102, 0100   |  | · · · ·             |                       | Tan 2008  | 0  | 5/   | 4 40   | 0.9%   | 0.08 (0.  | 00, 1.63)  |   |                   |     |
| Total affect 2 = 2.99 (P = 0.007)       0.01       0.1   | rogeneity: Tau   | = 0.00: Chi <sup>2</sup> =   | = 0.03. d  | f=1 (P=0.8  | (6):   <sup>2</sup> = 0                                       | %   |  | to t   |                     |                       | Total (95% CI)  | the strengt  | 4552   | 4582   | 100.0%   | 0.38 [0.  | 29, 0.50]  | •                                       |                   |     |
| $\frac{1}{10000 \text{ productions}} \frac{1}{10000 \text{ productions}} $   | for overall effe   | t Z = 2.69 (P  | = 0.007  | )   |   |   |  | 0.01 0.1<br>Eavoure lav                                    | nerimentall Eavours | 10 100<br>F (control) | Total events  | 68   |  | 197  |  |   | a state and an a   | And I have a                            |                   |     |
| Totak SKADIAL       TOTAK SKADIAL <th colspa<="" td=""><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>r atouts levt</td><td>pennental ratous</td><td>steomoit</td><td>Heterogeneity: Tau* = 0</td><td>.00; Chi#=1</td><td>0.77, df = 1</td><td>(P = 0.46); P =</td><td>= 0%</td><td></td><td>0.01 0.1</td><td>1 1 10</td><td>100</td></th>   | <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td>r atouts levt</td> <td>pennental ratous</td> <td>steomoit</td> <td>Heterogeneity: Tau* = 0</td> <td>.00; Chi#=1</td> <td>0.77, df = 1</td> <td>(P = 0.46); P =</td> <td>= 0%</td> <td></td> <td>0.01 0.1</td> <td>1 1 10</td> <td>100</td> |  |  |   |   |   |  |  | r atouts levt       | pennental ratous      | steomoit  | Heterogeneity: Tau* = 0  | .00; Chi#=1  | 0.77, df = 1   | (P = 0.46); P =  | = 0%  |  | 0.01 0.1                                | 1 1 10            | 100 |
| $\begin{array}{c c c c c c c c c c c c c c c c c c c $   |  |  |  |   |   |   |  |  |                     |                       | Test for overall effect. 2  | = 0.85 (P = 1  | 0.00001)   |  |  |   | Favours (e:  | xperimental) Favours (control)          |                   |     |
| $\begin{array}{c c c c c c c c c c c c c c c c c c c $   |  |  |  |   |   |   |  |  |                     |                       |   |  |  |  |  |   |  |   |                   |     |
| Minor bleeding           Teams ration:         Risk Ratio         Risk Ratio         Colspan="2">Colspan="2"           Vision Colspan="2">Colspan="2"         Colspan="2">Colspan="2"         Colspan="2">Colspan="2"         Colspan="2">Colspan="2"         Colspan="2"         Colspa="2"         Colspan="2"         Col   |  |  |  |   |   |   |  |  |                     |                       |   |  |  |  |  |   |  |   |                   |     |
| Stringer Deleteding         Trans Stringer Deleteding         Risk Ratio         Risk Ratio<   |  |  |  |   |   |   |  |  |                     |                       | 4 E Droudo  | 20011  | nicm   |  |  |   |  |   |                   |     |
| TANS SEAD/Line         TRANS FEMORAL         Risk Ratio         Risk Ratio           vib/group         ford  |  |  |  |   |   |   |  |  |                     |                       | 4.F FSeudo  | aneu   | rysin  |  |  |   |  |   |                   |     |
| Instruction         Textuber of the lowers         Total Vertified         MH, Random, 59% Cl         MH, Random,  | Minor  | bleedi   | ing  |   |   |   | Dick Datio   |  | Diek Datio          |                       |   |  |  |  |  |   |  |   |                   |     |
| int 2007     0     67     1     67     0.4%     0.33 [0,1], 0,0]       int 10     0.00     3507     11.6%     551 (0,1)     Field Allow       int 2012     0.00     3501     11.6%     0.5% [0,1]     Field Allow       int 2012     0.00     501     15.4%     0.58 [0,3], 0.5]     Int 2012       int 2012     1.60     500     1.64     0.58 [0,3], 0.5]       int 2012     1.60     4.50     0.58 [0,3], 0.5]       int 2012     1.60     4.59     0.57 [0,4], 1.27]       int 2012     1.60     1.60     0.23 [0,0], 1.41       int 2012     1.60     1.60     0.23 [0,0], 1.41       int 2012     1.60     1.60     0.58 [0,3]     0.77 [0,62,0.94]        int 5     1.79     1.79     1.79     1.60     1.60     2.50 [0,0]       int 60     0.77 [0,62,0.94]     1.70     1.70     1.60     1.60     2.50 [0,0]       int 61     1.70     1.79     1.70     1.70     1.70     1.70       int 61     1.70 <td>Minor</td> <td>bleedi</td> <td>ing</td> <td>TRANS FF</td> <td>MORAL</td> <td></td> <td>DISE DOUL</td> <td></td> <td>Tuoninauto</td> <td>5% CI</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td>   | Minor  | bleedi   | ing  | TRANS FF  | MORAL   |   | DISE DOUL  |  | Tuoninauto          | 5% CI                 |   |  |  |  |  |   |  |   |                   |     |
| 11     100     2507     118     3514     452.65     0.58 (105)     110     581.00       2020     61136     61156     3.95     0.78 (0.27.16)     -     -     -     MA Atandom, 59:01   | Minor  | bleedi<br>TRANS R  | ing<br>RADIAL  | TRANS FE  | MORAL   | Weight  | M.H. Random, 95%   | % CI   | M.H. Random, 9      |                       |   |  |  |  |  | Dist. D.  | tio  | Risk Ratio                              |                   |     |
| 2020 6 1136 8 1168 39% 078[027,218]<br>mol21012 20 500 36 501 15.4% 058[03,08]<br>gli 2015 24 4157 32 4207 15.7% 0.75[0,44,127]<br>yli 2015 24 4157 24 4157 4208 24 2010,128<br>yli 2015 24 4157 24 4157 24 4157 4208 24 2010,128<br>yli 2015 24 4157 24 4157 24 4157 444 4100.0% 0.39[0,20,07]<br>yli 2016 24 4157 24 4157 42 4157 444 4100.0% 0.39[0,20,07]<br>yli 2016 24 4157 24 4157 42 4157 444 4100.0% 0.39[0,20,07]<br>yli 2016 24 4157 42 4157 444 4100.0% 0.39[0,20,07]<br>yli 2016 24 4157 42 4157 42 4157 444 4100.0% 0.39[0,20,07]<br>yli 2016 24 4157 42 4157 42 4157 444 4100.0% 0.39[0,20,07]<br>yli 2016 24 4157 42 4157 444 4100.0% 0.39[0,20,07]<br>yli 2016 24 4157 42 4157 444 4100.0% 0.39[0,20,07]<br>yli 2016 24 4157 42 4157 42 4157 444 4100.0% 0.39[0,20,07]<br>yli 2016 24 4157 444 4100.0% 0.39[0,20,07]<br>yli 2016 24 4157 42 4157 444 4100.0% 0.39[0,20,07]<br>yli 2016 24 4157 444 4100.0  |  | bleedi<br>TRANS R<br>Events  | ing<br>RADIAL<br>Total   | TRANS FE  | MORAL<br>Tota   | Weight  | M-H, Random, 95%   | % CI   | M-H, Random, 9      | 5/10                  | The second second   | TRANS RAD  | IAL TRA  | IS FEMORAL   | and the second   | RISK Rd   |  |   |                   |     |
| non 2012 20 500 36 501 15.4% 0.58 033, 0.95]<br>j02105 24 4197 22 407 15.7% 0.75 (0.44, 127)<br>1012 1 60 4 59 0.9% 0.25 (0.03, 2.14)<br>9% c0) 9457 9494 100.0% 0.27 (0.62, 0.94)<br>wrts 151 199<br>10002 101 0, 1 0, 1 0, 1 0, 1 0, 1 0, 1  | Minor  | bleedi<br>TRANS R<br>Events<br>0   | ADIAL<br>Total   | TRANS FE<br>Events  | MORAL<br>Tota<br>5  | Weight  | M-H, Random, 955<br>0.33 (0.01, 8<br>0.85 (0.65, 1   | 5 CI   | M-H, Random, 9      |                       | Study or Subgroup   | Events   | Total Ev   | IS FEMORAL<br>Ints Total   | Weight M   | I-H, Randon   | n, 95% Cl  | M-H, Random, 95% CI                     |                   |     |
| jig 2016 24 4197 32 4207 15.7% 0.75 [0.44, 127]<br>1012 1 45 0.05 % 0.25 [0.02, 2.14]<br>400 2016 0 160 2 100 29% 0.25 [0.02, 2.14]<br>400 2016 0 160 2 100 29% 0.25 [0.02, 2.14]<br>400 2016 0 160 2 100 29% 0.25 [0.02, 2.14]<br>400 2016 0 160 2 100 29% 0.25 [0.02, 2.14]<br>400 2016 0 160 2 100 29% 0.25 [0.02, 2.14]<br>400 2016 0 160 2 100 29% 0.25 [0.02, 2.14]<br>400 2016 0 160 2 100 29% 0.25 [0.02, 2.14]<br>400 2016 0 160 2 100 29% 0.25 [0.02, 0.14]<br>400 2016 0 160 2 100 29% 0.25 [0.02, 0.14]<br>400 2016 0 160 2 100 29% 0.25 [0.02, 0.14]<br>400 2016 0 160 2 100 29% 0.25 [0.02, 0.14]<br>400 2016 0 160 2 100 29% 0.25 [0.02, 0.14]<br>400 2016 0 160 2 100 29% 0.25 [0.02, 0.14]<br>400 2016 0 160 2 100 29% 0.25 [0.02, 0.14]<br>400 2016 0 160 2 100 29% 0.25 [0.02, 0.14]<br>400 2016 0 160 2 100 29% 0.25 [0.02, 0.14]<br>400 2016 0 160 2 100 29% 0.25 [0.02, 0.14]<br>400 2016 0 160 2 100 29% 0.25 [0.02, 0.14]<br>400 2016 0 160 2 100 29% 0.25 [0.02, 0.14]<br>400 2016 0 160 2 100 20% 0.25 [0.02, 0.14]<br>400 2016 0 160 2 100 20% 0.25 [0.02, 0.14]<br>400 2016 0 160 2 100 20% 0.25 [0.02, 0.14]<br>400 2016 0 160 2 100 20% 0.25 [0.02, 0.14]<br>400 2016 0 160 2 100 20% 0.25 [0.02, 0.14]<br>400 2016 0 160 2 100 20% 0.25 [0.02, 0.14]<br>400 2016 0 160 2 100 20% 0.25 [0.02, 0.14]<br>400 2016 0 160 2 100 20% 0.25 [0.02, 0.14]<br>400 2016 0 160 2 100 20% 0.25 [0.02, 0.14]<br>400 2016 0 160 2 100 20% 0.25 [0.02, 0.14]<br>400 2016 0 160 2 100 20% 0.25 [0.02, 0.14]<br>400 2016 0 160 2 100 20% 0.25 [0.02, 0.14]<br>400 2016 0 160 2 100 20% 0.25 [0.02, 0.14]<br>400 2016 0 100 2 100 20% 0.25 [0.02, 0.14]<br>400 2016 0 100 2 100 20% 0.25 [0.02, 0.14]<br>400 2016 0 100 2 100 20% 0.25 [0.02, 0.14]<br>400 2016 0 100 2 100 20% 0 100 20   | Minor  | bleedi<br>TRANS R<br>Events<br>0<br>100<br>6   | ing<br>ADIAL<br>Total<br>57<br>3507<br>1138  | TRANS FE<br>Events<br>1<br>118<br>8   | MORAL<br>Tota<br>5<br>351<br>115                              | Weight  | M-H, Random, 95!<br>0.33 (0.01, 8<br>0.85 (0.65, 1<br>0.76 (0.27, 2  | 5 CI<br>.01]<br>.10]<br>.19]                               | M-H, Random, 9      |                       | Study or Subgroup<br>Cantor 2005  | Events   | AL TRA<br>Total Ev<br>25<br>50   | IS FEMORAL<br>ents Total   | Weight M   | 1.00 [0.0<br>0.22.00  | n, 95% Cl<br>17, 15.12]  | M-H, Random, 95% Cl                     |                   |     |
| 1     60     4     59     0.9%     0.25     [0.03, 2.14]     July (2711     7     2507     23     3314     64.85%     3320     13, 2711       150     9457     9494     100.0%     0.77     [0.62, 0.94]     Image: Transmit and tr   | Minor<br>or Subgroup<br>selet 2007<br>2011<br>ay 2020<br>aenoli 2012   | bleedi<br>TRANS R<br>Events<br>0<br>100<br>6<br>20   | ing<br>ADIAL<br>Total<br>57<br>3507<br>1138<br>500                                     | TRANS FE<br>Events<br>1<br>118<br>8<br>36   | MORAL<br>Tota<br>5<br>351<br>115<br>50                        | Weight<br>7 0.4%<br>1 63.6%<br>3 3.9%<br>15.4%  | M-H, Random, 95<br>0.33 [0.01, 8<br>0.85 [0.65, 1<br>0.76 [0.27, 2<br>0.56 [0.33, 0  | % CI<br>.01]<br>.10]<br>.19]<br>.95]                       | M-H, Random, 9      | <u> </u>              | Study or Subgroup<br>Cantor 2005<br>Etriby 2017<br>Gan 2009   | TRANS RAD<br>Events<br>1<br>0  | AL TRA<br>Total Ev<br>25<br>50<br>92                                     | IS FEMORAL<br>ents Total<br>1 25<br>1 50<br>6 1050   | Weight #<br>6.3%<br>4.6%   | HISK Ra<br>1-H, Randon<br>1.00 [0.0<br>0.33 [0<br>1.90 [0.2   | n, 95% Cl<br>7, 15.12]   | M-H, Random, 95% Cl                     |                   |     |
| 15% CD)     9457     9494 100.0%     0.77 [0.62, 0.94]     Weng 2012     0     0     1     59     45%     0.23 [0.01, 7.89]       werds     151     199     199     57     1     46     45%     0.27 [0.01, 64]       mends     151     199     0.01     0.1     0.1     10     10       mends (26% CD)     3891     4444 100.0%     0.39 [0.20, 67]       werds endletter = 25 (16 = 0.01)     0.01     0.1     10     10   | Minor<br>or Subgroup<br>selet 2007<br>2011<br>sy 2020<br>agnoli 2012<br>migli 2015   | bleedi<br>TRANS R<br>Events<br>0<br>100<br>6<br>20<br>24   | ing<br>Total<br>57<br>3507<br>1138<br>500<br>4197                                      | TRANS FE<br>Events<br>1<br>118<br>8<br>36<br>32                                   | MORAL<br>Tota<br>5<br>351<br>115<br>50<br>420                 | Weight<br>0.4%<br>63.6%<br>3.9%<br>15.4%<br>15.7%                                     | M-H, Random, 95!<br>0.33 (0.01, 8<br>0.85 (0.65, 1<br>0.76 (0.27, 2<br>0.56 (0.33, 0<br>0.75 (0.44, 1  | % CI<br>.001]<br>.10]<br>.19]<br>.95]<br>.27]              | M-H, Random, 9      |                       | Study or Subgroup<br>Cantor 2005<br>Etriby 2017<br>Gan 2009<br>Hou 2010   | TRANS RAD<br>Events<br>1<br>0<br>1<br>0  | IAL TRA<br><u>Total Ev</u><br>25<br>50<br>92<br>100                      | IS FEMORAL<br>ents Total<br>1 25<br>1 50<br>6 1050<br>2 100  | Weight #<br>6.3%<br>4.6%<br>10.4%<br>5.0%                                    | 1.00 [0.0<br>1.00 [0.0<br>0.33 [0<br>1.90 [0.2<br>0.20 [0   | n, 95% CI<br>77, 15.12]  | M-H, Random, 95% Cl                     |                   |     |
| 5% C1     9457     9441     100.0%     0.77 (0.62, 0.94)     ✓     Yun 3008     0.57 1     46     46%     0.27 (0.1, 64)       meths     151     198     000 (C)H <sup>2</sup> = 3.31 (F = 0.0%)     000 (C)H <sup>2</sup> = 3.01 (F = 0.0%)     3691     4644     100.0%     0.38 (0.20, 0.77)       meths     0.00 (C)H <sup>2</sup> = 3.01 (F = 0.0%)     0.01 (L)     0.01 (L)     0.01 (L)     100     100       meths     0.00 (C)H <sup>2</sup> = 3.01 (F = 0.0%)     0.01 (L)     0.01 (L)     0.01 (L)     100  | Minor<br>or Subgroup<br>selet 2007<br>2011<br>ay 2020<br>agnoli 2012<br>migli 2015<br>i 2012   | bleedi<br>TRANS R<br>Events<br>0<br>100<br>6<br>20<br>24<br>1  | ing<br>Total<br>57<br>3507<br>1138<br>500<br>4197<br>60                                | TRANS FE<br>Events<br>1<br>118<br>8<br>36<br>32<br>4                              | MORAL<br>Tota<br>5<br>351<br>115<br>50<br>420<br>5            | Weight<br>0.4%<br>63.6%<br>3.9%<br>15.4%<br>15.7%<br>0.9%                             | M-H, Random, 95!<br>0.33 (0.01, 8<br>0.85 (0.65, 1<br>0.76 (0.27, 2<br>0.56 (0.33, 0<br>0.75 (0.44, 1<br>0.25 (0.03, 1                                 | % CI<br>1.01]<br>1.10]<br>1.19]<br>1.95]<br>1.27]<br>1.14] | M-H, Random, 9      |                       | Study or Subgroup<br>Cantor 2005<br>Etriby 2017<br>Gan 2009<br>Hou 2010<br>Jolly 2011   | TRANS RAD<br>Events<br>1<br>0<br>1<br>0<br>7   | IAL TRA<br><u>Total Ev</u><br>25<br>50<br>92<br>100<br>3507              | IS FEMORAL<br>ents Total<br>1 25<br>1 50<br>6 1050<br>2 100<br>23 3514                               | Weight 1<br>6.3%<br>4.6%<br>10.4%<br>5.0%<br>64.6%                           | 1.00 [0.0<br>1.00 [0.0<br>0.33 [0.<br>1.90 [0.2<br>0.20 [0.<br>0.30 [0.   | n, 95% CI<br>(01, 7.99)<br>(01, 7.99)<br>(01, 4.11)<br>(01, 4.11)  | M-H, Random, 95% Cl                     |                   |     |
| vents 151 199<br>janeb; Tau <sup>2</sup> 0.00; Ch <sup>2</sup> = 3.31, df = 5 (P = 0.65); P <sup>2</sup> = 0%<br>0.01 0,1 0,1 10<br>Total (95% CI) 3891 4844 100.0% 0.39 (0.20, 0.77) ←<br>Total events 9 35<br>0.01 0,1 0,1 10<br>Total events 9 35<br>0.01 0,1 0,1 10<br>Helemanerska Tau <sup>2</sup> = 0.00; P <sup>2</sup> = 0%   | Minor<br>or Subgroup<br>selet 2007<br>2011<br>ay 2020<br>agnoli 2012<br>migli 2015<br>a 2012   | bleedi<br>TRANS R<br>Events<br>0<br>100<br>6<br>20<br>24<br>1  | ing<br>ADIAL<br>Total<br>57<br>3507<br>1138<br>500<br>4197<br>60                       | TRANS FE<br>Events<br>118<br>8<br>36<br>32<br>4                                   | MORAL<br>Tota<br>5<br>351<br>115<br>50<br>420<br>5            | Weight<br>7 0.4%<br>4 63.6%<br>3 3.9%<br>15.4%<br>7 15.7%<br>0.9%                     | M-H, Random, 95!<br>0.33 (0.01, 8<br>0.85 (0.65, 1<br>0.76 (0.27, 2<br>0.56 (0.33, 0<br>0.75 (0.44, 1<br>0.25 (0.03, 2                                 | \$ CI<br>.01]  | M-H, Random, 9      |                       | Study or Subgroup<br>Cantor 2005<br>Ethy 2017<br>Gan 2009<br>Hou 2010<br>Jolly 2011<br>Wang 2012  | TRANS RAD<br>Events<br>1<br>0<br>1<br>0<br>7<br>0<br>0   | IAL TRA<br>Total Ev<br>25<br>50<br>92<br>100<br>3507<br>60               | IS FEMORAL<br>Ints Total<br>1 25<br>1 50<br>6 1050<br>2 100<br>23 3514<br>1 59                       | Weight 1<br>6.3%<br>4.6%<br>10.4%<br>5.0%<br>64.8%<br>4.6%                   | 1.00 [0.0<br>0.33 [0<br>1.90 [0.2<br>0.20 [0<br>0.30 [0<br>0.33 [0  | n, 95% Cl<br>7, 15.12]   | M-H, Random, 95% Cl                     |                   |     |
| panely: Table and the second s   | or Subgroup<br>elet 2007<br>2011<br>w 2020<br>ggnoli 2012<br>nigli 2015<br>2012<br>(95% CI)  | bleedi<br>TRANS R<br>Events<br>0<br>100<br>6<br>20<br>24<br>1  | ing<br>Total<br>57<br>3507<br>1138<br>500<br>4197<br>60<br>9457                        | TRANS FE<br>Events<br>118<br>8<br>36<br>32<br>4                                   | MORAL<br>Tota<br>5<br>351<br>115<br>50<br>420<br>5<br>949     | Weight<br>0.4%<br>1 63.6%<br>3 3.9%<br>15.4%<br>1 5.7%<br>3 0.9%<br>100.0%            | M.H, Random, 95'<br>0.33 [0.01, 8<br>0.85 [0.86, 1<br>0.76 [0.27, 2<br>0.56 [0.33, 0<br>0.75 [0.44, 1<br>0.25 [0.03, 2<br>0.77 [0.62, 0.               | \$\$ CI<br>.10]<br>.19]<br>.95]<br>.27]<br>.14]<br>.94]    | M-H, Random, 9      | <u></u>               | Study or Subgroup<br>Cantor 2005<br>Etriby 2017<br>Gan 2009<br>Hou 2010<br>Jolly 2011<br>Wang 2012<br>Yan 2008                                  | IRANS RAD           Events           1           0           1           0           7           0           0 | IAL TRA<br>Total Ev<br>25<br>50<br>92<br>100<br>3507<br>60<br>57         | IS FEMORAL<br>ents Total<br>1 25<br>1 50<br>6 1050<br>2 100<br>23 3514<br>1 59<br>1 46               | Weight 1<br>6.3%<br>4.8%<br>10.4%<br>5.0%<br>64.6%<br>4.6%                   | Hosk Ra<br>1.H, Randon<br>1.00 [0.0<br>0.33 [0<br>1.90 [0.2<br>0.20 [0<br>0.30 [0<br>0.33 [0<br>0.27 [0                       | n, 95% Cl<br>77, 15.12]  | M.H., Randorn, 95% Cl                   |                   |     |
| overall effect Z = 2.51 (P = 0.01)   | Minor<br>or Subgroup<br>elet 2007<br>011<br>y 2020<br>gnoli 2012<br>nigli 2015<br>2012<br>95% CI)<br>events  | bleedi<br>TRANS R<br>Events<br>0<br>100<br>6<br>20<br>24<br>1<br>1<br>51                               | ing<br>Total<br>57<br>3507<br>1138<br>500<br>4197<br>60<br>9457                        | TRANS FE<br>Events<br>1<br>118<br>8<br>36<br>36<br>32<br>4<br>4<br>199            | MORAL<br>Tota<br>5<br>351<br>115<br>50<br>420<br>5<br>949     | Weight<br>0.4%<br>1 63.6%<br>3 .9%<br>1 15.4%<br>1 15.4%<br>3 .9%<br>1 0.9%<br>100.0% | N38 Katu<br>M-H, Random, 957<br>0.33 (0.01, 8<br>0.85 (0.85, 1)<br>0.76 (0.27, 2<br>0.56 (0.33, 0<br>0.75 (0.44, 1)<br>0.25 (0.03, 2<br>0.77 (0.62, 0. | % Cl<br>.01]   | M-H, Random, 9      |                       | Study or Subgroup<br>Cantor 2005<br>Ethity 2017<br>Gan 2009<br>Hou 2010<br>Jolly 2011<br>Wéng 2012<br>Yan 2008<br>Total (15% CP                 | TRANS RAD<br>Events<br>1<br>0<br>1<br>0<br>7<br>0<br>0<br>0  | IAL TRA<br>Total Ev<br>25<br>50<br>92<br>100<br>3507<br>60<br>57<br>3891 | IS FEMORAL<br>ents Total<br>1 25<br>1 50<br>6 1050<br>2 100<br>23 3514<br>1 59<br>1 46<br>4844       | Weight #<br>6.3%<br>4.6%<br>10.4%<br>5.0%<br>64.6%<br>4.6%<br>4.6%<br>100.0% | Husk Ra<br>1.H, Randon<br>1.00 [0.0<br>0.33 [0<br>1.90 [0.2<br>0.20 [0<br>0.30 [0<br>0.33 [0<br>0.33 [0<br>0.27 [0<br>0.39 I0 | n, 95% Cl<br>7, 15.12]   | M.H., Randorn, 95% Cl                   |                   |     |
|  | Minor<br>or Subgroup<br>elet 2007<br>211<br>y 2020<br>anoli 2012<br>igli 2015<br>2012<br>2012<br>2012<br>2012<br>2012  | bleedi<br>TRANS R<br>Events<br>0<br>100<br>6<br>20<br>24<br>1<br>1<br>151<br>*= 0.00; Chi <sup>2</sup> | Total<br>Total<br>Total<br>57<br>3507<br>1136<br>500<br>4197<br>60<br>9457<br>*= 3.31, | TRANS FE<br>Events<br>1<br>118<br>8<br>36<br>32<br>4<br>4<br>199<br>df = 5 (P = 0 | MORAL<br>Tota<br>5<br>351<br>115<br>50<br>420<br>5<br>949<br> | Weight<br>7 0.4%<br>4 63.6%<br>3 3.9%<br>1 15.4%<br>7 15.7%<br>3 0.9%<br>1 100.0%     | N-H, Random, 957<br>0.33 (0.01, 8<br>0.85 (0.85, 1<br>0.76 (0.27, 2<br>0.56 (0.33, 0<br>0.75 (0.44, 1<br>0.25 (0.03, 2<br>0.77 (0.62, 0.               | % Cl<br>.01]<br>.10]<br>.95]<br>.27]<br>.14]<br>.94]       | M.H, Random, 9      | 10 100                | Study or Subgroup<br>Canter 2005<br>Erbity 2017<br>Gan 2009<br>Hou 2010<br>Johy 2011<br>Weng 2012<br>Yan 2008<br>Total (95% Ct)<br>Total events | TRANS RAD<br>Events  1  0  1  0  7  0  7  0  9   | AL TRA<br>Total Ev<br>25<br>50<br>92<br>100<br>3507<br>60<br>57<br>3891  | IS FEMORAL<br>ents Total<br>1 25<br>1 50<br>6 1050<br>2 100<br>23 3514<br>1 59<br>1 46<br>4844<br>35 | Weight #<br>6.3%<br>4.6%<br>10.4%<br>5.0%<br>64.6%<br>4.6%<br>4.6%<br>100.0% | Hosk Ra<br>1.H, Randon<br>1.00 [0.0<br>0.33 [0.<br>1.90 [0.2<br>0.20 [0.<br>0.30 [0.<br>0.33 [0.<br>0.27 [0.<br>0.39 [0.      | n, 95% Cl<br>7, 15.12] —<br>(01, 7.99]<br>3, 15.63]<br>(01, 4.11] (<br>13, 0.71]<br>(01, 7.89] (<br>01, 6.48] (<br>20, 0.77] | MH, Random, 95% Cl                      |                   |     |

**Fig 4.** Comparison of Trans-radial approach (TRA) versus Trans-femoral approach (TFA) in patients with acute coronary syndrome showing reduced major bleeding (A), BARC-3-5 bleeding (B), minor bleeding (C), vascular complications (D), hematoma (E) and Pseudoaneurysm (F). BARC- Bleeding academic research consortium; M-H = Mantel-Haenszel; CI- = confidence interval.

https://doi.org/10.1371/journal.pone.0266709.g004

8.6%; RR: 0.76; 95% CI: 0.65–0.90; P = 0.0009;  $I^2 = 30\% Fig 5A$ ]. We did not observe any difference in re-infarction(3.8% versus 4.1%; RR: 0.92; 95% CI: 0.80–1.05; P = 0.20; I<sup>2</sup> = 0%), stroke  $(0.5\% \text{ versus } 0.4\%; \text{RR: } 1.29; 95\% \text{ CI: } 0.86-1.93; \text{P} = 0.22; \text{I}^2 = 0\%)$ , stent thrombosis(0.9% vs)0.9%; RR: 0.95; 95% CI: 0.71–1.28; P = 0.75; I<sup>2</sup> = 0%), and severe bleeding requiring blood transfusions between the groups (1.8% vs 2.2%; RR: 0.74; 95% CI: 0.53-1.04; P = 0.09; I<sup>2</sup> = 38%)[Fig 5B-5D & S12 Fig in S1 File]. Mortality was described as in-hospital mortality in 6 studies and hence, they were analyzed separately. It showed no difference in the in-hospital mortality between the two arms (1.5% versus 2.4%; RR: 0.68; 95% CI: 0.24-1.93; P = 0.47; I<sup>2</sup> = 0%), S13 Fig in S1 File]. As expected, we observed more access-site crossover with trans-radial procedures [(6.7% vs 2.1%; RR: 3.09; 95% CI: 2.41–3.94;  $P = \langle 0.00001; I^2 = 31\% \rangle$ ] S14 Fig in S1 File]. We noticed a small decreased contrast volume use (ml) [mean difference (95% CI): -4.6 (-8.5 to -0.7)], small but significantly increased procedural time {mean difference(95%) CI) 1.2 [0.1 to 2.3]} and fluoroscopy time {mean difference(95% CI) 0.8 [0.3 to1.4] min} in the trans-radial group (S15-S17 Figs in S1 File). There was no difference in arrival time at PCI to first balloon inflation (FBI) {mean difference(95% CI) 1.9 [-1.3; 5.1] min} (S18 Fig in S1 File). We studied the study defined acute kidney injury and mean difference in creatinine pre and post PCI between the TRA and TFA arms, and found no difference between the groups (S19 & S20 Figs in S1 File).

# Discussion

The main findings of our meta-analysis that included only randomized controlled trials involving patients with acute coronary syndrome are (i) trans-radial procedures were associated with decreased all-cause mortality in patients with ACS undergoing PCI (ii) they are

| 5.A-  | Net a  | adver   | se ca   | rdiac   | even  | ts  |  | 5.C Stroke   | 1   |   |  |   |   |   |   |     |
|---|--|---|---|---|---|---|--|--|---|---|--|---|---|---|---|-----|
|   | TRANS R  | ADIAL   | TRANS FEM   | IORAL   |   | Risk Ratio  | Risk Ratio   |  | TRANS R   | ADIAL   | TRANS FE   | MORAL   |   | Risk Ratio  | Risk Ratio  |     |
| Study or Subgroup   | Events   | Total   | Events  | Total   | Weight  | M-H. Random, 95% CI   | M-H. Random, 95% CI  | Study or Subgroup  | Events  | Total   | Events   | Total   | Weight  | M-H, Random, 95% Cl   | M-H, Random, 95% Cl   | _   |
| Bernat 2014   | 16   | 348   | 38  | 359   | 6.5%  | 0.43 (0.25. 0.76)   |  | Bernat 2014  | 1   | 348   | . 1  | 359   | 2.1%  | 1.03 [0.06, 16.43]  |   |     |
| Chodor 2009   | 4  | 50  | q   | 50  | 1.9%  | 0.44 (0.15, 1.35)   |  | Cantor 2005  | 0   | 25  | 0  | 25  |   | Not estimable   |   |     |
| Chodor 2011   | 5  | 49  | 7   | 59  | 2.0%  | 0.86 (0.29, 2.54)   |  | Chodor 2009  | 0   | 50  | 1  | 50  | 1.6%  | 0.33 [0.01, 7.99]   |   |     |
| How 2010  | 4  | 100   |   | 100   | 1 0 06  | 0.60 [0.25, 2.54]   |  | Chodor 2011  | 20  | 49  | 1  | 2514  | 1.0%  | 1 43 (0.72, 3.60)   |   |     |
| Ioly 2010   | 100  | 2607  | 120   | 2614  | 20.495  | 0.00 [0.10, 1.01]   | -  | Koltowski 2014   | 20  | 5007  | 1  | 57  | 2.9%  | 1 78 [0.17 19 13]   |   |     |
| Voltewold 2014  | 120  | 5307  | 139   | 5314  | 20.4%   | 0.02 [0.75, 1.17]   |  | Le may 2020  | 11  | 1136  | 5  | 1156  | 14.8%   | 2.24 [0.78, 6.42]   |   |     |
| Lo more 2020  | 57   | 1100  | 50  | 1150  | 12.0%   | 0.00 [0.30, 2.22]   |  | Mann 1998  | 0   | 65  | 0  | 77  |   | Not estimable   |   |     |
| Demographi 2012   | 57   | 500   | 105   | 504   | 13.0%   | 0.80 [0.08, 1.40]   |  | Romagnoli 2012   | 4   | 500   | 3  | 501   | 7.4%  | 1.34 [0.30, 5.94]   |   |     |
| Romagnon 2012   | 00   | 500   | 105   | 20  | 4.000   | 0.05 [0.49, 0.60]   |  | Valgimigli 2015  | 16  | 4197  | 16   | 4207  | 34.3%   | 1.00 [0.50, 2.00]   |   |     |
| Salto 2003  | 4  | 11  | 8   | /2  | 1.8%  | 0.47 [0.15, 1.49]   |  | Tetel (OEK CD  |   | 0044  |  | 40005   | 400.00  | 4 30 10 00 4 031  |   |     |
| Valgimigli 2015   | 410  | 4197  | 486   | 4207  | 30.2%   | 0.85 [0.75, 0.96]   |  | Total (95% CI)   | 51  | 9941  | 12   | 10005   | 100.0%  | 1.29 [0.86, 1.95]   |   |     |
| wang 2012   | 2  | 60  | g   | 59  | 1.1%  | 0.22 [0.05, 0.97]   |  | Heterogeneity Tou?   | - 0.00: Chiž  | - 2 07 d  | 92<br>(= 7 /P = 0  | 80) IF = 0  | 6   | (1) [1] [1] [1]   |   |     |
| Yan 2008  | 3  | 57  | 4   | 46  | 1.2%  | 0.61 [0.14, 2.57]   |  | Test for overall effect  | Z = 1.22 (F   | = 0.22)   |  | 00,1 - 0.   |   |   | D.01 0.1 1 10 100<br>Favours [experimental] Favours [control]   |     |
| Total (95% CI)  |  | 10145   |   | 10180   | 100.0%  | 0.76 [0.65, 0.90]   | •  |  |   |   |  |   |   |   |   |     |
| Total events  | 709  |   | 880   |   |   |   |  |  |   |   |  |   |   |   |   |     |
| Heterogeneity: Tau <sup>2</sup> =   | 0.02; Chi <sup>2</sup>   | = 15.71,  | df = 11 (P =  | 0.15); P=   | 30%   |   | 0.01 0.1 1 10 10   |  | . I   |   |  |   |   |   |   |     |
| Test for overall effect:  | Z = 3.32 (F  | = 0.0009  | 0   |   |   |   | Favours (experimental) Eavours (control)   | 5.D Stent  | thror   | npo   | SIS.   |   |   |   |   |     |
|   |  |   |   |   |   |   | ratears (experimental) ratears (centrol)   |  | TRANS RA  | DIAL T  | RANS FEM   | RAL   |   | Risk Ratio  | Risk Ratio  |     |
|   |  |   |   |   |   |   |  | Study or Subgroup  | Events  | Total   | Events   | Total W   | eight M-H   | I, Random, 95% Cl   | M-H, Random, 95% Cl   |     |
|   |  |   |   |   |   |   |  | Brasselet 2007   | 4   | 57  | 4  | 57  | 5.0%  | 1.00 (0.26, 3.81)   |   |     |
| 5 B. Po.infar   | rction   |   |   |   |   |   |  | Jolly 2011   | 16  | 3507  | 26   | 3514 2  | 3.0%  | 0.62 [0.33, 1.15]   |   |     |
| J.D- Ne-IIIIai  | ction  |   |   |   |   |   |  | Remanali 2012  | 6   | 500   | 0  | 501   | 0.4%  | 0.67 (0.24, 1.96)   |   |     |
|   | TRANS R  | ADIAL   | TRANS FEM   | IORAL   |   | Risk Ratio  | Risk Ratio   | Valgimigli 2015  | 42  | 4197  | 38   | 4207 4  | 6.4%  | 1.11 [0.72, 1.71]   |   |     |
| Study or Subgroup   | Events   | Total   | Events  | Total   | Weight  | M-H, Random, 95% Cl   | M-H, Random, 95% Cl  | Wang 2012  | 0   | 60  | 0  | 59  |   | Not estimable   |   |     |
| Bernat 2014   | 4  | 348   | 3   | 359   | 0.8%  | 1.38 (0.31, 6.10)   |  | Total (95% CI)   |   | 9457  |  | 9494 10   | 0.0%  | 0.95 [0.71, 1.28]   | •   |     |
| Centor 2005   | 0  | 25  | 0   | 25  |   | Not estimable   |  | Total events   | 85  |   | 90   |   |   |   |   |     |
| Chadar 2000   | 1  | 60  | ů   | 60  | 0.206   | 2 00 0 12 71 02   |  | Heterogeneity: Tau*=   | 0.00; Chi <sup>2</sup> =  | 3.64, df=   | 4 (P=0.46  | ; I <sup>e</sup> = 0%   |   | 0.01  | 01 10 100   |     |
| Chodor 2005   |  | 30  | 0   | 50  | 0.230   | 3.00 [0.13, 71.32]  |  | Test for overall effect:   | Z = 0.32 (P =   | 0.75)   |  |   |   | F   | avours (experimental) Favours (control)   |     |
| Chodor 2011   | U  | 49  | U   | 59  |   | Not estimable   |  |  |   |   |  |   |   |   |   |     |
| Gan 2009  | 0  | 90  | 2   | 105   | 0.2%  | 0.23 [0.01, 4.79]   |  |  |   |   |  |   |   |   |   |     |
| Hou 2010  | 0  | 100   | 0   | 100   |   | Not estimable   |  | and show many  |   |   |  |   |   |   |   |     |
| Jolly 2011  | 60   | 3507  | 65  | 3514  | 14.6%   | 0.92 [0.65, 1.31]   |  | 5.E- Sever   | e ble   | edin  | g rec  | uirir   | ng tra  | ansfusion   |   |     |
| Koltowski 2014  |  | 112 100 100   |   |   |   |   |  |  |   |   | 0  |   |   |   |   |     |
| 0000  | 0  | 64  | 0   | 57  |   | Not estimable   |  |  | TRANC   | ADIAL   | TRANCI   | EMODAL  |   | Dick Patio  | Pick Patio  |     |
| 0.00002.20.20   | 20   | 1126  | 0   | 57  | 4 696   | Not estimable   | in the test of tes | Study or Subgroup  | TRANS   | ADIAL   | TRANS I  | EMORAL  | d Weigh   | Risk Ratio  | Risk Ratio  |     |
| Le may 2020<br>Monn 1000  | 0<br>20  | 64<br>1136  | 0<br>19   | 57<br>1156<br>77  | 4.6%  | Not estimable<br>1.07 [0.57, 2.00]  |  | Study or Subgroup  | TRANS<br>Events   | ADIAL<br>Tota   | TRANS I<br>Events  | EMORAL<br>Tota  | Weigh   | Risk Ratio<br>t M-H, Random, 95% C<br>0 15 0 01 2 84  | Risk Ratio  | _   |
| Le may 2020<br>Mann 1998  | 0<br>20<br>0   | 64<br>1136<br>65  | 0<br>19<br>0  | 57<br>1156<br>77  | 4.6%  | Not estimable<br>1.07 (0.57, 2.00)<br>Not estimable   |  | Study or Subgroup<br>Bernat 2014<br>Brasselet 2007   | TRANS<br>Events<br>0  | ADIAL<br>Tota<br>348  | TRANS I<br>Events  | EMORAL<br>Tota<br>35  | Weigh<br>9 1.39<br>7 1.19   | Risk Ratio<br>t M-H, Random, 95% C<br>0.15 [0.01, 2.84<br>3.00 [0.12, 72.13   | Risk Ratio           I         M-H, Random, 95% CI           I  |     |
| Le may 2020<br>Mann 1998<br>Romagnoli 2012  | 0<br>20<br>0<br>6  | 64<br>1136<br>65<br>500   | 0<br>19<br>0<br>7   | 57<br>1156<br>77<br>501   | 4.6%<br>1.5%                                    | Not estimable<br>1.07 (0.57, 2.00)<br>Not estimable<br>0.86 (0.29, 2.54)  |  | Study or Subgroup<br>Bernat 2014<br>Brasselet 2007<br>Cantor 2005  | TRANS<br>Events<br>0<br>1<br>0  | ADIAL<br>Tota<br>348<br>51<br>26  | TRANS I<br>Events  | EMORAL<br>Tota<br>35<br>5<br>2  | 1 Weigh<br>3 1.39<br>7 1.19<br>5  | Risk Ratio<br>t M-H, Random, 95% C<br>0.15 (0.01, 2.84<br>3.00 (0.12, 72.13<br>Not estimable  | Risk Ratio           I         M-H, Random, 95% CI           I  | -1  |
| Le may 2020<br>Mann 1998<br>Romagnoli 2012<br>Saito 2003  | 0<br>20<br>0<br>6<br>0   | 64<br>1136<br>65<br>500<br>77   | 0<br>19<br>0<br>7<br>0  | 57<br>1156<br>77<br>501<br>72                                     | 4.6%<br>1.5%                                    | Not estimable<br>1.07 (0.57, 2.00)<br>Not estimable<br>0.86 (0.29, 2.54)<br>Not estimable   |  | Study or Subgroup<br>Bemat 2014<br>Brasselet 2007<br>Cantor 2005<br>Chodor 2009  | TRANS<br>Events<br>0<br>1<br>0<br>0   | ADIAL<br>Tota<br>348<br>51<br>26<br>50  | TRANS I<br>Events  | EMORAL<br>Tota<br>35<br>5<br>2<br>5   | 1 Weigh<br>9 1.39<br>7 1.19<br>5<br>0 1.39  | Risk Ratio           t         M-H, Random, 95% C           5         0.15 [0.01, 2.84           5         3.00 [0.12, 72.13           Not estimable         0.14 [0.01, 2.70   | Risk Ratio           I         M-H, Random, 95% CI           I         Image: Comparison of the second se |     |
| Le may 2020<br>Mann 1998<br>Romagnoli 2012<br>Saito 2003<br>Valgimigli 2015   | 0<br>20<br>0<br>6<br>0<br>299  | 64<br>1136<br>65<br>500<br>77<br>4197   | 0<br>19<br>0<br>7<br>0<br>330                                   | 57<br>1156<br>77<br>501<br>72<br>4207                             | 4.6%<br>1.5%<br>77.8%                           | Not estimable<br>1.07 (0.57, 2.00)<br>Not estimable<br>0.86 (0.29, 2.54)<br>Not estimable<br>0.91 (0.78, 1.06)  |  | Study or Subgroup<br>Bernat 2014<br>Brasselet 2007<br>Cantor 2005<br>Chodor 2009<br>Chodor 2011  | TRANS<br>Events<br>0<br>1<br>0<br>0<br>1  | ADIAL<br>Tota<br>348<br>51<br>26<br>50<br>45  | TRANS I<br>Events  | EMORAL<br>Tota<br>35<br>5<br>2<br>5<br>5<br>5   | I Weigh<br>3 1.39<br>7 1.19<br>5<br>0 1.39<br>9 1.19  | Risk Ratio           t         M-H, Random, 95% C           5         0.15 [0.01, 2.84           5         3.00 [0.12, 72.13           Not estimable         0.14 [0.01, 2.70           5         0.14 [0.01, 2.70           5         0.14 [0.01, 2.70   | Risk Ratio           M-H, Random, 95% Cl  |     |
| Le may 2020<br>Mann 1998<br>Romagnoli 2012<br>Saito 2003<br>Valgimigli 2015<br>Wang 2012  | 0<br>20<br>0<br>6<br>0<br>299<br>1   | 64<br>1136<br>65<br>500<br>77<br>4197<br>60                                     | 0<br>19<br>0<br>7<br>0<br>330<br>3                              | 57<br>1156<br>77<br>501<br>72<br>4207<br>59                       | 4.6%<br>1.5%<br>77.8%                           | Not estimable<br>1.07 (0.57, 2.00)<br>Not estimable<br>0.86 (0.29, 2.54)<br>Not estimable<br>0.91 (0.78, 1.06)<br>0.33 (0.04, 3.06)                                       |  | Study of Subgroup<br>Bernat 2014<br>Brasselet 2007<br>Cantor 2005<br>Chodor 2009<br>Chodor 2011<br>Jolly 2011  | TRANS<br>Events<br>0<br>1<br>0<br>0<br>1<br>99  | ADIAL<br>Tota<br>348<br>51<br>25<br>50<br>45<br>3501                                      | TRANS I<br>Events  | EMORAL<br>Tota<br>35<br>5<br>2<br>5<br>5<br>351                                       | I Weigh<br>9 1.39<br>7 1.19<br>5<br>0 1.39<br>9 1.19<br>4 32.99   | Risk Ratio           t         M-H, Random, 95% C           6         0.15 [0.01, 2.84           6         3.00 [0.12, 72.13           Not estimable         0.14 [0.01, 2.70           6         0.15 [0.01, 6.84           6         3.60 [0.15, 86.84           6         1.01 [0.77, 1.33   | Risk Ratio           1         M-H, Random, 95% C1           1  | -   |
| Le may 2020<br>Mann 1998<br>Romagnoli 2012<br>Saito 2003<br>Valgimigli 2015<br>Wang 2012<br>Van 2008  | 0<br>20<br>0<br>6<br>0<br>299<br>1   | 64<br>1136<br>65<br>500<br>77<br>4197<br>60                                     | 0<br>19<br>0<br>7<br>0<br>330<br>3                              | 57<br>1156<br>77<br>501<br>72<br>4207<br>59                       | 4.6%<br>1.5%<br>77.8%<br>0.4%                   | Not estimable<br>1.07 (0.57, 2.00)<br>Not estimable<br>0.86 (0.29, 2.54)<br>Not estimable<br>0.91 (0.78, 1.06)<br>0.33 (0.04, 3.06)                                       |  | Study of Subgroup<br>Bernal 2014<br>Brasselet 2007<br>Cantor 2005<br>Chodor 2009<br>Chodor 2011<br>Jolly 2011<br>Le may 2020   | TRANS  <br>Events<br>0<br>1<br>0<br>0<br>0<br>0<br>1<br>99<br>36                                      | ADIAL<br>Tota<br>348<br>57<br>26<br>50<br>49<br>3507<br>1138                              | TRANS I<br>Events  | EMORAL<br>Tota<br>35<br>5<br>2<br>5<br>5<br>351<br>115                                | I Weigh<br>9 1.39<br>7 1.19<br>5<br>0 1.39<br>9 1.19<br>4 32.99<br>6 24.79  | Risk Ratio           t         M-H, Random, 95% C           6         0.15 (0.01, 2.84)           5         3.00 [0.12, 72.13)           Not estimable         0.14 (0.01, 2.70)           6         3.60 [0.15, 86.44)           6         1.01 (0.71, 1.33)           6         0.89 [0.58, 1.39)   | Risk Ratio           1         MH, Random, 95% Cl           1         —           2         —           1         —           2         —           1         —           2         —           1         —   |     |
| Le may 2020<br>Mann 1998<br>Romagnoli 2012<br>Saito 2003<br>Valgimigli 2015<br>Wang 2012<br>Yan 2008  | 0<br>20<br>6<br>0<br>299<br>1<br>0   | 64<br>1136<br>500<br>77<br>4197<br>60<br>57                                     | 0<br>19<br>0<br>7<br>0<br>330<br>3<br>0                         | 57<br>1156<br>77<br>501<br>72<br>4207<br>59<br>46                 | 4.6%<br>1.5%<br>77.8%<br>0.4%                   | Not estimable<br>1.07 (0.57, 2.00)<br>Not estimable<br>0.86 (0.29, 2.54)<br>Not estimable<br>0.91 (0.78, 1.06)<br>0.33 (0.04, 3.06)<br>Not estimable                      |  | Study or Subgroup<br>Bernat 2014<br>Brasselet 2007<br>Cantor 2005<br>Chodor 2009<br>Chodor 2011<br>Joly 2011<br>Le may 2020<br>Romagnoll 2012  | TRANS  <br>Events<br>0<br>1<br>0<br>0<br>0<br>1<br>99<br>36<br>5                                      | ADIAL<br>Tota<br>348<br>55<br>26<br>50<br>40<br>3501<br>1136<br>500                       | TRANS I<br>Events  | EMORAL<br>Tota<br>35<br>5<br>2<br>5<br>351<br>115<br>50                               | I Weigh<br>9 1.39<br>7 1.19<br>5<br>9 1.39<br>9 1.19<br>4 32.99<br>6 24.79<br>1 9.29  | Risk Ratio           M.H, Random, 95% C           6         0.15 (0.01, 2.04)           3.00 [0.12, 72.13]           Not estimable           0.14 (0.01, 2.70)           3.60 [0.15, 86.44)           1.01 (0.77, 1.33)           0.03 [0.058, 1.39)           0.31 [0.12, 0.86)           0.31 [0.12, 0.86)  | Risk Ratio  |     |
| Le may 2020<br>Mann 1998<br>Romagnoli 2012<br>Saito 2003<br>Valgimigli 2015<br>Wang 2012<br>Yan 2008<br>Total (95% CD   | 0<br>20<br>6<br>0<br>299<br>1<br>0   | 64<br>1136<br>65<br>500<br>77<br>4197<br>60<br>57<br>10325                      | 0<br>19<br>0<br>7<br>0<br>330<br>3<br>0                         | 57<br>1156<br>77<br>501<br>72<br>4207<br>59<br>46<br>10387        | 4.6%<br>1.5%<br>77.8%<br>0.4%                   | Not estimable<br>1.07 (0.57, 2.00)<br>Not estimable<br>0.86 (0.29, 2.54)<br>Not estimable<br>0.91 (0.78, 1.06)<br>0.33 (0.04, 3.06)<br>Not estimable<br>0.92 (0.80, 1.05) |  | Study or Subgroup<br>Bernat 2014<br>Brasselet 2007<br>Cantor 2005<br>Chodor 2010<br>Jolly 2011<br>Ler may 2020<br>Romagnoli 2012<br>Valgimigli 2015<br>Wang 2012   | TRANS<br>Events<br>0<br>1<br>0<br>0<br>1<br>99<br>36<br>5<br>40<br>0<br>0                             | ADIAL<br>Tota<br>346<br>51<br>25<br>50<br>45<br>3501<br>1136<br>500<br>4191<br>60         | TRANS I<br>Events<br>(<br>)<br>(<br>)<br>(<br>)<br>(<br>)<br>(<br>)<br>(<br>)<br>(<br>)<br>(<br>)<br>(<br>)<br>( | EMORAL<br>Tota<br>35<br>5<br>2<br>5<br>5<br>351<br>115<br>50<br>420<br>5              | I Weigh<br>3 1.39<br>7 1.19<br>5<br>0 1.39<br>9 1.19<br>4 32.99<br>6 24.79<br>1 9.29<br>7 27.09<br>9 1.39   | Risk Ratio           M.H, Random, 95% C           0.015 [0.01, 2.84           5         3.00 [0.12, 72.13           Not estimable           6         0.15 [0.01, 2.84           5         3.00 [0.12, 72.13           Not estimable           6         3.60 [0.15, 86.44           5         0.16 [0.68, 1.38           6         0.31 [0.12, 0.05, 1.38           6         0.31 [0.12, 0.05, 1.38           6         0.63 [0.42, 0.93           6         0.02 [0.01, 4.01   | Risk Ratio  |     |
| Le may 2020<br>Mann 1998<br>Romagnoli 2012<br>Saito 2003<br>Valgimigli 2015<br>Wang 2012<br>Yan 2008<br>Total (95% CI)  | 0<br>20<br>6<br>0<br>299<br>1<br>0   | 64<br>1136<br>65<br>500<br>77<br>4197<br>60<br>57<br>10325                      | 0<br>19<br>0<br>7<br>0<br>330<br>3<br>0                         | 57<br>1156<br>77<br>501<br>72<br>4207<br>59<br>46<br>10387        | 4.6%<br>1.5%<br>77.8%<br>0.4%<br>100.0%         | Not estimable<br>1.07 (0.57, 2.00)<br>Not estimable<br>0.86 (0.29, 2.54)<br>Not estimable<br>0.91 (0.78, 1.06)<br>0.33 (0.04, 3.06]<br>Not estimable<br>0.92 (0.80, 1.05) |  | Study of Subgroup<br>Bernat 2014<br>Brasselet 2007<br>Cantor 2005<br>Chodor 2009<br>Chodor 2011<br>Jolly 2011<br>Le may 2020<br>Romagnoli 2012<br>Valgimgli 2015<br>Wang 2012  | TRANS<br>Events<br>0<br>1<br>0<br>0<br>1<br>99<br>36<br>5<br>40<br>0                                  | ADIAL<br>Tota<br>346<br>51<br>25<br>50<br>45<br>3501<br>1136<br>500<br>4191<br>60         | TRANS I<br>Events  | EMORAL<br>Tota<br>35<br>5<br>2<br>5<br>351<br>115<br>50<br>420<br>5                   | I Weigh<br>9 1.39<br>7 1.19<br>5<br>0 1.39<br>9 1.19<br>4 32.99<br>6 24.79<br>1 9.29<br>7 27.09<br>9 1.39   | Nisk Ratio           M.H., Random, 95% C           6         0.15 (0.01, 2.84           5         3.00 [0.12, 72.13           Not estimable         0.14 [0.01, 270           6         0.360 [0.15, 76.13           6         0.14 [0.01, 270           5         3.60 [0.15, 86.44           1.01 [0.77, 1.33         0.38 [0.58, 1.39           6         0.31 [0.12, 0.86           6         0.63 [0.42, 0.93           5         0.20 [0.01, 4.01   | Risk Ratio  |     |
| Le may 2020<br>Mann 1998<br>Romagnoli 2012<br>Saito 2003<br>Valgimigli 2015<br>Wang 2012<br>Yan 2008<br>Total (95% CI)<br>Total events  | 0<br>20<br>6<br>0<br>299<br>1<br>0<br>391                                      | 64<br>1136<br>65<br>500<br>77<br>4197<br>60<br>57<br><b>10325</b>               | 0<br>19<br>0<br>7<br>0<br>330<br>3<br>0<br>429                  | 57<br>1156<br>77<br>501<br>72<br>4207<br>59<br>46<br>10387        | 4.6%<br>1.5%<br>77.8%<br>0.4%<br>100.0%         | Not estimable<br>1.07 (0.57, 2.00)<br>Not estimable<br>0.86 (0.29, 2.54)<br>Not estimable<br>0.91 (0.78, 1.06)<br>0.33 (0.04, 3.06)<br>Not estimable<br>0.92 (0.80, 1.05) |  | Study of Subgroup<br>Bennat 2014<br>Brasselet 2007<br>Cantor 2006<br>Chodor 2009<br>Chodor 2011<br>Jolly 2011<br>Le may 2020<br>Romapoli 2012<br>Valgimigli 2015<br>Wang 2012<br>Total (95% CI)                                    | TRANS  <br>Events<br>0<br>1<br>0<br>0<br>1<br>99<br>36<br>5<br>40<br>0                                | ADIAL<br>Tota<br>348<br>51<br>24<br>50<br>45<br>3500<br>1138<br>500<br>4191<br>60<br>9925 | TRANS I<br>Events<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0 | EMORAL<br>Tota<br>355<br>5<br>5<br>351<br>115<br>50<br>420<br>5<br>998                | I         Weight           8         1.39           5         0           0         1.39           9         1.19           6         24.79           1         9.29           6         24.79           1         9.29           7         1.39           7         27.09           9         1.39           7         100.05                | Nisk Ratio           T MH, Random, 95% C           5         0.15 [0.01, 2.84           6         0.15 [0.01, 2.72, 13           Not estimable         0.14 [0.01, 270]           6         0.14 [0.01, 270]           6         0.30 [0.15, 86.44           6         0.14 [0.01, 270]           6         0.30 [0.15, 86.44           6         0.31 [0.77, 1.33]           6         0.31 [0.12, 0.86]           6         0.63 [0.42, 0.93]           6         0.63 [0.42, 0.93]           6         0.20 [0.01, 4.01]           5         0.74 [0.53, 1.04] | Pisk Ratio  |     |
| Le may 2020<br>Mann 1998<br>Romagnoli 2012<br>Saito 2003<br>Valgimigli 2012<br>Yan 2008<br>Total (95% CI)<br>Total events<br>Heterogeneity: Tau <sup>e</sup> =  | 0<br>20<br>0<br>299<br>1<br>0<br>391<br>€0.00; Chi <sup>≠</sup>                | 64<br>1136<br>65<br>500<br>77<br>4197<br>60<br>57<br><b>10325</b><br>= 2.69, dt | 0<br>19<br>0<br>7<br>0<br>330<br>3<br>0<br>429<br>'= 7 (P = 0.9 | 57<br>1156<br>77<br>501<br>72<br>4207<br>59<br>46<br><b>10387</b> | 4.6%<br>1.5%<br>77.8%<br>0.4%<br><b>100.0</b> % | Not estimable<br>1.07 (0.57, 2.00)<br>Not estimable<br>0.86 (0.29, 2.54)<br>Not estimable<br>0.91 (0.78, 1.06)<br>0.33 (0.04, 3.06]<br>Not estimable<br>0.92 [0.80, 1.05] |  | Study of Subgroup,<br>Bernat 2014<br>Brasselet 2007<br>Canbro 2003<br>Chodor 2009<br>Chodor 2011<br>Jolly 2011<br>Le may 2020<br>Romagnoli 2012<br>Valgimgli 2015<br>Wang 2012<br>Total events                                     | TRANS<br>Events<br>0<br>1<br>0<br>0<br>1<br>99<br>36<br>5<br>40<br>0<br>182                           | ADIAL<br>Tota<br>348<br>51<br>24<br>50<br>43<br>3500<br>1138<br>500<br>4191<br>60<br>9925 | TRANS I<br>Events<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0 | EMORAL<br>Tota<br>35<br>5<br>2<br>5<br>5<br>5<br>351<br>115<br>50<br>420<br>5<br>998  | I         Weight           8         1.39           5         0           0         1.39           9         1.19           6         24.79           6         24.79           1         9.29           7         1.39           7         27.09           9         1.39           7         100.09   | Nisk Ratio           t         M-H, Random, 95% C           6         0.15 (0.01, 2.84           5         3.00 [0.12, 72.13]           10         Not estimable           6         0.14 (0.01, 270, 13)           5         3.60 [0.15, 96.44           6         1.01 (0.77, 1.33)           6         0.38 [0.15, 91.44           6         0.31 (0.12, 0.85)           6         0.63 [0.42, 0.93)           6         0.20 [0.01, 4.01           6         0.74 [0.53, 1.04   | Risk Ratio  |     |
| Le may 2020<br>Mann 1998<br>Romagnoli 2012<br>Saito 2003<br>Valgimigli 2015<br>Wang 2012<br>Yan 2008<br>Total (95% CI)<br>Total events<br>Heterogenelly: Tau <sup>a</sup> =<br>Test for overall effect: | 0<br>20<br>0<br>299<br>1<br>0<br>391<br>:0.00; Chi <sup>2</sup><br>Z = 1.30 (F | 64<br>1136<br>65<br>500<br>77<br>4197<br>60<br>57<br><b>10325</b><br>= 2.69, dt | 0<br>19<br>0<br>7<br>0<br>330<br>3<br>0<br>*29<br>*= 7 (P = 0.9 | 57<br>1156<br>77<br>501<br>72<br>4207<br>59<br>46<br><b>10387</b> | 4.6%<br>1.5%<br>77.8%<br>0.4%<br><b>100.0%</b>  | Not estimable<br>1.07 (0.57, 2.00)<br>Not estimable<br>0.86 (0.29, 2.54)<br>Not estimable<br>0.91 (0.78, 1.06)<br>0.33 (0.04, 3.06)<br>Not estimable<br>0.92 [0.80, 1.05] |  | Study of Subgroup.<br>Bernat 2014<br>Brasseld 2007<br>Crador 2005<br>Chodor 2010<br>Joliy 2011<br>Let may 2020<br>Romagnol 2012<br>Valgimgil 2015<br>Wang 2012<br>Total (95% CI)<br>Total events<br>Hotoroceneti, Tau <sup>2</sup> | TRANS:<br>Events<br>0<br>1<br>0<br>0<br>1<br>99<br>36<br>5<br>40<br>0<br>1<br>1<br>82<br>= 0.07; Chit | ADIAL<br>Tota<br>50<br>50<br>45<br>50<br>45<br>50<br>419<br>60<br>9925<br>= 12.81         | TRANS I<br>Events<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0 | EMORAL<br>Tota<br>35<br>5<br>5<br>5<br>5<br>5<br>5<br>5<br>5<br>5<br>5<br>5<br>5<br>5 | I         Weight           9         1.39           7         1.19           5         0           0         1.39           9         1.19           6         24.79           1         9.29           6         24.79           1         9.29           7         27.09           9         1.39           7         100.05           :38% | Nisk Ratio           MH, Radrom, 95% C           0.15 [0.01, 246           0.00 [0.12, 72.13           Not estimable           0.14 [0.01, 270           0.3 00 [0.15, 86.44           0.10 [0.07, 1.33           0.03 [0.03, 81.38           0.03 [0.04, 20.93           0.020 [0.01, 4.01           6         0.37 [0.12, 0.85           0.30 [0.12, 0.42, 0.93           0.30 [0.01, 4.01  | Pisk Ratio  | 100 |

**Fig 5.** Comparison of Trans-radial approach (TRA) versus Trans-femoral approach (TFA) in patients with acute coronary syndrome showing reduced NACE favoring TRA (A). However, no difference was observed between TRA and TFA on reinfarction (B), stroke (C), stent thrombosis (D) and severe bleeding requiring transfusions (E). NACE- Net adverse cardiac outcomes; M-H = Mantel-Haenszel; CI = confidence interval.

https://doi.org/10.1371/journal.pone.0266709.g005

associated with decreased MACE, NACE, study-defined major bleeding, BARC class 3–5 bleeding, vascular complications, hematoma, and pseudoaneurysms without any difference in the in-hospital mortality rate, reinfarction, stroke, MACE, stent thrombosis, and severe bleeding requiring blood transfusions. We also found a significantly reduced 30-day mortality with trans-radial procedures in patients with STEMI alone. Such potential benefits of TRA may be due to reduced bleeding, early ambulation reducing infections and venous thromboembolisms. Our meta-analysis is holistic with separate analysis for the outcomes in patients with ACS and STEMI. We also analyzed the results based on the quality of studies in addition to the calculation for the power of the meta-analysis for clinically important outcomes along with meta-regression of various factors for those outcomes.

None of the included randomized studies were powered for all-cause mortality events. Hence, it is essential to do the metanalysis to know the effect of trans-radial procedures on outcomes. Though a large number of metanalysis is available comparing TRA with TFA, only a few of them are good quality metanalysis conducted in patients with ACS. The metanalysis performed by Ando et al [22] involving only high-quality studies with low risk of bias found reduced mortality, MACE, major bleeding in the trans-radial arm, similar to our results. Though the metanalysis by Ruiz-Rodriguez et al [23] was diluted by the amalgamation of data from RCTs and cohort studies, their result was similar to our results. However, the beneficial effects of trans-radial procedures were questioned by Le May et al who found no difference in 30 days all-cause mortality and MACE between trans-radial and transfemoral arms [4]. It was prematurely stopped, and event rates were lower than expected, resulting in a study underpowered to show any difference between the two arms in terms of mortality. It also needs to be emphasized that the above study used bivalirudin in most of the patients (Table 1), and vascular closure devices were used in more than 2/3<sup>rd</sup> of the patients in the transfemoral arm. A closer look also showed a significantly reduced use of GpIIb/IIIa inhibitors (only 6%) which is usually low as compared with other studies (Table 1) and real-world practice [24]. We included the above trial in our metanalysis. Despite adding that trial in our meta-analysis, the result did not change. This underscores the beneficial effect of trans-radial PCI in patients with ACS. Ando et al found reduced occurrence of AKI in the TRA as compared with TFA, and found that such a reduced AKI event was predominantly responsible for the reduction in the all-cause mortality [25, 26]. In contrast, in our metanalysis, we did not observe the same. Its needs to be emphasized that the above study was 2x2 factorial one. The sub-group analysis found that such a difference in acute kidney injury was observed in the heparin arm alone without any difference in the bivalirudin arm. This is a hypothesis generating finding as no difference between the arms was observed for the co-primary efficacy and safety end points in the MATRIX- Access or anti-thrombin program [19]. Whether the difference attributed could be because of heparin or bivalirudin needs to further studied in another RCT. Also, when studies were categorized based on  $\geq$ 25% of patients receiving GpIIb/IIIa inhibitors, no significant difference in adverse clinical outcomes was observed between TRA and TFA groups. This underscores importance of bleeding (access and non-access site) related to them resulting in worse clinical outcomes.

Both MI and bleedings were associated with mortality [27]. Reduction in major bleeding has been shown to have a reduction in ischemic events. Bleeding, not only leads to interruption in anti-platelets, but also causes activation of inflammatory pathways that might lead to increased ischemic events. This is especially important in patients with STEMI where more potent anti-thrombotic would be used. Similar to our metanalysis, Jhand et al [28] have shown that TRA procedures are associated with lower all-cause mortality and bleeding in patients with STEMI. In systems of care where pharmaco-invasive and rescue PCI therapy is utilized for STEMI, TRA acts as a boon to prevent access site-related bleeding complications. Any access site-related bleeding in such a clinical situation that warrants interference in anti-plate-let therapy will increase complications. Other possible benefits of TRA include early ambulation that will reduce hospital-related infections and venous-thromboembolism. Though we noticed increased procedural time with TRA, we did not find any difference in the arrival at PCI to the FBI which was in contrast to an analysis of the National Cardiovascular Disease Registry (NCDR) which revealed a modestly increased door-to-balloon time with TRA compared with TFA [29].

Vascular closure devices (VCDs) are increasingly used in interventional cardiology practice. VCDs may decrease the time to ambulation after the procedure. However, several studies including a recent metanalysis have shown that VCDs are not superior to manual compression in safety and efficacy [30, 31]. Also, a recent meta-analysis showed the superiority of the transradial procedure over trans-femoral procedures where VCDs were used [32]. Hence, we believe trans-radial procedures should be considered superior to VCD-assisted TFA procedures unless proved otherwise by a sufficiently powered RCT. All the studies included in our meta-analysis have excluded patients with **cardiogenic shock (CS)**. However, Gandhi et al [33] and Pancholy et al [34] showed that the trans-radial procedures reduced 30day mortality and MACE in patients with ACS **and CS** provided excellent operator experience is available. With the increase in the expertise of the operator and the institution, the ease of doing radial procedures will increase. Adopting a large volume radial procedural program even in patients with STEMI will lead to increasingly available expertise in patients with STEMI and **CS** that may improve patient outcomes.

# Limitations

First, our study is a study-level meta-analysis of randomized studies and the search strategy was restricted to only articles published in English language and only Pubmed and Embase databases were screened for our meta-analysis. Second, many salient outcomes are not studied by all the available studies (For e.g., BARC 3-5 bleeding was reported only in the MATRIX and SAFARI-STEMI trials), and the definition used for some of the outcomes like myocardial infarction and major bleeding differs between the included studies. Third, several of the studies included in the final analysis except five of them as described above had a high-risk of bias or had some-concerns. However, a sub-group analysis restricted to studies with a low risk of bias showed similar results. Fourth, the anti-coagulant used in these trials were not the same (Table 1). However, Valgimigli et al have shown that there was no difference in MACE between bivalirudin and heparin arms [19]. Fifth, variation in the use of GpIIb/IIIa inhibitors, second anti-platelet agent and VCDs were also noticed among the included studies. Sixth, outcomes of radial procedures depend on expertise which was not pre-defined in most of the trials. In spite having many limitations, our metanalysis is the first powered metanalysis that answers the effect of TRA on all-cause mortality. We have described the results separately for patients with ACS and STEMI. In addition, we also analyzed the results based on the quality of studies which is very important to understand the quality of the results. Meta-regression for various factors like mean age, % of females, % with diabetes, and % receiving GpIIb/IIIa inhibitor were also used. Lastly, a properly done ultrasound-guided femoral access with less usage of GpIIb/IIIa inhibitors versus radial access has not been randomly studied. Until then, we may not generalize the results.

## Conclusion

Our metanalysis conclude that in patients with ACS undergoing PCI, trans-radial approach is associated with reduced 30-day all-cause mortality (more so in patients with STEMI), MACE, NACE, study-defined major bleeding, BARC class 3–5 bleeding, vascular complications, hematoma, and pseudo-aneurysms. Hence, TRA should be considered as a default procedural access strategy in most of the patients with ACS undergoing PCI. All interventionists should strive hard to master TRA so as to improve patient outcomes.

## Supporting information

S1 File. (DOCX)

# **Author Contributions**

Conceptualization: Nagendra Boopathy Senguttuvan.

- **Data curation:** Nagendra Boopathy Senguttuvan, Pothireddy M. K. Reddy, PunatiHari Shankar, Rizwan Suliankatchi Abdulkader, Hanumath Prasad Yallanki, Vadivelu Ramalingam, Ravindran Rajendran, Kesavamoorthy Bhoopalan, Ankur Kalra, Ramamoorthi Jayaraj.
- **Formal analysis:** Nagendra Boopathy Senguttuvan, Pothireddy M. K. Reddy, PunatiHari Shankar, Rizwan Suliankatchi Abdulkader, Hanumath Prasad Yallanki, Monil Majmundar, Vadivelu Ramalingam, Ravindran Rajendran, Ankur Kalra, Ramamoorthi Jayaraj.

Funding acquisition: Kesavamoorthy Bhoopalan.

Investigation: Nagendra Boopathy Senguttuvan, Ramesh Daggubati.

- Methodology: Nagendra Boopathy Senguttuvan, Rizwan Suliankatchi Abdulkader, Vadivelu Ramalingam, Kesavamoorthy Bhoopalan, Sivasubramanian Ramakrishnan, Ramesh Daggubati, Sadagopan Thanikachalam.
- **Project administration:** Nagendra Boopathy Senguttuvan, Muralidharan T. R., Sivasubramanian Ramakrishnan, Ramesh Daggubati, Sadagopan Thanikachalam.
- **Resources:** Rizwan Suliankatchi Abdulkader, Ashish Kumar, Ravindran Rajendran, Kesavamoorthy Bhoopalan, Vinay Kumar Bahl.
- Software: Rizwan Suliankatchi Abdulkader, Vadivelu Ramalingam.
- Supervision: Nagendra Boopathy Senguttuvan, Kesavamoorthy Bhoopalan, Muralidharan T. R., Sivasubramanian Ramakrishnan, Ramesh Daggubati, Sadagopan Thanikachalam, Ashok Seth.
- Validation: Nagendra Boopathy Senguttuvan, Hanumath Prasad Yallanki, Ashish Kumar, Monil Majmundar, Muralidharan T. R., Ramamoorthi Jayaraj, Sivasubramanian Ramakrishnan, Sadagopan Thanikachalam, Ashok Seth, Vinay Kumar Bahl.
- Visualization: Nagendra Boopathy Senguttuvan, Vadivelu Ramalingam, Ashok Seth, Vinay Kumar Bahl.
- Writing original draft: Nagendra Boopathy Senguttuvan.
- Writing review & editing: Ashish Kumar, Monil Majmundar, Ravindran Rajendran, Kesavamoorthy Bhoopalan, Dhamodharan Kaliyamoorthy, Muralidharan T. R., Ankur Kalra, Ramamoorthi Jayaraj, Sivasubramanian Ramakrishnan, Ramesh Daggubati, Sadagopan Thanikachalam, Ashok Seth, Vinay Kumar Bahl.

#### References

- Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, et al. Global Burden of Cardiovascular Diseases and Risk Factors, 1990–2019: Update from the GBD 2019 Study. J Am Coll Cardiol. 2020 Dec 22; 76(25):2982–3021. https://doi.org/10.1016/j.jacc.2020.11.010 PMID: 33309175
- Mason PJ, Shah B, Tamis-Holland JE, Bittl JA, Cohen MG, Safirstein J, et al. An update on radial artery access and best practices for transradial coronary angiography and intervention in acute coronary syndrome: A scientific statement from the American Heart Association. Circ Cardiovasc Interventions. 2018; 11(9). https://doi.org/10.1161/HCV.00000000000035 PMID: 30354598
- Collet J-P, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J. 2020 Aug 29. https://doi.org/10.1093/eurheartj/ehaa624 PMID: 33085966
- Le May M, Wells G, So D, Chong AY, Dick A, Froeschl M, et al. Safety and Efficacy of Femoral Access vs Radial Access in ST-Segment Elevation Myocardial Infarction: The SAFARI-STEMI Randomized Clinical Trial. JAMA Cardiol. 2020 Feb 1; 5(2):126–34. https://doi.org/10.1001/jamacardio.2019.4852 PMID: 31895439
- Bernat I, Horak D, Stasek J, Mates M, Pesek J, Ostadal P, et al. ST-segment elevation myocardial infarction treated by radial or femoral approach in a multicenter randomized clinical trial: the STEMI-RADIAL trial. J Am Coll Cardiol. 2014 Mar 18; 63(10):964–72. https://doi.org/10.1016/j.jacc.2013.08. 1651 PMID: 24211309
- Brasselet C, Tassan S, Nazeyrollas P, Hamon M, Metz D. Randomized comparison of femoral versus radial approach for percutaneous coronary intervention using abciximab in acute myocardial infarction: results of the FARMI trial. Heart. 2007 Dec; 93(12):1556–61. https://doi.org/10.1136/hrt.2007.117309 PMID: 17639099
- Cantor WJ, Puley G, Natarajan MK, Dzavik V, Madan M, Fry A, et al. Radial versus femoral access for emergent percutaneous coronary intervention with adjunct glycoprotein IIb/IIIa inhibition in acute myocardial infarction—the RADIAL-AMI pilot randomized trial. Am Heart J. 2005 Sep; 150(3):543–9. <a href="https://doi.org/10.1016/j.ahj.2004.10.043">https://doi.org/10.1016/j.ahj.2004.10.043</a> PMID: 16169338

- Chodór P, Krupa H, Kurek T, Sokal A, Swierad M, Was T, et al. RADIal versus femoral approach for percutaneous coronary interventions in patients with Acute Myocardial Infarction (RADIAMI): A prospective, randomized, single-center clinical trial. Cardiol J. 2009; 16(4):332–40. PMID: 19653176
- Chodór P, Kurek T, Kowalczuk A, Świerad M, Wąs T, Honisz G, et al. Radial vs femoral approach with StarClose clip placement for primary percutaneous coronary intervention in patients with ST-elevation myocardial infarction. RADIAMI II: a prospective, randomised, single centre trial. Kardiol Pol. 2011; 69 (8):763–71. PMID: 21850615
- Etriby SE, Nassar A, Rifaie O, Mahmoudy AE, Missiry AE. The impact of transradial vs transfemoral approach for percutaneous coronary intervention on the outcome of patients presenting with acute coronary syndrome. J Invasive Cardiol. 2017; 29(10):E119.
- Gan L, Lib Q, Liuc R, Zhaoc Y, Qiuc J, Liao Y. Effectiveness and feasibility of transradial approaches for primary percutaneous coronary intervention in patients with acute myocardial infarction. Journal of Nanjing Medical University [Internet]. 2009 Jul 1 [cited 2021 Jan 18]; 23(4):270–4.
- Hou L, Wei Y-D, Li W-M, Xu Y-W. Comparative study on transradial versus transfemoral approach for primary percutaneous coronary intervention in Chinese patients with acute myocardial infarction. Saudi Med J. 2010 Feb; 31(2):158–62. PMID: 20174731
- Jolly SS, Yusuf S, Cairns J, Niemelä K, Xavier D, Widimsky P, et al. Radial versus femoral access for coronary angiography and intervention in patients with acute coronary syndromes (RIVAL): A randomised, parallel group, multicentre trial. Lancet [Internet]. 2011; 377(9775):1409–20. https://doi.org/10. 1016/S0140-6736(11)60404-2 PMID: 21470671
- Kołtowski L, Filipiak KJ, Kochman J, Pietrasik A, Rdzanek A, Huczek Z, et al. Access for percutaneous coronary intervention in ST segment elevation myocardial infarction: radial vs. femoral—a prospective, randomised clinical trial (OCEAN RACE). Kardiol Pol. 2014; 72(7):604–11. <u>https://doi.org/10.5603/KP. a2014.0071</u> PMID: 24671918
- Li W, Li Y, Zhao J, Duan Y, Sheng L, Yang B, et al. Safety and feasibility of emergent percutaneous coronary intervention with the transradial access in patients with acute myocardial infarction. Chin Med J (Engl). 2007 Apr 5; 120(7):598–600. PMID: 17442210
- Mann T, Cubeddu G, Bowen J, Schneider JE, Arrowood M, Newman WN, et al. Stenting in acute coronary syndromes: a comparison of radial versus femoral access sites. J Am Coll Cardiol. 1998 Sep; 32 (3):572–6. https://doi.org/10.1016/s0735-1097(98)00288-5 PMID: 9741495
- Romagnoli E, Biondi-Zoccai G, Sciahbasi A, Politi L, Rigattieri S, Pendenza G, et al. Radial versus femoral randomized investigation in st-segment elevation acute coronary syndrome: The rifle-steacs (radial versus femoral randomized investigation in st-elevation acute coronary syndrome) study. J Am Coll Cardiol. 2012; 60(24):2481–9. https://doi.org/10.1016/j.jacc.2012.06.017 PMID: 22858390
- 18. Saito S, Tanaka S, Hiroe Y, Miyashita Y, Takahashi S, Tanaka K, et al. Comparative study on transradial approach vs. transfemoral approach in primary stent implantation for patients with acute myocardial infarction: results of the test for myocardial infarction by prospective unicenter randomization for access sites (TEMPURA) trial. Catheter Cardiovasc Interv. 2003 May; 59(1):26–33. https://doi.org/10.1002/ ccd.10493 PMID: 12720237
- Valgimigli M, Frigoli E, Leonardi S, Rothenbühler M, Gagnor A, Calabrò P, et al. Bivalirudin or Unfractionated Heparin in Acute Coronary Syndromes. N Engl J Med. 2015 Sep 10; 373(11):997–1009. <u>https://</u> doi.org/10.1056/NEJMoa1507854 PMID: 26324049
- Wang Y-B, Fu X-H, Wang X-C, Gu X-S, Zhao Y-J, Hao G-Z, et al. Randomized comparison of radial versus femoral approach for patients with STEMI undergoing early PCI following intravenous thrombolysis. J Invasive Cardiol. 2012 Aug; 24(8):412–6. PMID: 22865313
- Yan Z-X, Zhou Y-J, Zhao Y-X, Liu Y-Y, Shi D-M, Guo Y-H, et al. Safety and feasibility of transradial approach for primary percutaneous coronary intervention in elderly patients with acute myocardial infarction. Chin Med J [Internet]. 2008; 121(9):782–6. PMID: 18701040
- Andò G, Capodanno D. Radial Access Reduces Mortality in Patients with Acute Coronary Syndromes Results from an Updated Trial Sequential Analysis of Randomized Trials. JACC Cardiovasc Interventions [Internet]. 2016; 9(7):660–70. https://doi.org/10.1016/j.jcin.2015.12.008 PMID: 27056303
- Ruiz-Rodriguez E, Asfour A, Lolay G, Ziada Khaled M., Abdel-Latif A. Systematic Review and Metaanalysis of Major Cardiovascular Outcomes for Radial Versus Femoral Access in Patients with Acute Coronary Syndrome. South Med J. 2016 Jan; 109(1): 61–76. <u>https://doi.org/10.14423/SMJ.</u> 000000000000404 PMID: 26741877
- 24. Völz S, Petursson P, Odenstedt J, Ioanes D, Haraldsson I, Angerås O, et al. Ticagrelor is Not Superior to Clopidogrel in Patients With Acute Coronary Syndromes Undergoing PCI: A Report from Swedish Coronary Angiography and Angioplasty Registry. J Am Heart Assoc. 2020 Jul 21; 9(14):e015990. https://doi.org/10.1161/JAHA.119.015990 PMID: 32662350

- 25. Andò G, Cortese B, Russo F, Rothenbühler M, Frigoli E, Gargiulo G, et al. Acute Kidney Injury After Radial or Femoral Access for Invasive Acute Coronary Syndrome Management: AKI-MATRIX. J Am Coll Cardiol. 2017 May 11;S0735-1097(17)36897-3. <u>https://doi.org/10.1016/j.jacc.2017.02.070</u> PMID: 28528767
- 26. Rothenbühler M, Valgimigli M, Odutayo A, Frigoli E, Leonardi S, Vranckx P, et al. Association of acute kidney injury and bleeding events with mortality after radial or femoral access in patients with acute coronary syndrome undergoing invasive management: secondary analysis of a randomized clinical trial. Eur Heart J. 2019 Apr 14; 40(15):1226–32. https://doi.org/10.1093/eurheartj/ehy860 PMID: 30689825
- 27. Mehran R, Pocock SJ, Stone GW, Clayton TC, Dangas GD, Feit F, et al. Associations of major bleeding and myocardial infarction with the incidence and timing of mortality in patients presenting with non-STelevation acute coronary syndromes: a risk model from the ACUITY trial. Eur Heart J. 2009 Jun; 30 (12):1457–66. https://doi.org/10.1093/eurheartj/ehp110 PMID: 19351691
- Jhand A, Atti V, Gwon Y, Dhawan R, Turagam M, Mamas M, et al. Meta-Analysis of Transradial vs Transfemoral Access for Percutaneous Coronary Intervention in Patients With ST Elevation Myocardial Infarction. Am J Cardiol. 2021 Feb 15; 141:23–30. <u>https://doi.org/10.1016/j.amjcard.2020.11.016</u> PMID: 33220324
- 29. Baklanov DV, Kaltenbach LA, Marso SP, Subherwal SS, Feldman DN, Garratt KN, et al. The Prevalence and Outcomes of Transradial Percutaneous Coronary 20 Intervention for ST-Segment Elevation Myocardial Infarction: Analysis From the National Cardiovascular Data Registry (2007 to 2011). J Am Coll Cardiol 2013; 61:420–426. https://doi.org/10.1016/j.jacc.2012.10.032 PMID: 23265340
- Schulz-Schüpke S, Helde S, Gewalt S, Ibrahim T, Linhardt M, Haas K, et al. Comparison of vascular closure devices vs manual compression after femoral artery puncture: the ISAR-CLOSURE randomized clinical trial. JAMA. 2014 Nov 19; 312(19):1981–7. <u>https://doi.org/10.1001/jama.2014.15305</u> PMID: 25399273
- Noori VJ, Eldrup-Jørgensen J. A systematic review of vascular closure devices for femoral artery puncture sites. J Vasc Surg. 2018 Sep; 68(3):887–99. <u>https://doi.org/10.1016/j.jvs.2018.05.019</u> PMID: 30146036
- 32. Chugh Y, Bavishi C, Mojadidi MK, Elgendy IY, Faillace RT, Brilakis ES, et al. Safety of transradial access compared to transfermoral access with hemostatic devices (vessel plugs and suture devices) after percutaneous coronary interventions: A systematic review and meta-analysis. Catheter Cardiovasc Interv. 2020 Aug; 96(2):285–95. https://doi.org/10.1002/ccd.29061 PMID: 32521099
- **33.** Gandhi S, Kakar R, Overgaard CB. Comparison of radial to femoral PCI in acute myocardial infarction and cardiogenic shock: a systematic review. J Thromb Thrombolysis. 2015 Jul; 40(1):108–17. <u>https://doi.org/10.1007/s11239-014-1133-y PMID: 25183512</u>
- 34. Pancholy SB, Palamaner Subash Shantha G, Romagnoli E, Kedev S, Bernat I, Rao SV, et al. Impact of access site choice on outcomes of patients with cardiogenic shock undergoing percutaneous coronary intervention: A systematic review and meta-analysis. Am Heart J. 2015 Aug; 170(2):353–61. <u>https://doi.org/10.1016/j.ahj.2015.05.001</u> PMID: 26299234