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Systematic Review and Meta-analysis of Major Cardiovascular Outcomes for Radial Versus Femoral Access in Patients with Acute Coronary Syndrome

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Abstract

Objectives—Radial artery access (RA) for left heart catheterization and percutaneous coronary interventions (PCIs) has been demonstrated to be safe and effective. Despite consistent data showing less bleeding complications compared with femoral artery access (FA), it continues to be underused in the United States, particularly in patients with acute coronary syndrome (ACS) in whom aggressive anticoagulation and platelet inhibition regimens are needed. This systematic review and meta-analysis aims to compare major cardiovascular outcomes and safety endpoints in patients with ACS managed with PCI using radial versus femoral access.

Methods—Randomized controlled trials and cohort studies comparing RA versus FA in patients with ACS were analyzed. Our primary outcomes were mortality, major adverse cardiac event, major bleeding, and access-related complications. A fixed-effects model was used for the primary analyses.

Results—Fifteen randomized controlled trials and 17 cohort studies involving 44,854 patients with ACS were identified. Compared with FA, RA was associated with a reduction in major bleeding (odds ratio [OR] 0.45, 95% confidence interval [CI] 0.33–0.61; $P < 0.001$), access-related complications (OR 0.27, 95% CI 0.18–0.39; $P < 0.001$), mortality (OR 0.64, 95% CI 0.54–0.75; $P < 0.001$), and major adverse cardiac event (OR 0.70, 95% CI 0.57–0.85; $P < 0.001$). These significant reductions were consistent across different study designs and clinical presentations.

Conclusions—Based on this large meta-analysis, RA for primary PCI in the setting of ACS is associated with reduction in cardiac and safety endpoints when compared with FA in both urgent and elective procedures. This should encourage a wider adoption of this technique among centers and interventional cardiologists.

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Keywords

radial artery access; femoral artery access; percutaneous coronary interventions; acute coronary syndrome; complications

Radial artery access (RA) has been demonstrated to be a safe and effective technique for coronary angiography and percutaneous coronary interventions (PCIs).[1–4] Although performing PCI via RA requires the development of specific skills and involves a significant learning curve, success rates are similar and bleeding complications are lower when compared with femoral artery access (FA).[5–9] The possible reduction in bleeding and vascular complications is clinically relevant because studies have demonstrated a relation between major bleeding and morbidity and mortality.[10–13] Despite consistent evidence in the literature showing the benefits of RA over FA, particularly when an aggressive anticoagulation and platelet inhibition regimen is needed, RA continues to be significantly underused in this setting, especially in certain areas of the United States.[14,15] This may be the result of unfamiliarity with the technique, the need for skill-set development, and possibly the lack of dedicated catheters.

The Society for Cardiac Angiography and Interventions, the European Association of Percutaneous Cardiovascular Interventions, and the European Society of Cardiology have published expert consensus documents favoring RA as the vascular access of choice in conjunction with current recommendations regarding optimal antithrombotic strategies.[16,17] Studies examining the use of RA in PCI, particularly in the setting of acute coronary syndromes (ACSs) and ST-elevation myocardial infarction (STEMI) have been small and could not reach solid conclusions, however. This meta-analysis aims to compare major cardiovascular outcomes and safety profile in patients with ACS managed with PCI using RA versus FA.

Methods

Review Question and Study Protocol

We report this protocol-driven systematic review and meta-analysis according to the Preferred Reported Items for Systematic Reviews and Meta-Analyses.[18] Our review question was whether PCIs in patients with ACSs performed using the RA are as safe and efficacious as those performed using the FA.

Search Strategy and Eligibility Criteria

We searched MEDLINE, the Cochrane databases, EMBASE and CINAHL (September 1998–June 2014), using the following database-appropriate Medical Subject Heading terms: *radial access, transradial, femoral access, transfemoral, percutaneous coronary intervention, ST-segment elevation myocardial infarction, acute coronary syndrome*, and *clinical outcomes*. We sought additional studies by reviewing the reference lists of eligible studies, relevant review articles, and published abstracts of major international annual meetings. Two reviewers (A.A. and E.R.R.) independently judged the eligibility of all of the studies. Eligible studies included randomized controlled trials (RCTs) and cohort studies that

compared RA and FA during PCI in patients with ACS and measured at least one of the following cardiovascular outcomes: mortality, major adverse cardiac events (MACE), major bleeding, and access-related complications. We excluded studies with fewer than 100 patients because of the small sample size that may influence the results. We also excluded studies and registries that examined the outcome retrospectively.[19]

Data Abstraction

Two reviewers working in duplicate and independently used a standardized form to abstract the data from each study. Any discrepancies were resolved by consensus and arbitration by a third investigator (A.A.L.). For each outcome, absolute event numbers were extracted and results are expressed as a ratio of total participants with complete follow-up. The longest follow-up data available were used for each study.

Quality Assessment

The criterion of Jüni et al[20] was used to ascertain the methodological quality and the potential for bias of included randomized trials. A modified Newcastle-Ottawa scale[21] was used to assess the quality of registry studies (details included in the online-only supplemental material). Briefly, the authors evaluated the study quality based on the following criteria: adequacy of allocation, appropriate description of randomization method, similarity of groups at the onset of the study, blinding for both participants and caregivers, blind ascertainment of outcomes, attrition, and intention to treat analysis. The authors' statements regarding blinding and other methods in the original manuscripts were accepted verbatim.

Data Analyses

We performed a meta-analysis of the RCTs and cohort studies comparing clinical outcomes of patients with ACSs undergoing PCI using either RA or FA for their index procedure. The prespecified outcomes of our analyses were all-cause mortality, MACE, major bleeding, and access-related complications. Given the inherent difference in study design, we performed separate meta-analyses for the RCTs and the cohort studies.[22] This was followed by a pooled estimate for all of the studies. Because MACE had different definitions in the incorporated studies, we only included studies that specifically reported the outcome and used a traditional definition of its components. For mortality, some studies used all-cause mortality, whereas others used cardiac mortality. Given the observed heterogeneity in the study methods, we conducted random effects meta-analyses to obtain estimated odds ratios (ORs) for the prespecified main clinical outcomes comparing radial versus femoral access and their associated 95% confidence intervals (CIs). The estimated OR from separate studies was combined according to the DerSemonian-Laird method.[23] We calculated the number needed to treat (NNT) and the number needed to harm (NNH) to assess clinical relevance of the results. The NNT and NNH are the reciprocal of the estimated risk difference calculated based on the Mantel-Haenzel method. NNT denotes the number of patients who would need to be treated with radial access PCI instead of FA PCI to prevent one adverse event, whereas NNH denotes the number of patients who would need to be treated with FA PCI instead of RA PCI to cause one adverse outcome in this analysis. We estimated the proportion of between-study inconsistency resulting from true differences among studies (rather than

differences from chance) using the I^2 statistic,[24] with values of 25%, 50%, and 75% considered low, moderate, and high, respectively. Funnel plots were graphically explored for evidence of publication bias. RevMan version 5.1.2 (Copenhagen, Denmark) was used for these analyses.

Results

Search Results

Of 295 articles retrieved during the initial search (Fig. 1[A]), 46 were not original investigations (review articles and editorials) and 217 were not pertinent to the study question (study design was not pertinent to the meta-analysis question or the clinical outcomes were not reported adequately). Thirty-two studies (15 RCTs and 17 cohorts) containing 44,854 patients were found eligible for inclusion in the meta-analysis. Of these 44,854 patients, 10,482 (23%) underwent RA and 34,372 (77%) underwent FA PCI. Interreviewer agreement on study eligibility was 100%.

Study Characteristics

The main characteristics of the included trials for both RCTs and cohort studies are presented in Table 1. Overall, the median number in cohort studies was larger than that in the RCTs (306 vs 63 patients per group). The age reflects the general clinical practice for patients with ACS and was equal in RCTs and cohort studies (median age 62 years in RCTs and 61.75 in cohort studies). Twelve of the 15 RCTs and 14 of the 17 cohort studies included patients with STEMI exclusively. None of the RCTs included patients with cardiogenic shock, whereas 6 of the 17 cohort studies included this patient category.

Study Quality

Several metrics were used to assess the data quality and reliability of this meta-analysis result. Supplemental Table 1 (http://links.lww.com/SMJ/A42) presents the well-balanced methodological quality of the RCTs. Because blinding to the access site is not logistically feasible, it was not achieved in any of the included studies. We judged whether the follow-up was adequate based on the expected time frame of occurrence of major bleeding and access site complications; however, 12 of the 17 studies had a follow-up duration of ≤30 days, which may not be adequate to assess the rates of mortality or MACE. Follow-up was complete in all of the included RCTs except in the study by Gan et al,[26] in which 12% to 16% of the study population was lost to follow-up. Supplemental Table 2 (http://links.lww.com/SMJ/A43) presents the quality of the cohort studies. All 17 observational studies received favorable ratings on 6 of the 8 domains, but ratings were lower on assessment of outcome and comparability. None of the studies blinded the caregivers to access assignment. The interreviewer agreement on these quality domains was 90%.

[A]There were no figure callouts after this point in text as received. The copyeditor inserted callouts for Figs 2–5 based on best estimates, but guessed at the placement of Figs 6–9. Please check and move/reorder the callouts if needed. The callouts must occur in numerical/consecutive order.

Meta-analyses

Overall Sample—A total of 1378 patients (3.2%) died during follow-up: RA was associated with a significant reduction in mortality (2.1% vs 3.4%, OR 0.64, 95% CI 0.54–0.75, $P < 0.001$); this reduction was observed in both RCTs (1.9% vs 2.7%, OR 0.69, 95% CI 0.53–0.90, $P = 0.006$) and cohort studies (2.3% vs 3.6%, OR 0.61, 95% CI 0.50–0.74, $P < 0.001$). MACE was observed in 2788 patients (6.7%) and RA was associated with a significant reduction in MACE as compared with FA (5.0% vs 7.2%, OR 0.84, 95% CI 0.76–0.94, $P < 0.01$). This reduction was significant only in cohort studies (6.2% vs 7.6%, OR 0.85, 95% CI 0.75–0.97, $P < 0.01$).

A total of 38,522 patients were analyzed for major bleeding, 10,709 of whom (28%) underwent RA procedures and 27,813 (72%) underwent FA procedures (Fig. 2). Major bleeding was observed in 1047 patients (2.7%). Among those, RA reduced the risk of major bleeding by 55% compared with FA (1.4% vs 3.2%, OR 0.45, 95% CI 0.33–0.61, $P < 0.001$). This reduction was significant in both RCTs (1.0% vs 2.0%, OR 0.54, 95% CI 0.37–0.80, $P = 0.002$) and cohorts (1.8% vs 3.5%, OR 0.39, 95% CI 0.25–0.61, $P < 0.001$).

Furthermore, 31,409 patients were analyzed for access-related complications, 8952 of whom underwent RA and 22,457 of whom underwent FA (Fig. 3). Access-related complications were observed in 909 patients (2.9%). RA was superior to FA in terms of the risk of access-related complications (1.2% vs 3.6%, OR 0.27, 95% CI 0.18–0.39, $P < 0.001$). This benefit was observed in both RCTs (1.9% vs 4.9%, OR 0.38, 95% CI 0.30–0.49, $P < 0.001$) and cohorts (1.2% vs 3.1%, OR 0.12, 95% CI 0.06–0.27, $P < 0.001$).

Analysis of the STEMI Population—We conducted a separate analysis for studies involving only patients with STEMI to evaluate potential differences in outcomes when compared with non-ST elevation ACS. A total of 12,944 patients were analyzed for mortality outcomes. Of these patients, 4329 (33%) underwent RA and 8615 (67%) underwent FA. A total of 520 patients (4%) died during follow-up. Among them, RA was associated with an overall reduction in mortality (2.8% vs 4.6%, OR 0.61, 95% CI 0.49–0.76, $P < 0.001$). This reduction was observed in both RCTs (3.4% vs 5.8%, OR 0.57, 95% CI 0.39–0.82; $P = 0.003$) and cohort studies (2.6% vs 4.4%, OR 0.63, 95% CI 0.48–0.84, $P = 0.002$). A total of 12,931 patients were analyzed for MACE, 5081 of whom (39%) underwent RA and 7850 (61%) underwent FA (Fig. 4). MACE was observed in a total of 657 patients (5.8%). RA was associated with a significant reduction in MACE as compared with FA (4.3% vs 6.4%, OR 0.55, 95% CI 0.45–0.68, $P < 0.001$), both in RCTs (5.8% vs 8.1%, OR 0.67, 95% CI 0.49–0.90, $P < 0.01$) and cohorts (3.3% vs 6.1%, OR 0.45, 95% CI 0.34–0.60, $P < 0.001$). A total of 14,026 patients were analyzed for major bleeding, 4868 (34.7%) of whom underwent RA and 9158 (65.3%) of whom underwent FA. Major bleeding was observed in 432 patients (3.0%). Among those, RA reduced the risk of major bleeding significantly compared with FA (1.7% vs 3.8%, OR 0.38, 95% CI 0.26–0.57, $P < 0.001$), both in RCTs (1.9 % vs 4.7%, OR 0.45, 95% CI 0.29–0.70 $P = 0.0004$) and cohorts (1.6% vs 3.6%, OR 0.31, 95% CI 0.16–0.59, $P = 0.0004$). Furthermore, 6913 patients were analyzed for access-related complications; 3111 (45%) underwent RA and 3802 (55%) underwent FA. Access-related complications were observed in 320 patients (4.6%). RA was significantly

superior to FA in reducing the risk of access-related complications (1.5% vs 7.2%, OR 0.25, 95% CI 0.15–0.39, $P < 0.001$), both in RCTs (2.6% vs 7.1%, OR 0.36, 95% CI 0.24–0.54, $P < 0.001$) and cohorts (0.5% vs 7.2%, OR 0.09, 95% CI 0.03–0.29, $P < 0.001$).

Sensitivity Analyses—We also conducted sensitivity analyses comparing randomized with cohort studies to explore the possibility of selection bias in our results. There were no significant differences between the outcomes in both arms and we did not observe any significant interactions (Table 2). Similarly, we did not observe significant interactions among studies that enrolled patients with STEMI compared with studies that included patients with ACS (Table 3). Our findings were unchanged when we again performed the meta-analysis using the fixed-effects instead of the random-effects model (data not shown). The heterogeneity observed in our analyses was generally in the low-to-moderate range, and we elected to present the data from the random-effects model.

The absolute risk difference in major bleeding was 2% (CI 3%–1%, $P < 0.001$) with NNT of 50 individuals. The absolute risk difference in access site complications was 4% (CI 6%–3%, $P = 0.001$) with NNT of 25 individuals. The absolute risk difference in MACE was 2% (CI 3%–1%, $P = 0.01$) with NNT of 50 individuals. The absolute risk difference in mortality was 1% (CI 2%–1%, $P < 0.001$) with NNT of 100 individuals. This reduction in absolute risk difference and subsequent NNT was consistent among RCTs and cohort studies.

Heterogeneity Analysis—Tests for heterogeneity were performed for each of the clinical endpoints using the I^2 statistic. We also examined funnel plots to assess publication bias (supplemental Fig. 1, http://links.lww.com/SMJ/A44 [Funnel plots of the included studies showing the lack of publication bias and the consistency of the study results around the overall odds ratio estimate. The plots were constructed for each outcome separately.]). Overall, the heterogeneity in our analyses based on the I^2 statistic was moderate (approximately 40%) except for mortality, for which the heterogeneity was low (0%). We drew funnel plots to seek evidence of publication bias; where inconsistency was high, the funnel plots were not interpretable and where inconsistency was low, the funnel plots were inconclusive.

Discussion

This comprehensive meta-analysis including RCTs and cohort studies demonstrates that RA access for PCI in the setting of ACS is safer and associated with better cardiovascular outcomes compared with FA (Figs. 5–9). We demonstrated a significant reduction in mortality, MACE, major bleeding, and access-related complications with RA. This benefit was consistent across multiple study designs, clinical scenarios, and patient populations. This is the largest and most comprehensive meta-analysis to date to address this important clinical scenario, and the results presented herein support the adoption of RA for PCI even in the setting of emergency primary PCI.

We included data from 32 studies and found significant reduction in mortality from RA when PCI was performed in ACS in both RCTs and cohort studies. The mechanism by which RA reduces mortality and MACE in patients with ACS may be directly related to the

prevention of both major bleeding and access-related complications. Although the responsible mechanism of increased mortality in populations with major bleeding is uncertain, bleeding complications have been strongly linked to mortality in patients undergoing coronary angiography and PCI.[10–13] Data from the Acute Catheterization and Urgent Intervention Triage strategY trial demonstrated that the increased risk of mortality associated with significant bleeding events is comparable to those experiencing a recurrent myocardial infarction.[11] FA has been associated with higher rates of bleeding and vascular access complications as compared with RA. The cardinal finding of our analyses is the significant reduction in vascular access complications as well as bleeding. These reductions were consistent both in RCTs and cohort studies. In addition, when we limited the analyses to patients with STEMI who traditionally have higher incidences of bleeding and vascular complications, these reductions in bleeding and access site complications remained significant. Our findings are consistent with results from a study based on the National Cardiovascular Data (CathPCI) registry examining 2,820,874 procedures ranging from elective (40%) to urgent (40%) to emergent (20%) and salvage (0.4%) PCI.[14] The results demonstrated the superiority of RA, which was associated with lower adjusted risk of bleeding (OR 0.51, 95% CI 0.49–0.54) and vascular access complications (OR 0.39, 95% CI 0.31–0.50). These reductions were consistent among different age groups, sexes, and clinical presentations. Of note, the registry population included significant percentage of patients with STEMI (18%) and patients with non-ST elevation ACS (62%).[14]

Although the cumulative data showed a reduction in MACE with adopting RA, some of the studies included did not show consistent benefit in terms of MACE. When we restricted the analysis to patients with STEMI, we observed greater reduction in MACE when adopting RA. We believe that patients with STEMI benefit more because of the greater reduction in bleeding, particularly with the higher dose of antithrombotic/antiplatelet therapy used in this group. Overall, the benefit was observed more in cohort studies compared with RCTs and this can be explained by selection bias in these studies. It is important to point out that RA is associated with a learning curve, and it is essential that before adopting an RA ACS/STEMI program, operators and institutions must develop their skills in less challenging, low-acuity patient populations. There is evidence that operator and institutional expertise play a major role in the relation between RA and prevention of MACE. This suggests that adopting a high-volume radial program will bring additional benefits to a wide range of patients.[35]

Many of the studies contained in our meta-analysis were intention to treat and were associated with significant crossover rates between RA and FA (5.6% and 1.2%, respectively). The RadIal Vs femorAL access for coronary intervention study, one of the largest RCTs in our analysis, had a crossover rate of 7.3%, and when significant access-related bleeding events were analyzed, the location of these bleeding events was found to be in the FA site, mainly in the crossover group when RA access was not possible. Of note, this study was excluded from our STEMI-focused analysis because it included patients with STEMI and non-STEMI diagnoses. We repeated the analyses excluding studies that had significant crossover, and the significant benefits of RA persisted (data not shown). Overall, the rates of crossover also were higher in the RA-assigned group.

Our meta-analysis has a number of potential limitations. We relied on published data because we did not have access to patient-level data that could have allowed for more accurate and detailed analysis of subgroups. We also included both RCTs and cohort studies; however, we analyzed each subset separately and our sensitivity analysis did not find any significant interactions between the results of RCTs and cohort studies except for access site complications, which were significantly lower in cohort studies. This can be explained by possible selection bias in cohort studies—operators may have selected RA in patients with a higher risk of access site complications, for instance. Finally, although the analyzed studies included mostly patients with STEMI, we opted to use the term ACS with or without ST-elevation, because this broadly represented the overall population. We conducted a sensitivity analysis among studies that exclusively enrolled patients with STEMI compared with those that included all patients with ACS, and there was no significant interaction between the two groups.

Conclusions

This meta-analysis of randomized and cohort studies showed that among patients with ACS with or without ST-elevation undergoing primary PCI, RA is associated with consistent reductions in mortality, MACE, major bleeding, and access site–related complications. As such, RA should be considered the default approach in patients with ACS, as recommended in expert consensus documents.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Key Points

- Radial artery access (RA) for coronary angiography and interventions offers equivalent success rates to femoral artery access in patients with acute coronary syndromes.
- RA access for coronary angiography and interventions is associated with significantly lower access-related complication and bleeding rates compared with femoral artery access in patients with acute coronary syndromes.
- The benefits of RA access for coronary angiography and interventions extend across different study designs, patient populations, and clinical scenarios. As such, these data should encourage the wide adoption of RA in clinical practice.

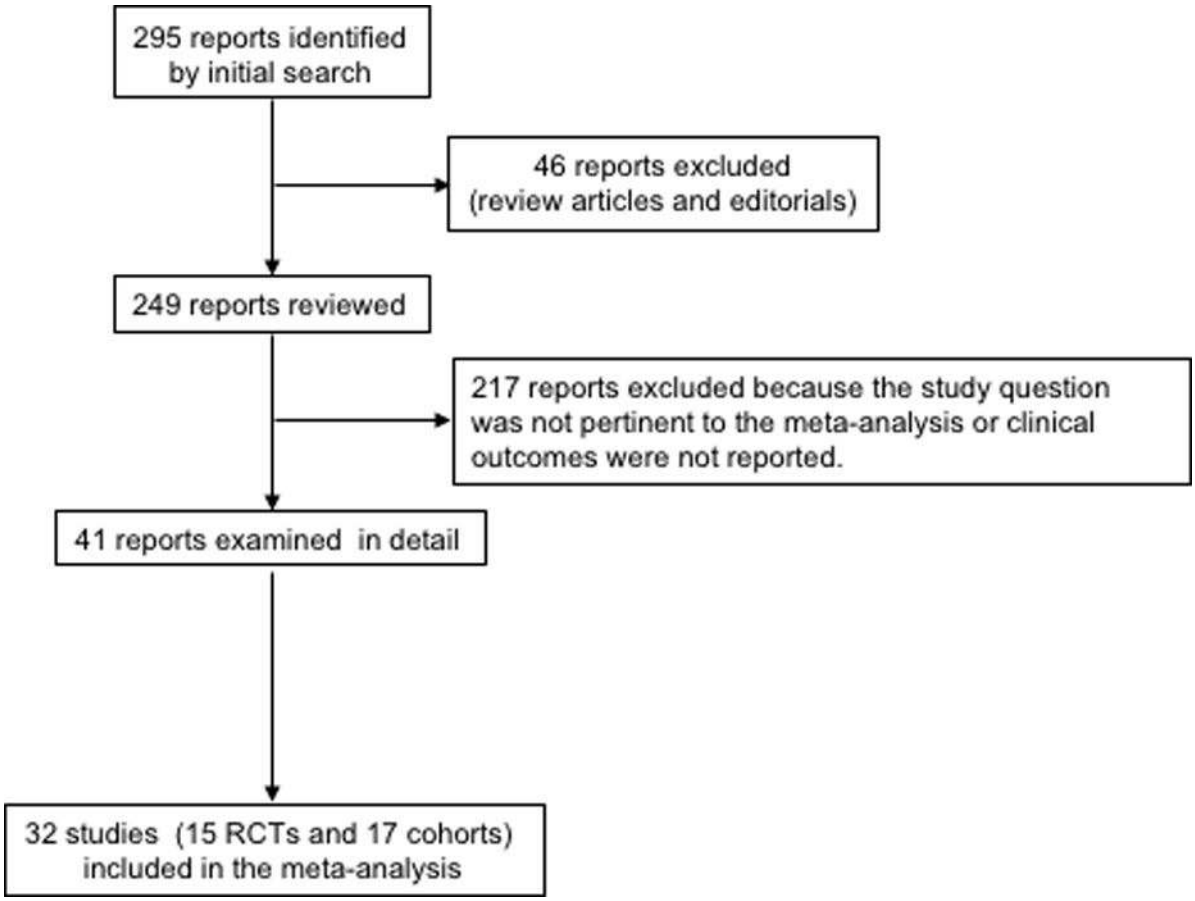

Fig. 1.
Selection of trials for inclusion in the meta-analysis. RCTs, randomized controlled trials.

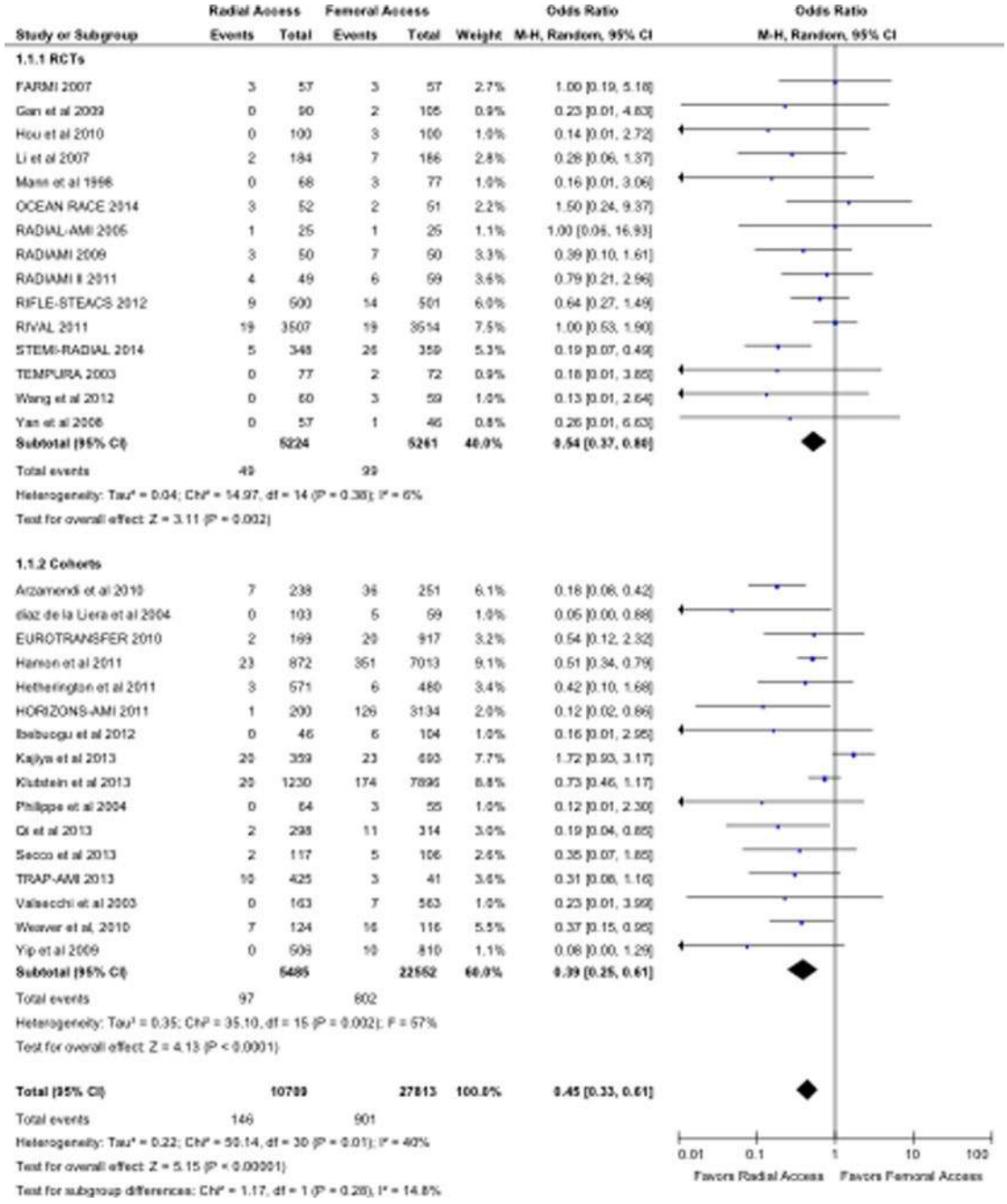

Fig. 2.

Forest plot of unadjusted odds ratios (ORs; 95% confidence intervals [CIs]) for major bleeding after percutaneous coronary intervention in patients with acute coronary syndromes undergoing radial artery access (RA) compared with femoral artery access (FA). A total of 38,522 patients were analyzed for major bleeding, 10,709 of whom (28%) underwent RA and 28,976 (75%) underwent FA. Major bleeding was observed in a total of 1047 patients (2.7%). RA was associated with a reduction in major bleeding as compared with FA (1.4% vs 3.2%, OR 0.45, 95% CI 0.33–0.61; $P < 0.001$), similarly in both randomized controlled

trials (1.0% vs 2.2%, OR 0.54, 95% CI 0.37–0.80, $P = 0.002$) and cohorts (1.8% vs 3.5%, OR 0.39, 95% CI 0.25–0.61, $P < 0.001$).

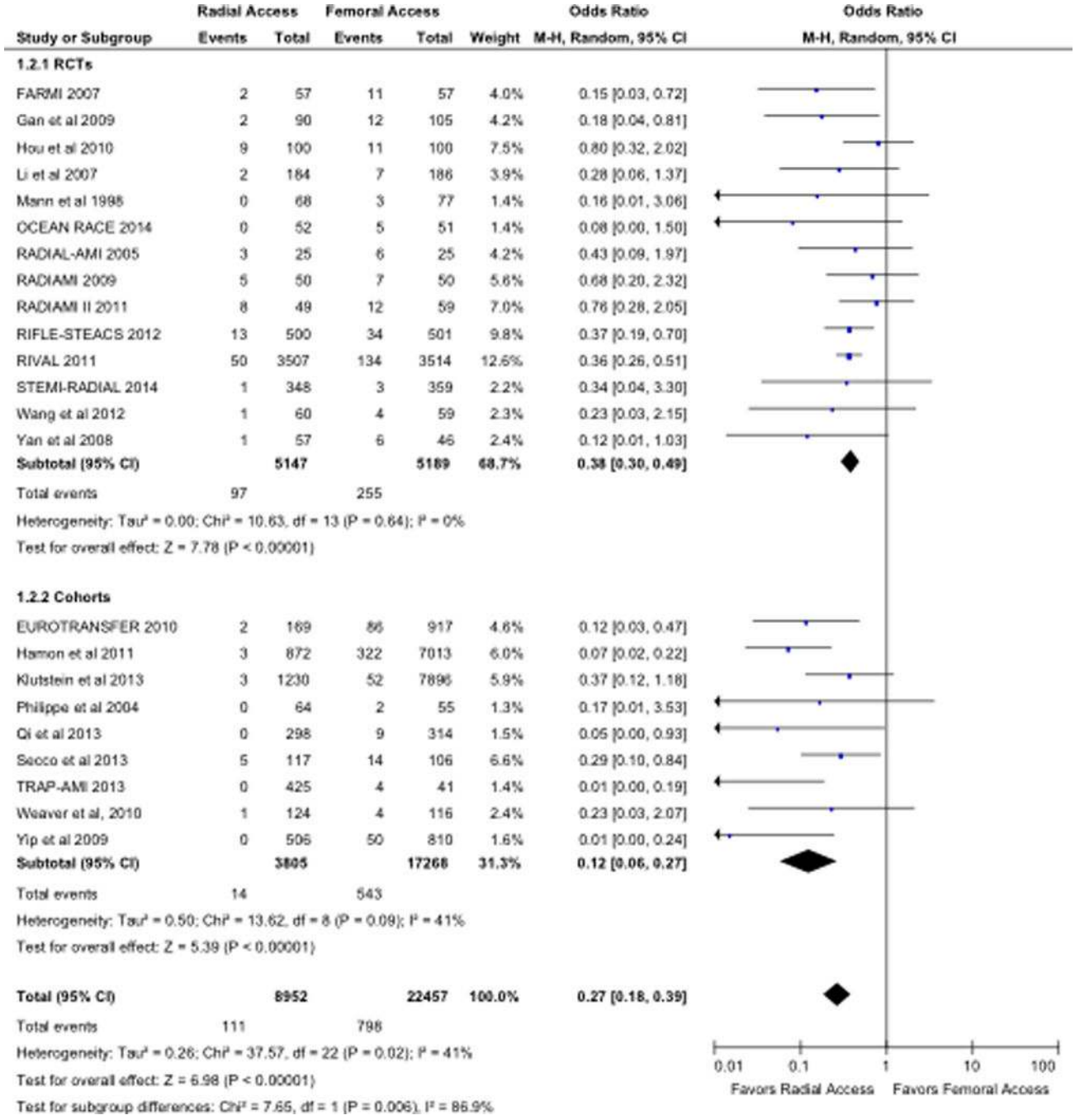

Fig. 3.

Forest plot of unadjusted odds ratios (ORs; 95% confidence intervals [CIs]) for access-related complications after percutaneous coronary intervention in patients with acute coronary syndromes undergoing radial artery access (RA) compared with femoral artery access (FA). A total of 31,409 patients were analyzed for access-related complications, 8952 of whom underwent RA and 22,457 underwent FA. Access-related complications were observed in 909 patients (2.9%). RA was associated with a reduction in access-related complications compared with FA (1.2% vs 3.6%, OR 0.27, 95% CI 0.18–0.39, $P < 0.001$),

similarly in both randomized controlled trials (1.9% vs 4.9%, OR 0.38, 95% CI 0.30–0.49, $P < 0.001$) and cohorts (0.4% vs 3.1%, OR 0.12, 95% CI 0.06–0.27, $P < 0.001$).

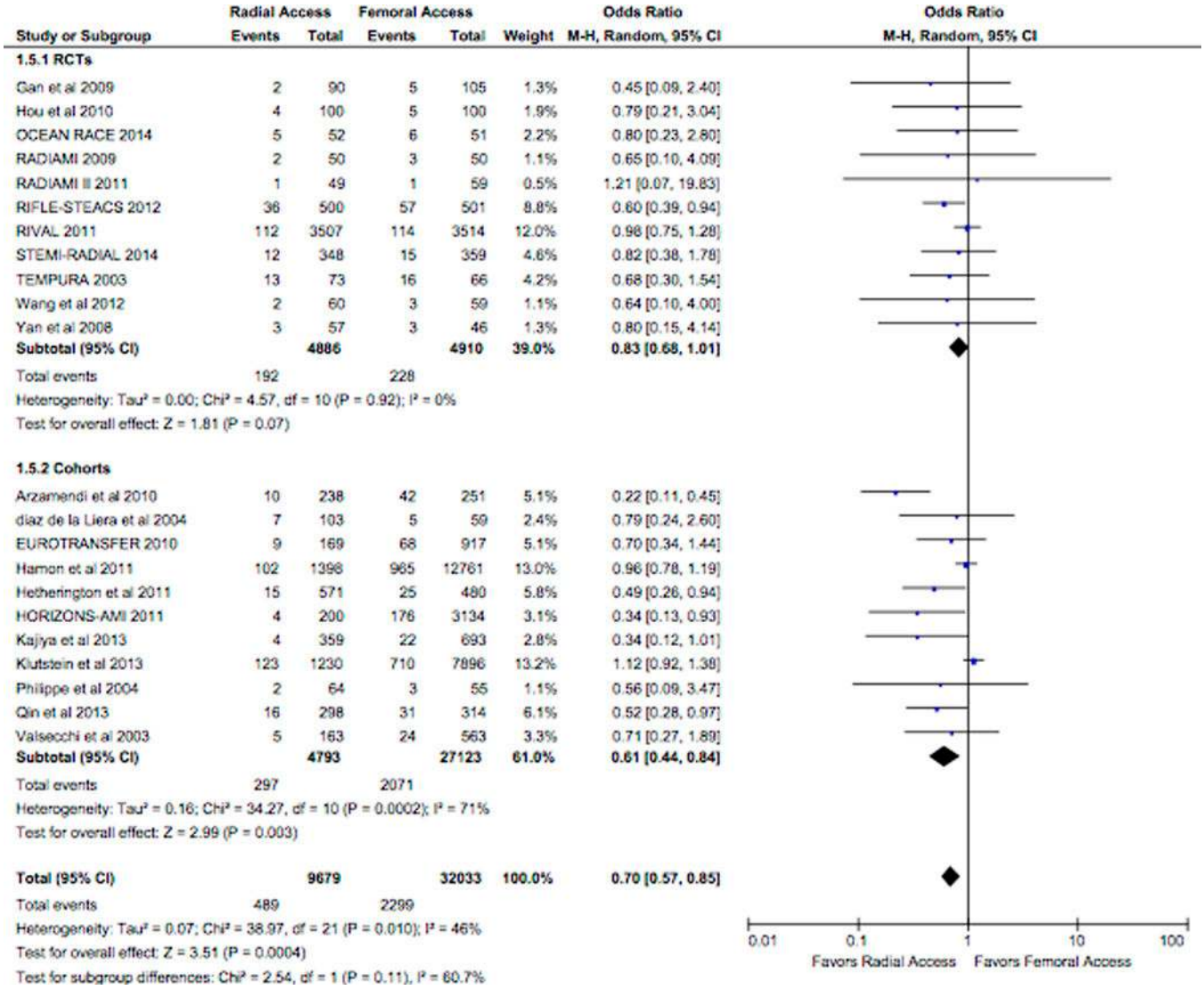

Fig. 4.

Forest plot of unadjusted odds ratios (ORs; 95% confidence intervals [CIs]) for major adverse cardiovascular events (MACE) after percutaneous coronary intervention in patients with acute coronary syndromes undergoing radial artery access (RA) compared with femoral artery access (FA). A total of 38,520 patients were analyzed for MACE, 9544 (25%) of whom underwent RA and 28,976 (75%) underwent FA. MACE was observed in a total of 2608 patients (6.8%). RA was associated with a reduction in MACE as compared with FA (5.0% vs 7.3%, OR 0.70, 95% CI 0.57–0.85, $P < 0.001$). This significant reduction was only observed in cohort studies (6.4% vs 7.9%, OR 0.61, 95% CI 0.44–0.84, $P < 0.01$), however.

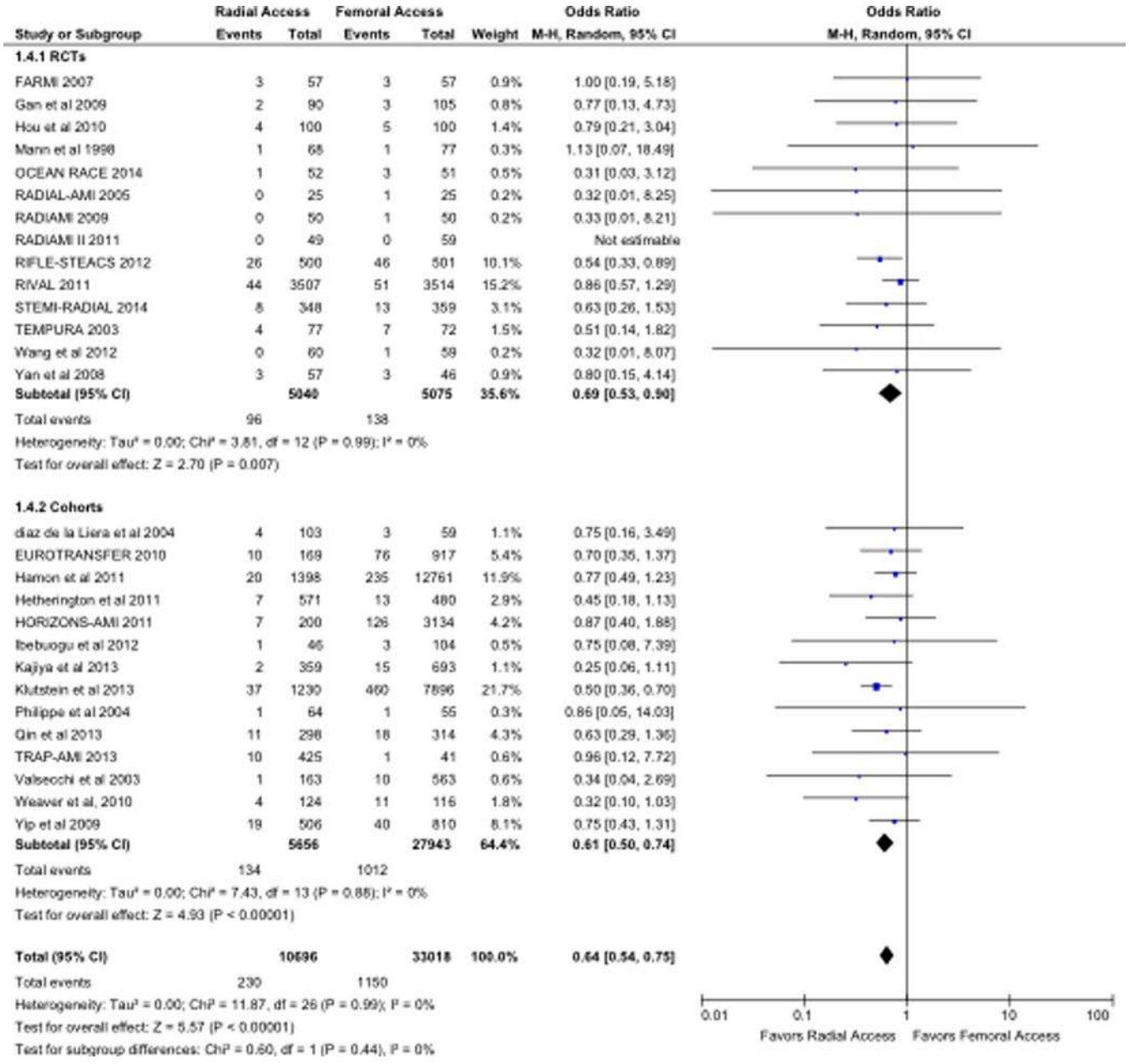

Fig. 5.

Forest plot of unadjusted odds ratios (ORs; 95% confidence intervals [CIs]) for mortality after percutaneous coronary intervention in patients with acute coronary syndromes undergoing radial artery access (RA) compared with femoral artery access (FA). A total of 43,714 patients were analyzed for mortality, 10,696 (25%) of whom underwent RA and 33,018 (75%) underwent FA. A total of 1378 patients (3.2%) died during follow-up. RA was associated with an overall reduction in mortality (2.1% vs 3.4%, OR 0.64, 95% CI 0.54–0.75, $P < 0.001$). Benefits were observed in both randomized controlled trials (1.9% vs 2.7%, OR 0.69, 95% CI 0.53–0.90, $P = 0.006$) and cohort studies (2.3% vs 3.6%, OR 0.61, 95% CI 0.50–0.74, $P < 0.001$).

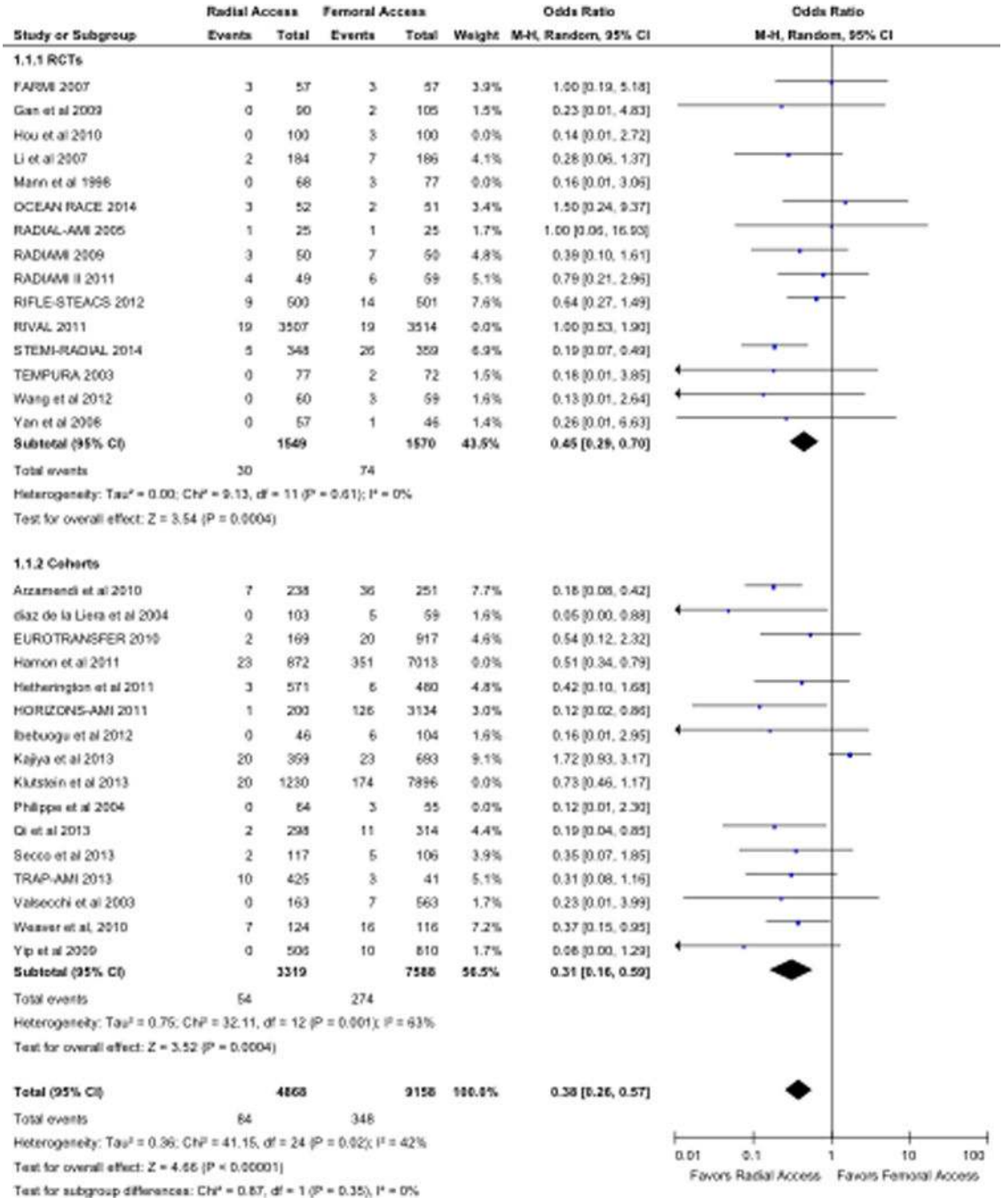

Fig. 6.

Forest plot of unadjusted odds ratios (ORs; 95% confidence intervals [CIs]) for major bleeding after primary percutaneous coronary intervention in patients with ST-elevation myocardial infarction undergoing radial artery access (RA) compared with femoral artery access (FA). A total of 107,208 patients were analyzed for major bleeding, 4868 of whom (34.7%) underwent RA and 9158 (65.3%) underwent FA. Major bleeding was observed in a total of 432 patients (3.0%). RA was associated with a reduction in major bleeding as compared with FA (1.7% vs 3.8%, OR 0.38, 95% CI 0.26–0.57, $P < 0.001$), similarly in both

randomized controlled trials (1.9 % vs 4.7%, OR 0.45, 95% CI 0.29–0.70, $P < 0.001$) and cohorts (1.6% vs 3.6%, OR 0.31, 95% CI 0.16–0.59, $P < 0.001$).

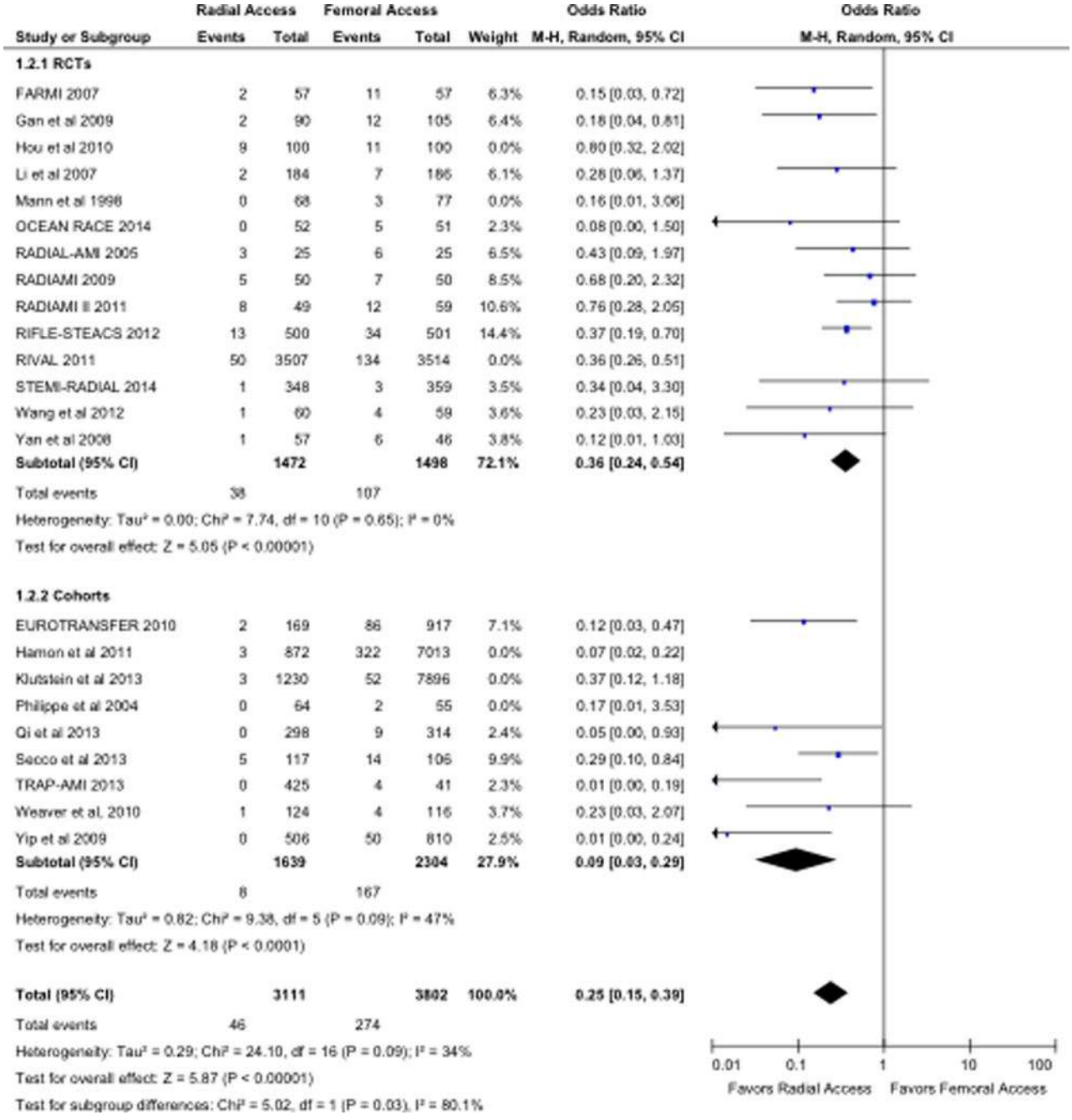

Fig. 7.

Forest plot of unadjusted odds ratios (ORs; 95% confidence intervals [CIs]) for access-related complications after primary percutaneous coronary intervention in patients with ST-elevation myocardial infarction undergoing radial artery access (RA) compared with femoral artery access (FA). A total of 6913 patients were analyzed for access-related complications, 3111 (45%) of whom underwent RA, and 3802 (55%) of whom underwent FA. Access-related complications were observed in 320 patients (4.6%). RA was associated with a reduction in access-related complications compared with FA (1.5% vs 7.2%, OR 0.25, 95% CI 0.15–0.39, $P < 0.001$), similarly in both randomized controlled trials (2.6% vs 7.1%, OR

0.36, 95% CI 0.24–0.54, $P < 0.001$) and cohorts (0.5% vs 7.2%, OR 0.09, 95% CI 0.03–0.29 $P < 0.001$).

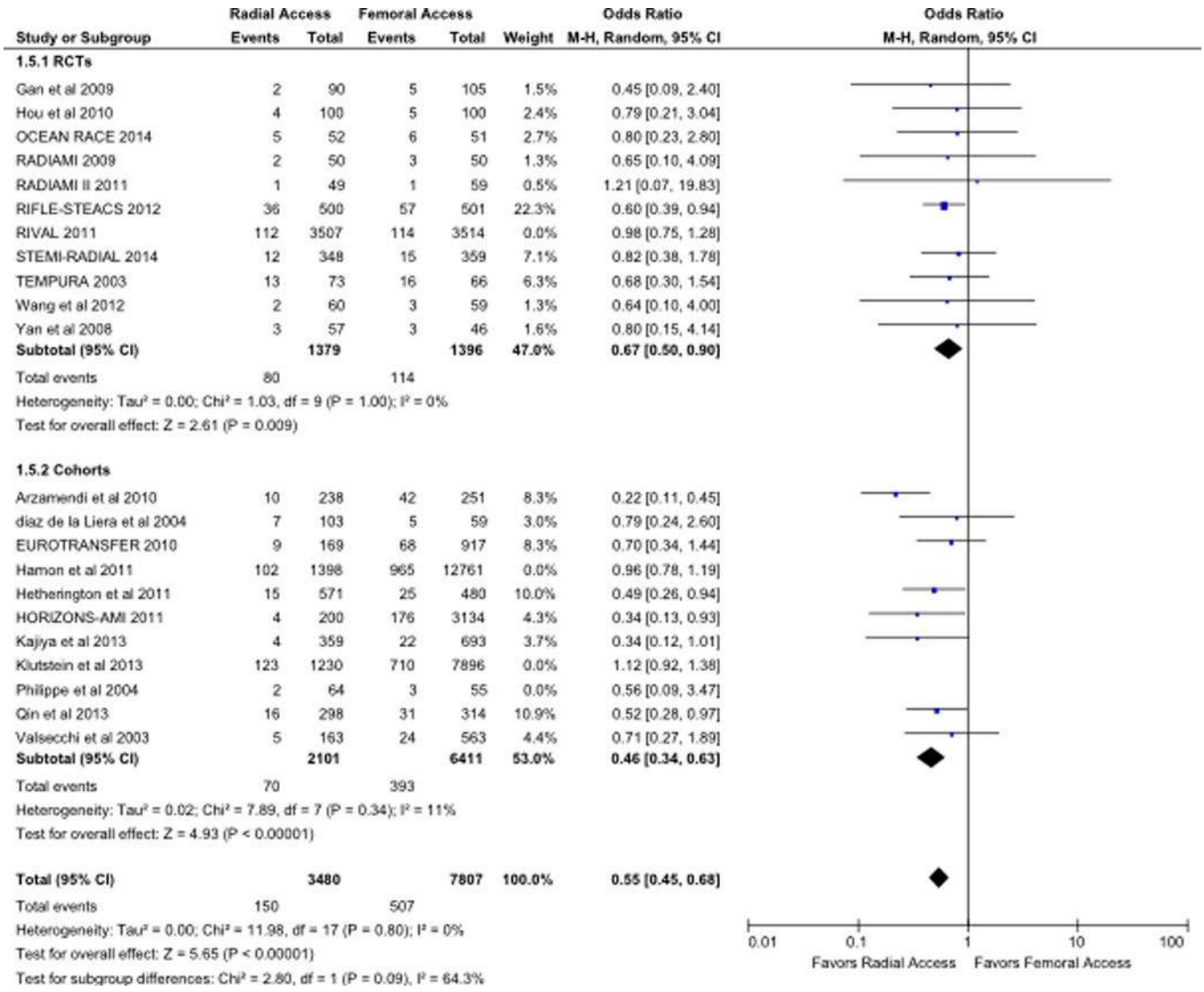

Fig. 8.

Forest plot of unadjusted odds ratios (ORs; 95% confidence intervals [CIs]) for major adverse cardiovascular events (MACE) after primary percutaneous coronary intervention in patients with ST-elevation myocardial infarction undergoing radial artery access (RA) compared with femoral artery access (FA). A total of 12,931 patients were analyzed for MACE, 5081 (39%) of whom underwent RA and 7850 (61%) of whom underwent FA. MACE was observed in a total of 751 patients (5.8%). RA was associated with a reduction in MACE as compared with FA (4.5% vs 7.1%, OR 0.55, 95% CI 0.45–0.68, $P < 0.001$), similarly in both randomized controlled trials (3.4% vs 6.6%, OR 0.67, 95% CI 0.5–0.90, $P = 0.009$) and cohorts (3.5% vs 6.6%, OR 0.46, 95% CI 0.34–0.63, $P < 0.001$).

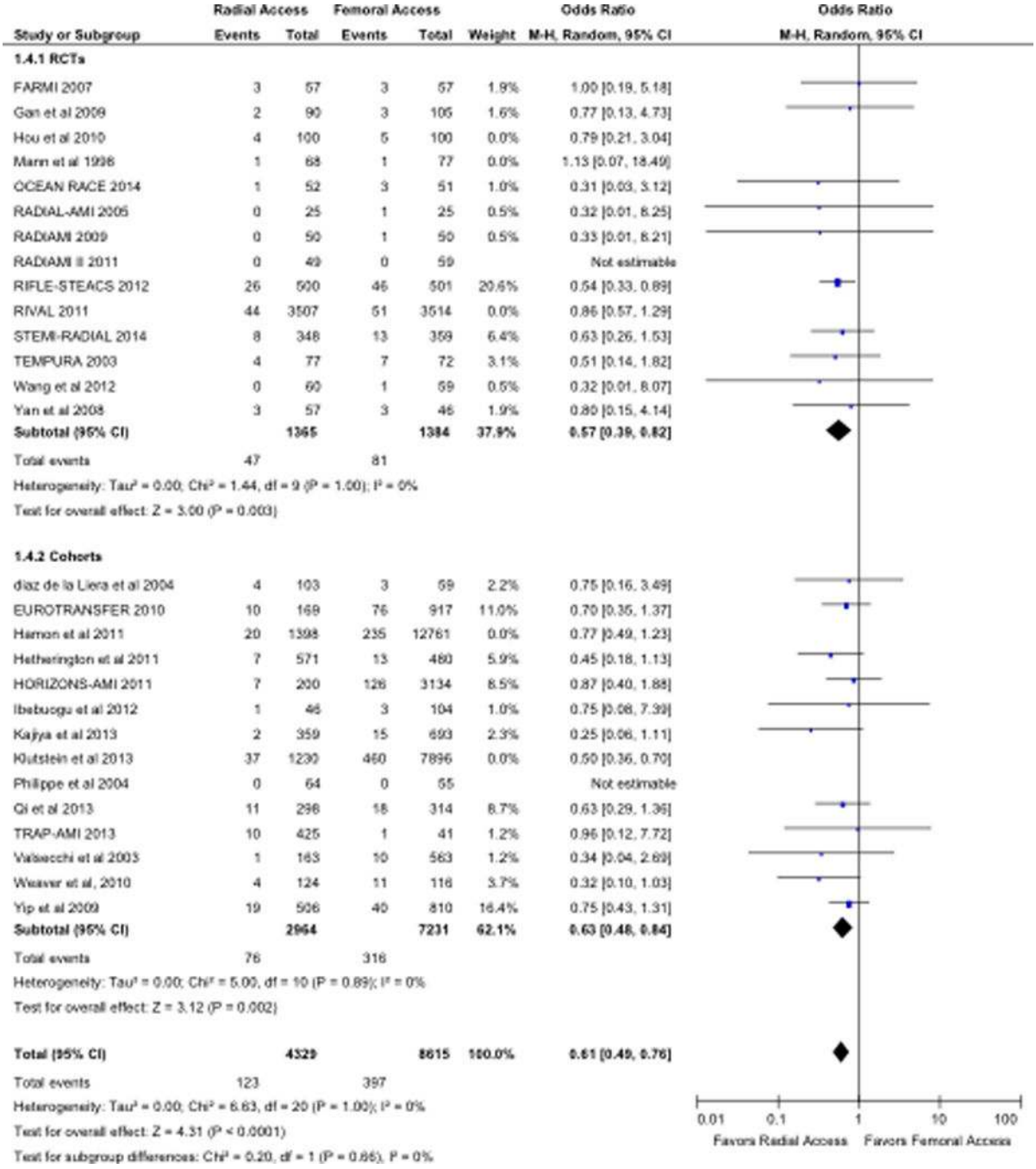

Fig. 9.

Forest plot of unadjusted odds ratios (ORs; 95% confidence intervals [CIs]) for mortality after primary percutaneous coronary intervention in patients with ST-elevation myocardial infarction undergoing radial artery access (RA) compared with femoral artery access (FA). A total of 12,944 patients were analyzed for mortality outcomes, 4329 (33%) of whom underwent RA and 8615 (67%) of whom underwent FA. A total of 520 patients (4%) died during follow-up. In the meta-analysis, RA was associated with an overall reduction in mortality (2.8% vs 4.6%, OR 0.61, 95% CI 0.49–0.76, $P < 0.001$). Benefits were observed in

both randomized controlled trials (3.4% vs 5.8%, OR 0.57, 95% CI 0.39–0.82, $P < 0.003$) and cohort studies (2.6% vs 4.4%, OR 0.63, 95% CI 0.48–0.84, $P = 0.002$).

Table 1

Patient characteristics[A]

Study	Year	Design	No.	Age	Male, %	Clinical scenario	Follow-up	Primary outcome	MACE definition	Definition of complication	Cardiogenic shock
RCTs											
FARMI[25]	2007	RCT, single center	57 57	60 ± 12 58 ± 13	86 82	STEMI	In-hospital	Incidence of peripheral arterial complication	NR	TIMI major	No
Gan et al[26]	2009	RCT, multicenter	90 105	54 ± 12.5 52 ± 12	73 84	STEMI	In-hospital and 6 mo	NR	Death, CABG, MI, and TLR	NR	No
Hou et al[27]	2010	RCT, single center	100 100	65 ± 8 66 ± 8	72 69	AMI	30 d	NR	Death, recurrent MI, and TVR	Hemoglobin loss of at least 2 mmol/L, administration of blood transfusions, and needing vascular repair	No
Li et al[28]	2007	RCT, single center	184 186	56.5 ± 11 55 ± 13	76 64	STEMI	In-hospital	NR	NR	Local hematoma	No
Mann et al[29]	1998	RCT, single center	65 77	63 62	65 68	ACS	In-hospital	NR	NR	Access site complications were defined as a vascular bleeding that prolonged hospitalization	No
OCEAN RACE[30]	2014	RCT, single center	52 51	61 (50–72) 63 (50–75)	NR	STEMI	12 mo	Major bleeding by the REPLACE-2 scale and minor bleeding by EASY scale (TR arm) or the FEMORAL scale (TF arm)	Cardiovascular death, recurrent MI, stroke, repeat revascularization, and (non-CABG) bleedings	REPLACE-2 scale	No
RADIAL-AMI[31]	2005	RCT, multicenter	25 25	52 (48–60) 58 (49–72)	76 100	STEMI	30 d	Primary efficacy: reperfusion time (time from local anesthesia infiltration to first balloon inflation) Primary safety: major bleeding and access site complications	NR	Intracranial or retroperitoneal bleeding, drop in hemoglobin level >5 g/dL, hematocrit z[B] 15%, or bleeding requiring blood transfusion	No
RADIAMI[32]	2009	RCT, single center	50 50	60 ± 9 59 ± 9	51.5 48.5	STEMI	In-hospital	NR	Death, MI	Intracranial hemorrhage, fatal bleeding, bleeding requiring blood transfusion, operation, or resulting in drop in hemoglobin count >3 g/dL	No
RADIAMI II[33]	2011	RCT, single center	49 59	62 ± 9 58 ± 10	65 63	STEMI	In-hospital	NR	Death, CABG, MI, and TLR	Intracranial hemorrhage, fatal bleeding, bleeding requiring blood transfusion, operation, or resulting in drop in hemoglobin count >3 g/dL	No
RIFLE-STEACS[34]	2012	RCT, multicenter	500 501	65 (56–75) 65 (55–77)	75 72	STEMI	30 d	(NACEs) Cardiac death, stroke, myocardial infarction, target lesion revascularization, and bleeding	Cardiac death, nonfatal MI, TLR, and stroke	Non-CABG bleeding with 3 g/dL decrease in hemoglobin, leading to increased level of care	No
RIVAL[35]	2011	RCT, multicenter	3507 3514	62 (12) 62 (12)	74 73	STEMI NSTEMI	30 d	composite of death, myocardial infarction, stroke, or (non-CABG)-related major bleeding	Death, MI, and stroke	TIMI major	No

Study	Year	Design	No.	Age	Male, %	Clinical scenario	Follow-up	Primary outcome	MACE definition	Definition of complication	Cardiogenic shock
STEMI-RADIAL[36]	2014	RCT, multicenter	348 359	63 ± 11 61.5 ± 11	75 79	STEMI	30 d and 6 mo	Cumulative incidence of major bleeding and vascular access site complications	Death, MI, and stroke	HORIZONS-AMI	No
TEMPURA[3]	2003	RCT, single center	77 72	66 ± 12 67 ± 10	80.5 82	STEMI	In-hospital and 9 mo	MACE	Death, recurrent MI, or TVR	Bleeding requiring blood transfusion and/or surgical repair or cerebral bleeding	No
Wang et al[37]	2012	RCT, single center	60 59	60 ± 12 60 ± 11	87 83	STEMI	In hospital	NR	Death, recurrent MI, and repeat TLR	TIMI major	No
Yan et al[38]	2008	RCT, single center	57 46	70 ± 7.5 71 ± 8	75 74	STEMI	30 d	NR	Death, recurrent MI, and repeat TVR	TIMI major	No
Cohorts											
Arzamendi et al[39]	2010	Prospective cohort, single center with propensity-matched analysis	238 251	59 ± 13 64 ± 13	81 59	STEMI	In-hospital, 30 d and 1 y	Time to revascularization and the incidence of major bleeding.	Cardiac death, MI, and TVR	Intracranial or intraocular bleeding, access site hemorrhage requiring intervention, hematoma with diameter of ≥5 cm, a reduction in hemoglobin level of ≥4 g/dL without overt bleeding source or ≥3 g/dL with an overt bleeding source, reoperation for bleeding, or transfusion of blood product	Yes
Diaz de la Llera et al[40]	2004	Prospective cohort, single center	103 59	55 ± 11 61 ± 12	90 78	STEMI	30 d	MACE and local complications	Death, new MI, and need for new revascularization	Vascular repair and hemorrhage requiring blood transfusion and hematomas requiring prolonged hospitalization	No
EURO TRANSFER[41]	2010	Post hoc analysis of multicenter, multinational EUROTRANSFER registry	169 917	63 ± 13 63 ± 0.512	76 75	STEMI	In-hospital bleeding, death at 1 y	Main outcomes death and in-hospital bleeding	Death, MI, or TLR	Blood transfusion during hospital stay after index PCI procedure and intracranial hemorrhage	No
Hamon et al[42]	2011	Post hoc analysis of multicenter, multinational OASIS-5 trial with propensity-matched analysis	1,398 12,761	64 ± 11 65 ± 11	71 65	UA NSTEMI	9 d, 30 d, and 6 mo	Death, myocardial infarction and refractory ischemia	Death, MI, and TVR	Fatal bleeding, intracranial, retroperitoneal, intraocular, drop in hemoglobin ≥3 g/dL or requiring transfusion ≥2 U RBC	NR
Hetherington et al[43]	2009	Prospective cohort, single center	571 480	62 ± 13 65 ± 13	75 66	STEMI	In-hospital	Procedural success, major vascular complication and failed initial access strategy	Death, stroke, CABG, MI, or TVR	Access site hemorrhage/hematoma requiring transfusion or delaying hospital discharge or proved false aneurysm formation	No
HORIZONS-AMI[44]	2011	Post hoc analysis of multicenter, multinational HORIZONS-AMI trial	200 3134	59[a] (52–68) 60[a] (53–67)	73 77	STEMI	30-d and 1 y	NACE (MACE or major bleeding)	Death, MI, stroke, or TVR	Intracranial or intraocular hemorrhage, hematomas ≥5 cm in diameter, access site hemorrhage requiring intervention, reoperation for bleeding, clinically overt bleeding with decrease in hemoglobin by ≥3 g/dL, reduction in hemoglobin concentration of ≥4 g/dL without an overt source of bleeding, or need for any blood product transfusion	Yes
Ibebuogu et al[45]	2012	Prospective cohort, single center	46 104	62 ± 12 65 ± 14	76 72	STEMI	In-hospital	NR	NR	Hematoma and vascular complications	Yes
Kajiya et al[46]	2012	Prospective cohort, single center with propensity-	350 693	56 ± 11 57 ± 12	87 85	STEMI	30 d	DTB time, major and minor bleeding, and MACE	Death, MI, and TVR	Intracranial or intraocular bleeding, hemorrhage at access site requiring intervention, hematoma with diameter of at least 5 cm, reduction in hemoglobin	Yes

Study	Year	Design	No.	Age	Male, %	Clinical scenario	Follow-up	Primary outcome	MACE definition	Definition of complication	Cardiogenic shock
		matched analysis, ACUITY trial								levels of at least 4 g/dL without an overt bleeding source or at least 3 g/dL with such a source, reoperation for bleeding, or transfusion of blood product	
Klutstein et al[47]	2013	Post hoc analysis of multicenter, multinational RCT EARLY-ACS trial with propensity-matched analysis	1230 7896	65[a] (56–73) 68[a] (60–75)	74 68	NSTEMI	30-d death/MI 1−y death	Bleeding occurring within 120 h of the catheterization procedure	Death, MI, and TVR at 3 d	TIMI major	Yes
Philippe et al[2]	2004	Prospective cohort, single center	64 55	59 ± 20 60 ± 10	75 72	ACS	30 d	Major access site bleeding and major cardiac events	Death, MI, CABG, or TVR	TIMI major	No
Qin et al[48]	2013	Prospective cohort, single center	298 314	66 ± 10 65 ± 12	72 74	STEMI	30 d	MACE	Death, MI, or TLR	Fatal bleeding, resulted in transfusion of ≥2 U of blood; caused substantial hypotension with need for inotropes; required surgical intervention; caused severely disabling sequelae; was intracranial and symptomatic or intraocular and led to significant visual loss or led to decrease in hemoglobin of at least 5 g/dL	No
Secco et al[49]	2013	Prospective cohort, single center	177 106	82 ± 4 83 ± 4	57 42.5	STEMI	In-hospital	Main outcome of interest was time to dilatation	NR	TIMI criteria	Yes
TRAP-AMI[50]	2013	Prospective cohort, single center	425 41	61 ± 14 62 ± 19	76 49	STEMI	In-hospital	NR	NR	Bleeding necessitating blood transfusion	No
Valsecchi et al[51]	2003	Prospective cohort, single center	163 563	61.5± 12 61.5 ±13	87 86	STEMI	30 d	MACE	Death, MI, ventricular arrhythmias, heart failure, or TLR	TIMI major	No
Weaver et al[52]	2010	Prospective cohort, single center	124 116	60 ± 12 61 ± 13	82 79	STEMI	In-hospital	NR	NR	TIMI major	No
Yip et al[53]	2009	Prospective cohort, single center	506 810	61 ± 12 62 ± 12	82 84	STEMI	30 d	NR	NR	Bleeding related to the procedure with fall in hemoglobin >3 g/dl requiring blood transfusion	No

CABG, coronary artery bypass grafting; DTB, door-to-balloon; MACE, major adverse cardiac events; MI, myocardial infarction; NACE,[C]; NR, no result[D]; PCI, percutaneous coronary interventions; RBC, red blood cell count; RCT, randomized controlled trial; STEMI, ST-elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction; TF, femoral; TLR, target lesion revascularization; TR, radial; TVR, target vessel revascularization.

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South Med J. Author manuscript; available in PMC 2017 January 01.

Table 2

Estimated ORs and 95% CIs of MACEs in RA vs FA in RCTs vs cohort studies

	RCTs		Cohort studies		
	OR	**95% CI**	**OR**	**95% CI**	***P***
Major bleeding	0.52	0.34–0.79	0.39	0.25–0.61	0.4
Access site complications	0.38	0.30–0.49	0.12	0.06–0.27	0.01
All-cause mortality	0.69	0.53–0.90	0.61	0.50–0.74	0.5
MACE	0.83	0.68–1.01	0.61	0.44–0.84	0.1

CI, confidence interval; FA, femoral artery access; MACE, major adverse cardiac event OR, odds ratio; RA, radial artery access; RCT, randomized controlled trial.

Table 3

Estimated ORs and 95% CIs of MACEs in RA vs FA in studies including patients with STEMI vs studies including all patients with ACS

	STEMI studies		All ACS studies		
	OR	**95% CI**	**OR**	**95% CI**	***P***
Major bleeding	0.38	0.25–0.57	0.44	0.32–0.60	0.6
Access site complications	0.25	0.15–0.39	0.27	0.18–0.39	0.8
All-cause mortality	0.62	0.50–0.77	0.64	0.54–0.75	0.1
MACE	0.55	0.45–0.68	0.70	0.57–0.85	0.1

ACS, acute coronary syndrome; CI, confidence interval; FA, femoral artery access; MACE, major adverse cardiac event; OR, odds ratio; RA, radial artery access; STEMI, ST-elevation myocardial infarction.