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Radial Access Reduces Mortality in Patients With Acute Coronary Syndromes

Results From an Updated Trial Sequential Analysis of Randomized Trials

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ABSTRACT

OBJECTIVES The authors sought to investigate whether the cumulative evidence coming from randomized studies has reached the necessary power to consider radial access as a bleeding avoidance strategy that reduces mortality and ischemic endpoints in patients with acute coronary syndromes (ACS).

BACKGROUND Studies in ACS patients have reached conflicting conclusions about the impact of radial access in improving ischemic outcomes in addition to the established bleeding benefit.

METHODS English-language publications and abstracts of major cardiovascular meetings until October 2015 were scrutinized. Study quality, patient characteristics, procedural data, and outcomes were extracted. Data were pooled in random effects meta-analyses with classic and trial sequential techniques. Trial sequential analysis combines the a priori information size calculation needed to allow for clinically meaningful statistical inference with the adjustment of thresholds for which results are considered significant.

RESULTS Seventeen studies, encompassing data from 19,328 patients, were pooled. Radial access was found to reduce mortality (relative risk [RR]: 0.73; 95% confidence interval [CI]: 0.60 to 0.88; $p = 0.001$), major adverse cardiovascular events (RR: 0.86; 95% CI: 0.77 to 0.95; $p = 0.005$), and major bleeding (RR: 0.60; 95% CI: 0.48 to 0.76; $p < 0.001$). Multiple sensitivity analyses showed consistent results, and trial sequential analysis suggested firm evidence for a meaningful reduction in mortality with radial access.

CONCLUSIONS Radial access reduces mortality compared with femoral access in ACS patients undergoing invasive management. This benefit is paralleled by consistent reductions in major adverse cardiovascular events and major bleeding, supporting radial access as the default strategy for cardiac catheterization in patients with ACS.
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Combined use of potent antithrombotic drugs and early invasive management in patients with ACS have prompted a substantial reduction in adverse ischemic events, at the cost of increased bleeding (1). From being traditionally regarded as an inherent shortcoming of implementing life-saving procedures, bleeding is now appreciated as an important cause of negative outcomes (2).

The radial access site has been increasingly used as an alternative to the femoral access site both for diagnostic and interventional purposes. An earlier meta-analysis conducted across the broad spectrum of percutaneous coronary intervention (PCI) concluded that radial access reduces major bleeding (3). Yet, studies conducted in ACS have come to conflicting conclusions with respect to the efficacy of the radial approach in reducing ischemic events, or the

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composite of ischemic or bleeding events, by parallel reductions in bleeding (4–10). A more recent meta-analysis (11) suggested a mortality benefit of radial access in patients with ST-segment elevation myocardial infarction (STEMI), although the significant heterogeneity of the studies included prevented a clear understanding of the mechanistic relation between bleeding and mortality (12). Notably, none of such meta-analyses has included data from the most recent trials in the field, and 1 recent article—including a concise meta-analysis of ACS trials—did not report pooled results of procedural outcomes nor explored potential sources of heterogeneity with sensitivity analyses (10).

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On this background, we conducted an updated, comprehensive meta-analysis of randomized studies comparing radial and femoral access in invasively managed patients with ACS. Given the small sample size of many of the earlier trials and to explore any chance of false-positive or false-negative findings in previous meta-analyses (13), we used a trial sequential methodology to critically evaluate whether the amount of the accumulated information has now reached the necessary power to support the systematic and routine use of radial access as a bleeding avoidance strategy to reduce mortality or other ischemic endpoints in patients with ACS undergoing invasive management.

METHODS

PROTOCOL AND REGISTRATION. The protocol of this study has been registered in the PROSPERO database (Time Sequential Meta-Analysis of Radial Versus Femoral Access in Invasively Managed Patients With Acute Coronary Syndromes; CRD42015022031) in compliance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards (14). Study selection, data sources and searches, data extraction and quality assessment, and data synthesis and analysis are reported in the Methods section of the Online Appendix.

TRIAL SEQUENTIAL ANALYSIS. The trial sequential analysis (TSA) combines the a priori information size (IS) calculation for a meta-analysis with the adjustment of the thresholds for which the results are considered statistically significant (15,16). The IS calculation is analogous to sample size calculation in a single trial aimed at estimating the number of events and patients needed to allow for reliable statistical inference. Similarly, in a meta-analysis, the IS calculation is on the basis of the expected incidence of events in the control group and the expected relative risk (RR) reduction of the experimental intervention. Estimating the IS for the purpose of a TSA is instrumental in quantifying the reliability of data pooled in the meta-analysis itself, as a function of the strength of the accumulating evidence over time, and the heterogeneity across included trial populations, interventions, and methods.

The TSA methodology is on the basis of the assumption that data will accumulate until the required IS has been exceeded and requires pre-specifying meaningful thresholds to control for the risk of false-positive (type I error) or false-negative (type II error) results. To that end, a monitoring boundaries methodology was used. Briefly, such approach has been originally developed for repeated significance testing in clinical trials in order to evaluate the accumulating data before the sample size has been reached and to avoid false-positive statistical test results, a phenomenon commonly known as "multiplicity due to repeated significance testing" (17). In other words, adjusted significance thresholds may eliminate early false-positive findings due to repeated significance testing when pooled estimates are on the basis of a still insufficient number of events and patients. Indeed, the possibility to calculate adjusted confidence intervals (CIs) serves to guard against spurious inferences at early stages of a meta-analysis: adjusted confidence intervals appropriately converge to resemble conventional CIs as the accrued number of patients approaches the required IS.

z-Curves were constructed for each explored outcome, and alpha conventional thresholds for significance testing at the 5% and 1% levels were displayed. Adjusted significance monitoring boundaries, as described above, were added by using the O'Brien-Fleming alpha-spending method under the assumption that significance testing may have been performed each time a new trial was sequentially added to the meta-analysis (16). Given the considerable amount of attention given to the access site debate over the last decade, this assumption appeared reasonable. The IS was calculated (Online Table 1) with 99% power for major adverse cardiovascular events (MACE) (defined as the composite of death, myocardial infarction, or stroke), access site bleeding and major bleeding, and 90% power for each of the MACE components. The control event rate was set to the proportion observed in the

ABBREVIATIONS AND ACRONYMS

CI = confidence interval

IS = information size

MACE = major adverse cardiovascular event(s)

PCI = percutaneous coronary intervention

PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses

RR = relative risk

STEMI = ST-segment elevation myocardial infarction

TSA = trial sequential analysis

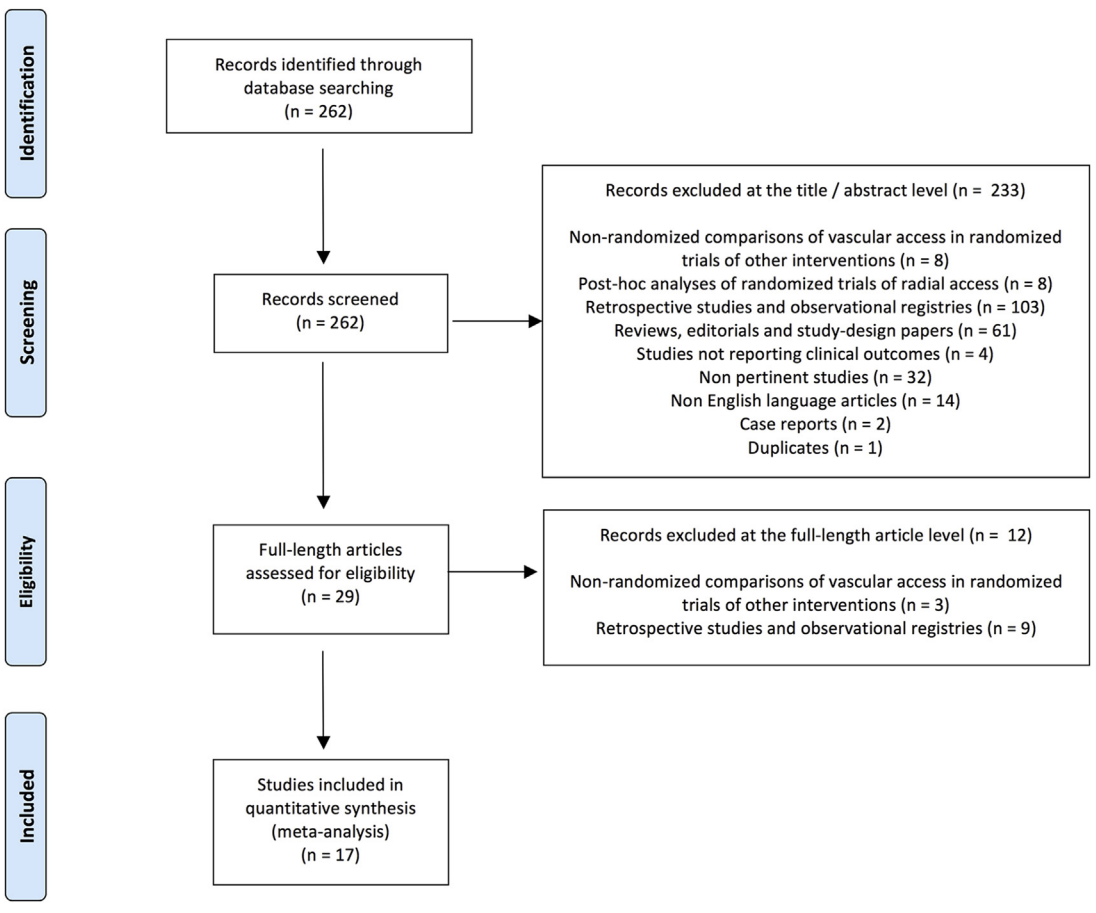
femoral group. In terms of treatment effect, we set a 30% RR reduction for MACE and its components, resembling the design of the MATRIX (Minimizing Adverse Hemorrhagic Events by Transradial Access Site and Systemic Implementation of Angiox) trial (18). Accordingly, alpha was set at 2.5% for MACE (18), and at 1% for death, myocardial infarction, and stroke. For access site and major bleeding, we set a 50% RR reduction with 1% alpha, a clinically relevant effect size that is consistent with the expected benefit of the radial access. Futility boundaries were calculated to provide a threshold for "no effect" and to reflect the uncertainty of obtaining a chance negative finding in relation to the accumulated number of patients (16).

The standard meta-analyses were performed using the meta (version 4.3-2) and metafor (version 1.9-8) packages for R (version 3.2.2) (The R Foundation for Statistical Computing, Vienna, Austria). The TSAs were performed with Trial Sequential Analysis, version 0.9 Beta (Copenhagen Trial Unit, Rigshospitalet, Copenhagen, Denmark).

RESULTS

SEARCH RESULTS AND RISK OF BIAS. The study search (**Figure 1**) identified 17 trials (4-10,19-28) that met all inclusion criteria, encompassing data from up to 19,328 ACS patients (9,638 randomized to radial access and 9,690 randomized to femoral access). Of these trials, 10 were single-center and 7 were multicenter (Online Table 2). Studies that did not report numerical data for myocardial infarction and stroke only were maintained. One single-center study reporting only procedural results was included in the meta-analysis of access-site bleeding and crossover

FIGURE 1 Study Flow Diagram



Selection process for studies to be included in the meta-analysis in compliance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards.

(24). One multicenter trial was reported as an abstract and later, in extenso, as a doctoral thesis (28). All included studies shared a high risk of performance bias because participants could not be blinded to the access site (Online Figure 1). Overall, 7 studies were judged at "low risk" of bias.

Table 1 provides key details of the studies included. Heparin was the most commonly used anticoagulant agent, and the use of glycoprotein IIb/IIIa inhibitors ranged widely across different studies and indications. Most trials mandated for a discrete level of expertise in radial procedures. Data about procedural duration were reported in 13 trials. Radial procedures lasted significantly longer than femoral procedures, although the difference was clinically trivial (standardized difference in means 0.16 min, 95% CI: 0.06 to 0.26; $Z = 3.02$; $p = 0.003$) and affected by moderate heterogeneity ($p = 0.028$; $I^2 = 48\%$).

CLASSIC META-ANALYSIS. On the basis of conventional standards for significance testing, radial access was found superior to femoral access in reducing death (RR: 0.73; 95% CI: 0.60 to 0.88; $p = 0.001$) (**Figure 2**), MACE (RR: 0.86; 95% CI: 0.77 to 0.95; $p = 0.005$) (Online Figure 2), access site (RR: 0.38; 95% CI: 0.31 to 0.47; $p < 0.001$) (Online Figure 3), and major bleeding (RR: 0.60; 95% CI: 0.48 to 0.76; $p < 0.001$) (Online Figure 4), although it was not superior in reducing either recurrent myocardial infarction or stroke (**Table 2**). There was no significant heterogeneity as assessed by the Cochran Q test, and the inconsistency was $I^2 = 0$ for all these outcomes (**Table 2**). Compared with femoral access, radial access was associated with a higher risk of crossover (RR: 3.38; 95% CI: 2.09 to 5.49; $p < 0.001$), with severe observed heterogeneity ($p < 0.001$; $I^2 = 62\%$) (**Table 2**, Online Figure 5). However, the rates of crossover were low in both groups (6.2% in the radial arm, 1.6% in the femoral arm).

SENSITIVITY ANALYSIS. Multiple sensitivity analyses restricted to multicenter studies, studies at low risk of bias, studies enrolling only patients with STEMI, studies with expert radial operators, and recent trials conducted in the last 5 years were consistent with the pooled analyses of all studies (**Table 2**). No remarkable variations in heterogeneity were observed in these sensitivity analyses with the exception of access site and major bleeding (**Table 2**), likely reflecting differences in bleeding definitions across studies (Online Table 2). Interestingly, the heterogeneity observed for access site crossover in the meta-analysis of all studies (**Table 2**) was much lower in magnitude in analyses restricted to patients with STEMI ($p = 0.24$; $I^2 = 20\%$) and in trials where operators were required to have a minimal expertise of >200 radial procedures ($p = 0.54$; $I^2 = 0\%$) (Online Figure 5), although corresponding tests for interaction proved to be negative.

STUDY REMOVAL ANALYSIS AND PUBLICATION BIAS. Removing individual studies did not result in significant deviations of the pooled RR for all-cause death, myocardial infarction, stroke, access site bleeding, major bleeding, access site crossover, or procedural duration. Conversely, radial access was consistently associated with a significant reduction in MACE at each step of the study removal analysis until MATRIX trial was removed, although the magnitude of the treatment effect remained similar (RR: 0.85; 95% CI: 0.71 to 1.02; $p = 0.08$). Visual inspection of the funnel plots revealed a minimal asymmetry only for major bleeding, and the corresponding Egger test was statistically significant ($p = 0.028$), likely reflecting the "small-study effect" (29) of trials conducted in the early 2000s.

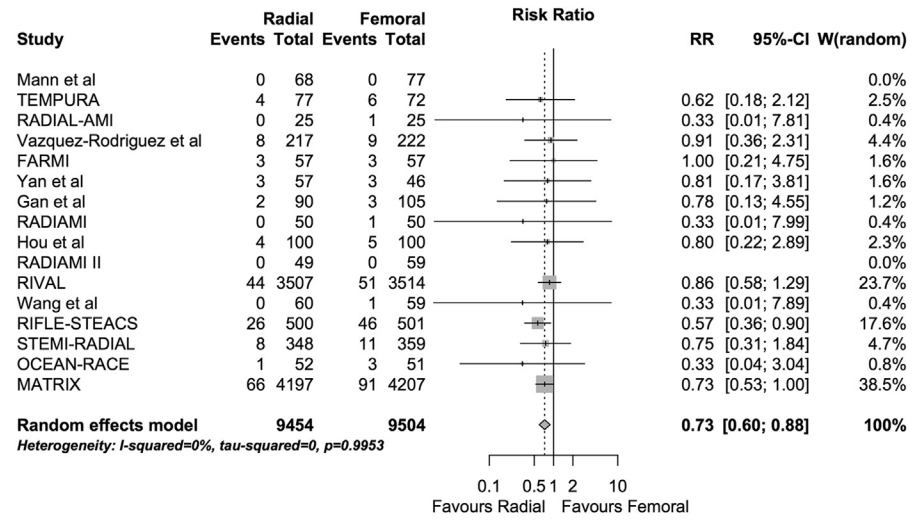
IS CALCULATIONS AND TSA FOR EFFICACY ENDPOINTS. The IS for death was estimated at 22,007 patients (**Figure 3**). The incidence of death in patients receiving femoral PCI was 2.5%. After the RIFLE-STEACS (Radial Versus Femoral Randomized Investigation in ST-Elevation Acute Coronary Syndrome) trial (8) and after the MATRIX trial (10), the cumulative *z*-statistic crossed the conventional statistical thresholds for significance testing at the 5% and 1% alpha level, respectively. After the MATRIX trial (10), it also crossed the upper monitoring boundary. For myocardial infarction, the IS was estimated at 12,298 patients, a cumulative sample size that had not been reached before the MATRIX trial (10). The incidence of recurrent myocardial infarction in patients receiving femoral PCI was 4.4%. The cumulative *z*-statistic after the RIVAL trial (A Trial of Trans-Radial Versus Trans-Femoral Percutaneous Coronary Intervention Access Site Approach in Patients With Unstable Angina or Myocardial Infarction Managed With an Invasive Strategy) (7) consistently crossed the futility boundaries without any change over time, implying neutral results unlikely to be changed by a new trial (data not shown). The incidence of stroke was as low as 0.4% in the femoral access group and 0.5% in the radial access group, with no signals of benefit or harm by either group (data not shown). For the composite of MACE (Online Figure 6), the IS was estimated at 10,591 patients, a pooled sample size that had not been reached before the MATRIX trial (10). The cumulative incidence of MACE in the femoral group was 7.0%. Notably, before the MATRIX trial (10), the cumulative *z*-statistic was well below

TABLE 1 Characteristics of Radial and Femoral Patients in the Trials Included in the Meta-Analysis

	Access, n		Crossover, %		≥7-F Sheath, %		Sheath Management		Anticoagulant		GPI Use, %		
First Author/Study (Ref. #)	Radial	Femoral	Radial	Femoral	Radial	Femoral	Radial	Femoral	Radial	Femoral	Radial	Femoral	Operator Radial Experience
Mann et al. (4)	68	77	8	0	0	74	RCD	CMC	UFH	UFH	15	10	NR
TEMPURA (5)	77	72	0	1.4	0	0	NR	CMC	UFH	UFH	0	0	NR
RADIAL-AMI (6)	25	25	4	0	0	12	NR	CMC 92%, VSD 8%	UFH	UFH	96	92	>100 previous TRCP
Li et al. (24)	184	186	1.6	1.1	0	0	RCD	CMC	UFH	UFH	NR	NR	Not reported
FARMI (19)	57	57	12.3	1.8	0	0	NR	CMC	UFH	UFH	100	100	>100 previous TRCP
Vazquez-Rodriguez (28)	217	222	9	0	NR	NR	RCD	CMC 11%, VSD 89%	UFH	UFH	60.2	58.6	>200 previous TRCP
Yan et al. (26)	57	46	1.8	0	NR	NR	RCD	CMC	UFH	UFH	100	100	>500 previous TRCP
RADIAMI (20)	50	50	8	2	0	0	RCD	CMC	UFH	UFH	44	42	>50 previous TRCP
Gan et al. (27)	90	105	1.1	0	NR	NR	NR	CMC	UFH	UFH	31.1	34.3	NR
Hou et al. (22)	100	100	4	0	NR	NR	RCD	CMC	LMWH, UFH	LMWH	28	20	>200 previous TRCP
RADIAMI II (21)	49	59	4.1	1.7	0	0	RCD	VCD	UFH 100%	UFH 100%	51	54	Several years' experience
RIVAL (7)	3507	3514	6.9	0.9	1.0	6.0	PLP	PLP	LMWH 51.5% FON 33.3%, UFH 10.9% BIV 2.2%	LMWH 51.8% FON 31.6%, UFH 10.8% BIV 3.1%	25.3	24	>50 TRCP within the previous year
Wang et al. (25)	60	59	6.6	1.7	NR	NR	RCD	CMC	UFH 100%	UFH 100%	55	50.8	>500 previous TRCP
RIFLE-STEACS (8)	500	501	9.4	2.8	9.2	18.6	PLP	PLP	UFH 92% BIV 8%	UFH 92.8% BIV 7.2%	67.4	69.9	>150 PCIs/year with adequate expertise in both approaches, minimal proficiency criteria of >50% TRCP per year
STEMI-RADIAL (9)	348	359	3.7	0.6	0	0.8	RCD	PLP	UFH 100%	UFH 100%	45	45	>200 PCIs/ year in high-volume radial centers (>80% cases/year)
OCEAN-RACE (23)	52	51	9.6	7.8	NR	NR	NR	NR	NR	NR	59.2	66.7	>200/year TRCP and operators in training (<200/year)
MATRIX (10)	4,197	4207	5.7	2.3	NR	NR	PLP	PLP	UFH 49.9% BIV 40.1%	UFH 45.5% BIV 40.7%	13.7	12.4	>75 TRCP within the previous year

BIV = bivalirudin; CMC = conventional manual compression; FON = fondaparinux; GPI = glycoprotein IIb/IIIa inhibitor; LMWH = low-molecular-weight heparin; PCI = percutaneous coronary intervention; PLP = per local practice; RCD = radial compression device; TRCP = transradial coronary procedures; UFH = unfractionated heparin; VSD = vascular closure device.

FIGURE 2 Meta-Analysis of Radial Versus Femoral Access for Mortality



The forest plot shows a significant 27% relative risk reduction with radial compared with femoral access. CI = confidence interval.

the conventional threshold for statistical significance at the 5% level and within the futility boundaries. After the MATRIX trial (10), it crossed the threshold for statistical significance at the 1% level.

IS CALCULATIONS AND TSA FOR SAFETY ENDPOINTS. For access site bleeding, the IS was estimated at 9,087 patients (Online Figure 7). The incidence of access site bleeding in the femoral group was 3.1%. The cumulative *z*-statistic had already crossed the significance level of 1% early before the RIVAL trial (7) and crossed the upper monitoring boundary soon after the RIVAL trial (7). For major bleeding, the IS was estimated at 12,892 patients (Online Figure 8). The incidence of major bleeding in the femoral group was 2.2%. Again, the cumulative *z*-statistic had crossed the significance level of 1% well before the RIVAL trial (7), and the monitoring boundaries were already truncated after 10,504 patients had been included in the meta-analysis. After STEMI-RADIAL (Trial Comparing Radial and Femoral Approach in Primary Percutaneous Coronary Intervention) (9), the cumulative *z*-statistic also crossed the upper monitoring boundary.

DISCUSSION

SUMMARY OF STUDY RESULTS. The main findings of this study can be summarized as follows. First, pooling data from randomized trials of invasively managed ACS with the conventional approach, radial access was shown to significantly reduce mortality by 27%, MACE by 14%, access site bleeding by 63% and major bleeding by 40%, with no significant effects noted on recurrent myocardial infarction and stroke. Second, the accompanying TSA suggests that after the MATRIX trial (10), there is now firm evidence supporting the observed reduction in death and MACE with the radial access, whereas firm evidence showing a reduction in access site and major bleeding was apparent already before the RIVAL trial (7). The role of the MATRIX trial in driving the statistical significance for MACE was consistent with the study removal analysis. Third, the statistically significant reduction in MACE obtained after inclusion of MATRIX in the meta-analysis was driven by the most important single component of MACE, that is, mortality. Indeed, after pooling the MATRIX trial data, the cumulative evidence supporting radial access for mortality reduction crossed both the conventional threshold of $p < 0.01$ and the monitoring boundaries of the TSA. Importantly, this reduction in mortality was not flawed by heterogeneity and remained consistent after running multiple sensitivity analyses, including those restricted to multicenter studies, patients with STEMI, studies at low risk of bias, studies with a minimum of radial proficiency required, and more recent studies conducted in the last 5 years.

RATIONALE OF THE TSA. Early trials of radial versus femoral access for cardiac catheterization were

TABLE 2 Pooled Effects of Radial Access on Study Outcomes and Sensitivity Analyses

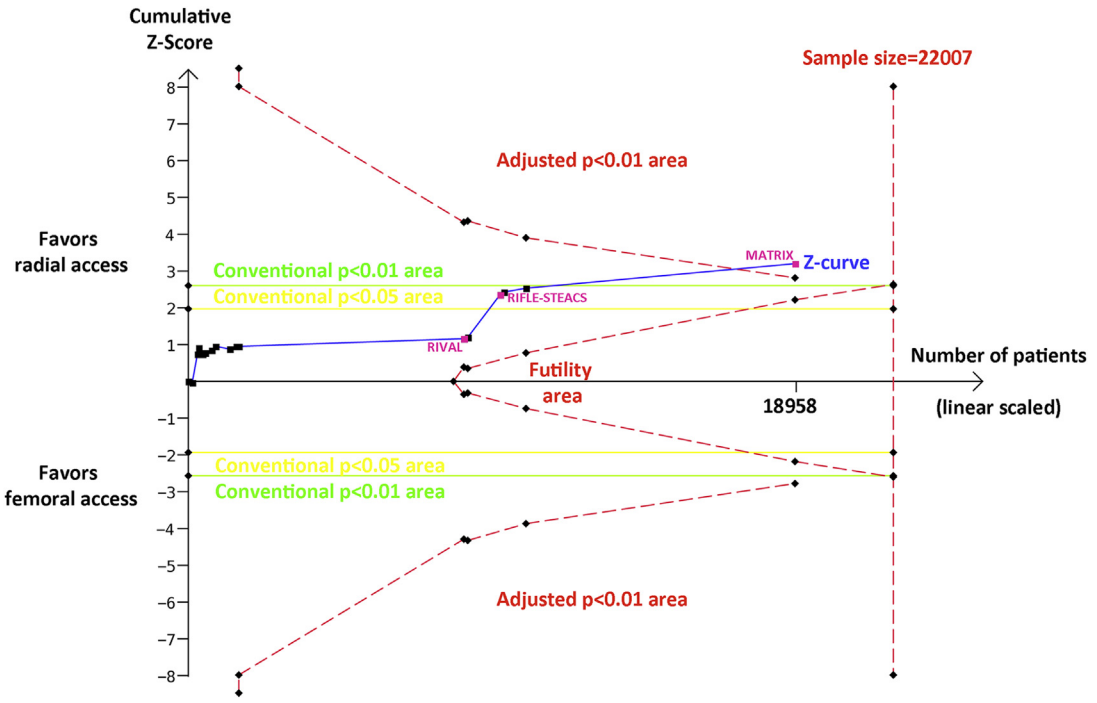
			Test for Overall Effect				Heterogeneity				
Outcome	Studies, N	Patients, N	RR	95% CI	*z*-Test	p Value	Chi-Square	df	p Value	I^2	τ^2
Death											
All studies	16	18,958	0.73	0.60–0.88	3.21	0.001	3.52	13	1.00	0%	0.00
Multicenter studies	7	17,817	0.73	0.60–0.90	2.98	0.003	2.29	6	0.89	0%	0.00
Low risk of bias studies	7	17,446	0.72	0.59–0.89	3.06	0.002	2.29	6	0.89	0%	0.00
STEMI studies	13	3,388	0.65	0.47–0.89	2.66	0.008	2.33	11	1.00	0%	0.00
Expert operators (>200 TRCP)	6	2,569	0.66	0.46–0.93	2.36	0.02	1.28	5	0.94	0%	0.00
Recent studies (2011–2015)	7	17,463	0.72	0.58–0.89	3.08	0.002	2.55	5	0.77	0%	0.00
Myocardial infarction											
All studies	15	18,855	0.91	0.79–1.04	1.39	0.16	2.56	8	0.92	0%	0.00
Stroke											
All studies	9	17,933	1.19	0.77–1.84	0.80	0.42	2.13	7	0.95	0%	0.00
MACE											
All studies	16	18,958	0.86	0.77–0.95	2.83	0.005	6.74	14	0.94	0%	0.00
Multicenter studies	7	17,817	0.86	0.77–0.96	2.63	0.009	4.65	6	0.59	0%	0.00
Low risk of bias studies	7	17,446	0.86	0.77–0.96	2.67	0.008	4.04	6	0.67	0%	0.00
STEMI studies	13	3,388	0.72	0.55–0.93	2.46	0.01	3.85	12	0.99	0%	0.00
Expert operators (>200 TRCP)	6	2,569	0.71	0.53–0.96	2.21	0.03	2.65	5	0.75	0%	0.00
Recent studies (2011–2015)	7	17,463	0.86	0.77–0.96	2.71	0.007	4.89	6	0.56	0%	0.00
Access site bleeding											
All studies	17	19,328	0.37	0.30–0.46	9.09	<0.001	14.49	16	0.56	0%	0.00
Multicenter studies	7	17,817	0.35	0.27–0.45	8.39	<0.001	3.77	6	0.71	0%	0.00
Low risk of bias studies	7	17,446	0.35	0.27–0.45	8.36	<0.001	3.85	6	0.70	0%	0.00
STEMI studies	14	3,758	0.35	0.25–0.51	5.55	<0.001	14.41	13	0.35	10%	0.05
Expert operators (>200 TRCP)	6	2,569	0.28	0.17–0.45	5.27	<0.001	3.69	5	0.59	0%	0.00
Recent studies (2011–2015)	7	17,463	0.40	0.28–0.58	4.92	<0.001	9.40	6	0.15	36%	0.08
Major bleeding											
All studies	16	18,958	0.60	0.48–0.76	4.41	<0.001	12.91	14	0.53	0%	0.00
Multicenter studies	7	17,817	0.56	0.39–0.80	3.18	0.001	7.48	5	0.19	33%	0.06
Low risk of bias studies	7	17,446	0.59	0.41–0.85	2.81	0.005	7.25	5	0.20	31%	0.06
STEMI studies	13	3,388	0.45	0.30–0.69	3.77	<0.001	9.33	11	0.59	0%	0.00
Expert operators (>200 TRCP)	6	2,569	0.36	0.21–0.60	3.88	<0.001	4.30	5	0.51	0%	0.00
Recent studies (2011–2015)	7	17,463	0.61	0.43–0.87	2.77	0.006	8.35	6	0.21	28%	0.06
Access site crossover											
All studies	17	19,328	3.38	2.09–5.49	4.94	<0.001	42.09	16	<0.001	62%	0.35
Multicenter studies	7	17,817	4.63	2.43–8.80	4.67	<0.001	28.99	6	<0.001	79%	0.38
Low risk of bias studies	7	17,446	3.47	1.81–6.66	3.75	<0.001	34.53	6	<0.001	83%	0.44
STEMI studies	14	3,758	2.83	1.66–4.84	3.81	<0.001	16.16	13	0.24	20%	0.18
Expert operators (>200 TRCP)	6	2,569	4.06	2.45–6.71	5.45	<0.001	4.09	5	0.54	0%	0.00
Recent studies (2011–2015)	7	17,463	3.60	1.99–6.52	4.22	<0.001	28.53	6	<0.001	79%	0.35

CI = confidence interval; df = degrees of freedom; MACE = major adverse cardiovascular events; RR = relative risk; STEMI = ST-segment elevation myocardial infarction; TRCP = transradial coronary procedures.

limited by their single-center nature and lacked sufficient power to provide meaningful conclusions. More recently, 4 larger multicenter trials have been conducted in ACS, with mixed results (7–10). Notably, none of the trials conducted so far was powered for the hard outcome of mortality, hence the rationale behind a new meta-analysis. The understanding that even previous meta-analyses on this topic (3,11) were underpowered for the mortality endpoint is consistent with the results of our TSA, showing that the mortality RR reduction with radial access becomes statistically significant at the 5% and 1% alpha level after data from the RIFLE-STEACS (8) and MATRIX (10) trials are included, respectively, and clinically significant (i.e., the cumulative *z*-curve crosses the adjusted monitoring boundary) after the addition of the MATRIX trial (10).

The interpretation of a TSA resembles that of interim analyses of clinical trials. In our case, the interim analysis is sequentially performed with every published trial of radial versus femoral access and can dictate whether a sufficient level of evidence for

FIGURE 3 TSA for All-Cause Death



The required information size to demonstrate or reject a 30% relative risk reduction with an incidence in the femoral (control) group of 2.5% (alpha 1%, power 90%) is 22,007 patients **(vertical red dotted line)**. The horizontal axis represents the number of patients included in the meta-analysis and is linear scaled, hence the distance of a new trial from the previous one on the axis represents the new trial population. The vertical axis represents the cumulative *z*-score. The **red dotted lines** represent the trial sequential monitoring boundaries (inward sloping) and the futility boundaries (outward sloping). The **solid blue line** represents the cumulative *z*-curve. The **yellow and the green lines** represent the conventional thresholds for statistical significance techniques at $p = 0.05$ and $p = 0.01$, respectively. After the MATRIX trial (10), when all 18,958 patients have been included in the meta-analysis, the *z*-curve crossed the monitoring boundaries, constructed from IS calculations. This occurrence demonstrates conclusive evidence for a reduction in mortality with radial access. According to the trial sequential analysis (TSA) methodology, crossing the monitoring boundaries for the *z*-curve indicates a clinically meaningful effect of a specific intervention that is also supported by statistical significance.

benefit, harm, or futility has been reached. For death, the *z*-curve crossed the monitoring boundaries, which in a randomized trial of radial access powered for mortality would suggest the opportunity to stop the trial due to a clear evidence of superiority. According to the TSA methodology, crossing the monitoring boundaries for the *z*-curve indicates a clinically meaningful effect of a specific intervention that is also consolidated by statistical significance (15,16).

These findings in aggregate support the understanding that there is no need for further trials of radial versus femoral access powered for mortality after the MATRIX trial (10), and that the current body of evidence is sufficient to consider the radial access as a life-saving procedure in invasively managed patients with ACS, warranting both an upgrade of current recommendations and every effort to maximize the proportion of radial procedures (30). Recently released European Society of Cardiology guidelines for the management of ACS in patients presenting without persistent ST-segment elevation now support this concept with a Class I, Level of Evidence: A recommendation for the use of the radial approach, if performed in experienced center, and thereby promote a transition to preferential use of the radial approach in patients presenting with an ACS (31).

BLEEDING AND MORTALITY. The observed reduction in mortality with radial access was achieved in parallel with significant reductions in MACE and bleeding (both access site related and major). A link between bleeding and ischemic events (including fatal ischemic events) has increasingly emerged in interventional studies over time, supported by the understanding that any strategy aimed at reducing bleeding is also associated with improved survival in

patients with ACS (32), particularly in those undergoing PCI (33). Consistent with this concept, in the MATRIX trial, the magnitude of the reduction in major bleeding was similar to the observed reduction in mortality (10). Interestingly, in a nested case-control post hoc study of the MATRIX trial (10) focusing on 137 cases of death not directly attributed to a bleeding event and 1,370 matched control subjects, the occurrence of a BARC (Bleeding Academic Research Consortium) actionable bleeding was associated with a twice-higher mortality risk (adjusted odds ratio 2.35; $p = 0.015$). Several mechanisms may contribute to explain the association of bleeding events and mortality from ischemic causes, including anemia, abrupt discontinuation of antiplatelet and anticoagulant therapies, and prothrombotic states related to bleeding, or the effects of blood transfusions (34).

IMPACT OF OPERATORS' EXPERIENCE. It may be perceived that the safety benefits of radial access are outweighed by technical challenges, which may discourage interventional cardiologists from adopting a new strategy which may lead, at the initial stages of the learning curve, to longer procedures and, ultimately, access site crossover. This is also suggested by subgroup analyses from the 2 largest randomized trials available (7,10). Consistently, restricting our findings to studies where a minimum expertise of 200 radial cases was required resulted in larger point estimates for most of the clinical outcomes explored (**Table 2**), which confirm that the benefit of radial access may be larger in (but not confined to) cases performed by expert operators. Noteworthy, radial procedures were only marginally longer than femoral procedures; there was no interaction between the risk of crossover with radial access and operators' experience ($p = 0.36$); and the risk of crossover was larger in trials in which a minimal radial expertise of 200 cases was required, which could be mostly attributable to the possibility of more complex patients randomized in trials in which a high proficiency in radial procedures was mandated. Accordingly, large U.S. registry data demonstrate that as operators' radial volume increases, higher-risk patients are chosen for radial procedures and that the larger the radial procedural volume, the higher the proficiency (35).

STUDY LIMITATIONS. Specific limitations of our study that cannot be totally addressed by the TSA methodology are as follows. First, we could not use any standardized definition of bleeding (36) across the studies. Second, patients with non-STEMI mainly belong to 2 multicenter trials, which have come to conflicting conclusions (10,37). It was not possible to perform a sensitivity analysis restricted to patients with non-STEMI due to lack of published data, although the benefit of radial access in these patients in registries (38) seems consistent with randomized studies. Finally, we cannot exclude that the differences in bleeding and mortality shown in our study may be influenced by variable use of glycoprotein IIb/IIIa inhibitors, a source of consistent heterogeneity across studies comparing radial and femoral access (39).

CONCLUSIONS

The updated pooled and trial sequential analysis of the available information to date indicates that radial access reduces mortality in patients with ACS undergoing invasive management. This benefit is paralleled by significant reductions in MACE, access site bleeding, and major bleeding as compared with femoral access, thus supporting the use of radial access as the default strategy for cardiac catheterization in patients with ACS.

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PERSPECTIVES

WHAT IS KNOWN? The radial vascular access has been increasingly used for cardiac catheterization and interventions compared with the femoral approach. The main advantage, consisting in the lower incidence of access site bleeding and complications, is typically paralleled by patients' preference.

WHAT IS NEW? Studies conducted in patients with ACS have come to conflicting conclusions with respect to the efficacy of the radial approach in reducing the composite of net adverse cardiovascular events by parallel reductions in bleeding. This trial sequential analysis of all randomized studies to date suggests that the body of evidence is now sufficient to recommend radial access as a life-saving procedure.

WHAT IS NEXT? This study supports the notion that radial artery should be the vascular access of choice for experienced centers treating patients with ACS and that femoral-oriented centers should promote a transition to radial approach.

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APPENDIX For an expanded Methods section and supplemental figures and tables, please see the online version of this paper.