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Anticoagulant vs. antiplatelet therapy in patients with cryptogenic stroke and patent foramen ovale: an individual participant data meta-analysis

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Aims The preferred antithrombotic strategy for secondary prevention in patients with cryptogenic stroke (CS) and patent foramen ovale (PFO) is unknown. We pooled multiple observational studies and used propensity score-based methods to estimate the comparative effectiveness of oral anticoagulation (OAC) compared with antiplatelet therapy (APT).

Methods and results Individual participant data from 12 databases of medically treated patients with CS and PFO were analysed with Cox regression models, to estimate database-specific hazard ratios (HRs) comparing OAC with APT, for both the primary composite outcome [recurrent stroke, transient ischaemic attack (TIA), or death] and stroke alone. Propensity scores were applied via inverse probability of treatment weighting to control for confounding. We synthesized database-specific HRs using random-effects meta-analysis models. This analysis included 2385 (OAC = 804 and APT = 1581) patients with 227 composite endpoints (stroke/TIA/death). The difference between OAC and APT was not statistically significant for the primary composite outcome [adjusted HR = 0.76, 95% confidence interval (CI) 0.52–1.12] or for the secondary outcome of stroke alone (adjusted HR = 0.75, 95% CI 0.44–1.27). Results were consistent in analyses applying alternative weighting schemes, with the exception that OAC had a statistically significant beneficial effect on the composite outcome in analyses standardized to the patient population who actually received APT (adjusted HR = 0.64, 95% CI 0.42–0.99). Subgroup analyses did not detect statistically significant heterogeneity of treatment effects across clinically important patient groups.

Conclusion We did not find a statistically significant difference comparing OAC with APT; our results justify randomized trials comparing different antithrombotic approaches in these patients.

Keywords Cryptogenic stroke • Patent foramen ovale • Secondary stroke prevention • Medical stroke treatment • Cardiogenic stroke

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Clinical perspective

The preferred antithrombotic strategy for secondary prevention in patients with cryptogenic stroke and patent foramen ovale is unknown. Current practice reflects this uncertainty, with antiplatelet therapy used in about two-thirds of patients and anticoagulation used in the remainder. Our results show low outcome rates with both forms of antithrombotic therapy in these patients. The comparison between treatments was not statistically significant in our main analyses but the treatment effect estimates favored oral anticoagulation, suggesting that this approach deserves further investigation, particularly for novel oral anticoagulants with better therapeutic profiles than warfarin.

Introduction

With the exception of cardio-embolic stroke, in which oral anticoagulation (OAC) is the preferred antithrombotic strategy for secondary prevention, guideline-recommended care for ischaemic stroke patients generally includes antiplatelet therapy (APT).[1] However, there is considerable disagreement over the best antithrombotic approach in patients with cryptogenic stroke (CS) and patent foramen ovale (PFO), in which paradoxical embolism is a suspected mechanism. Although the clinical syndrome caused by paradoxical embolism is arterial occlusion, the thrombus arises from a venous source. Thus, response to therapy may be more analogous to that of venothromboembolic disease in which OAC is superior.[2]

There has been no definitive study assessing the comparative effectiveness of OAC vs. APT in this population. Recent trials comparing mechanical PFO closure with 'best medical therapy' have generally left the choice of medical therapy to the treating physicians[3–5] and included a substantial minority of patients receiving warfarin instead of APT, indicating continued uncertainty.

A recent meta-analysis comparing OAC vs. APT using published data from both randomized and (mostly) observational studies[6] suggested substantial benefits from OAC; however, the total number of included patients was small ($n = 629$) and the component observational studies made no attempt to control for confounding. It has been shown that patients receiving different antithrombotic regimens are non-comparable.[7] Herein, we present the findings of the Targeted Antithrombotic Therapy in Cryptogenic Stroke with PFO (TAcTiCS-PFO) study, which addresses the limitations of the prior analyses by obtaining individual participant data (IPD) from studies included in the original meta-analysis; substantially augmenting the data set with studies participating in the Risk of Paradoxical Embolism (RoPE) study[8,9]; and using rigorous methods to control confounding.

Methods

Construction of the IPD database

Study selection criteria

The studies included in the TAcTiCS-PFO study partially overlap with those included in the RoPE study.[8,9] Studies were eligible for the present investigation if they enrolled CS patients systematically investigated for PFO (with transoesophageal echocardiography or transcranial Doppler), included at least 15 patients with PFO and CS receiving APT and at least 15 patients with PFO and CS receiving OAC, and obtained 1-year follow-up data for transient ischaemic attack (TIA), stroke, or death on at least 90% of the consenting subjects.

Identifying studies meeting selection criteria and obtaining data

Appropriate studies were identified by literature search and through direct contact with RoPE study investigators. Although the literature included only 8 studies that reported comparative data on APT vs. OAC, we identified 18 studies that potentially had collected data appropriate for comparative analysis. Seven of these were already included in the RoPE study (five other RoPE databases did not meet inclusion criteria). Of the remaining 11 studies, only 2 met our inclusion criteria, had sufficient available data, and agreed to participate. Finally, we were also able to obtain the medical arms of the three randomized clinical trials testing mechanical closure.[3–5] Thus, the final TAcTiCS-PFO data set included 12 component databases (*Table 1*).

Harmonizing data across contributed databases

Common variable definitions established for the RoPE study formed the basis for harmonization of data in TAcTiCS-PFO and have been described previously.[8,9]

Our primary outcome was a composite of stroke, TIA, or death from any cause; stroke alone was considered as a secondary outcome. We defined stroke as a sudden onset neurological deficit in a vascular territory presumed to be due to focal ischaemia lasting >24 h or accompanied by acute neuroimaging changes in the appropriate location; TIA was defined as a deficit lasting <24 h, unaccompanied by acute neuroimaging changes in the appropriate location. Our definition of CS conformed to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification,[10] which requires a complete work-up to identify underlying causes including (at minimum) magnetic resonance or computed tomography imaging; vascular imaging with angiography; and cardiac rhythm study (by electrocardiography, Holter, or telemetry). Cardio-embolic stroke in the TOAST classification is considered 'probable' if a high-risk source is identified and 'possible' if medium-risk sources are present. This latter category includes PFO and atrial septal aneurysms (ASAs). Study subjects with medium-risk sources were considered cryptogenic. All included studies conformed to this CS definition.

Safety was examined by comparing major bleeding classified as serious adverse events, using the definitions in the component studies. This information was reliably obtained only in the four randomized trials (PICSS, CLOSURE, RESPECT, and the PC Trial).

Exposure to treatment was determined on the basis of the initial oral antithrombotic regimen after the index event. Thus, the OAC treatment group included the strategy of initial OAC treatment, with eventual switching to APT. We describe switching behaviour in the three trials examining PFO closure (CLOSURE, RESPECT, and the PC Trial), in which ascertainment of these data was most complete. For patients started on OAC, switching was defined as the first visit without an anticoagulant but with an antiplatelet. For patients started on APT, switching was defined as any visit with an OAC, either as monotherapy or as dual antithrombotic therapy. OAC included only warfarin. APT included aspirin, clopidogrel, ticlopidine, and aspirin combined with

Table 1 Component databases of the TAcTiCS-PFO study

Study	Subjects (*n*)	Antiplatelets *n* (%)	Anticoagulants *n* (%)	Outcomes of interest (*n*)			
				Stroke	Stroke/TIA	Death	Stroke/TIA/death
RESPECT (medical arm)[3]	438	332 (75.8%)	106 (24.2%)	13	17	1	17
CLOSURE 1 (medical arm)[5]	379	265 (69.9%)	114 (30.1%)	12	25	3	27
German[31]	296	161 (54.4%)	135 (45.6%)	16	27	11	33
CODICIA[32]	294	212 (72.1%)	82 (27.9%)	6	16	3	19
PC Trial (medical arm)[4]	205	141 (68.8%)	64 (31.2%)	7	11	0	11
Bern Published[33]	146	67 (45.9%)	79 (54.1%)	16	28	9	33
FORI[34]	117	93 (79.5%)	24 (20.5%)	8	10	1	11
Sapienza[35]	115	80 (69.6%)	35 (30.4%)	4	7	5	9
Schuclenz, 2005[36]	113	66 (58.4%)	47 (41.6%)	8	29	2	31
PICSS[25]	98	56 (57.1%)	42 (42.9%)	10	16	4	20
Tufts[37]	95	46 (48.4%)	49 (51.6%)	3	4	0	4
Toronto[38]	89	63 (70.8%)	26 (29.2%)	6	11	2	12
Total	2385	1582 (66.3%)	803 (33.7%)	109	201	41	227

Patients treated with both antiplatelets and anticoagulants were excluded from this table.

dipyridamole. In our main analysis, we excluded patients who were initially placed on combination antiplatelet/anticoagulant therapy. We assessed the stability of our results by repeating the analysis after reclassifying these patients as anticoagulant-treated.

Database-specific treatment effects and average effects across studies

Propensity score analyses

We estimated the effect of OAC vs. APT on the outcomes of interest using a two-stage process. In the first stage, database-specific analyses were used to estimate marginal hazard ratios (HRs) comparing the two treatments. In the second stage, the HR estimates were pooled across databases.

To adjust for confounding bias within each of the included studies, database-specific HRs were estimated using inverse probability of treatment-weighted Cox regression.[11] First, we derived propensity scores via logistic regression (with OAC use as the response) to estimate each patient's probability of being assigned to OAC.[12] In the next step, this score is applied to weight patients by the inverse of the probability of receiving the treatment that they actually received. This method creates balance for all the covariates across the two treatments, to efficiently control for confounding. Supplementary material online, *Table S1A–L* describes the variables included in each database-specific propensity score model. Briefly, variables with >20% missing data were excluded from these analyses, except for categorical variables, in which an indicator variable was created for missingness where missingness was no greater than 40%. All variables that might plausibly influence treatment choice and the outcome of interest were included in the propensity score model; variable selection was based on clinical reasoning and not statistical signficance.[13]

Patients receiving OAC were weighted by inverse probability of treatment weights calculated as p_{OAC}/p_i and patients receiving APT were weighted by $(1-p_{OAC})/(1-p_i)$; here p_{OAC} is the probability of receiving OAC in the sample and p_i is the individual's propensity for receiving OAC (estimated on the basis of patient characteristics).[14] These weights yield an estimate of the average treatment effect standardized to the overall study population. For each database, we assessed whether the estimated propensity score produced balance (in each of the studies separately and in the overall database) by examining the standardized mean difference for all covariates included in the propensity model.

In all analyses, the standard error of the database-specific HR was obtained using the robust covariance matrix estimate.[15] Because extreme weights can influence the estimate of the treatment effect, the distributions of propensity weights in each database were examined; individuals assigned weights greater than 10 or less than 0.1 were trimmed or truncated in sensitivity analyses.[16]

Meta-analyses

We estimated summary treatment effects across studies using a two-level univariate random-effects meta-analysis model to combine the propensity score-weighted estimates of the log HR from each of the included studies.[17] We assessed between-study heterogeneity by calculating the I^2 index for each meta-analysis.[18]

Exploring treatment effect heterogeneity

RoPE strata-specific effects and other subgroups

The 10-point RoPE score (Supplementary material online, Table S2) was used to stratify the population based on the estimated probability that the index stroke was PFO-attributable, as opposed to a stroke of another (occult) cause with an incidentally discovered PFO.[19] The calculation of the attributable fraction is based on a comparison of PFO prevalence between CS patients and similar patients without CS. Generally, with a decreasing number of conventional stroke risk factors and younger age (resulting in a higher RoPE score and an increasing PFO prevalence in CS patients), the PFO-attributable fraction increases.

To examine whether OAC treatment effects might differ between patients with high vs. low RoPE scores, we excluded two databases for which neuroradiology variables were not obtained (Sapienza and PC Trial) and calculated RoPE scores on all the remaining patients. Because some patients had missing data for RoPE score variables, we used multiple imputation within each data set. We stratified patients within

each imputed data set into strata with RoPE score ≥7 and <7. In the RoPE study, patients with a score of 7 were estimated to have a >70% PFO-attributable fraction, and this value separated patients into similarly sized groups.

To control for confounding, propensity scores for treatment were created for each stratum within each imputed data set[20] and used to weight observations as described earlier. HRs were calculated within each imputed data set and combined.[21] Database- and stratum-specific HRs were then meta-analyzed. Stratified analyses were similarly performed to estimate differential effects across the following subgroups: age groups (≤45 and >45); sex; presence vs. absence of ASA; presence vs. absence of a superficial lesion on neuroimaging; and presence vs. absence of large shunt (defined as >10 microbubbles in left atrium within three cardiac cycles).

In stratified analyses, some of the studies did not have adequate data to estimate effects in all subgroups. To make maximal use of the available data, we used a bivariate random-effects meta-analysis model. This model allows for heterogeneity of the 'true' treatment effects across studies (within each subgroup) and accounts for possible correlations of these effects across studies.[22] All meta-analysis models were fit with restricted maximum likelihood methods.[23]

Sensitivity analyses

We performed extensive sensitivity analyses. First, because clinicians may recommend a specific therapy based on clinical characteristics associated with treatment response, we explored alternative propensity weighting schemes that standardized treatment effects to the patient populations who actually received OAC or APT.[24] Secondly, we performed a meta-analysis that included treatment effect estimates from studies that did not provide individual-level data for TAcTiCS PFO, but provided enough information to approximate them from published data. Thirdly, we performed analyses limited to data from the four randomized trials participating in TAcTiCS,[3–5,25] assuming that outcome ascertainment methods were more rigorous in these studies.

Software

Study-level analyses were conducted using SAS software, version 9.4 TS Level 1 M1 (SAS Institute Inc., Cary, NC, USA). Meta-analyses were conducted using Stata, version SE/13.1 (Stata Corp., College Station, TX, USA).

Results

We obtained data from 2385 patients (OAC = 803 and APT = 1582) followed for a total of 6116 person-years with 227 composite endpoint events (stroke/TIA/death) (*Figure 1*) . The crude outcome rates were 3.7% events per person-year for the composite outcome and 1.8% for recurrent stroke. The rate of OAC use among those receiving antithrombotic treatment ranged from 20.5% (in FORI) to 54.1% (in Bern) (*Table 1*). Among patients in the medical arms of the three device trials, 30% of those initiated on OAC eventually switched to APT (i.e. at least one follow-up visit with only APT), whereas only 7% on those initiated on APT subsequently received OAC (either as an additional agent or as monotherapy for at least one visit).

Patient characteristics are summarized in *Table 2* (database-specific comparisons are presented in Supplementary material online, *Tables S1A–L*). Compared with patients initially receiving APT, patients receiving OAC were older, more likely to have an index stroke, more likely to have a history of stroke, and greater stroke severity. On neuroimaging, patients receiving OAC were more likely to have superficial, anterior, multiple, and large lesions. Echocardiographic characteristics also differed, with patients receiving OAC being more likely to have an ASA and larger shunt. Overall, there was no substantial difference in the distribution of vascular risk factors or RoPE scores across treatment groups. Despite the substantial differences seen between the treatment groups, inverse probability weighting achieved balance in the covariates in the individual databases and overall.

Database-specific propensity models contained from 10 to 34 variables and had *C*-statistics ranging from 0.66 (RESPECT) to 0.82 (Tufts). Although propensity adjustment had considerable influence over the HR estimate in individual studies, confounding bias appeared to affect study-level effects in both directions; summary results were similar in adjusted and unadjusted analyses and not statistically significant in either (adjusted HR for the primary composite outcome = 0.76, 95% CI 0.52–1.12) (shown in *Figure 2* and *Table 3*). Similar results were seen for the outcome of stroke alone (adjusted HR = 0.75, 95% CI 0.44–1.27) (Supplementary material online, *Figure S1*). Results were similar when the 114 patients treated on combination therapy (excluded from the primary analysis) were included in the OAC group.

Overall, results were similar across alternative weighting schemes (*Table 3*), with the exception that OAC had a statistically significant beneficial effect on the primary composite outcome in analyses standardized to the patient population who actually received APT (adjusted HR = 0.64, 95% CI 0.42–0.99). Point estimates of the treatment effect standardized to the OAC-treated population did not favor either antithrombotic approach. Results were similar to the main analysis when estimates from the four literature-based studies with unavailable individual patient data were included (summary HR for primary composite outcome = 0.76, 95% CI 0.54–1.07; summary HR for stroke alone = 0.67, 95% CI 0.42–1.08). Results were also similar in analyses restricted to data from randomized trials (PICSS and the medically treated groups from the three randomized trials of PFO closure). We subsequently stratified patients by their RoPE score. About 1061 patients with 39 outcomes were in the high RoPE score group, and 1196 patients with 115 composite outcomes were in the low RoPE score group. Of the 128 patients who could not be classified because of missing RoPE score variables, 77 patients were classifiable using imputation and 49 patients were not (as they came from studies without neuroimaging data).

We did not find statistically significant heterogeneity of treatment effects (i.e., effect modification) in any of the subgroup analyses for the primary composite outcome (*Figure 3*). We obtained similar results for stroke (Supplementary material online, *Figure S2*). Of note, outcome rates were very low among the high RoPE score group, making the database-specific HRs inestimable in some studies and resulting in imprecise effect estimates in others.

Bleeds classified as serious adverse events were ascertained in 1120 patients across four studies. There were only 10 such bleeds in total, with very similar event rates in both groups (unadjusted HR = 0.91, 95% CI 0.22–3.74; adjusted HR = 0.80, 95% CI 0.21–3.1) (analysis details are provided in the Supplementary material online, *Table S3*).

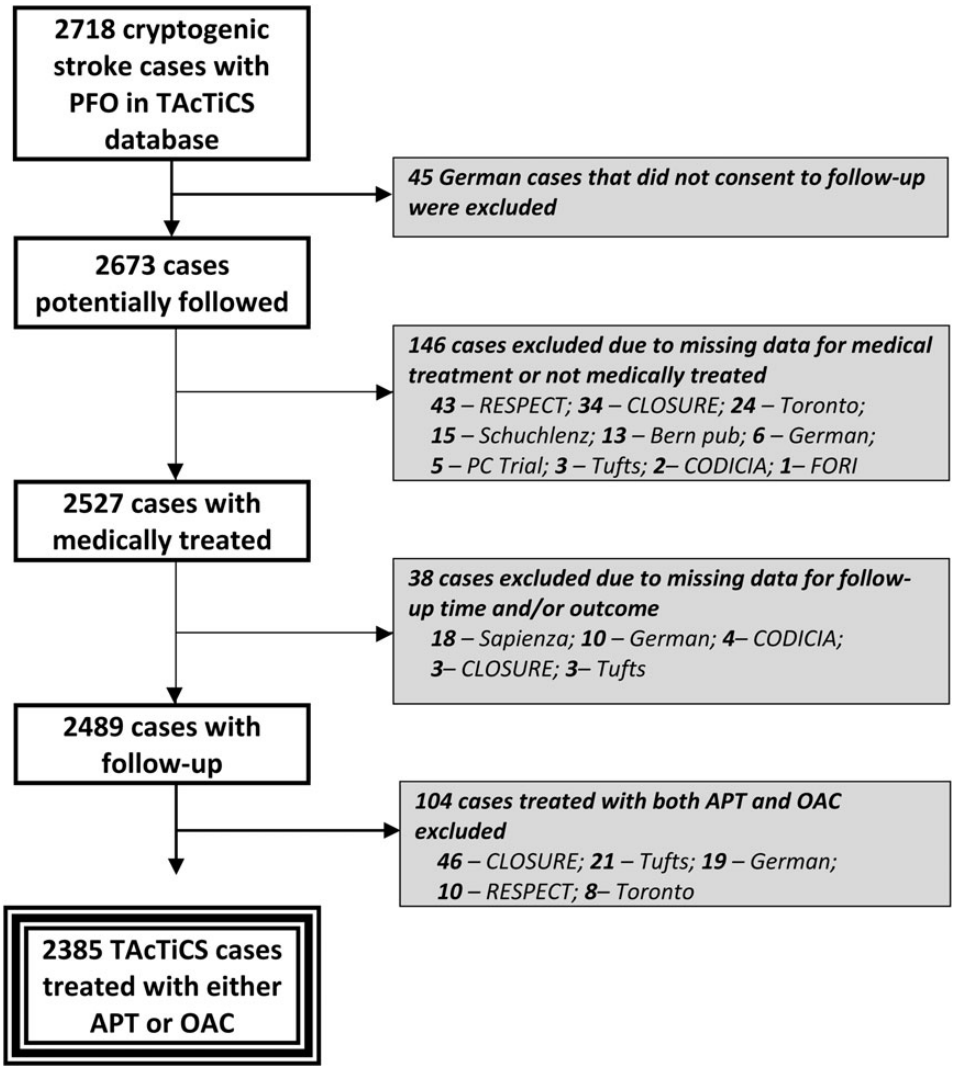

Figure 1 Flow diagram showing cases included in the TAcTiCS analysis and detailing reasons for exclusion of potentially eligible participants from the 12 component studies.

Discussion

Our individual patient data meta-analysis incorporating 12 studies with over 2000 patients did not detect a statistically significant difference in the composite outcome of stroke, TIA, or death with OAC vs. APT in patients with CS and PFO. This is the largest study to date examining medical therapy in this population. In general, point estimates favoured OAC, with an estimated effect showing about 25% relative reduction in the hazard of the composite outcome, but these estimates were imprecise and confidence intervals did not exclude the null. As the crude outcome rate overall was 3.7% per person-year, we note that such a difference might be clinically important. Sensitivity analyses were generally consistent with these overall results, and subgroup analyses did not identify statistically significant heterogeneity of treatment effects.

Prior evidence was suggestive that warfarin may be more effective for secondary stroke prevention in these patients. Although the randomized trial PICSS[25] (which examined the subgroup of patients from WARSS[26] investigated for PFO) found no benefit for warfarin over aspirin, it included only 98 patients with both PFO and CS. Among these patients, a clinically substantial, but not statistically significant, benefit was observed for warfarin (stroke or death in 9.5 vs. 17.9% of warfarin- and ASA-treated patients, respectively; HR = 0.52, $P = 0.28$). We recently synthesized the published evidence on secondary stroke prevention in patients with PFO and CS and found a clinically impressive and statistically significant 50% reduction in recurrence risk with warfarin.[6] Finally, in the RESPECT trial, patients with APT but not with OAC fared significantly worse than those with device closure in a prospectively planned subgroup analysis.[4]

The TAcTiCS study reported here has several advantages over prior meta-analyses using published data. Most importantly, although the seven previously published comparative studies did not control for confounding by indication (because outcomes within

Table 2 Patient characteristics across TAcTiCS component databases using non-imputed data

Variable	Treated with anticoagulants ($n = 803$)	Treated with antiplatelets ($n = 1582$)	*P*-value[a]	Full cohort ($n = 2385$)
Clinical variables				
Age[b]	50.1 ± 13.2 (803)	48.4 ± 13.1 (1576)	0.0034	49.0 ± 13.2 (2379)
Male gender	57.9% (465/803)	56.6% (895/1580)	0.5562	57.1% (1360/2383)
White race	87.5% (210/240)	85.2% (381/447)	0.4143	86.0% (591/687)
Index event of stroke	81.5% (626/768)	76.9% (1155/1501)	0.0123	78.5% (1781/2269)
Prior stroke/TIA	19.1% (153/803)	15.2% (239/1576)	0.0156	16.5% (392/2379)
Initial NIHSS[b]	2.7 ± 3.7 (546)	1.5 ± 2.5 (992)	<0.0001	1.9 ± 3.0 (1538)
Initial Rankin[b]	0.7 ± 1.1 (506)	0.7 ± 0.9 (1025)	0.078	0.7 ± 1.0 (1531)
Current smoker	23.0% (184/801)	22.3% (350/1572)	0.3615	22.5% (534/2373)
History of hypertension	31.2% (250/802)	32.4% (511/1577)	0.5428	32.0% (761/2379)
History of diabetes	7.9% (63/800)	7.5% (119/1578)	0.7724	7.7% (182/2378)
Hypercholesterolaemia	29.9% (202/675)	34.1% (446/1309)	0.0621	32.7% (648/1984)
Migraine	24.5% (140/572)	24.1% (300/1246)	0.8539	24.2% (440/1818)
Body mass index[b]	27.4 ± 5.1 (285)	27.4 ± 5.4 (515)	0.8981	27.4 ± 5.3 (800)
Neuroradiology				
Superficial (vs. deep)	54.1% (320/592)	47.2% (573/1215)	0.0059	49.4% (893/1807)
Anterior infarct	44.1% (200/454)	34.2% (290/848)	0.0005	37.6% (490/1302)
Multiple strokes (vs. not)	11.5% (55/478)	4.9% (46/933)	<0.0001	7.2% (101/1411)
Large infarct (vs. small)	33.0% (169/512)	22.5% (218/971)	<0.0001	26.1% (387/1483)
Echocardiography				
Hypermobile septum	36.4% (285/783)	26.2% (401/1532)	<0.0001	29.6% (686/2315)
Large PFO	62.8% (389/619)	56.9% (684/1202)	0.0147	58.9% (1073/1821)
RoPE score[b]	6.3 ± 1.7 (588)	6.4 ± 1.8 (1201)	0.3439	6.4 ± 1.7 (1789)
RoPE ≥ 7, % (*n*)[c]	43.1% (341/791)	46.1% (720/1561)	0.1652	45.1% (1061/2352)

[a]*P*-value from two-sample *t*-test when mean ± standard deviation (*n*) shown, non-parametric Kruskal–Wallis test when median <25th–75th percentile (*n*) shown, and χ^2 test otherwise when data shown are presented as % (ratio) or % (*n*).
[b]Mean ± standard deviation.
[c]Includes cases with missing data needed for RoPE score, but still classifiable as ≥7 vs. ≤6.

component studies were too few to support conventional risk adjustment), we used methods for confounding control that rely on exposure (rather than outcome) modeling. Our analyses showed that the treatment groups in the component databases differed with respect to many potential confounding variables, making unadjusted analyses suspect. Moreover, previous meta-analyses included only 629 patients; the current analysis included almost four-fold the number of patients.[6] Finally, because studies enrolled patients at or near the time of the index event, our study approximates a 'new (incident) user' design.

Analysis of individual patient data also permitted the examination of the effect of treatment in population subgroups. Our hypothesis that OAC would be especially beneficial for patients in the 'purer' high RoPE score group (who have a low burden of vascular risk factors) was not borne out. Although this group presumably is enriched with patients whose index event was caused by paradoxical embolism, the low RoPE score group may have been enriched with occult atrial fibrillation, given the strong association of this dysrhythmia with age and vascular risk factors and variability across component studies in the duration electrocardiograph monitoring to rule out atrial fibrillation as a stroke aetiology. Regardless, the treatment effect was not statistically significant in either subgroup.

Although this study represents the best-available evidence on the comparative effectiveness of APT compared with OAC for patients with CS and PFO, some limitations need to be considered. First, our results estimate the effect of initial antithrombotic choice; they are analogous to an intention-to-treat analysis in a randomized trial. However, a substantial minority of patients who started OAC subsequently switched to APT, potentially attenuating the difference between treatment groups. Second, safety outcomes were not consistently obtained across most of the studies. Third, this was a non-randomized observational study. Although propensity score-based weighting achieved balance in the observed covariates across component databases, the effect of unmeasured covariates cannot be assessed. Although theory and simulations support the advantage of propensity score-based methods over conventional regression methods, empirical work has shown that the results of propensity score-based observational comparative effectiveness studies

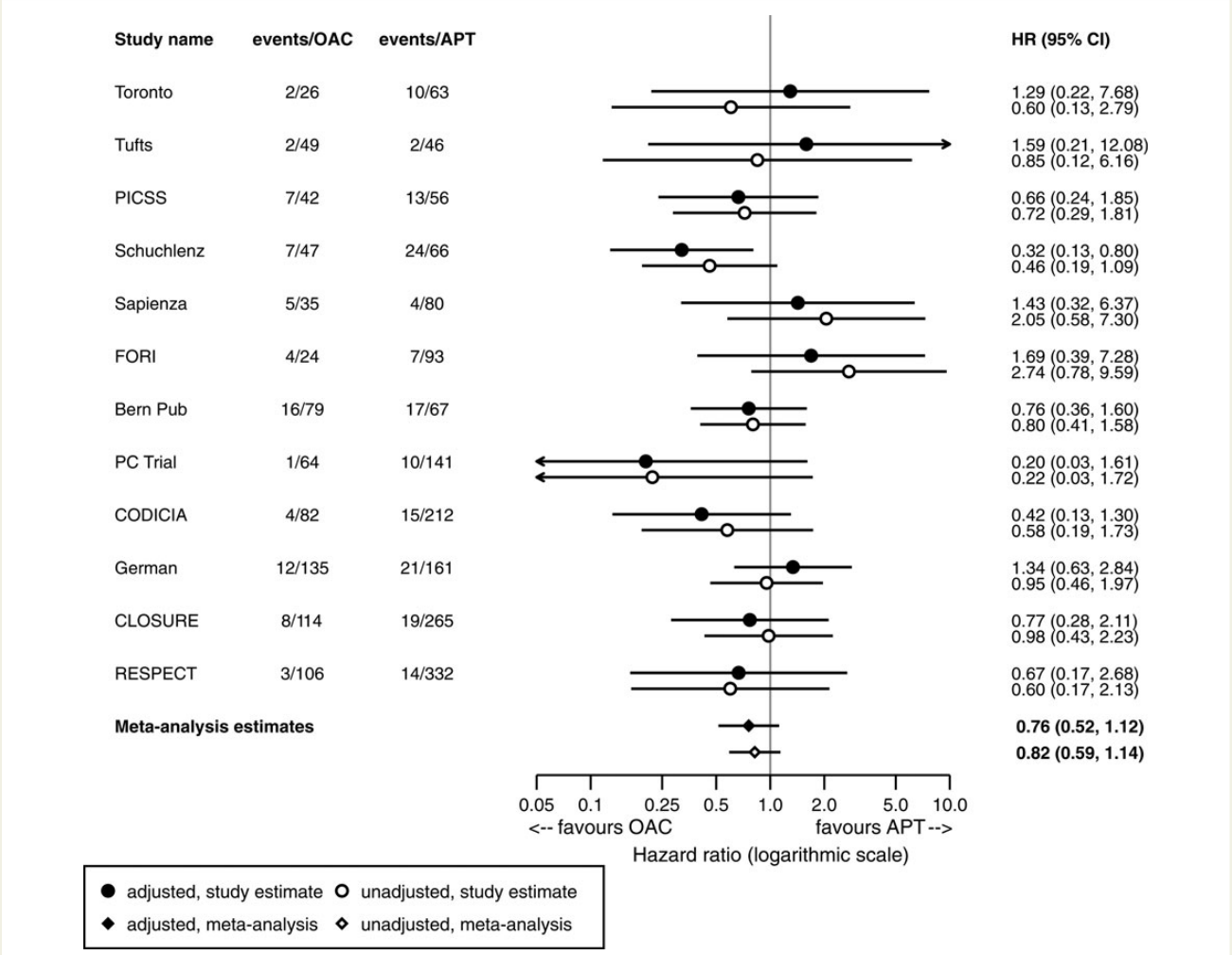

Figure 2 Summary results for composite outcome by study. Open circles represent crude HRs for individual studies; solid circles represent the adjusted HRs in individual studies. Pooled estimates, represented by diamonds, were computed from a random-effects model. Horizontal lines through the circles and diamonds denote the 95% CIs for individual studies and summary results, respectively.

Table 3 Main and sensitivity analyses

Weighting schemes	Stroke/TIA/death		Stroke alone	
	HR (95% CI)	*P*-index (%)	HR (95% CI)	*P*-index (%)
Main analysis				
Standardized to the overall population	0.76 (0.52–1.12)	0	0.75 (0 44–1.27)	0
Sensitivity analyses				
Standardized to the antiplatelet-treated	0.64 (0 42–0.99)	0	0.60 (0.33–1.10)	19
Standardized to the anticoagulant-treated	1.01 (0.60–1.69)	40	1.04 (0.47–2.30)	45
Standardized to the overall population, limited to RCTs	0.63 (0.23–1.71)	0	0.53 (0.14–2.04)	0
Standardized to the overall population, including data from published studies[a]	0.76 (0.54–1.07)	0	0.67 (0 42–1.08)	0

CI, confidence interval; HR, hazard ratio; reference category is APT; TIA, transient ischaemic attack.
[a]These analyses include data from published studies that did not contribute IPD to the RoPE database (for stroke/death/TIA: Harrer,[39] Hausmann,[40] and Cerrato[41]; for stroke alone: Hausmann,[40] Cerrato,[41] and Lee.[42])

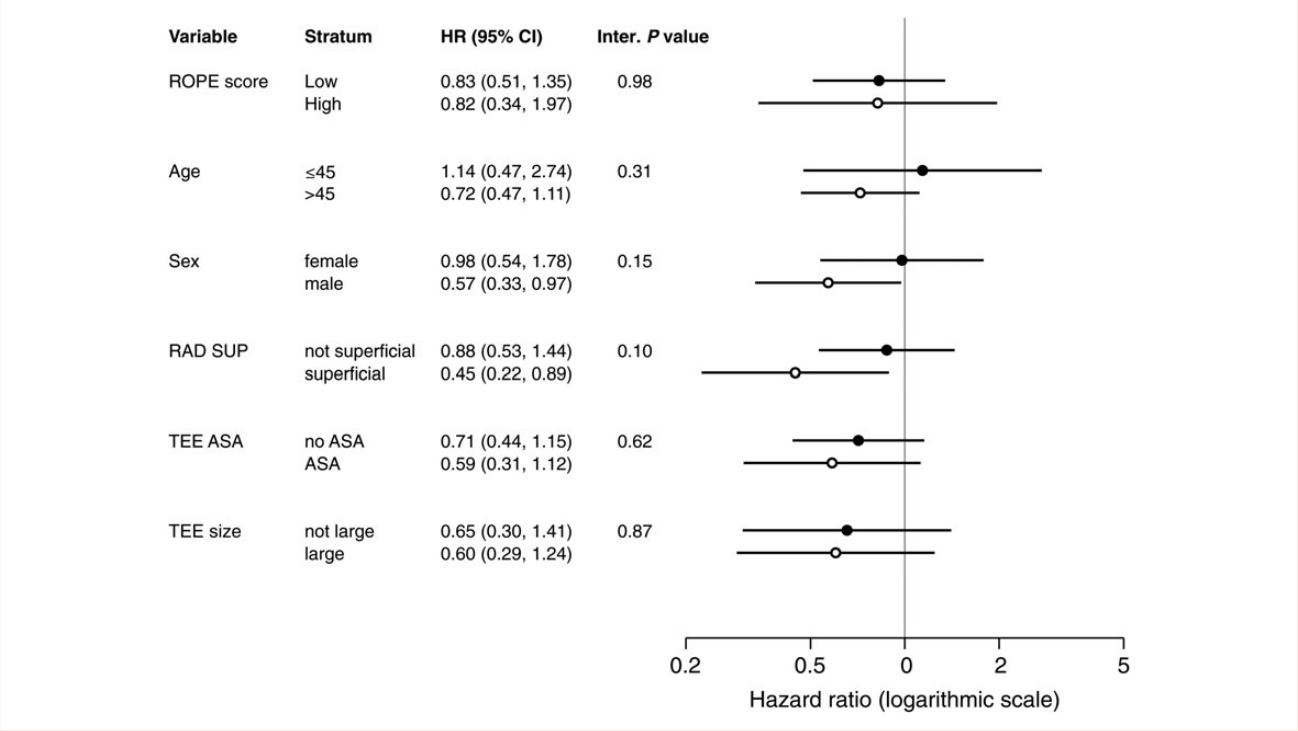

Figure 3 Summary results for composite outcome by subgroup. Circles represent adjusted stratum-specific HRs pooled across studies using a random-effects model. Horizontal lines through the circles denote the 95% CIs. Inter. *P* value, interaction p-value comparing treatment effects between strata; RAD SUP, superficial lesion on neuroimaging; TEE, trans-esophageal echocardiography.

sometimes disagree with randomized study results.[27,28] Fourth, the quality of study procedures can vary from database to database, with variable patient selection criteria, rates of loss to follow-up, and outcome ascertainment methods across databases. However, for a sensitivity analysis based on the databases derived from randomized clinical trials, the results remained not statistically significant although the point estimate favoured OAC more strongly.

Despite the fact that this is the largest study comparing antithrombotic strategies for secondary prevention of CS in patients with PFO, the confidence intervals of our effect estimates were wide and did not rule out clinically important benefits of OAC over APT. This was particularly the case for key subgroups, such as patients with high RoPE scores, in which outcome rates in both treatment groups were very low. The imprecision of treatment effect estimates was in part due to the need to adjust for a large number of potential confounders that differed in distribution between the treatment groups. Randomized clinical trials would be anticipated to provide more precise treatment effect estimates, even with similar sample sizes and event rates.

Despite our results, the pathophysiological rationale supporting OAC over APT for patients with non-lacunar ischaemic stroke without a defined source (including those with PFO) is compelling. For thrombo-embolic syndromes thought to be due to platelet-poor thrombus formation occurring at venous flow rates (deep venous thrombosis and pulmonary embolism) and in areas of haemostasis (e.g. left atrial appendage in atrial fibrillation), warfarin has shown consistent superiority to APT.[2,29] The advent of novel anticoagulants has renewed interest in the potential advantages of OAC for secondary prevention in the CS population and has led to the newly proposed diagnostic category of embolic stroke of undetermined source as a potential therapeutic target.[30] Although our results have not ruled out these benefits, the low outcome rates on APT, particularly in younger patients without atherosclerotic risk factors, limit the magnitude of the potential absolute benefit of OAC in this setting.

Conclusion

In summary, currently available data do not provide definitive evidence on the comparative benefits of OAC vs. APT in patients with CS and PFO. Low outcome rates and the non-comparability of treatment groups resulted in imprecise estimates of the comparative effectiveness of antithrombotic treatments in this patient population. These results support the need for additional comparative studies, including randomized trials.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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