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MATA-ANALYSIS

Short-term risk of periprocedural stroke relative to radial vs. femoral access: systematic review, meta-analysis, study sequential analysis and meta-regression of 2,188,047 real-world cardiac catheterizations

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ABSTRACT

Objectives: To verify whether transradial (TRA) compared to transfemoral (TFA) cardiac catheterization reduces the risk of periprocedural stroke (PS).

Methods: We reviewed (CRD42021277918) published real-world cohorts reporting the incidence of PS within 3 days following diagnostic or interventional catheterization. Meta-analyses and meta-regressions of odds ratios (OR) performed using the DerSimonian and Laird method were checked for publication bias (Egger test) and adjusted for false-positive results (study sequential analysis SSA).

Results: The pooled incidence of PS from 2,188,047 catheterizations (14 cohorts), was 193 (105 to 355) per 100,000. Meta-analyses of adjusted estimates (OR = 0.66 (0.49 to 0.89); p = 0.007; I^2 = 90%), unadjusted estimates (OR = 0.63 (0.51 to 0.77; I^2 = 74%; p = 0.000)), and a sub-group of prospective cohorts (OR = 0.67 (0.48 to 0.94; p = 0.022; I^2 = 16%)) had a lower risk of PS in TRA (without indication of publication bias). SSA confirmed the pooled sample size was sufficient to support these conclusions. Meta-regression decreased the unexplained heterogeneity but did not identify any independent predictor of PS nor any effect modifier.

Conclusion: Periprocedural stroke remains a rare and hard-to-predict adverse event associated with cardiac catheterization. TRA is associated with a 20% to 30% lower risk of PS in real-world/common practice settings. Future studies are unlikely to change our conclusion.

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Stroke; catheterization; radial; femoral; incidence; observational; cohort; real-world; accession site; meta-analysis; meta-regression; trial sequential analysis

1. Background

The transradial approach (TRA) to cardiac catheterization has been demonstrated to be superior in terms of vascular complications, access site complications, short-term net adverse events, major bleeding, and mortality from numerous randomized controlled trials and registries [1,2]. The 2018 European Society of Cardiology (ESC)/European Association for Cardio-Thoracic Surgery (EACTS) [3], 2020 ESC [4], and 2021 American College of Cardiology (ACC)/American Heart Association (AHA)/Society for Cardiovascular Angiography and Interventions (SCAI) Guidelines [5] on myocardial revascularization recommend TRA as the standard approach for cardiac angiography and coronary intervention, the only exception being cases with overriding procedural considerations (class I, level A recommendation).

Catheterization-related periprocedural stroke (PS) is a rare but potentially devastating complication of diagnostic and interventional procedures in cardiology. These events are associated with a high rate of mortality and morbidity [6], thus having the potential to impact the benefit-risk profile of the procedure significantly.

For over 25 years, the best choice of access site (to decrease the risk of PS [7]) has been debated, yet, none of the 12 meta-analyses of randomized trials (RT) published since 2009 have shown a significant difference between TRA and transfemoral access (TFA) [1,2,7–16]. Nonetheless, no significant difference in PS incidence was observed in data pooled from RTs does not necessarily mean that no difference exists in the real world. The recent systematic review by Chiarito et al. [2] described four major obstacles to answering this question. First, with PS being such a rare event, no single RT had the power to show a significant difference between access sites; hence, there is doubt as to whether the entire meta-analysis of RTs has *á priori* statistical power to detect any difference. Second, a significant small-study effect strongly suggests that the overall estimate derived from the RTs suffers

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from publication bias (Supplementary Figure 8 in [2]). Third, there has been significant unexplained heterogeneity in the overall incidence of PS reported by individual RTs; this between-study variability could not be explained by the type of procedure, age, gender, or comorbidities (Supplementary Figure 7 in [2]). Last but not least, Chiarito et al. [2] highlight that most RTs published to date had neither systematic post-procedural neurological evaluations nor formal neurological event adjudications, leading to a probable underreporting of non-disabling cerebral ischemic events. Still, we believe that, from the perspective of detection and reporting bias, these RTs represent a lower risk than observational studies.

Since level A evidence cannot be used to assess the relative incidence of PS between TRA and TFA, we decided to pool relative estimates from real-world cohorts. Although one meta-analysis of this kind was published in 2016 [10], the aim of our study is not only to provide an updated review but also to use more stringent inclusion/exclusion criteria, ensuring greater certainty regarding the association between catheterization and PS. We additionally address the question of statistical power.

2. Methods

2.1. Systematic review

Reports published in the English language were identified as cross-references from the 2016´s Sirker et al. review [10], in PubMed/NCBI ('Cardiac Catheterization'[Mesh] OR 'Percutaneous Coronary Intervention'[Mesh] OR coronarography OR 'Angiography'[Mesh] OR 'Angioplasty'[Mesh]) AND (femoral OR 'Femoral Vein'[Mesh] OR radial OR 'Radial Artery'[Mesh] OR 'accession site') AND ('Stroke'[Mesh]), and via manual searches with no publication date restrictions. The review was done for publications indexed until July 2022. We included both retrospective and prospective real-world observational cohorts describing the following POPULATION: patients undergoing a first or repeated diagnostic or an interventional cardiac catheterization with no restriction on age or reason for admission. INTERVENTION: TRA catheterization; COMPARATOR: TFA catheterization; OUTCOME: short-term hemorrhagic and ischemic stroke/transient ischemic attack up to 3 days after the catheterization or if indicated in the text as 'in hospital' or 'within the index hospitalization.' Studies reporting stroke after 3 days or during follow-up were excluded because these are less likely to represent complications from the vascular access site but rather a manifestation of the elevated vascular risk of patients undergoing these procedures. We considered published articles only. Conference abstracts were not searched for. In one instance [17], the full text was not available and we extracted the relevant information from a publicly accessible thesis.

The studies were screened, and all available data on study characteristics (Table 1) cohort baseline characteristics (Table 2), and outcomes (Table 1) were independently extracted by two reviewers, one of whom was an interventional cardiologist and was one statistician, both with previous experience in literature review and evidence synthesis. We extracted the overall incidence of stroke, crude, and adjusted relative incidence between TRA and TFA. There was no restriction on the adjustment method (e.g. multivariate regression, propensity score matching, etc.). Authors reporting only crude estimates were additionally contacted via e-mail, but we were not provided with the adjusted estimates.

The quality of the individual reports was assessed by both reviewers using the Joana Briggs Institute (JBI) critical appraisal checklist for cohort studies [18]. The protocol was published prospectively in PROSPERO under the identifier CRD42021277918. We report in line with the PRISMA 2020 statement [19] and the MOOSE 2020 reporting standards [20]. Details on the systematic review are available for the reader in the Supplementary material.

2.2. Meta-analysis and meta-regression

The overall incidence of PS was calculated from the absolute counts, and confidence intervals were derived assuming the Poisson distribution. Odds ratios were calculated with conservative exact confidence intervals. In a single instance, we used the Haldane continuity correction for a zero cell [21,22]; however, the contribution of this cohort to the overall estimate was only 0.02% [23]. Meta-analyses were performed using *metan, metareg*, and *metabias* packages (STATA 15.0 software, StataCorp LP, USA). Publication bias was estimated using the Egger test [24] and plotted with a *confunnel* package.

The random effect meta-analysis was calculated using log-transformed odds ratios from the individual cohorts according to the DerSimonian and Laird method (21). The significance of the overall effect was calculated using a z-score and assuming a normal distribution; the heterogeneity was quantified via the I^2 statistic [25]. Study-level meta-regressions were calculated using log-transformed estimates (reported by individual authors) weighted according to the log-transformed confidence interval; the between-study variance was estimated using the restricted maximum likelihood algorithm. It did not escape to our attention that with rare events like PS, the incidence of PS in individual studies determines the confidence interval of the respective odds ratio to a greater extent than the actual study size. The confidence interval is determined by the number of events more than by the number of observations. In other words, small primary studies with more frequent PS would appear more precise (narrow confidence interval) compared to large primary with lower PS incidence. As a result, the small studies could have disproportionally more weight in the meta-analysis and may influence the overall estimate more than they would if the patients came from one single large trial. From the perspective of causal inference, this could be perceived as adjusting for future events. With that in mind, we employed an alternative weighting scheme where each overall estimate was also presented for a meta-analysis in which weights are proportional to the size of the cohort.

2.3. Study sequential analysis

The idea behind a meta-analysis is to estimate *post hoc* what would have happened if all subjects from the primary studies were observed in one single study. This idea is however

Table 1. **Characteristics of included publications and the reported incidence of PS**. The incidence was calculated assuming a Poisson distribution. Odds ratios are calculated with conservative exact confidence intervals. The publication by Kwok [47] reported only unadjusted estimates from the same registry as Ratib [39], who reported adjusted estimates; thus, the estimate of Kwok was used for the meta-analysis of unadjusted estimates and Ratib for the meta-analysis of adjusted estimates. UK means United Kingdom, TIA means transient ischemic attack, CVA means cerebrovascular accident, CT means computed tomography, TRA means transradial approach, TFA means transfemoral approach, PS means periprocedural stroke.

Author	Reference	Date	Region	Design	Sample	Data collection	Stroke definition (Author´s wording)	Adjusted OR TRA vs. TFA	Unadjusted TRA vs. TFA	Overall Incidence of PS per 100 000
Cruden	[41]	2007	Scotland	Retrospective	287	2003 to 2005	during the index admission		0,77 (0,04–14,74)	1045 (216–3055)
Jaffe	[42]	2007	Canada	Prospective	228	2000 to 2004	in-hospital		0,45 (0,05–4,26)	439 (11–2444)
Pristipino	[43]	2009	Italy	Prospective	1052	2008 to 2008	in-hospital		0,36 (0,01–8,75)	95 (2–530)
Defteros	[44]	2010	Greece	Retrospective	98	2009 to 2011	in-hospital both intracranial bleeding and ischemic CVA		0,51 (0,08–3,45)	4081 (1112–10,451)
Rodrigues	[45]	2012	Spain	Prospective	122	2007 to 2012	in-hospital		0,51 (0,04–7,36)	3278 (900–8182)
Ratib	[39]	2013	UK	Retrospective	348,092	2006 to 2010	periprocedural ischemic stroke, hemorrhagic stroke, or transient ischemic attack occurring before hospital discharge	0,99 (0,79–1,23)	1,01 (0,82–1,24)	111 (100–123)
Dangoisse	[46]	2013	Belgium	Prospective	3600	2002 to 2007	In-hospital disabling		1,92 (0,46–8,03)	222 (96–438)
He	[36]	2015	China	Retrospective	21,242	2006 to 2011	CT-confirmed in-hospital	0,33 (0,03–3,20)	0,50 (0,12–2,84)	56 (29–99)
Raposo	[37]	2015	Portugal	Prospective	16,710	2006 to 2012	within 48 hours of the procedure	1,3 (0,55–3,54)	1,03 (0,37–2,54)	161 (110–235)
Kwok	[47]	2015	UK	Retrospective	426,297	2007 to 2012	in-hospital ischemic stroke/TIA, hemorrhagic stroke		0,98 (0,82–1,17)	120 (110–130)
Jurga	[17]	2016	Sweden	Retrospective	336,836	2003 to 2011	within 24 h of the procedure in theabsence of atrial fibrillation.	1,3 (1,04–1,62)	0,91 (0,75–1,08)	162 (149–176)
Huyut	[23]	2018	Turkey	Retrospective	358	2012 to 2017	in-hospital		0,33 (0,10–8,12)	279 (7–1556)
Staszczak	[40]	2021	Poland	Prospective	1,177,161	2014 to 2019	stroke occurring at the catheterization laboratory	0,48 (0,30–0,78)	0,45 (0,32–0,64)	13 (11–15)
Matejka	[38]	2021	Czechia	Prospective	14,139	2009 to 2015	within index hospitalization	0,81 (0,38–1,72)	0,91 (0,43–2,08)	290 (208–393)
Reifart	[48]	2022	Germany	Prospective	189,917	2012 to 2018	stroke/TIA during hospitalization		0,81 (0,41–1,52)	33 (25–42)

Table 2. **Characteristics of included cohorts and the prevalence of risk factors**. BMI means body mass index, PCI means percutaneous coronary intervention, CABG means Coronary Artery Bypass Graft, CKD means chronic kidney disease, ACS means acute coronary syndrome, CAD means coronary artery disease, TRA means transradial approach, TFA means transfemoral approach, PS means periprocedural stroke.

Author	Reference	Date	Mean age	% Male gender	BMI	% Dyslipidemia	% Hypertension	% Smoking	% With prior PCI	% With prior CABG	% With known CAD	% With prior stroke	% Admission for ACS	% Diagnostic procedure	% CKD	% Diabetes	Note
Cruden	[41]	2007	59	82.9	27.9	65.9	37.60	46.3			33.1		100	0		10.8	
Jaffe	[42]	2007	82	59.2	26.7		83.80		14.00	6.1		6.1	28.1	0	21.9	19.3	
Pristipino	[43]	2009	66	71.0	27			16.0	20.00	9		4	41.2	60	8	21	
Defteros	[44]	2010	65	75.0		40.0	49.00	38.0	19.00	2			100	0		30	
Rodrigues	[45]	2012	65	83.6	27	54.9	57.40	32.8	17.20	4.1			100	0		35.2	There was a notable difference in the number of diabetics between TRA and TFA. The number from the larger arm is reported.
Ratib	[39]	2013	65	73.8		53.2	48.70	20.8	19.60	8.1		3.4	55.5	0	0.8	18.8	This reference should be used only as a substitute for the adjusted estimate for Kwok 2015 (similar cohort)
Dangoisse	[46]	2013	65	75.6		43.9	48.80	26.5			11.3			0	7.6	20.4	
He	[36]	2015	58	78.1		53.5	58.20		14.00	2.2		4.1	66.2			24.2	
Raposo	[37]	2015	66	67.3	28	59.9	72.00	38.2	24.00	11.6		8.1	38	63.4	2.1	27.5	
Kwok	[47]	2015		74.0		54.7	51.60	56.9	21.28	8.07		3.77	59.4	0	2.54	18.05	Ischemic and hemorrhagic put together for our analysis
Jurga	[17]	2016							76.00				52				Neurological complications were categorized as stroke or TIA (ischemic stroke and intracerebral hemorrhage but not subarachnoid hemorrhage. The thesis reports the risk ratio; we consider it comparable to the odds ratio.
Huyut	[23]	2018	59	89.7	29	51.4	69.60	56.4	63.10	19.8		1.7	0	0		40	Haldan correction
Staszczak	[40]	2021		61.9			69.40	17.4	25.88	5.64		3.01	61.4	55.27	5.27	21.76	
Matejka	[38]	2021	67	62.9	30	74.7	85.50	17.1	17.70	5.2	33	9.1	18	53	8	32	
Reifart	[48]	2022	68										30	12			
Weighted mean			66	67	28	54	62	27	31	7	29	3	56	32	4	21	

complicated by the fact that the authors of each study already tested the difference between the TRA and the TFA. If there were, for instance, 14 publications of primary studies and one meta-analysis published in the past, the hypothesis of lower PS incidence in TRA was tested 15 times.

When testing a hypothesis by meta-analysis, the pooled sample size should at least equal the sample size of an adequately powered trial. If the estimate is subjected to significance testing before the pooled sample has surpassed the required information size, the threshold for statistical significance can be adjusted to account for the elevated risk of random error. This idea is equivalent to repeated testing encountered in interim analyses of clinical trials. Thus, a question naturally arises whether definitive conclusions can be drawn based on the conventional frequentist significance level (e.g. $p < 0.05$), when primary studies are published over time and when previous meta-analyses were employed/published to estimate the pooled effect size [26–29].

Study sequential analysis is a transparent tool for better control of type I and type II errors (compared to traditional meta-analysis) using confidence intervals adjusted in the light of statistical power (sample size) required to detect or refute the assumed intervention effect [30]. For our purposes, study sequential analysis [30] was designed (similarly to Lan and DeMets approach [31]) to verify whether the pooled number of catheterizations was sufficient to show the difference between TRA and TFA. More specifically, a two-sided O´Brien-Fleming alpha-spending boundary was set to confirm/reject the hypothesis of 20% relative risk reduction in TRA with 80% power at 5% alpha (significance level). The incidence in the control (TFA) arm and the heterogeneity were taken from the random-effect meta-analysis. The previous testing by Sirker et al. in 2016 [10] was accounted for. Based on this analysis, a definitive conclusion could be drawn if the cumulative Z-curve (Figure 3) crosses either the study sequential monitoring boundary or the futility boundaries or if the accumulated sample size used for meta-analysis is larger than the required sample size. The computation and graphic output were generated using Copenhagen Trial Unit's Trial Sequential Analysis Software (TSA Software; Center for Clinical Intervention Research, Rigshospitalet, Copenhagen, Denmark.) [32].

2.4. Sensitivity analyses

For sensitivity analyses, we (I) meta-analyzed only estimates from studies with the highest JBI rating (with strict end-point adjudication), (II) observed the sensitivity of the overall estimate toward a stepwise exclusion of individual reports (so-called leave-one-out analysis), (III) analyzed a subgroup of the prospective cohorts, and (IV) analyzed a subgroup of the cohorts that clearly stated the type of PS used in the analysis was ischemic.

2.5. E-values

The assumption of unmeasured confounding is a fundamental concern of causal inference based on observational data. A recommended reporting standard for meta-analyses is to conduct a post-estimation sensitivity analysis to assess how strong a relationship would have to be between an unmeasured confounder and the treatment assignment, as well as between the unmeasured confounder and the outcome, to explain away an observed treatment effect [33,34]. In addition to the abovementioned sub-group analyses, we calculated e-values [35]. E-value characterizes the extent of bias which would be required, hypothetically, to shift the pooled estimate to the null [34], in our case the risk ratio expressing the association that an unmeasured confounder(s) would need to have with both the treatment assignment and the outcome to 'explain away' the observed treatment-outcome effect. E-values for the point estimate and the confidence range were calculated using Stata immediate command *evalue* assuming the relative outcomes on the risk ratio scale.

3. Results

3.1. Systematic review and study characteristics

Sirker et al. [10] previously carried out a meta-analysis of 21 real-world (i.e. observational) cohorts, out of which we included ten observational cohorts fulfilling our inclusion criteria (reasons for exclusion of individual studies are summarized in Supplementary Table 1). Out of 223 publications identified via manual and database searches, we included four additional cohorts fulfilling the inclusion criteria (see PRISMA flowchart in Supplementary Figure 1), bringing the total to 14. No publications in other than the English language were encountered. The 14 cohorts were reported in 15 publications; 8 were prospective, and 6 were retrospective studies. Eleven cohorts were from Europe, one from Canada, one from Turkey, and one from China. All reports were considered to be of good quality according to the JBI checklist (Supplementary Table 2); however, only four publications provided sufficient descriptions of the neurological examinations used in PS cases [17,36–38], and only six authors reported adjusted estimates (i.e. controlling for third factors, such as age, previous stroke or acute coronary syndrome) [17,36–40].

The sample size was variable, ranging from 98 to 1,177,161 catheterizations. The weighted mean (as if all patients came from the same cohort) age was 66 years; 31% of patients had previously undergone PCI, 3% had a previous stroke, and 56% had been admitted for the acute coronary syndrome (Table 2).

3.2. Meta-analysis and meta-regression of the overall PS incidence

The overall incidence of PS, i.e. irrespective of the access site, was variable between individual reports (Figure 1), with an I^2 of 98.7%. The pooled incidence derived from a total of 2,188,047 catheterizations was 193 PS (105 to 355) per 100,000 when studies were weighted according to the inverse of the confidence interval and 34 PS (31 to 37) per 100,000 when studies were weighted according to sample size (i.e. the number of catheterizations). A meta-regression (with the aim to identify the sources of differences between

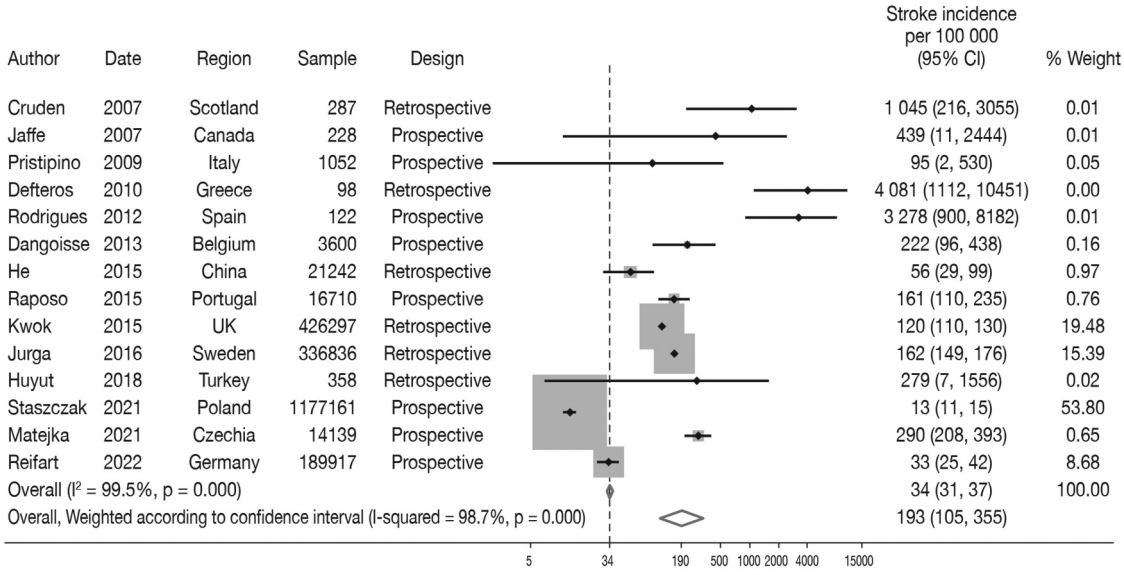

Figure 1. Meta-analysis of the overall incidence of PS irrespective of the access site.

The incidence is expressed per 100,000 catheterizations. The overall estimate is calculated using the DerSimonian and Laird random-effects model weighted according to the inverse of the confidence interval. Additionally, we present the overall estimate from meta-analyses weighted according to study size. PS means periprocedural stroke, and the UK means the United Kingdom.

individual studies) predicting overall incidence estimates (Supplementary Table 3) showed that residual heterogeneity could be substantially reduced when considering individual study characteristics; only the sample size of the studies proved to be an independent predictor (with an adjusted p = 0.009), and a residual heterogeneity of 15%. This means that the larger the primary study was, the less likely was the PS to occur.

3.3. Meta-analysis of the adjusted estimates of relative PS incidence

The adjusted relative incidence of PS between TRA vs. TFA (reported by six papers (1,914,180 catheterizations) [17,36–40]) varied between individual reports (Figure 2) with an I^2 of 67.8%. The pooled odds ratio was not significant when studies were weighted according to the inverse of the confidence interval (OR = 0.91 (0.65 to 1.27); p = 0.584) but was significant when studies were weighted according to sample size (OR = 0.66 (0.49 to 0.89); p = 0.007). The e-value for point estimate (further as e_{point}) was 2.40 and the e-value for confidence limit (further as e_{limit}) was 1.50. The Funnel plot and Egger regression (Supplementary Figure 2 and Supplementary Figure 3) showed no publication bias (p = 0.340).

(a) Estimates are calculated using the DerSimonian and Laird random-effects model weighted according to the inverse of the confidence interval. Additionally, we present the overall estimate from the meta-analysis weighted according to study size.

(b) To reflect potential false positive estimates resulting from taking account of new studies published over time and before reaching the required information size, we employed study sequential analysis [32]. A two-sided O´Brien-Fleming alpha-spending sequential monitoring boundary was constructed based on 80% power to detect a 20% relative risk reduction in TRA at alpha 5%. A previous meta-analysis by Sirker et al. in 2016 [10] was accounted for. The cumulative Z-curve avoids the futility boundary (grey inner wedge) and crosses the adjusted boundary for benefit meaning that the

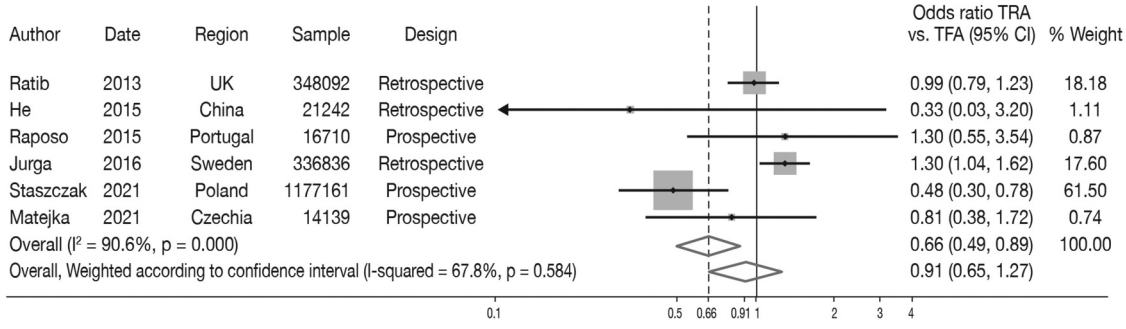

Figure 2. Meta-analysis of adjusted odds ratios of the incidence of PS between TRA and TFA acces

The overall estimate is calculated using the DerSimonian and Laird random-effects model weighted according to the inverse of the confidence interval. Additionally, we present the overall estimate from meta-analyses weighted according to study size. PS means periprocedural stroke, UK means United Kingdom, TRA means transradial and TFA means transfemoral.

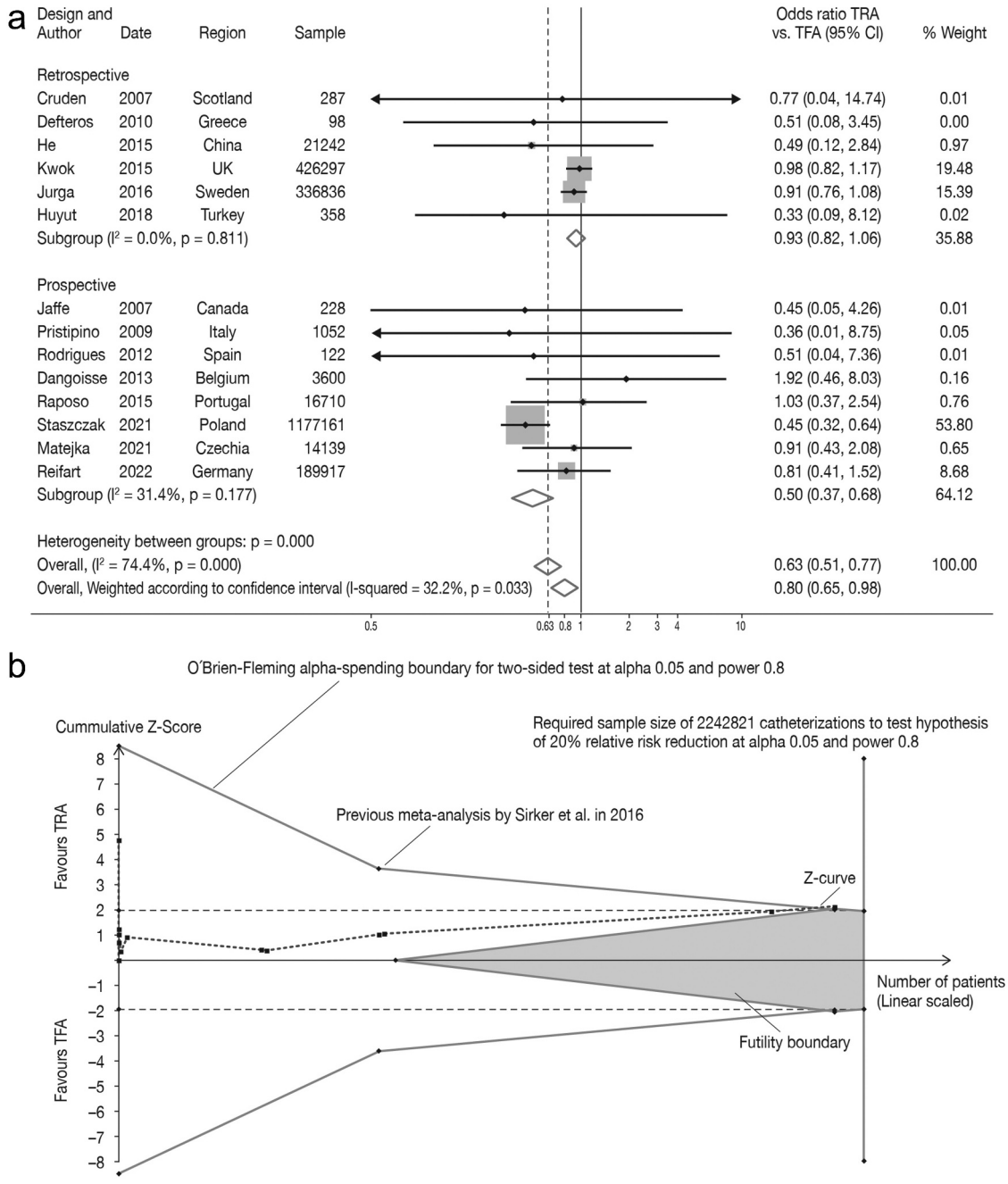

Figure 3. Meta-analysis (a) and study sequential analysis (b) of unadjusted odds ratios of the incidence of PS between TRA and TFA access. (a) Estimates are calculated using the DerSimonian and Laird random-effects model weighted according to the inverse of the confidence interval. Additionally, we present the overall estimate from the meta-analysis weighted according to study size. (b) To reflect potential false positive estimates resulting from taking account of new studies published over time and before reaching the required information size, we employedstudy sequential analysis [32]. A two-sided O'Brien-Fleming alpha-spending sequential monitoring boundary was constructed based on 80% power to detect a 20% relative risk reduction in TRA at alpha 5%. A previous meta-analysis by Sirker et al. in 2016 [10] was accounted for. The cumulative Z-curve avoids the futility boundary(grey inner wedge) and crosses the adjusted boundary for benefit meaning that the conclusion of our meta-analysis holds. Of note, our systematic review did not reach the sample size required á priori (2,242,821) catheterizations by only 2.4%. This means that future studies are unlikely to change our conclusion. PS means periprocedural stroke, UK means United Kingdom, TRA means transradial and TFA means transfemoral.

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3.4. Meta-analysis and meta-regression of the unadjusted estimates of relative PS incidence

The unadjusted relative incidence of PS between TRA vs. TFA (reported by 14 papers (2,188,047 catheterizations) [17,23,36–38,40–48]) was less heterogeneous (Figure 2) with an I^2 of 32.2%. The pooled odds ratio was significant irrespective of

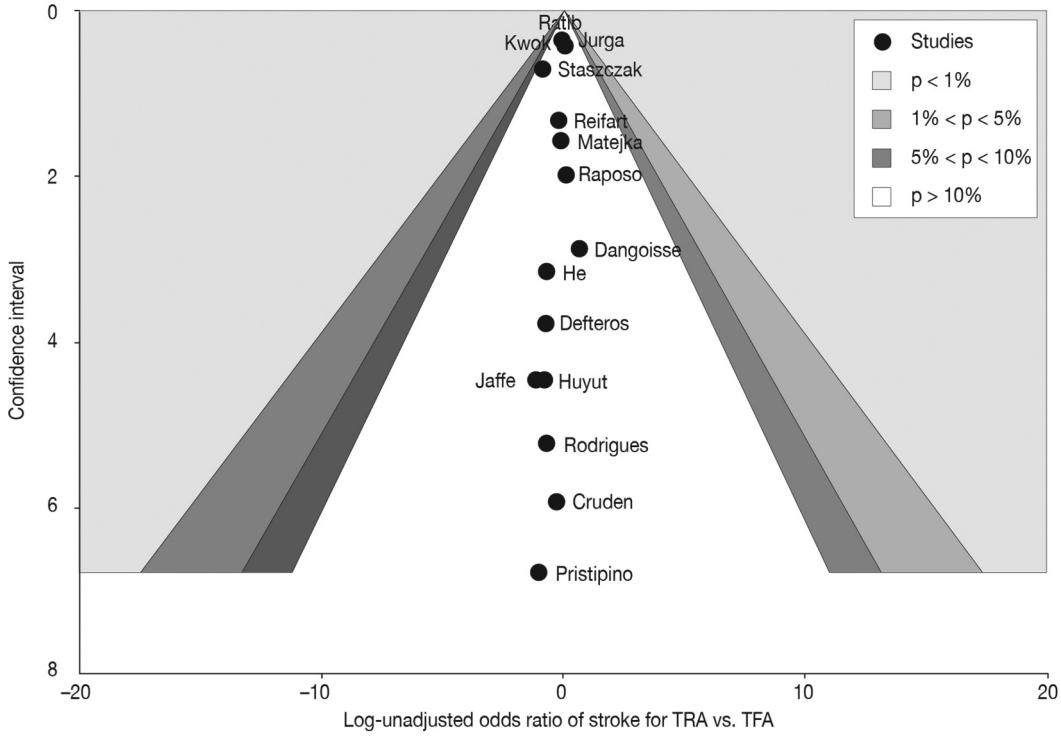

Figure 4. Funnel plot for the meta-analysis of unadjusted odds ratios. The cohorts are plotted with respect to the log-transformed odds ratio for TRA vs. TFA and the respective confidence interval. TRA means transradial and TFA means transfemoral.

whether studies were weighted according to the inverse of the confidence interval (OR = 0.80 (0.65 to 0.98); p = 0.033) or according to study sample size (OR = 0.63 (0.51 to 0.77); p = 0.000; e_{point} = 2.55; e_{limit} = 1.92). The Funnel plot and Egger regression (Figure 4 and Supplementary Figure 4) showed no indication of publication bias (p = 0.229).

The cohorts are plotted with respect to the log-transformed odds ratio for TRA vs. TFA and the respective confidence interval. TRA means transradial and TFA means transfemoral.

Meta-regression predicting unadjusted estimates (Supplementary Table 4) showed that the residual heterogeneity (difference between results of individual primary studies) could be reduced to 0% when considering individual study characteristics, yet none of the study characteristics were an independent predictor of the relative estimate, i.e. able to modify the risk resulting from the choice of the access site.

3.5. Study sequential analysis

To control for false positivity and to verify that the pooled sample size (i.e. number of catheterizations) was sufficient to show at least a 20% difference between TRA and TSA, we employed study sequential analysis [32]. From Figure 3, it is clear that the cumulative Z-curve avoids the futility boundary (gray inner wedge) and crosses the adjusted O´Brien-Fleming alpha-spending boundary for benefit of TRA meaning that the conclusion of our meta-analysis holds (i.e. the results are significant even in the light of multiple testing by the previously published reports). The pooled sample of 2,188,047 catheterizations did not reach the á *priori* required sample size (2,242,821) by only 2.4% meaning that future studies are unlikely to change our conclusion.

3.6. Sensitivity analysis

For sensitivity analysis I, we meta-analyzed unadjusted estimates from the cohorts with valid neurological assessments of PS cases (Supplementary Figure 5). Although the point estimate was similar to the estimates from previous meta-analyses, the odds ratio did not reach statistical significance (OR = 0.91 (0.77 to 1.07; p = 0.255)). However, it should be noted that this meta-analysis pooled only 388,927 catheterizations and it is unlikely to be sufficiently powered (i.e. the sample size was not large enough).

For sensitivity analysis II, we tested the stability of the overall estimate with respect to the stepwise exclusion of individual reports, in other words, whether our conclusions are dependent on one single primary study. Nonselective exclusion of reports did not change the direction and significance of the overall estimate except for the study by Staszczak et al. [40], which was the largest cohort and included 1,177,161 catheterizations, representing 54% of the pooled sample size. The exclusion of this cohort did not change the direction of the overall point estimate, but it did affect the statistical significance (Supplementary Table 5).

For sensitivity analysis III, we separately meta-analyzed a subgroup of prospective cohorts (Figure 3). Both weighting schemes provided significant estimates with low heterogeneity; OR = 0.50 (0.37 to 0.68; p = 0.000; I^2 = 31%) for weights derived from the study sample and OR = 0.67 (0.48 to 0.94; p = 0.022; I^2 = 16%) for weights derived from the inverse of the confidence interval. For sensitivity analysis IV, we pooled only the three cohorts/sub-cohorts that specified precisely the type of PS as ischemic [37,38,44,47], these estimates were unadjusted. The odds ratio did not reach statistical significance (OR = 1.17 (0.98 to 1.41; p = 0.087, I^2 = 0%)). Of note, this does not mean that these are the only cohorts that included exceptionally ischemic events, rather, these authors specified the type of PS in the manuscript.

4. Discussion

The radial approach has been shown to reduce major access site-related bleeding complications, is associated with a reduction in mortality, and has a class 1A recommendation as the default access site for PCI in the acute coronary setting. However, TRA necessitates passage of the catheter and guide wire adjacent to the ostia of either the innominate or vertebral arteries, which might predispose to atheromatous plaque embolization from the more proximal subclavian artery and therefore contribute to an increase in the theoretical risk of PS. Our analysis of 2,188,047 cardiac catheterizations (14 real-world cohorts) shows that TRA was associated with a 20% to 30% reduction in the odds of PS, within 72 hours following cardiac catheterization. Our analysis overcomes the limitations of prior studies that reported longer-term stroke outcomes that are less likely to represent complications from the vascular access site but rather a manifestation of the elevated vascular risk of patients undergoing these procedures. With PS being a very rare event, one can assume the OR does provide a close estimate of the risk ratio and thus we can conclude that TRA is associated with a reduced risk of PS in practice by about one quarter [49].

Despite the more stringent inclusion criteria, our sample size was fivefold greater than the previous meta-analysis by Sirker [10]. We estimated both the overall and relative incidence of PS resulting from 2,188,047 real-world cardiac catheterizations. Our pooled overall incidence of PS of 193 per 100,000 is largely in agreement with the estimate of 140–190 per 100,000 reported by Sirker [10]. Our pooled relative incidence for TRA vs. TFA with OR = 0.80 (0.65 to 0.98) also supports the estimate OR = 0.71 (0.52 to 0.98) by Sirker [10].

Unlike Sirker et al. [10], our protocol did not include data originating in the controlled environment of an RT. One might argue that a mixed meta-analysis of both RT and observational cohorts would or at least could increase the level of evidence generated. To assess this, we calculated that the inclusion of all to-date published RTs into our analysis would only increase the sample size by 1.2%, making it unlikely to have changed the pooled estimate. Furthermore, RTs are less likely to recruit multi-morbid elderly patients that are at increased risk of sustaining a PS, and therefore any safety estimates derived from RT may not be directly applicable to them.

Our results are consistent across meta-analyses, yet the pooled estimates appear affected by the study sample size and the weighting scheme employed. This is not unexpected when rare events are analyzed. Sensitivity analysis I suggest that limiting the analysis to only studies with strict end-point adjudication may decrease the effect size and reduce statistical significance, although this could have also been due to the limited sample size of the analysis. Sensitivity analysis II suggests that the cohort reported by Staszczak et al. [40] is the only one that independently impacted the pooled estimate. To what extent this was due only to the large Staszczak et al. sample size is unclear. Sensitivity analysis III has two crucial features; first, the inclusion of only prospective cohorts preserves the significance of the estimate; and second, the heterogeneity among prospective cohorts is much less significant than in retrospective cohorts.

There are several potential mechanisms by which TRA may be associated with a decreased risk of PS. Firstly, we must recognize the possibility of unmeasured confounders. For instance, patients undergoing diagnostic cardiac catheterization through the radial approach are more likely to receive heparin than those in whom the femoral approach is utilized, to decrease the risk of radial artery occlusion. Only two primary studies adjusted the relative incidence of PS for the differences in heparin usage [38,40]. This may potentially contribute to the lower PS rates seen in the radial arm, although should not account for any differences in patients undergoing PCI who will all receive heparin during the procedure. Also, patients undergoing TFA in the real world are generally at higher risk and more comorbid, which would also place them at higher risk of stroke complications. In contrast to previous work, we have restricted analyses that reported PS outcomes within 72 hours of the cardiac catheterization procedure, as longer-term stroke events may not relate to cardiac catheterization but the inherent vascular risk of the cohorts which would tend to magnify any potential differences between the cohorts. Previous analyses have suggested that 80% of PS occurs within 48 hours [50], so limiting our analysis to 72 hours would minimize any differences driven by inherent differences in vascular risk between the 2 groups of patients. Whilst some of the observational studies used in the current analysis adjusted for differences in comorbidity, procedural and clinical indications, we cannot exclude residual confounding driving the worse outcomes of TFA. Secondly, the burden of atheroma is often far greater in the descending aorta compared to the subclavian arch/ascending aorta, which may place patients undergoing TFA at greater risk from cholesterol/plaque embolization than those undergoing TRA. Indeed previous work has postulated that this mechanism may contribute to the lower rates of acute kidney injury associated with TRA [51]. On the other hand, atheroma in the descending aorta should not contribute to PS unless the catheter picks up atheroma from the wall of the infrarenal aorta and carries it to the ascending aorta from which it embolizes to the brain. Finally, TRA may impact the occurrence of PS by reducing procedure-related major bleeding and vascular access site complications that are risk factors for the development of PS, mediated through blood loss, the presence (and worsening) of anemia, periprocedural hypotension, and blood transfusions.

Another way of assessing the risk of unmeasured/unobserved confounding is to abandon all underlying assumptions about the number and type of confounders and to consider their hypothetical joint impact. To estimate the minimal level of unmeasured confounding that would shift the pooled estimate to the null, we employed e-values [35]. Obtaining values of 2.40 for the pooled adjusted point estimate and 1.50 for its confidence limit, we assume that unmeasured confounding was unlikely to affect the results [52]. Similarly, e-values of 2.55 and 1.92 for pooled unadjusted point estimate and its confidence limit, respectively, suggest low sensitivity of the conclusion toward an unmeasured confounding.

Our work is subject to a number of limitations. The main limitation of our work is that the meta-analyses are based on published studies with a generally poor description of the endpoint adjudication. Only four authors provided sufficient descriptions of the neurological examinations used in PS cases [17,36–38], although this could have been done in other studies as well, notably those based on the nationwide registries, the information was not readily available from the manuscripts. The lack of information on valid outcome assessment in the primary studies represents an important limitation of our analysis. Another limitation is that we pooled together a wide and heterogeneous group of patients undergoing various procedures. We did not differentiate, for instance, patients according to the severity of coronary syndromes [16], or catheterizations performed via left or right radial access which are likely to change the effect size [53]. We also did not differentiate between hemorrhagic and ischemic PS [47] as many of the studies did not report on these outcomes separately. Nevertheless, our previous work has demonstrated that ischemic PS is 3 fold more common than hemorrhagic PS [47] in PCI and so any differences between the 2 groups of patients are likely to be driven by ischemic events. Nevertheless, we undertook a sensitivity analysis with only those studies that clearly reported the type of PS was ischemic and showed no difference between TRA and TFA. Similarly to the other three sensitivity analyses, the insignificant estimate may result from the limited number of observations pooled.

5. Conclusion

The incidence of short-term PS is highly heterogeneous among populations, i.e. tens to hundreds can be expected per 100,000 procedures. We did not identify any single characteristic that would predict this rare adverse cardiac catheterization event. Across several analyses, our results consistently show that TRA confers an ~20% lower risk of PS in real-world/common practice settings. We failed to identify any single characteristic/risk factor that could modify this effect. According to study sequential analysis, future studies are unlikely to change our conclusions.

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Author contributions

J.M. designed the hypothesis and J.T. wrote the protocol and the draft manuscript, both reviewed literatures, extracted data, interpreted results and developed the manuscript. J.T. designed and performed the statistical analyses. M.M. and T.D. revised and interpreted the results and continuously revised the manuscript.

Data statement

All analyses can be easily reproduced using the information provided in Table 1, Table 2, and Supplementary Table 2.

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