

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

David M. Kent<sup>1,2\*</sup>, Issa J. Dahabreh<sup>1,3,4</sup>, Robin Ruthazer<sup>1</sup>, Anthony J. Furlan<sup>5</sup>, Christian Weimar<sup>6</sup>, Joaquín Serena<sup>7</sup>, Bernhard Meier<sup>8</sup>, Heinrich P. Mattle<sup>9</sup>, Emanuele Di Angelantonio<sup>10</sup>, Maurizio Paciaroni<sup>11</sup>, Herwig Schuchlenz<sup>12</sup>, Shunichi Homma<sup>13</sup>, Jennifer S. Lutz<sup>1</sup>, and David E. Thaler<sup>2</sup>

<sup>1</sup>Predictive Analytics and Comparative Effectiveness Center, Institute for Clinical Research and Health Policy Studies, Tufts Medical Center/Tufts University School of Medicine, 800 Washington St, Box 63, Boston, MA 02111, USA; <sup>2</sup>Department of Neurology, Tufts Medical Center/Tufts University School of Medicine, Boston, MA, USA; <sup>3</sup>Center for Evidence-Based Medicine, School of Public Health, Brown University, Providence, RI, USA; <sup>4</sup>Department of Health Services, Policy, and Practice, School of Public Health, Brown University, Providence, RI, USA; <sup>5</sup>Department of Neurology, Case Western Reserve University, Cleveland, OH, USA; <sup>6</sup>Department of Neurology, University of Duisburg—Essen, Essen, Germany; <sup>7</sup>Neurology Department, Hospital Universitari Doctor Josep Trueta Institut D'Investigació Biomèdica de Girona, Girona, Spain; <sup>8</sup>Department of Cardiology, Swiss Cardiovascular Center, Inselspital, University of Bern, Bern, Switzerland; <sup>9</sup>Inselspital, University of Bern, Bern, Switzerland; <sup>10</sup>Department of Public Health and Primary Care, Cambridge University, Cambridge, UK; <sup>11</sup>Stroke Unit and Division of Cardiovascular Medicine, University of Perugia, Perugia, Italy; <sup>12</sup>Department of Medicine, LKH—Graz West, Graz, Austria; and <sup>13</sup>Division of Cardiology, Columbia University, New York, NY, USA

Received 16 January 2015; revised 20 April 2015; accepted 20 May 2015; online publish-ahead-of-print 3 July 2015

## 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

\* Corresponding author. Tel: +1 617 636 3234, Fax: +1 617 636 0022, Email: [dkent1@tuftsmedicalcenter.org](mailto:dkent1@tuftsmedicalcenter.org)

Published on behalf of the European Society of Cardiology. All rights reserved. © The Author 2015. For permissions please email: [journals.permissions@oup.com](mailto:journals.permissions@oup.com).

## 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).<sup>1</sup> 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.<sup>2</sup>

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<sup>3–5</sup> 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<sup>6</sup> 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.<sup>7</sup> 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<sup>8,9</sup>; 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.<sup>8,9</sup> 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.<sup>3–5</sup> 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.<sup>8,9</sup>

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,<sup>10</sup> 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) <sup>3</sup>	438	332 (75.8%)	106 (24.2%)	13	17	1	17
CLOSURE 1 (medical arm) <sup>5</sup>	379	265 (69.9%)	114 (30.1%)	12	25	3	27
German <sup>31</sup>	296	161 (54.4%)	135 (45.6%)	16	27	11	33
CODICIA <sup>32</sup>	294	212 (72.1%)	82 (27.9%)	6	16	3	19
PC Trial (medical arm) <sup>4</sup>	205	141 (68.8%)	64 (31.2%)	7	11	0	11
Bern Published <sup>33</sup>	146	67 (45.9%)	79 (54.1%)	16	28	9	33
FORI <sup>34</sup>	117	93 (79.5%)	24 (20.5%)	8	10	1	11
Sapienza <sup>35</sup>	115	80 (69.6%)	35 (30.4%)	4	7	5	9
Schuelenz, 2005 <sup>36</sup>	113	66 (58.4%)	47 (41.6%)	8	29	2	31
PICSS <sup>25</sup>	98	56 (57.1%)	42 (42.9%)	10	16	4	20
Tufts <sup>37</sup>	95	46 (48.4%)	49 (51.6%)	3	4	0	4
Toronto <sup>38</sup>	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.<sup>11</sup> 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.<sup>12</sup> 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 significance.<sup>13</sup>

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).<sup>14</sup> 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.<sup>15</sup> 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.<sup>16</sup>

### 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.<sup>17</sup> We assessed between-study heterogeneity by calculating the  $I^2$  index for each meta-analysis.<sup>18</sup>

## 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.<sup>19</sup> 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  $\geq 7$  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<sup>20</sup> and used to weight observations as described earlier. HRs were calculated within each imputed data set and combined.<sup>21</sup> Database- and stratum-specific HRs were then meta-analyzed. Stratified analyses were similarly performed to estimate differential effects across the following subgroups: age groups ( $\leq 45$  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.<sup>22</sup> All meta-analysis models were fit with restricted maximum likelihood methods.<sup>23</sup>

## 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.<sup>24</sup> 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,<sup>3–5,25</sup> 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

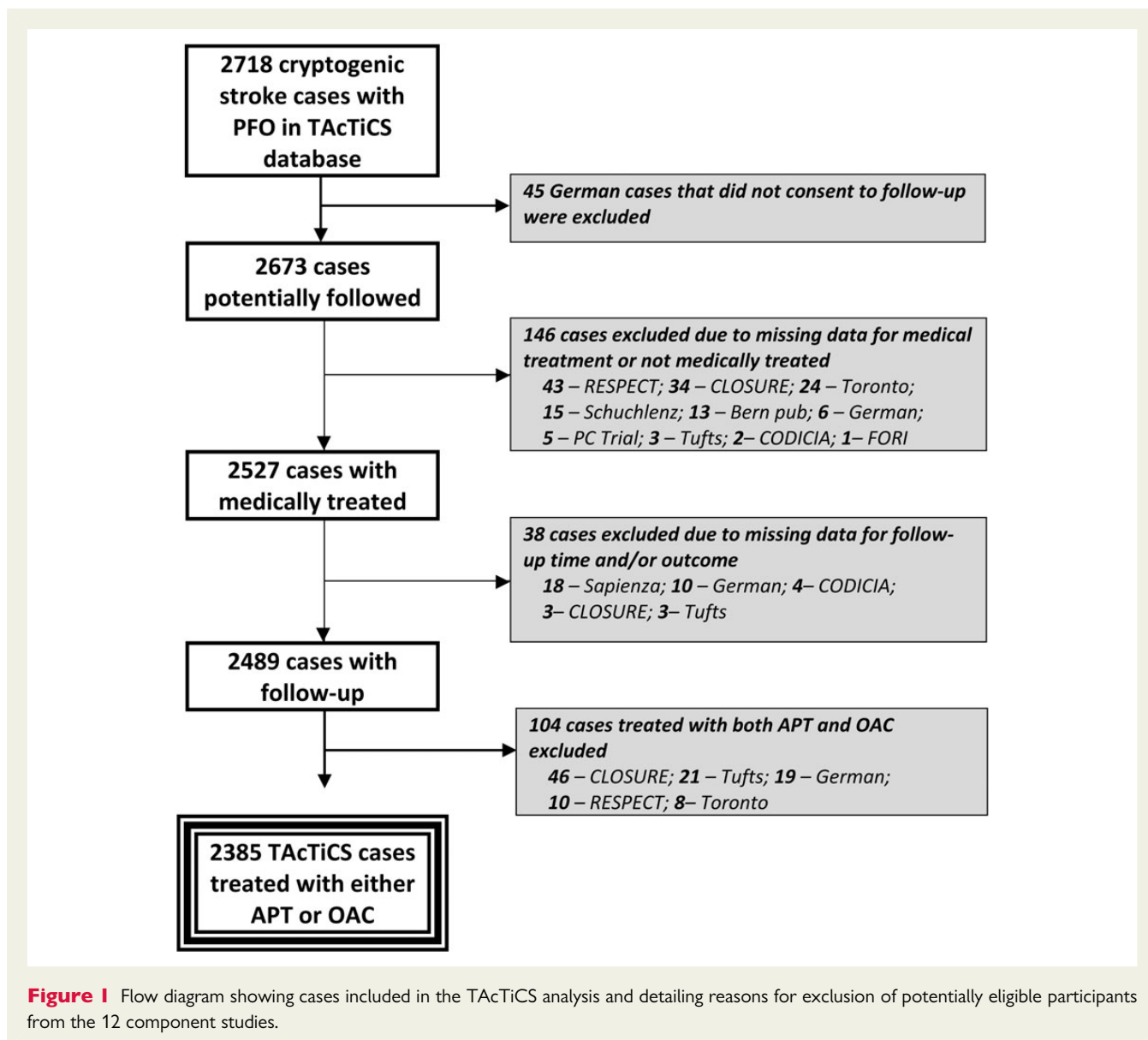
index stroke, more likely to have a history of stroke, and greater stroke severity. On neuroimaging, patients receiving OAC were more likely to have superficial, anterior, multiple, and large lesions. Echocardiographic characteristics also differed, with patients receiving OAC being more likely to have 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).



## 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<sup>25</sup> (which examined the subgroup of patients from WARSS<sup>26</sup> 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.<sup>6</sup> 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.<sup>4</sup>

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 <sup>a</sup>	Full cohort (n = 2385)
Clinical variables				
Age <sup>b</sup>	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 <sup>b</sup>	2.7 ± 3.7 (546)	1.5 ± 2.5 (992)	<0.0001	1.9 ± 3.0 (1538)
Initial Rankin <sup>b</sup>	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 <sup>b</sup>	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 <sup>b</sup>	6.3 ± 1.7 (588)	6.4 ± 1.8 (1201)	0.3439	6.4 ± 1.7 (1789)
RoPE ≥ 7, % (n) <sup>c</sup>	43.1% (341/791)	46.1% (720/1561)	0.1652	45.1% (1061/2352)

<sup>a</sup>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  $\chi^2$  test otherwise when data shown are presented as % (ratio) or % (n).

<sup>b</sup>Mean ± standard deviation.

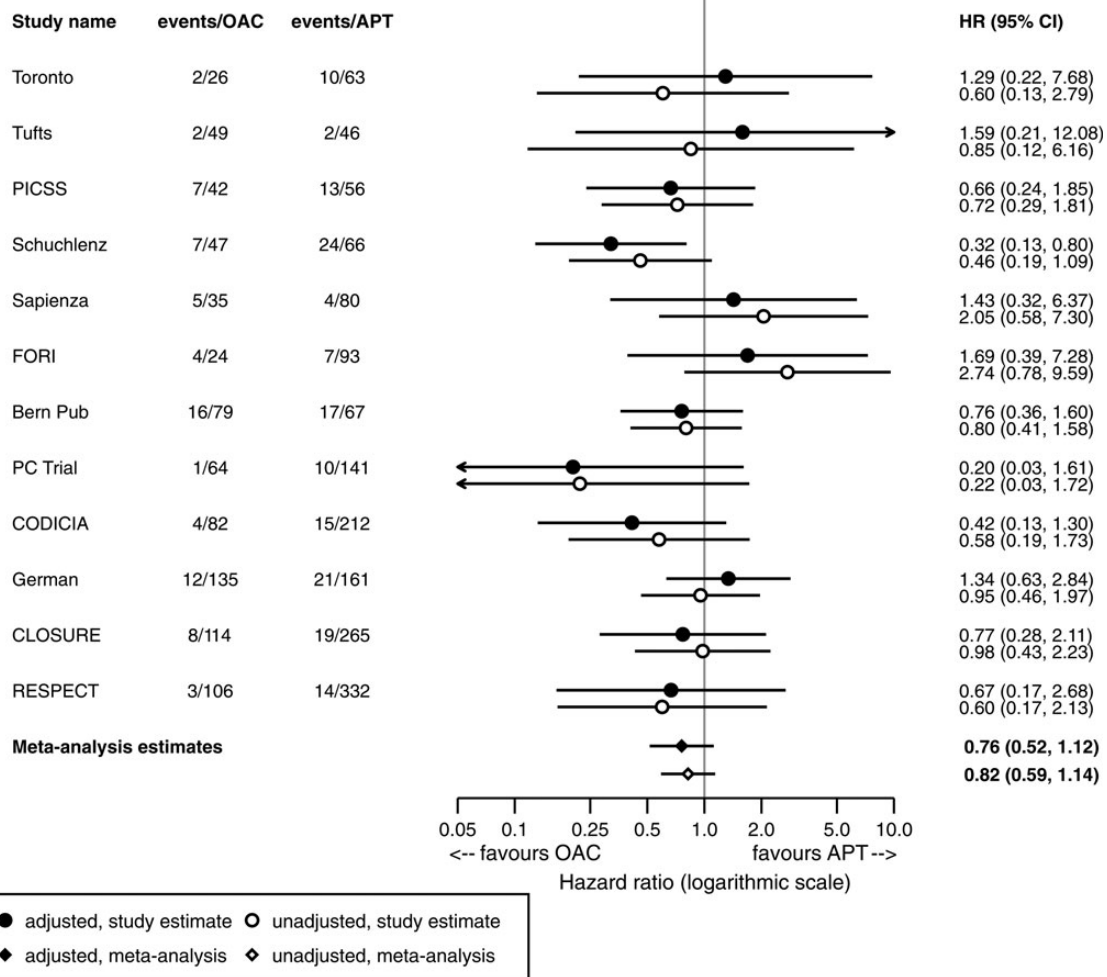
<sup>c</sup>Includes cases with missing data needed for RoPE score, but still classifiable as ≥7 vs. ≤6.

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.<sup>6</sup> 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



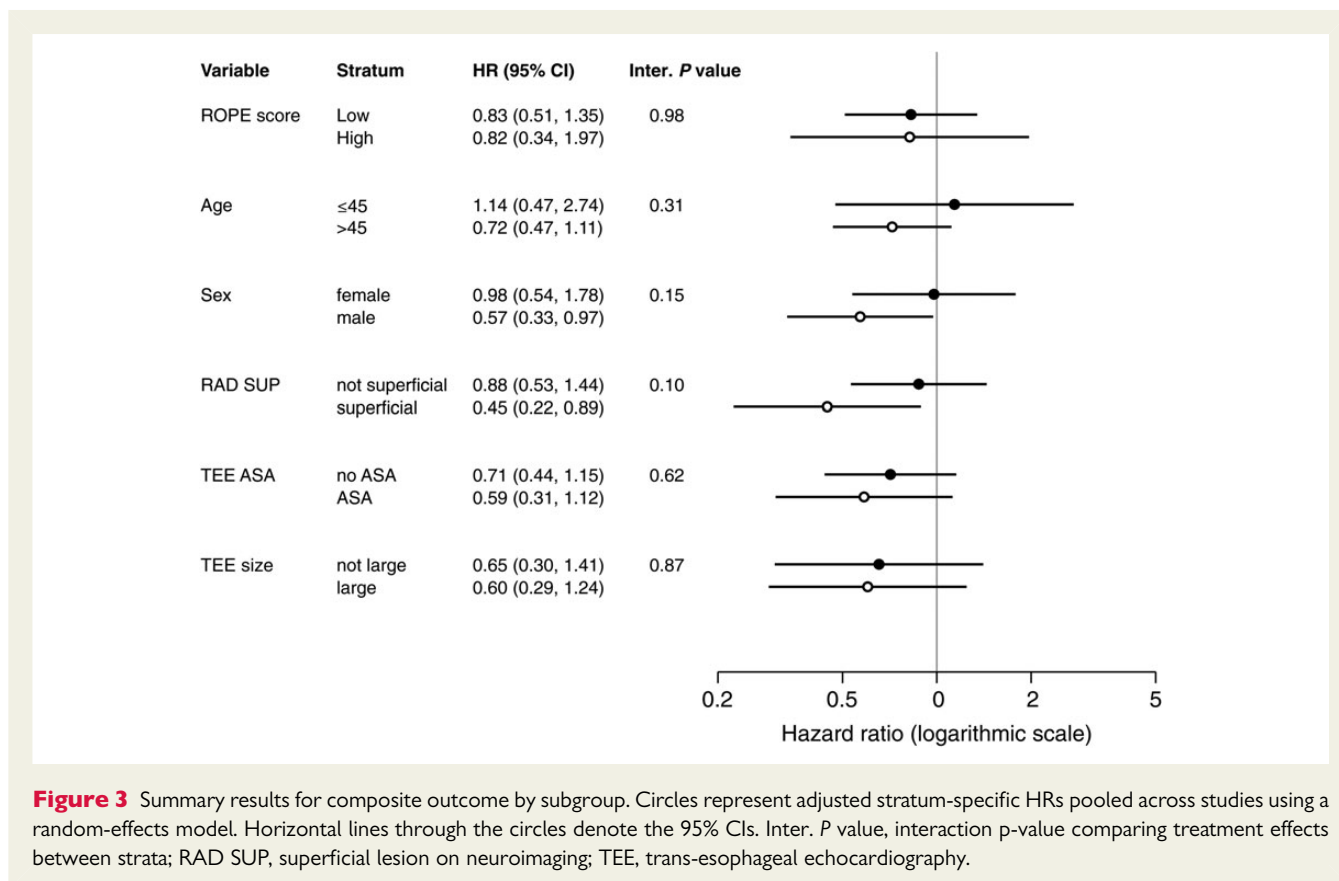
**Figure 2** Summary results for composite outcome by study. Open circles represent crude HRs for individual studies; solid circles represent the adjusted HRs in individual studies. Pooled estimates, represented by diamonds, were computed from a random-effects model. Horizontal lines through the circles 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 <sup>a</sup>	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.

<sup>a</sup>These analyses include data from published studies that did not contribute IPD to the RoPE database (for stroke/death/TIA: Harrer,<sup>39</sup> Hausmann,<sup>40</sup> and Cerrato<sup>41</sup>; for stroke alone: Hausmann,<sup>40</sup> Cerrato,<sup>41</sup> and Lee.<sup>42</sup>)



**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.<sup>27,28</sup> 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.<sup>2,29</sup> 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.<sup>30</sup> 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.

## Acknowledgement

We would like to thank the investigators in all the component studies for their contributions without which this secondary analysis would not be possible.



## Funding

This work was supported by the National Institutes of Health [UL1RR025752, R01 NS062153, and R21 NS079826].

**Conflict of interest:** D.E.T. is on National Steering Committees for two trials sponsored by St Jude Medical (RESPECT and ACP Trial) and one trial sponsored by CohereX (WWaveCrest). B.M. is supported by the following research grants to his institution and speaker bureau: AstraZeneca, Bayer BMS, Boehringer Ingelheim, Daiichi Sankyo, Eli Lilly, Pfizer, and St Jude Medical. M.P. received honoraria as a member of the speaker bureau of Sanofi-Aventis, Bayer, and Boehringer Ingelheim. A.J.F. is Principal Investigator of Closure I NMT Medical Boston. S.H. is a DSMB Member for the St Jude Medical RESPECT Trial and a consultant for Boehringer Ingelheim Pharma and Pfizer, BMS Pharmaceutical. No other authors have any relevant disclosures to report.

## References

- Furie KL, Kasner SE, Adams RJ, Albers GW, Bush RL, Fagan SC, Halperin JL, Johnston SC, Katzan J, Kernan WN, Mitchell PH, Ovbiagele B, Palesch YY, Sacco RL, Schwamm LH, Wassertheil-Smoller S, Turan TN, Wentworth D. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2011;**42**:227–276.
- Snow V, Qaseem A, Barry P, Hornbake ER, Rodnick JE, Tobolic T, Ireland B, Segal JB, Bass EB, Weiss KB, Green L, Owens DK. Management of venous thromboembolism: a clinical practice guideline from the American College of Physicians and the American Academy of Family Physicians. *Ann Intern Med* 2007;**146**:204–210.
- Carroll JD, Saver JL, Thaler DE, Smalling RW, Berry S, MacDonald LA, Marks DS, Tirschwell DL. Closure of patent foramen ovale versus medical therapy after cryptogenic stroke. *N Engl J Med* 2013;**368**:1092–1100.
- Meier B, Kalesan B, Mattle HP, Khattab AA, Hildick-Smith D, Dudek D, Andersen G, Ibrahim R, Schuler G, Walton AS, Wahl A, Windecker S, Juni P. Percutaneous closure of patent foramen ovale in cryptogenic embolism. *N Engl J Med* 2013;**368**:1083–1091.
- Furlan AJ, Reisman M, Massaro J, Mauri L, Adams HP, Albers GW, Felberg R, Herrmann H, Kar S, Landzberg M, Raizner A, Wechsler L. Closure or medical therapy for cryptogenic stroke with patent foramen ovale. *N Engl J Med* 2012;**366**:991–999.
- Kitsios GD, Dahabreh IJ, Abu Dabrh AM, Thaler DE, Kent DM. Patent foramen ovale closure and medical treatments for secondary stroke prevention: a systematic review of observational and randomized evidence. *Stroke* 2012;**43**:422–431.
- Thaler DE, Ruthazer R, Weimar C, Serena J, Mattle HP, Nedeltchev K, Mono ML, Di AE, Elkind MS, Di Tullio MR, Homma S, Michel P, Meier B, Furlan AJ, Lutz JS, Kent DM. Determinants of antithrombotic choice for patent foramen ovale in cryptogenic stroke. *Neurology* 2014;**83**:1954–1957.
- Kent DM, Thaler DE. The Risk of Paradoxical Embolism (RoPE) study: developing risk models for application to ongoing randomized trials of percutaneous patent foramen ovale closure for cryptogenic stroke. *Trials* 2011;**12**:185.
- Thaler DE, Di Angelantonio E, Di Tullio MR, Donovan JS, Griffith J, Homma S, Jaigobin C, Mas JL, Mattle HP, Michel P, Mono ML, Nedeltchev K, Papetti F, Ruthazer R, Serena J, Weimar C, Elkind MS, Kent DM. The Risk of Paradoxical Embolism (RoPE) study: initial description of the completed database. *Int J Stroke* 2013;**8**:612–619.
- Adams HP, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, Marsh EE III. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke* 1993;**24**:35–41.
- Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology* 2000;**11**:550–560.
- Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika* 1983;**70**:41–55.
- Robins JM. Data, design, and background knowledge in etiologic inference. *Epidemiology* 2001;**12**:313–320.
- Xu S, Ross C, Raebel MA, Shetterly S, Blanchette C, Smith D. Use of stabilized inverse propensity scores as weights to directly estimate relative risk and its confidence intervals. *Value Health* 2010;**13**:273–277.
- Lin DY, Wei LJ. The robust inference for the proportional hazards model. *J Am Stat Assoc* 1989;**84**:1074–1078.
- Lee BK, Lessler J, Stuart EA. Weight trimming and propensity score weighting. *PLoS One* 2011;**6**:e18174.
- DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;**7**:177–188.
- Thompson SG, Higgins JP. How should meta-regression analyses be undertaken and interpreted? *Stat Med* 2002;**21**:1559–1573.
- Kent DM, Ruthazer R, Weimar C, Mas JL, Serena J, Homma S, Di AE, Di Tullio MR, Lutz JS, Elkind MS, Griffith J, Jaigobin C, Mattle HP, Michel P, Mono ML, Nedeltchev K, Papetti F, Thaler DE. An index to identify stroke-related vs. incidental patent foramen ovale in cryptogenic stroke. *Neurology* 2013;**81**:619–625.
- Green KM, Stuart EA. Examining moderation analyses in propensity score methods: application to depression and substance use. *J Consult Clin Psychol* 2014;**82**:773–783.
- Yuan Y. Multiple imputation using SAS software. *J Stat Softw* 2011;**45**:1–25.
- van Houwelingen HC, Arends LR, Stijnen T. Advanced methods in meta-analysis: multivariate approach and meta-regression. *Stat Med* 2002;**21**:589–624.
- Normand SL. Meta-analysis: formulating, evaluating, combining, and reporting. *Stat Med* 1999;**18**:321–359.
- Kurth T, Walker AM, Glynn RJ, Chan KA, Gaziano JM, Berger K, Robins JM. Results of multivariable logistic regression, propensity matching, propensity adjustment, and propensity-based weighting under conditions of nonuniform effect. *Am J Epidemiol* 2006;**163**:262–270.
- Homma S, Sacco RL, Di Tullio MR, Sciacca RR, Mohr JP. Effect of medical treatment in stroke patients with patent foramen ovale: patent foramen ovale in Cryptogenic Stroke Study. *Circulation* 2002;**105**:2625–2631.
- Mohr JP, Thompson JL, Lazar RM, Levin B, Sacco RL, Furie KL, Kistler JP, Albers GW, Pettigrew LC, Adams HP, Jackson CM, Pullicino P. A comparison of warfarin and aspirin for the prevention of recurrent ischemic stroke. *N Engl J Med* 2001;**345**:1444–1451.
- Dahabreh IJ, Kent DM. Can the learning health care system be educated with observational data? *JAMA* 2014;**312**:129–130.
- Dahabreh IJ, Sheldrick RC, Paulus JK, Chung M, Varvarigou V, Jafri H, Rassen JA, Trikalinos TA, Kitsios GD. Do observational studies using propensity score methods agree with randomized trials? A systematic comparison of studies on acute coronary syndromes. *Eur Heart J* 2012;**33**:1893–1901.
- The Atrial Fibrillation Investigators. The efficacy of aspirin in patients with atrial fibrillation. Analysis of pooled data from 3 randomized trials. *Arch Intern Med* 1997;**157**:1237–1240.
- Hart RG, Diener HC, Coutris SB, Easton JD, Granger CB, O'Donnell MJ, Sacco RL, Connolly SJ. Embolic strokes of undetermined source: the case for a new clinical construct. *Lancet Neurol* 2014;**13**:429–438.
- Weimar C, Holle DN, Benemann J, Schmid E, Schminke U, Haberb RL, Diener HC, Goertler M. Current management and risk of recurrent stroke in cerebrovascular patients with right-to-left cardiac shunt. *Cerebrovasc Dis* 2009;**28**:349–356.
- Serena J, Marti-Fabregas J, Santamarina E, Rodriguez JJ, Perez-Ayuso MJ, Masjuan J, Segura T, Gallego J, Davalos A. Recurrent stroke and massive right-to-left shunt: results from the prospective Spanish multicenter (CODICIA) study. *Stroke* 2008;**39**:3131–3136.
- Nedeltchev K, Arnold M, Wahl A, Sturzenegger M, Vella EE, Windecker S, Meier B, Mattle HP. Outcome of patients with cryptogenic stroke and patent foramen ovale. *J Neurol Neurosurg Psychiatr* 2002;**72**:347–350.
- Paciaroni M, Agnelli G, Bertolini A, Pezzini A, Padovani A, Caso V, Venti M, Alberti A, Palmiero RA, Cerrato P, Silvestrelli G, Lanari A, Previdi P, Corea F, Balducci A, Ferri R, Falcinelli F, Filippucci E, Chiocchi P, Grandi FC, Ferigo L, Musolino R, Bersano A, Ghione I, Sacco S, Carolei A, Baldi A, Ageno W. Risk of recurrent cerebrovascular events in patients with cryptogenic stroke or transient ischemic attack and patent foramen ovale: the FORI (Foramen Ovale Registro Italiano) study. *Cerebrovasc Dis* 2011;**31**:109–116.
- De Castro S, Papetti F, Di AE, Razmovska B, Truscetti G, Tuderti U, Puca E, Correnti A, Fiorelli M, Prencipe M, Toni D. Feasibility and clinical utility of transeophageal echocardiography in the acute phase of cerebral ischemia. *Am J Cardiol* 2010;**106**:1339–1344.
- Schuchlenz HW, Weihs W, Berghold A, Lechner A, Schmidt R. Secondary prevention after cryptogenic cerebrovascular events in patients with patent foramen ovale. *Int J Cardiol* 2005;**101**:77–82.
- Kitsios GD, Lasker A, Singh J, Thaler DE. Recurrent stroke on imaging and presumed paradoxical embolism: a cross-sectional analysis. *Neurology* 2012;**78**:993–997.
- Casaubon L, McLaughlin P, Webb G, Yeo E, Merker D, Jaigobin C. Recurrent stroke/TIA in cryptogenic stroke patients with patent foramen ovale. *Can J Neurol Sci* 2007;**34**:74–80.
- Harrer JU, Wessels T, Franke A, Lucas S, Berlit P, Klotsch C. Stroke recurrence and its prevention in patients with patent foramen ovale. *Can J Neurol Sci* 2006;**33**:39–47.
- Hausmann D, Mugge A, Daniel WG. Identification of patent foramen ovale permitting paradoxical embolism. *J Am Coll Cardiol* 1995;**26**:1030–1038.
- Cerrato P, Priano L, Imperiale D, Bosco G, Destefanis E, Villar AM, Ribezzo M, Trevi GP, Bergamasco B, Orzan F. Recurrent cerebrovascular ischaemic events in patients with interatrial septal abnormalities: a follow-up study. *Neurol Sci* 2006;**26**:411–418.
- Lee JY, Song JK, Song JM, Kang DH, Yun SC, Kang DW, Kwon SU, Kim JS. Association between anatomic features of atrial septal abnormalities obtained by omniplane transeophageal echocardiography and stroke recurrence in cryptogenic stroke patients with patent foramen ovale. *Am J Cardiol* 2010;**106**:129–134.