EuroIntervention 2018;14:857-867 published online June 2018

Long-term effectiveness and safety of transcatheter closure of patent foramen ovale compared with antithrombotic therapy alone: a meta-analysis of six randomised clinical trials and 3,560 patients with reconstructed time-to-event data

Daniele Giacoppo[1,2,3]*, MD; Nicola Caronna[3], MD; Antonio H. Frangieh[1,2], MD, MPH; Jonathan Michel[1,2], MBBS; Giuseppe Andò[4], MD, PhD; Giuseppe Tarantini[5], MD, PhD; Albert M. Kasel[1,2], MD; Davide Capodanno[6,7], MD, PhD; Robert A. Byrne[1,8], MB, BCh, PhD

1. Deutsches Herzzentrum München, Technische Universität München, Munich, Germany; 2. Munich Structural Heart Institute, Munich, Germany; 3. Azienda Ospedaliero-Universitaria "Policlinico Giaccone", University of Palermo, Palermo, Italy; 4. Azienda Ospedaliero-Universitaria "Policlinico Martino", University of Messina, Messina, Italy; 5. Department of Cardiac, Thoracic and Vascular Sciences, University of Padua, Padua, Italy; 6. Cardio-Thoracic-Vascular Department, Azienda Ospedaliera Universitaria "Policlinico-Vittorio Emanuele", Catania, Italy; 7. Department of General Surgery and Medical-Surgical Specialties, University of Catania, Catania, Italy; 8. DZHK (German Center for Cardiovascular Research), Partner Site Munich Heart Alliance, Munich, Germany

GUEST EDITOR: Alec Vahanian, MD, PhD; *Department of Cardiology, Hôpital Bichat-Claude Bernard, and University Paris VII, Paris, France*

This paper also includes supplementary data published online at: http://www.pcronline.com/eurointervention/141st_issue/154

KEYWORDS

- PFO closure
- prior stroke
- prior transient ischaemic attack
- stroke

Abstract

Aims: Although three recent trials have shown a significant stroke risk reduction after tPFOc, the individual statistical power is limited and the impact on pooled evidence needs to be explored. We aimed to pool data from available randomised clinical trials (RCT) to assess whether tPFOc is more effective and safe than antithrombotic therapy alone (ATA).

Methods and results: Major electronic databases and tangential sources were searched. Six trials (3,560 patients) were identified. At a median follow-up of 3.6 (2.0-5.2) years (13,930 person-years), the risk of stroke was significantly lower after tPFOc compared with ATA (HR 0.28, 95% CI: 0.12-0.64, p=0.003). Significant heterogeneity was detected (I^2=66.1%), although single trials did not significantly influence the results. Reconstructed time-to-event data revealed that tPFOc benefits accrue after approximately one year and persist over time without significant variations (96.4% versus 88.0%; HR 0.25, 95% CI: 0.09-0.66, p=0.005; NNT=11). Although results showed a greater benefit in patients <45 years old, male, and with substantial shunt, interaction between subgroups was not significant. Trial sequential analysis showed that accumulated evidence appeared to be sufficient. However, tPFOc did not confer protection against transient ischaemic attack (TIA; HR 0.69, 95% CI: 0.31-1.54, p=0.365) and a significant excess in the risk of atrial fibrillation was observed (OR 4.99, 95% CI: 1.99-10.10, p<0.001), though generally early and transient. Major bleeding and migraine were comparable between treatments.

Conclusions: Compared with ATA, tPFOc significantly reduces the risk of stroke at long-term follow-up but no benefit is observed in terms of TIA. Atrial fibrillation is higher after tPFOc, though generally early and transient. The risks of major bleeding and migraine are comparable between the groups.

*Corresponding author: Deutsches Herzzentrum München, Lazarettstrasse 36, 80636 Munich, Germany.
E-mail: giacoppomd@gmail.com

SUBMITTED ON 29/03/2018 - REVISION RECEIVED ON 05/05/2018 - ACCEPTED ON 06/06/2018

DOI: 10.4244/EIJ-D-18-00341

Abbreviations

ATA	antithrombotic therapy alone
CI	confidence interval
HR	hazard ratio
NNT	number needed to treat
OR	odds ratio
PFO	patent foramen ovale
RCT	randomised clinical trials
tPFOc	transcatheter patent foramen ovale closure
TIA	transient ischaemic attack

Introduction

Patent foramen ovale (PFO) is associated with an increased risk of stroke as a result of paradoxical cerebral embolism[1,2]. Transcatheter PFO closure (tPFOc) is an attractive preventive approach but its effectiveness compared with antithrombotic therapy alone (ATA) has remained a matter of debate for a long time[3,4]. Indeed, early randomised clinical trials (RCT) did not prove a significant reduction in stroke compared with ATA[4-7], although later a pooled analysis and observational data fostered a possible benefit of tPFOc[4,8,9]. Currently, the European Stroke Organisation indicates tPFOc only in patients with cryptogenic stroke and PFO with high-risk features, while the American Heart Association/American Stroke Association guidelines consider tPFOc a viable alternative to ATA only in patients with PFO and recurrent deep vein thrombosis[10,11].

Recently, the results of the CLOSE, Gore REDUCE, and DEFENSE-PFO trials[12-14] showed significant risk reductions in stroke after tPFOc. Because all of the existing trials have low statistical power to detect difference in stroke rates and questions on secondary efficacy and safety endpoints remain unanswered, an updated systematic review represents a relevant undertaking. The several meta-analyses on the topic published over time present (with mixed proportions) the following limitations: absence of one or more of the available RCT, biased selection of reports, evidence based mostly on observational studies, inappropriate definition of the risk by estimates not accounting for time, missing or incomplete assessment of the risk variation over time, insufficient exploration of the heterogeneity across trials and clinical subgroups, omitted quantification of statistical power of the accumulated evidence, and incomplete definition of the net benefit of tPFOc[5,15-19].

Against this background, we aimed to provide an updated meta-analysis on tPFOc versus ATA to quantify the impact of the three newer trials, and to provide a proper description of risk variation in relation to time, and a critical assessment of the net benefit of tPFOc.

Methods

We conducted a frequentist pairwise meta-analysis in keeping with the recommendations of PRISMA **(Supplementary Table 1)** and the Cochrane Collaboration[20,21]. This meta-analysis was registered with PROSPERO (www.crd.york.ac.uk/prospero/; CRD42017081518).

ELIGIBILITY CRITERIA AND LITERATURE SEARCH

Three authors (N. Caronna, A.H. Frangieh, J. Michel) independently searched PubMed, Scopus, Web of Knowledge, ScienceDirect and Ovid electronic databases from the inception to 1 December 2017. No language restrictions or specific clinical subsets were imposed. A complementary search was performed by accessing major scientific websites with interest in the topic (www.clinicaltrials.gov, www.clinicaltrialresults.org, www.tctmd.com, www.pcronline.com, www.acc.org, www.heart.org) and screening of bibliographies of relevant reviews and book chapters. Duplicates due to the multiple-database search were removed. The retrieved data set was used for preliminary assessment of the feasibility of the meta-analysis and for qualitative definition of each of the included trials **(Supplementary Appendix 1)**.

According to PRISMA recommendations[20], after data extraction, performance of the statistical analysis, and manuscript drafting, a last search was made on 15 March 2018. The identification of an additional trial that met eligibility criteria required an update of the meta-analysis.

ENDPOINTS

The primary endpoint was stroke at the longest available follow-up. The secondary endpoints included transient ischaemic attack (TIA), atrial fibrillation, major bleeding and migraine at the longest available follow-up.

DATA EXTRACTION

Authors involved in the search (N. Caronna, A.H. Frangieh, J. Michel, D. Giacoppo) extracted trial-level qualitative and quantitative data. Trial-level risk estimates, incidences of events, and numbers of patients were exported for statistical analysis. Intention-to-treat analyses were considered. All the authors had full access to the data.

STATISTICAL ANALYSIS

Categorical variables are presented as proportions (counts) and were tested using the χ^2 test. Continuous variables are presented as means (standard deviations) and were compared using the t-test or ANOVA. Within-trial and between-trial means and standard deviations were weighted.

According to original long-term time-to-event analyses, trial-level hazard ratios (HRs) and 95% confidence intervals (CIs) were used for stroke and TIA. Pooled risk estimates were computed by fixed-effect and random-effects models with inverse variance weighting[21,22]. Risk distribution across trials was illustrated by forest plots with weighting according to a random-effects model[21,22]. The number needed to treat (NNT) was estimated as previously described for survival analysis[22,23].

We assessed heterogeneity by using Cochran's Q test with significance set at 0.10, between-study variance τ^2, and the I^2 statistic[21,22,24]. I^2 values <25% expressed low heterogeneity, 25-50% moderate heterogeneity, and >50% high heterogeneity[24].

We reconstructed time-to-event data for the primary endpoint of stroke by extreme-magnification digitisation of the original

high-quality Kaplan-Meier curves and then by modelling of retrieved spatial information along with numbers of events and numbers at risk for each time interval[25,26]. Additional information is provided in **Supplementary Appendix 2**. Retrieved data were used to carry out Kaplan-Meier analyses. According to a "one-stage" meta-analysis, a mixed-effect Cox proportional hazard regression model taking into account the original clustering of patients across trials was used to provide risk estimates alternative to those obtained by standard aggregate-data meta-analysis[27]. A "two-stage" meta-analysis with trial-level estimates according to Cox regression was also performed. Differences between treatments were compared by log-rank test.

A restricted maximum likelihood random-effects multiple-outcome meta-analysis was performed to provide a joint estimate of the risk of ischaemic stroke and TIA[28]. We decided to apply such a type of inference because it can provide estimates taking into account the correlation between outcomes and overcome missing values ("borrowing of strength")[28].

Risks of atrial fibrillation, major bleeding and migraine between groups were expressed by odds ratios (ORs) and 95% CIs, since these outcomes were not uniformly reported according to time-to-event analyses across trials and most of them occurred early.

Analyses were performed using R 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria) and Stata 13 (StataCorp, College Station, TX, USA).

SENSITIVITY AND SUBGROUP ANALYSES

The influence of individual trials on pooled estimates and heterogeneity was explored by removing each one at a time ("leave-one-out")[29].

Time-to-event landmark analyses were performed to compare the distributions of the events between groups from enrolment to two-year follow-up and from two years after enrolment to maximum available follow-up. In addition, after excluding trials having shorter follow-up, we assessed the risk of stroke between groups at five years to remove possible influences of trials designed to assess outcomes at earlier time points and mitigate the impact of very late follow-up variations across trials.

A cumulative meta-analysis was conducted to inspect the variations after addition of each trial in a chronological order and an O'Brien-Fleming monitoring boundary by using the Lan-DeMets alpha spending function approach ("trial sequential analysis") was computed to exclude spurious effects[30]. In addition, pooled effects of earlier and newer trials were compared to quantify the contrast between early and recent results.

Consistency of main results was assessed across the subgroups of age <45 versus ≥45 years, male versus female, and substantial versus non-substantial shunt according to large or mild-to-moderate transit of microbubbles, respectively. Interaction between effects was assessed with significance set at 0.05.

Finally, the risk of TIA was also assessed by using OR according to the reported number of events.

BIAS ASSESSMENT

Trial-level qualitative assessment was performed by using the Cochrane Collaboration tool[21], and the robustness of the meta-analysis conclusions was defined according to GRADE[31]. Further specifications on the two tools are reported in **Supplementary Appendix 2**.

Results

The search process is illustrated in **Supplementary Figure 1** and details of the strategy applied are shown in **Supplementary Table 2**. Six RCT[5-7,12,13,32] including 3,560 patients (1,889 tPFOc versus 1,671 ATA) were included in the meta-analysis. The main characteristics are reported in **Table 1**, while eligibility criteria are listed in **Supplementary Table 3**. Baseline characteristics were balanced between groups **(Supplementary Table 4)**, though there were differences across trials **(Supplementary Table 5)**. Overall, the included patients were middle-aged adults (45.3±9.9 years), with similar distribution between genders and low cardiovascular risk profile. Almost all patients had a recent cryptogenic stroke as qualifying event and frequently had large shunting. Devices and ATA regimens across trials are reported in **Table 1** and **Supplementary Table 6**.

STROKE

At a median follow-up time of 3.6 [2.0-5.2] years, 116 events occurred, 37 after tPFOc and 79 after ATA. Regardless of the model applied, the risk of stroke was significantly lower after tPFOc compared with ATA (HR 0.28, 95% CI: 0.12-0.64, p=0.003) **(Figure 1)**. The relative weight of trials was balanced

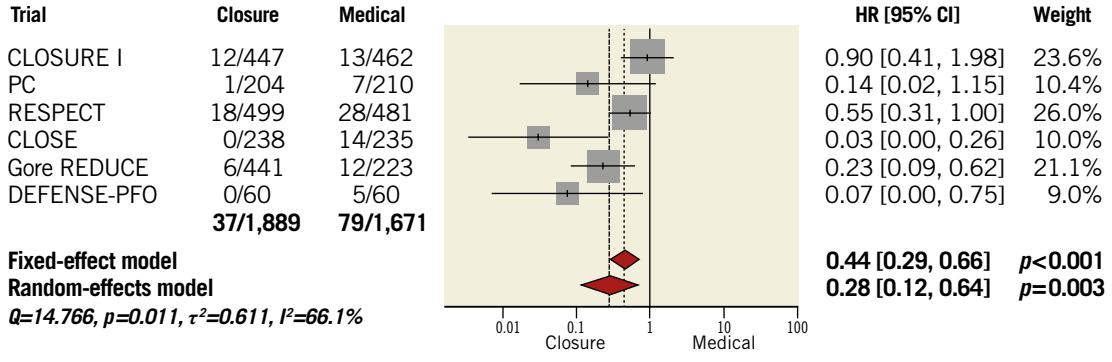


Figure 1. *Comparison between tPFOc and ATA at the longest available follow-up.*

Table 1. Main characteristics of included RCT.

	CLOSURE I	PC	RESPECT	CLOSE	Gore REDUCE	DEFENSE-PFO
Masking	Open-label	Open-label	Open-label	Open-label	Open-label	Open-label
Design	Superiority[a,b]	Superiority[b]	Superiority[b]	Superiority[a]	Superiority[a,b]	Superiority[a,b]
Randomisation	1:1	1:1	1:1	1:1:1[c]	2:1	1:1
Centres	87	29	69	34	63	2
Region	USA and Canada	Switzerland, Germany, Austria, Belgium, Poland, Slovakia, United Kingdom, Australia, Canada, Brazil	USA and Canada	France and Germany	USA, Canada, Denmark, Finland, Sweden, United Kingdom	South Korea
Duration	June 2003-Oct 2008	Feb 2000-Feb 2009	Aug 2003-Dec 2011	Dec 2008-Dec 2016	Dec 2008-Feb 2015	June 2011-Oct 2017
Adjudication	Blinded	Blinded	Blinded	Blinded	Blinded	Not specified
Registration	NCT00201461	NCT00166257	NCT00465270	NCT00562289	NCT00738894	NCT01550588
Protocol	Published	Published	Published	Published	Published	Not available
Sponsor	NMT Medical	St. Jude Medical	St. Jude Medical	French Ministry of Health	W.L. Gore and Associates	Research Foundation
Qualifying event	TIA or ischaemic stroke <180 days	TIA with brain infarct at imaging or ischaemic stroke or extra-cranial embolism	Ischaemic stroke <270 days	Ischaemic stroke <180 days	TIA with new brain infarct at imaging and ischaemic stroke <180 days	Ischaemic stroke <180 days
Patients total (device/medical)	909 (447/462)	414 (204/210)	980 (499/481)	473 (238/235)	664 (441/223)	120 (60/60)
Device type	STARFlex septal occluder (100%)	AMPLATZER PFO Occluder (100%)	AMPLATZER PFO Occluder (100%)	– AMPLATZER PFO Occluder (51.5%) – Intrasept PFO occluder (13.2%) – Premere (9.4%) – STARFlex septal occluder (8.9%) – AMPLATZER Cribriform Occluder (6.4%) – Figulla Flex II PFO occluder (6.4%) – Other device (4.3%)	– HELEX septal occluder (38.7%) – Cardioform septal occluder (61.3%)	AMPLATZER PFO Occluder (100%)
Primary endpoint	Stroke or TIA, any-cause death within 30 days, or neurological death between 30 days and 2 years	Stroke, TIA, peripheral embolism, or death	Stroke, TIA, early any-cause death or neurological death	Stroke	Stroke or new lesion >3 mm[d]	Stroke, vascular death, TIMI major bleeding
Follow-up[e]	2.0 [1.5-2.0]	4.9 [3.5-5.0]	5.9 [4.2-8.0]	5.6 [3.8-7.1]	3.2 [2.2-4.8]	2.8 [0.9-4.1][f]
Person-years total (device/medical)	1,593 (798/795)	1,655 (841/814)	5,688 (3,080/2,608)	2,572 (1,338/1,234)	2,232 (1,529/703)	190 (97/93)[f]

[a] Original estimated sample size was not reached. [b] Lower than expected incidences. [c] Random assignment of treatments was based on patients' eligibility to PFO closure, antiplatelet therapy, and oral anticoagulation: no contraindications (Group 1); contraindication to anticoagulation (Group 2); contraindication to PFO closure (Group 3), but data were presented as 2×2-cohort study. [d] Brain imaging (97.7% MRI, 2.1% CT). [e] Unit is year and values are expressed as median [interquartile range]. [f] The median follow-up is reported as described in the paper. However, analyses were performed at 2-year follow-up and no information is disclosed after this time point, thus person-year estimates refer to time-to-event analysis. CT: computed tomography; MRI: magnetic resonance imaging

overall. However, a high degree of heterogeneity was observed (I^2=66.1%), reflecting the different magnitude of trial-level effects and 95% CIs rather than direction. Indeed, all point estimates were to the left of the null: the CLOSURE I trial[5] showed no difference between strategies, the PC and RESPECT trials[6,7,32] showed a numerical benefit of the interventional treatment, while the CLOSE and Gore REDUCE trials[12,13] showed a significant risk reduction after tPFOc. Regardless of the model applied, no single trial could significantly influence pooled estimates **(Figure 2)** and between-trial heterogeneity remained high in any case.

Kaplan-Meier curves showed that difference between treatments emerged after approximately one year **(Figure 3)**. The survival free from stroke at the maximum available follow-up (13,930 person-years) was 96.4% after tPFOc (7,683 person-years) and 88.0% after ATA (6,247 person-years). The annualised incidence of stroke was 0.48/100 person-years after tPFOc and 1.26/100 person-years after ATA. The meta-analysis of reconstructed time-to-event data provided results consistent with aggregate-data meta-analysis (HR 0.25, 95% CI: 0.09-0.66, p=0.005). It was estimated that approximately 11 patients needed to undergo PFO closure to prevent one stroke as compared with ATA (NNT 11.3, 95% CI: 9.2-25.6). The landmark analysis showed uniform distributions over time, and risk estimates by "one-stage" meta-analyses were consistent with "two-stage" meta-analyses **(Figure 4)**.

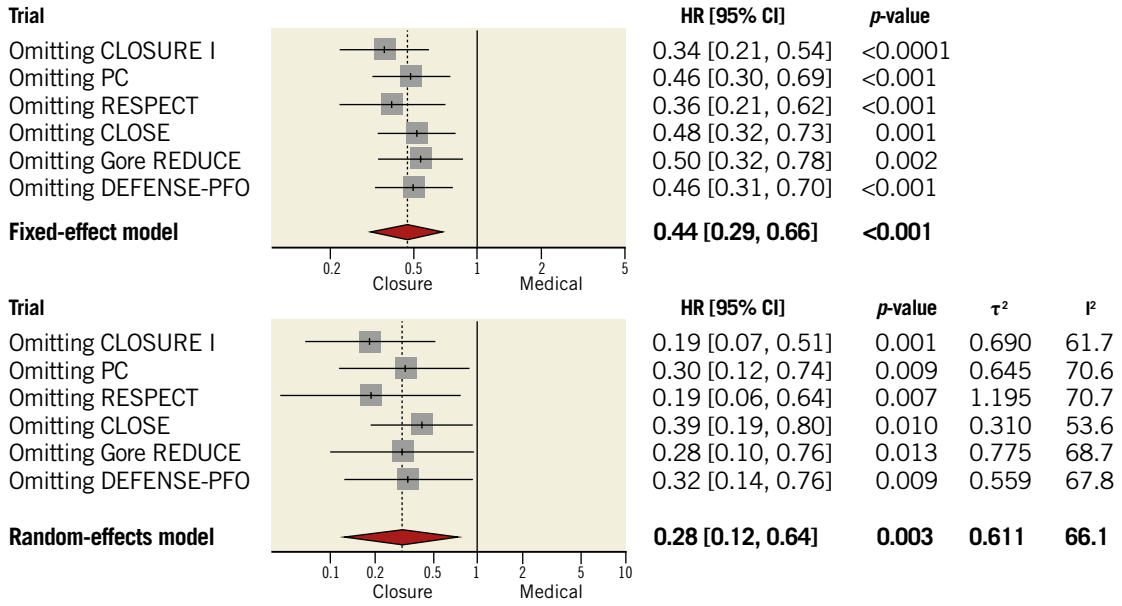


Figure 2. *Influence analysis.*

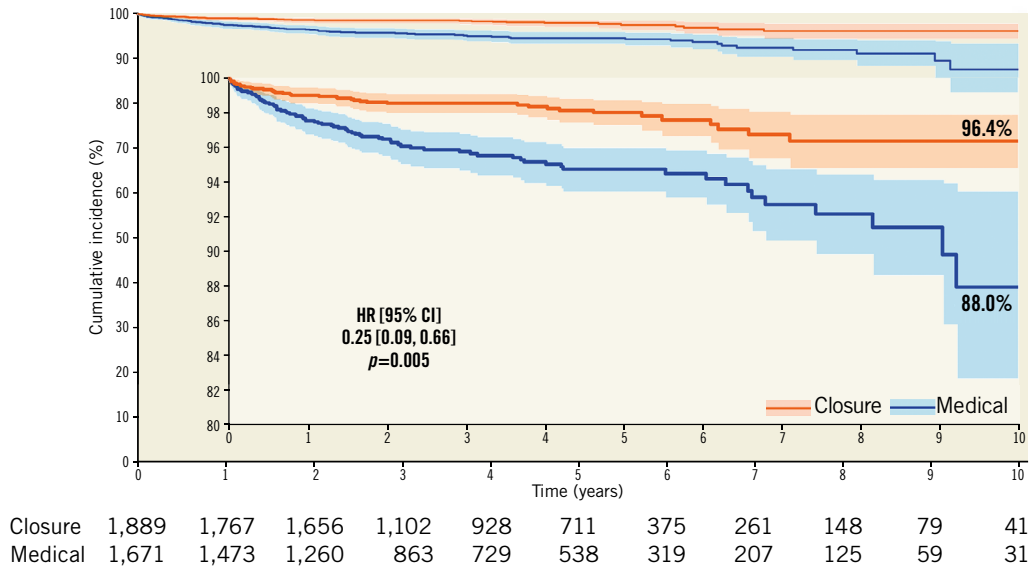


Figure 3. *Survival free from stroke.*

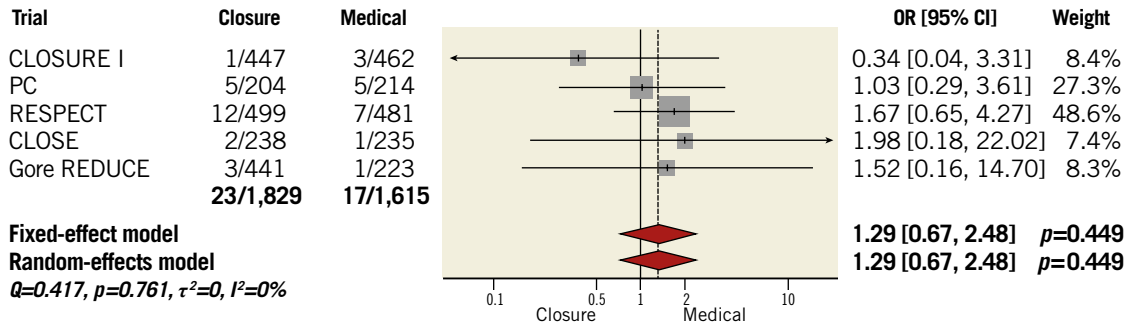


Figure 4. *Landmark analysis. The risk estimates within Kaplan-Meier graphs are derived from mixed-effects Cox proportional hazards regression accounting for the original clustering of patients ("one-stage"). The forest plots illustrate sensitivity analyses according to standard Cox proportional hazards regression and subsequent combination of trial-level outcomes by fixed-effect or random-effects models ("two-stage").*

The definition of stroke showed acceptable consistency across trials **(Supplementary Table 7)**. Events, events/100 person-years, and Kaplan-Meier estimates across trials and time points are reported in **Supplementary Table 8**.

With the aim of excluding investigations implying outdated and potentially ineffective devices and including only trials achieving very long-term data, we excluded the CLOSURE I and DEFENSE-PFO trials[5,14]. At five-year follow-up, no significant changes in the main conclusion were noted regardless of the method applied ("one-stage", mixed-effects Cox regression: HR 0.22, 95% CI: 0.09-0.54, p=0.001; "two-stage" random-effects: HR 0.23, 95% CI: 0.09-0.58, p=0.002) **(Figure 5)**. Results by including all trials were consistent **(Supplementary Table 8)**.

Trial sequential analysis was performed to exclude spurious results due to type I error and to assess the statistical power of pooled data **(Figure 6)**. While a conventional significance threshold (z=1.96; solid green line) was not reached by pooling the three earlier trials[5-7], at cumulative analysis the addition of the CLOSE trial[12] produced a significant variation (p=0.043) that would be spurious when accounting for type I error. After the addition of the Gore REDUCE trial[13], the cumulative z curve (z=2.599) crossed the alpha spending function monitoring boundary (z=2.075; dashed red line). The relative weight of the Gore REDUCE trial[13] on cumulative effect was greater than that of the CLOSE trial[12] **(Supplementary Figure 2)** and, after switching the order of addition of the two trials, the cumulative z curve (z=2.284) crossed the monitoring boundary earlier (z=2.243).

At subgroup analysis **(Figure 7)**, the stroke risk reduction after tPFOc seemed to be larger in patients <45 years old, males, with substantial shunt. However, no interaction between subgroups was observed.

TIA

The risk of TIA was not significantly reduced after tPFOc compared with ATA (HR 0.69, 95% CI: 0.31-1.54, p=0.365) **(Figure 8)**. The univariate sensitivity analysis using the number of events (ORs) was consistent **(Supplementary Figure 3)**. No heterogeneity across trial-level estimates was observed (I^2=0%; p=0.984).

ATRIAL FIBRILLATION AND MAJOR BLEEDING

Compared with ATA, tPFOc was associated with a more than fourfold increase in the risk of atrial fibrillation **(Figure 9A)**. Heterogeneity was moderate (I^2=44.8%; p=0.124). The risk of major bleeding was overall low and comparable between treatments **(Figure 9B)**. Heterogeneity was not significant (I^2=34.5%; p=0.191). Rates of other major cardiovascular adverse events are summarised in **Supplementary Table 9**.

MIGRAINE

Compared with ATA, tPFOc did not seem to produce any benefit in terms of migraine **(Supplementary Figure 4)**.

BIAS ASSESSMENT AND STUDY RELIABILITY

Overall, the quality of the included trials was moderate-to-high, but some possible sources of bias need to be taken into account,

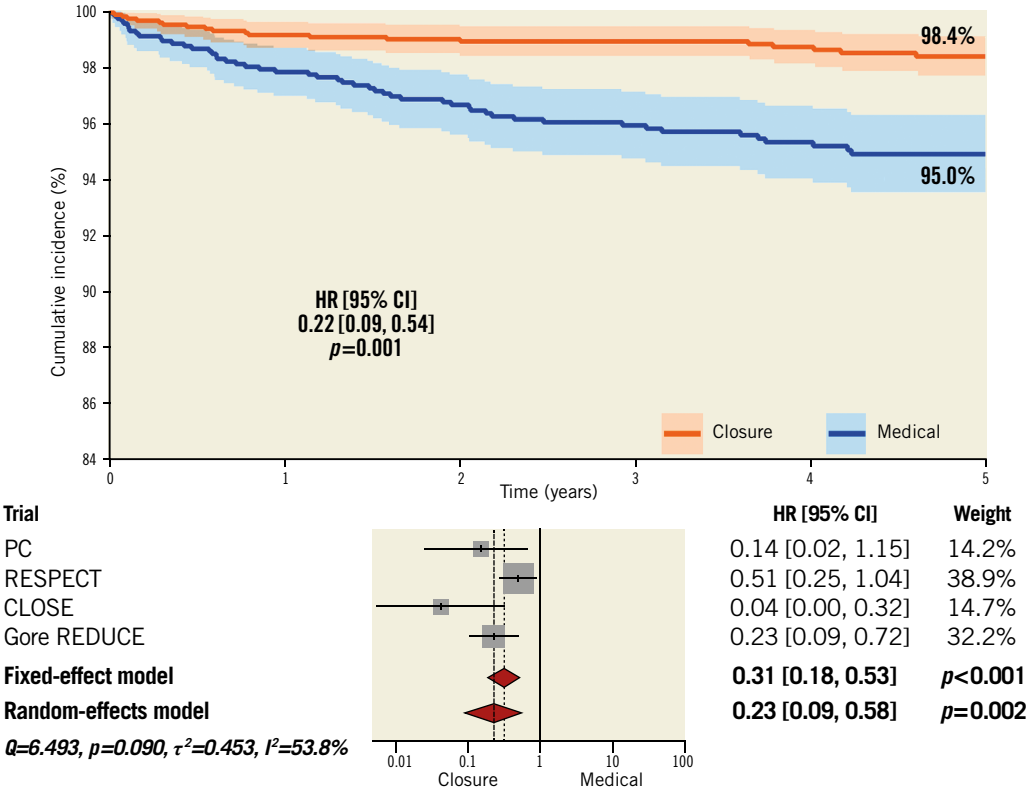
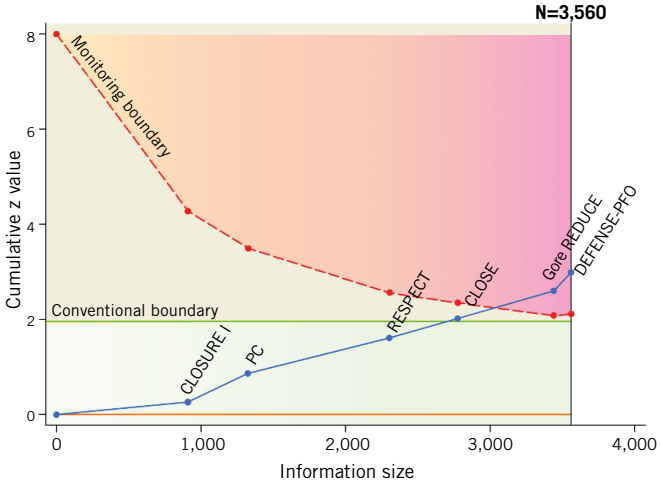


Figure 5. *Five-year analysis after exclusion of trials with outdated devices and limited follow-up.*



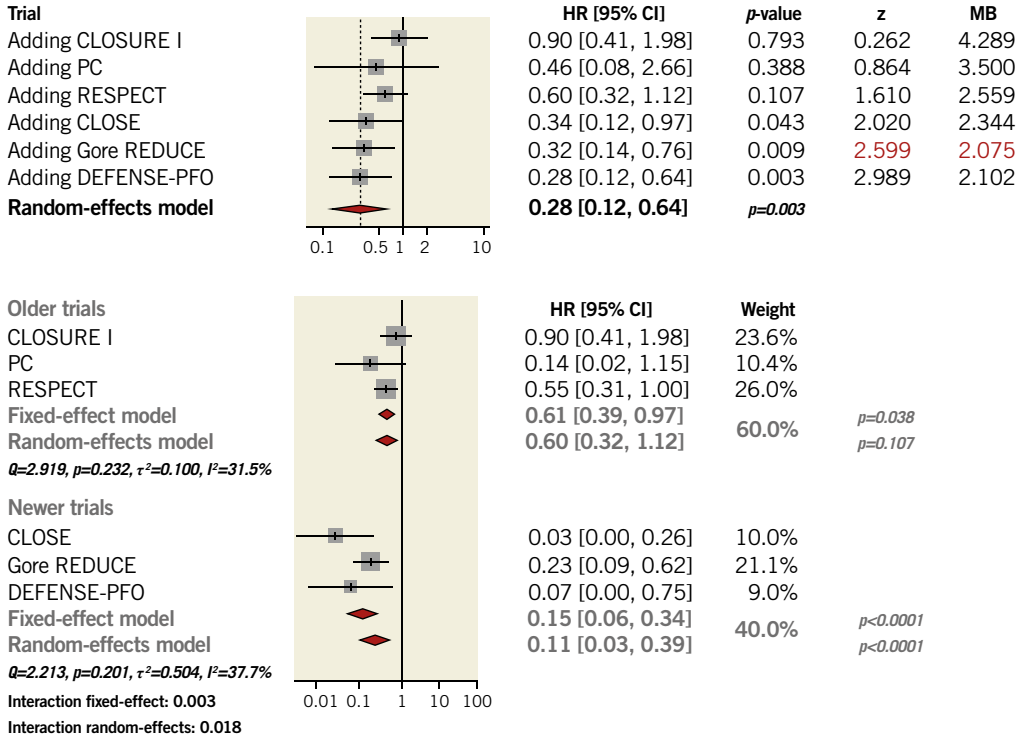


Figure 6. *Trial sequential analysis, cumulative meta-analysis and comparison between earlier and newer trials. Red numbers indicate when the cumulative risk reaches statistical significance. MB: monitoring boundary*

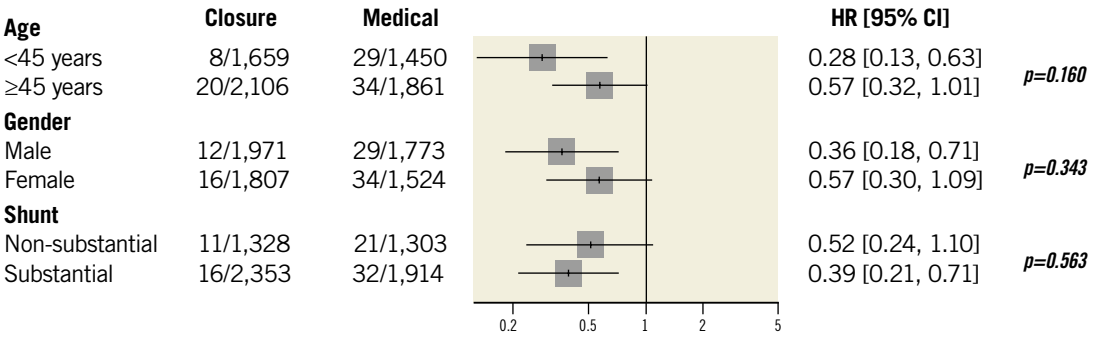


Figure 7. *Subgroup analyses.*

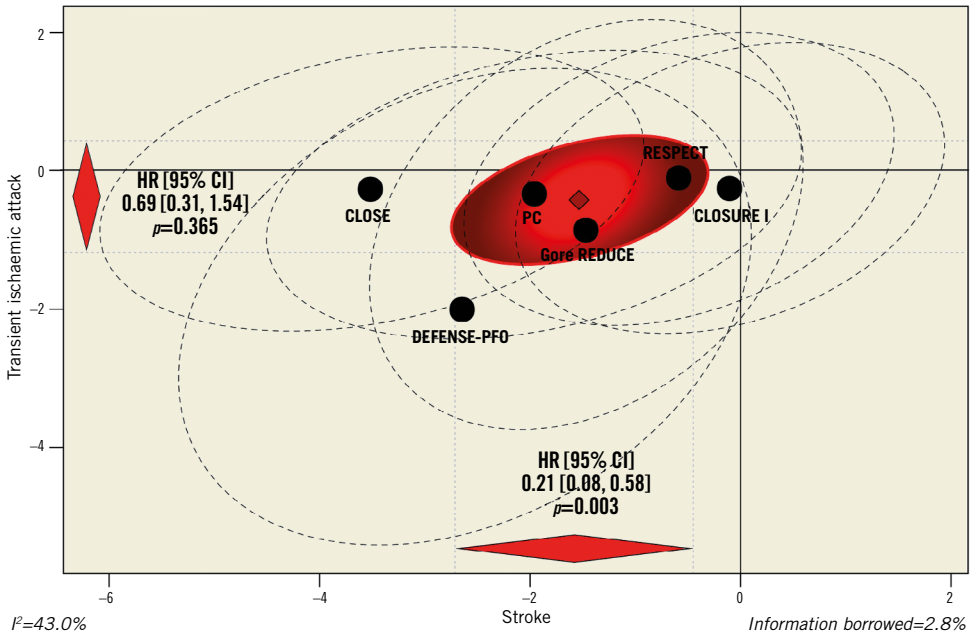


Figure 8. *Multiple-outcome meta-analysis of stroke and TIA.*

as illustrated in **Supplementary Figure 5**. According to GRADE[31], the reliability of our conclusions is acceptable **(Supplementary Table 10)**.

Discussion

The findings of this meta-analysis can be summarised as follows: 1) compared with ATA, tPFOc reduces the risk of stroke at very long-term follow-up; 2) the results are robust, do not depend on individual trials and do not change across analyses accounting for multiple testing and clinical subgroups; 3) although substantial heterogeneity was observed, this depended on differences in magnitude rather than direction of treatment effects; 4) although pathophysiologically correlated with stroke, tPFOc does not

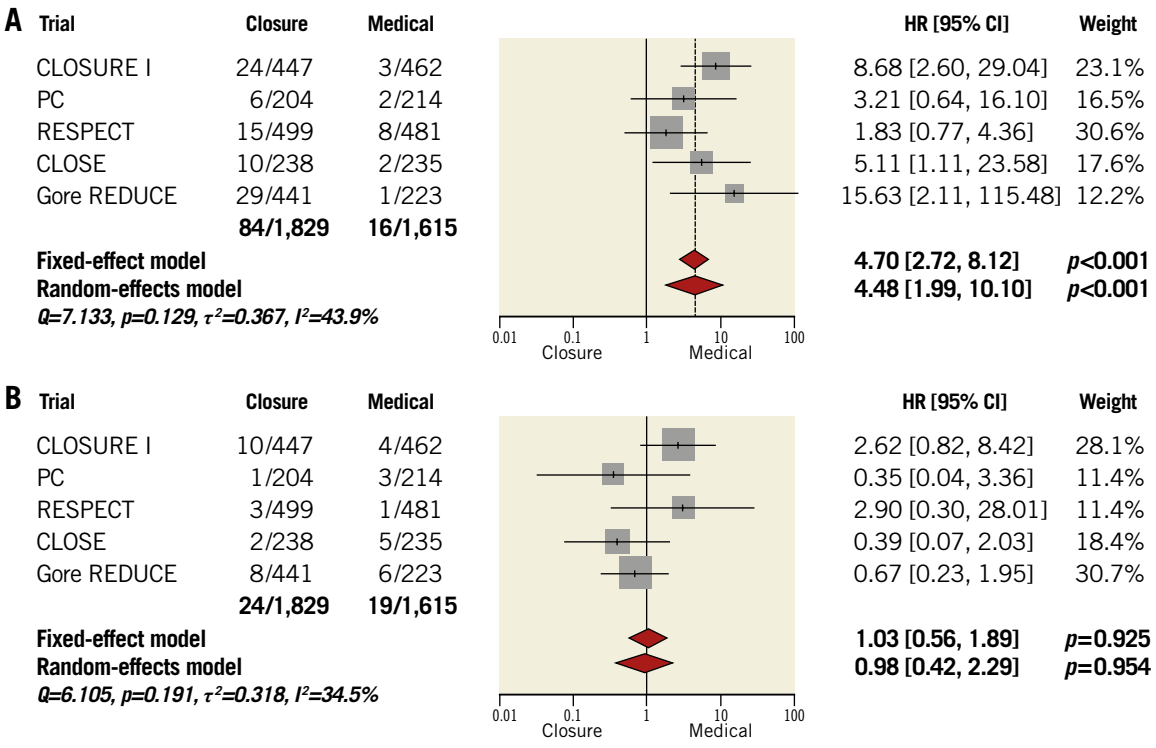


Figure 9. *Atrial fibrillation and major bleeding. A) Atrial fibrillation. B) Major bleeding.*

protect from TIA; 5) tPFOc imposes a higher post-procedural risk of atrial fibrillation, while no difference in major bleeding was observed; 6) no benefit of tPFOc against migraine is observed.

A major finding of our study was that the relative risk reduction of stroke was detectable after approximately one year after enrolment and continued to accrue with increasing duration of surveillance. Considering that each trial has no power for stroke (i.e., design for composite endpoints, anticipated termination, lower than expected incidence of events), extended follow-up enables capturing a larger number of events. The non-significant results observed in the primary analyses of the PC and RESPECT trials[6,7,32] should be interpreted against this background; over a short-to-medium time horizon, the incidence of stroke was insufficient to prove the benefit of tPFOc, as suggested by secondary analyses with extended follow-up[4,32].

However, this finding can only partially explain the different results observed between earlier and newer trials. Indeed, several factors might have contributed to the strong conclusions of the recent CLOSE, Gore REDUCE, and DEFENSE-PFO trials[12-14], despite sample size or follow-up time comparable with previous trials. First, the selection of patients in newer trials may have played a key role. In the CLOSURE I and PC trials[5,6], a recent TIA or peripheral embolism could justify enrolment, while in the other trials[7,12-14,32] almost exclusively patients who experienced cryptogenic stroke were considered for inclusion. Moreover, in earlier trials[5-7], a relevant proportion of patients - about 50% in the CLOSURE I trial[5] - had a small shunt, while in recent trials[12-14] patients with a substantial shunt were mostly enrolled. Second, in the CLOSE and in other recent trials[12-14], the longer experience gained may have led to more effective procedures by proper anatomic assessment and device size selection. Third, differences in devices and medical therapy may have influenced the results of trials. The CLOSURE I trial[5] employed the use of a double umbrella-like occluder comprised of a nickel-cobalt framework with attached polyester fabric that might not have worked as well as other devices[5,33,34]. Consistent with observational data, the three trials[7,14,32] based on a double-disc occluder device comprising a self-expanding nitinol mesh with a sewn polyester patch showed not only improved results but also fewer complications. Similarly, the Gore REDUCE trial[13], which tested double-disc occluders comprising a platinum-filled nitinol wire frame covered with expanded polytetrafluoroethylene, showed a strong reduction in the risk of stroke after tPFOc. However, in the CLOSE trial[12] – the investigation showing the most pronounced stroke risk reduction and the absence of stroke in the tPFOc group – several available devices were implanted in mixed proportions.

The impact of different ATA regimens in patients allocated to conservative treatment should also be considered. In the CLOSURE I, PC, and RESPECT trials[5-7], as well as in observational studies[35], outcomes were comparable between patients receiving anticoagulation and antiplatelet therapy. In the CLOSE trial[12], the randomised comparison of anticoagulation versus antiplatelet therapy showed a numerical trend favouring anticoagulation. Conversely, in the RESPECT trial[7,32], there was a significant risk reduction associated with antiplatelet therapy, although interaction testing was borderline. No information was provided for the DEFENSE-PFO trial[14].

We also performed landmark time-to-event analysis to provide estimates accounting for the overall significant loss of patients at follow-up and to assess consistency of results over time. Indeed, a significant proportion of patients were right-censored from two to five years, probably as a result of the limited per-protocol follow-up requirements of the CLOSURE I, Gore REDUCE and DEFENSE-PFO trials[5,13,14] and originally unplanned very late follow-up in the RESPECT trial[32]. In addition, the proportion of patients who were lost at follow-up was higher in the ATA group[4]. The significant proportion of patients with incomplete follow-up represents an important limitation of trials and must be borne in mind when interpreting very late outcomes. Nevertheless, our analysis showed evidence that the curves continue to diverge after two years and the number of events in the ATA group increases over time.

Importantly, some authors might argue about the inclusion of the CLOSURE I trial[5] because, after disclosure of the results, the tested device was labelled as ineffective. From a meta-analytic point of view, the exclusion of a trial from the main analysis based on the missing detection of differences between groups or the subjective experience of the investigator would imply a publication bias. However, we performed a sensitivity analysis with the aim of reducing factors potentially inflating the imprecision of pooled estimates. In this analysis, we excluded the CLOSURE I and DEFENSE-PFO trials[5,14] – since conclusions about specific device performance might be fair and trials with significantly shorter follow-up lengths could influence results – and applied a five-year right-censoring time to reduce inference based on limited numbers at risk. Despite these restrictions, pooled estimates were quite consistent with those computed in the main analysis.

Importantly, tPFOc cannot abolish the risk of recurrent stroke in patients with PFO and, although a significant proportion of cerebrovascular events in the interventional group may be related to suboptimal closure, causal relationships with additional factors, such as microembolism or thrombus formation on the implanted device, cannot be completely excluded[2,36]. In support of that, we found that the risk of TIA was comparable between groups without signals of heterogeneity. The diagnosis of TIA can be challenging compared with stroke. However, in the included trials, the occurrence of TIA was based on clinical and brain imaging data, acute cerebrovascular events during follow-up needed to be assessed by the neurologist, and atypical or unclear symptoms were not considered if not supported by further evidence. The comparable risk of TIA between groups perhaps implies the persistence in some patients who underwent tPFOc of imperceptible shunting that is not able to produce stroke but maintains some predisposition to embolisation through the interatrial septum. In addition, some anatomic characteristics, such as interatrial septal aneurysm, may confound the correlation between the significant stroke risk reduction and the lack of benefit in terms of TIA.

An important finding was that the development of atrial fibrillation is significantly higher in patients who undergo tPFOc compared with those receiving ATA. Nevertheless, the results of our analysis suggest that the net benefit of tPFOc is clear in spite of this. The review of data from the included trials shows that atrial fibrillation had onset generally limited to the early post-procedural time and in most cases was paroxysmal or treated successfully by electrical or pharmacologic cardioversion without recurrence over follow-up (59-100%). In addition, only a very small proportion of strokes in the tPFOc group had a causal relationship with atrial fibrillation. However, although the available results have acceptable follow-up length, the impact of a permanent implant on the overall risk of stroke, propensity to develop persistent atrial fibrillation and need for anticoagulation after several decades remains unexplored[37]. Procedural safety is further confirmed by similar incidences of major bleeding between groups. The young and low-risk profile of the enrolled patients did not lead to an excess of events in the ATA group.

The review of other major adverse events after tPFOc did not raise concerns[4-7,12-14,32], with the exception of a higher incidence of pulmonary embolism in the RESPECT trial[7,32], which was probably not related to the device and could be explained by the persistence of the source of embolism after successful tPFOc. Procedure- and device-related serious adverse events were very low across trials, ranging from 3.9% to 7.9%, and no differences in cumulative rates of any type of serious adverse event emerged between groups. Yet, heterogeneous reporting of information across trials was observed. Mortality over time was very low in both groups, and frequently events had a non-cardiac and non-neurologic cause.

Early observational reports suggested a possible secondary benefit of tPFOc in terms of reduction of the incidence of migraine[38]. However, a recent small trial has not shown a significant reduction in monthly migraine days[38]. Although it is mandatory to consider that in trials included in our meta-analysis the appropriate assessment of migraine was not among endpoints and the clinical subset did not necessarily comprise patients with a history of migraine, our meta-analysis indicates no benefit from tPFOc.

In aggregate, our review highlights that tPFOc can significantly reduce the risk of stroke over time compared with ATA, but the benefit seems to depend significantly on proper selection of patients in terms of clinical history and high-risk PFO characteristics. Currently, procedures performed for TIA or migraine do not present acceptable evidence-based support.

Limitations

As with any meta-analysis, regardless of aggregate data or reconstructed time-to-event data, our results depend on original investigations and share the same limitations. We did not have access to the full data set. However, we reconstructed original data according to a validated methodology having a minimal – but unavoidable – margin of imprecision[25,26]. The very large margin of significance/non-significance of pooled estimates as well as the strong consistency observed across multiple rigorous analyses make our conclusions robust and reliable.

In addition, the following limitations should be considered. First, with respect to the endpoints of atrial fibrillation and major bleeding, the mixed reporting across trials imposed the use of ORs as outcome measure instead of HRs. In addition, in the Gore REDUCE trial[13], events were provided as atrial fibrillation or atrial flutter. Yet, the number of atrial flutters was described as being extremely low. Second, in the report of the Gore REDUCE trial[13], the endpoint of TIA was not reported as an HR. We overcame this limitation by the "borrowing of strength" of multiple-outcome meta-analysis. In addition, we performed a sensitivity analysis by using counts (ORs) – reported for all the trials; results did not change. Third, in the CLOSURE I trial[5], atrial fibrillation and major bleeding were shown according to per-protocol analysis. We handled denominators according to as-randomised values to be consistent with the other trials that presented results according to intention-to-treat analysis. Fourth, in the subgroup analyses of the CLOSE and Gore REDUCE trials[12,13] (<44.6 versus ≥44.6 and ≤45 versus >45, respectively), the age cut-off differed trivially from the one we used (<45 versus ≥45), but the impact is considered insignificant. Moreover, with respect to subgroup analyses, in the CLOSE trial[12] data were shown as any shunt plus atrial septal aneurysm, thus were not considered in our study, while in the DEFENSE-PFO trial[14] no result was presented according to major clinical subgroups, thus data could not be pooled. Finally, in the DEFENSE-PFO trial[14], atrial fibrillation, major bleeding, and migraine were not shown.

Conclusions

Compared with ATA, tPFOc significantly reduces the risk of stroke at long-term follow-up. However, no difference was observed in terms of TIA. The risk of atrial fibrillation is higher after tPFOc but generally early and transient. Major bleeding and migraine are comparable with ATA.

Impact on daily practice

Currently, the European Stroke Organisation indicates tPFOc only in patients with cryptogenic stroke and PFO with high-risk features, while the American Heart Association/American Stroke Association guidelines consider tPFOc a viable alternative to ATA only in patients with PFO and recurrent deep vein thrombosis. This meta-analysis shows that accumulated evidence from randomised clinical trials is robust enough to prove a significant stroke risk reduction after tPFOc compared with ATA in patients with history of cryptogenic stroke confirmed by brain imaging. The safety profile of tPFOc is good overall but associated with a higher risk of atrial fibrillation, though mostly paroxysmal or successfully cardiovertible and with onset limited to the first period. No advantage of tPFOc in terms of TIA and migraine was observed.

Guest Editor

This paper was guest edited by Alec Vahanian, MD, PhD; Department of Cardiology, Hôpital Bichat-Claude Bernard, and University Paris VII, Paris, France.

Conflict of interest statement

All the authors declare no support from any organisation for the submitted work, no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, and no other relationships or activities that could appear to have influenced the submitted work. D. Giacoppo has received grants from the European Association of Percutaneous Cardiovascular Interventions (EAPCI). R. Byrne has received lecture fees from B. Braun Melsungen AG, Biotronik and Boston Scientific, and institutional research grants from Boston Scientific and HeartFlow. The other authors have no conflicts of interest to declare. The Guest Editor is a consultant for Edwards Lifesciences.

References

The complete list of references can be found in the online version of this paper.

Supplementary data

Supplementary Appendix 1. List of included trials.
Supplementary Appendix 2. Supplementary methods.
Supplementary Figure 1. Flow diagram.
Supplementary Figure 2. Trial sequential analysis after switching the order of addition of two simultaneously disclosed trials, Gore REDUCE and CLOSE.
Supplementary Figure 3. Sensitivity analysis of TIA.
Supplementary Figure 4. Risk of migraine.
Supplementary Figure 5. Bias assessment across the included trials.
Supplementary Table 1. PRISMA checklist.
Supplementary Table 2. Literature search.
Supplementary Table 3. Key eligibility criteria across the included trials.
Supplementary Table 4. Main clinical and anatomic characteristics by group.
Supplementary Table 5. Main clinical and anatomic characteristics by trial.
Supplementary Table 6. Antiplatelet and anticoagulant medications in patients assigned to tPFOc and ATA across the included trials.
Supplementary Table 7. Primary endpoints and definitions of stroke across the included trials.
Supplementary Table 8. Ischaemic stroke across trials and follow-up time points.
Supplementary Table 9. Main adverse cardiovascular events other than atrial fibrillation and major bleeding across the included trials.
Supplementary Table 10. Evaluation according to GRADE of the overall reliability of the conclusions provided.

The supplementary data are published online at: http://www.pcronline.com/eurointervention/141st_issue/154

Supplementary data

Supplementary Appendix 1. List of included trials.

- **CLOSURE I**[4,5,39,40]
  Evaluation of the STARFlex Septal Closure System in Patients with a Stroke and/or Transient Ischemic Attack due to Presumed Paradoxical Embolism through a Patent Foramen Ovale.

- **PC**[6,41]
  Clinical Trial Comparing Percutaneous Closure of Patent Foramen Ovale Using the Amplatzer PFO Occluder with Medical Treatment in Patients with Cryptogenic Embolism.

- **RESPECT**[4,7,32]
  Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment.

- **CLOSE**[12]
  Patent Foramen Ovale Closure or Anticoagulants versus Antiplatelet Therapy to Prevent Stroke Recurrence.

- **Gore REDUCE**[13]
  GORE® HELEX® Septal Occluder / GORE® CARDIOFORM Septal Occluder for Patent Foramen Ovale Closure in Stroke Patients.

- **DEFENSE-PFO**[14]
  Device Closure Versus Medical Therapy for Cryptogenic Stroke Patients with High-Risk Patent Foramen Ovale.

Supplementary Appendix 2. Supplementary methods.

Reconstruction of time-to-event data and risk estimation

High-quality Kaplan-Meier graphs were downloaded for each trial. Each curve was digitised at extreme magnification in order to retrieve spatial information. Data on the x and y axes were modelled along with number of events, numbers at risk, and thus number of right-censoring for each time interval (year) to estimate the survival function. The process was individually applied to each curve (treatment group) and performed for each trial. Reconstructed time-to-event analyses were used to draw the cumulative incidence of events over time[42]. Reconstructed data for the CLOSURE I trial[5] derived from a Kaplan-Meier curve describing the composite endpoint of stroke or transient ischaemic attack (TIA). We obtained data related to stroke by subtracting from the reconstructed time-to-event data of the pooled analysis by Kent and colleagues[4] the components of the PC and RESPECT trials[6,7,32]. With respect to the DEFENSE-PFO trial[14], a Kaplan-Meier curve was available only for the primary composite endpoint (6 events) but, given a difference of a single event compared with ischaemic stroke (5 events), we identified the outcome of interest guided by the agreement between computed and reported log-rank test p-values after sequential removal of each event at a time.

Supplementary specifications on statistical analysis

According to a “one-stage” meta-analysis, the risk of stroke between groups was obtained directly by mixed-effects Cox hazards regression accounting for the original clustering of patients across trials[27]. As generally recommended, Cox proportional hazards regressions were carried out

for each trial to obtain trial-level risk estimates which were subsequently pooled by random-effects models ("two-stage" meta-analysis). Proportional assumption was graphically inspected by the "log minus log" plot and tested according to the Schoenfeld residuals[43]. Given the absence of events in the tPFOc group of the CLOSE and DEFENSE-PFO trials[12,14], the estimation of the risk of stroke between treatments was performed by Firth's penalised maximum likelihood bias reduction method for Cox regression[44]. In the DEFENSE-PFO trial[14], similar methodology was applied for the outcome of TIA.

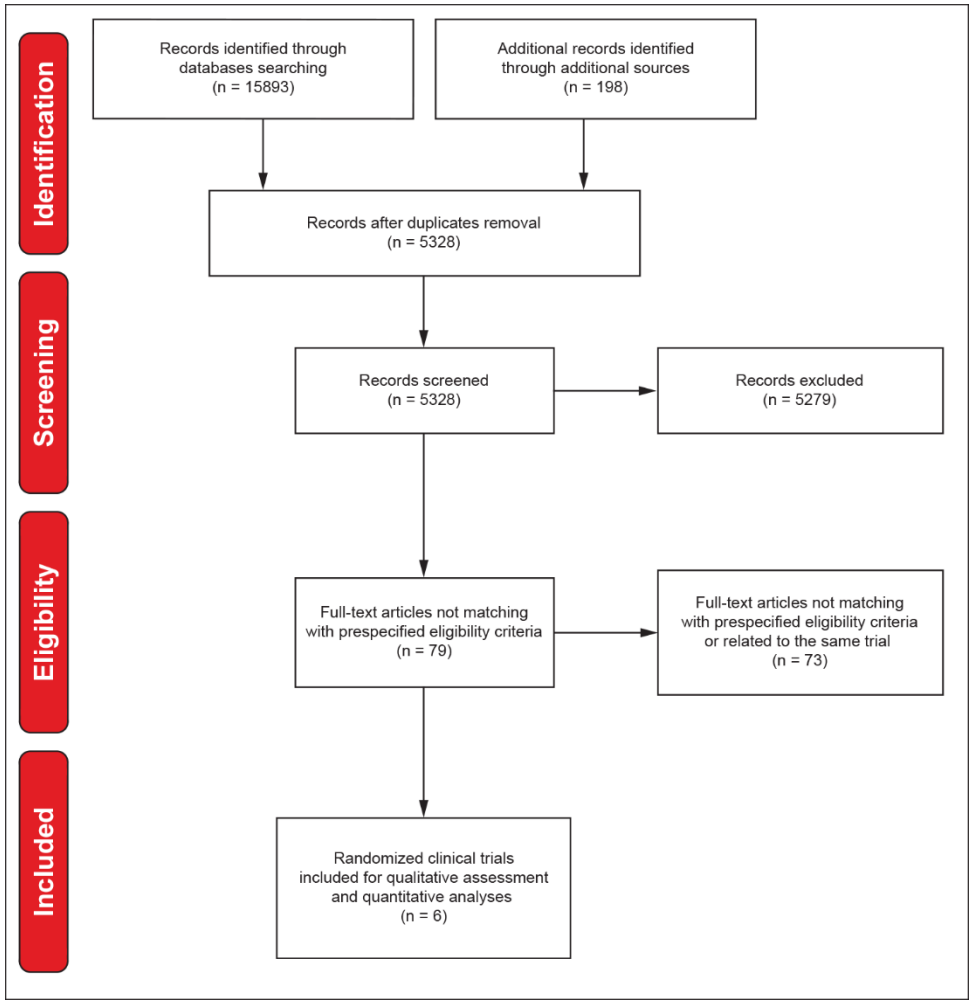
In the Gore REDUCE trial[13], the hazard ratio (HR) and 95% confidence interval (CI) for TIA was not reported and only counts in the two groups were available. This limitation was overcome by the borrowing of information of multiple-outcome meta-analysis. According to univariate analyses, a low correlation (0.3) between stroke and TIA was primarily assumed. In the DEFENSE-PFO trial[14], HR and 95% CI for TIA were indirectly estimated as described elsewhere[45].

Zero cells in fixed-effect and random-effects aggregate data meta-analyses were managed by "continuity correction" as recommended elsewhere[46].

Bias assessment

Trial-level qualitative assessment was performed by using the Cochrane Collaboration tool[21]. Seven domains were individually assessed: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, completeness of outcome data,

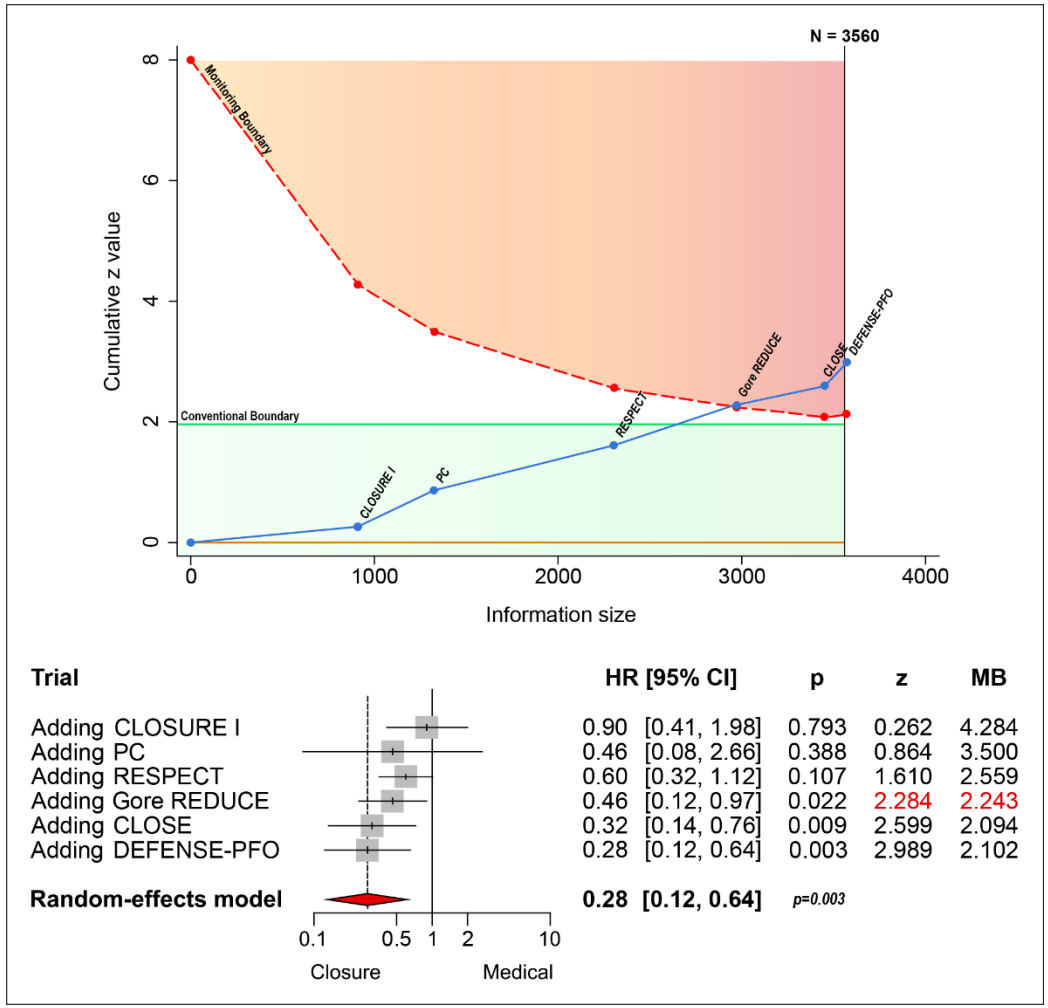
selective reporting of outcome, and other potential sources of bias such as, for example, remarkable conflict of interests or selective financial support from industries or anticipated study termination. The risk of bias was graded as “low”, “unclear”, or “high” according to the individual review of the included trials[21]. The robustness of the conclusions of the meta-analysis was inspected according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE)[31]. The degree of confidence was graded as “very low”, “low”, “moderate” or “high”[22].



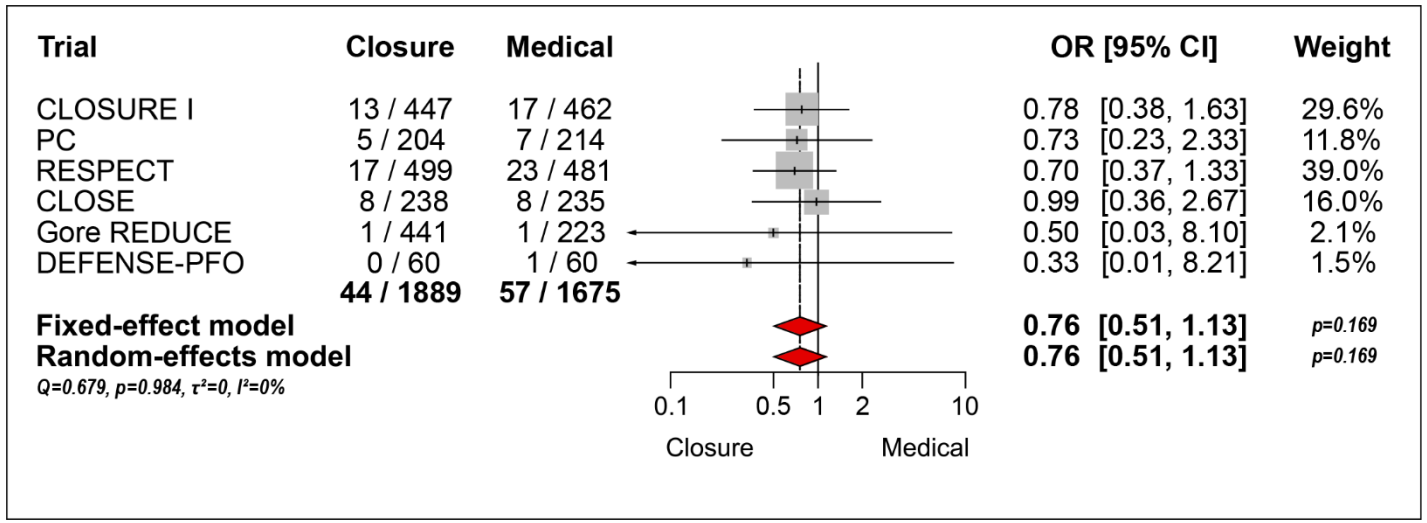
Supplementary Figure 1. Flow diagram.

In aggregate, a total of 15,893 reports were retrieved by multiple-database search, while 198 reports were identified by tangential exploration. After removal of duplicates, 5,328 reports underwent title- and abstract-level screening with exclusion of 5,279 of them because they did not match pre-specified eligibility criteria. Divergences among investigators were solved by consensus (N.C., A.H.F., J.M., D.G.). The other 79 reports

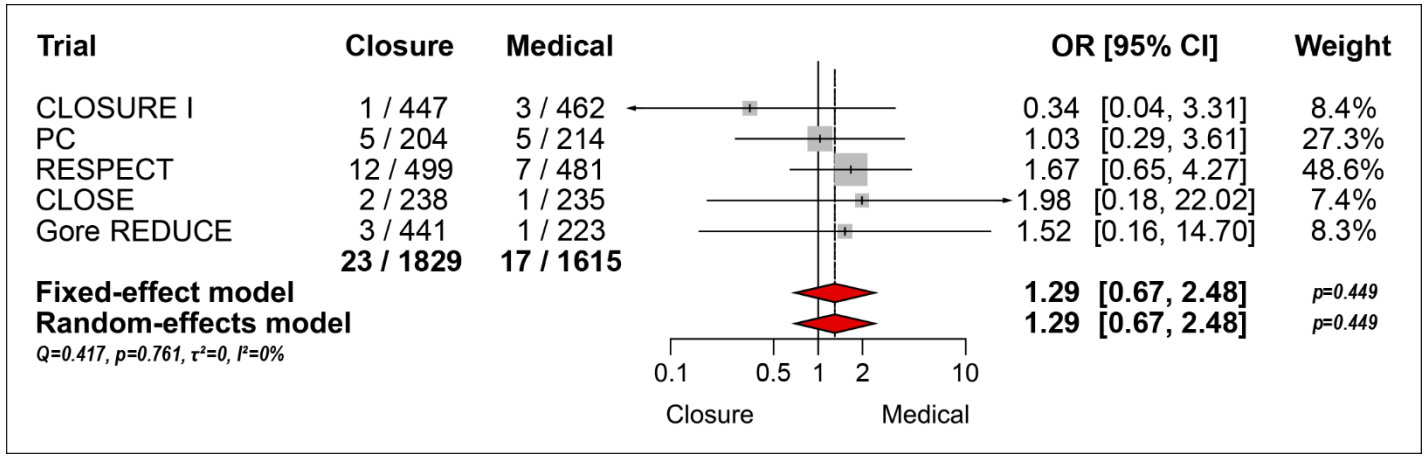
underwent full-text screening and, when related to the same trial (i.e., study protocol, secondary analysis, pooled analysis, etc.) were appended to the main investigation and considered as part of a single unit.



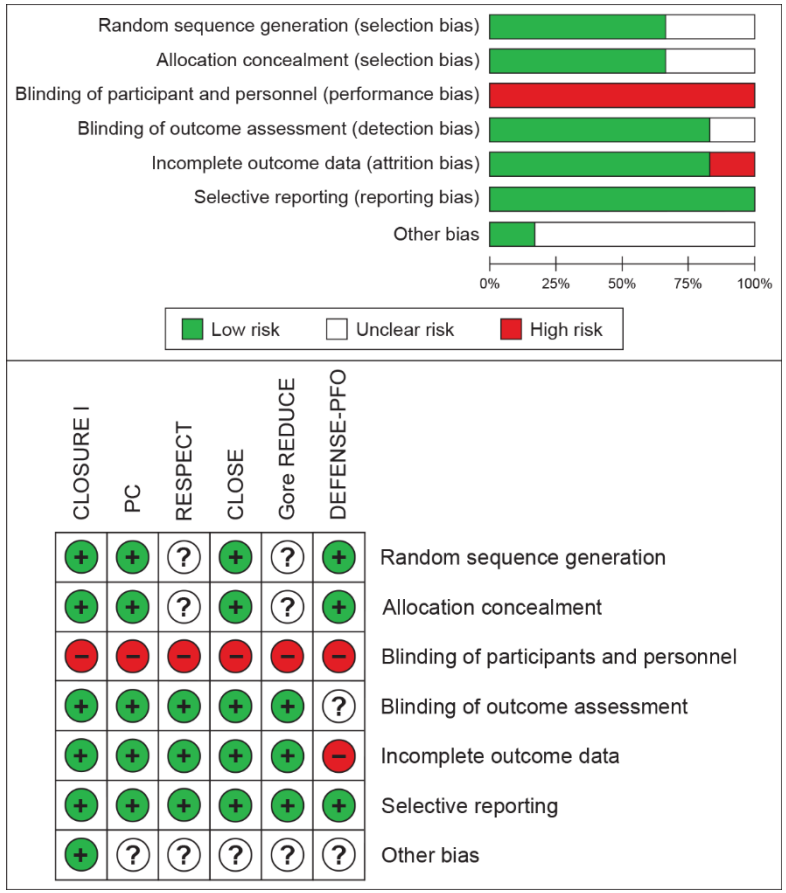
Supplementary Figure 2. Trial sequential analysis after switching the order of addition of two simultaneously disclosed trials, Gore REDUCE and CLOSE.



Supplementary Figure 3. Sensitivity analysis of TIA.



Supplementary Figure 4. Risk of migraine.



Supplementary Figure 5. Bias assessment across the included trials.

Given the dissimilar strategies under investigation, all the trials were open-label. In the RESPECT and Gore REDUCE trials[7,13], the description of random sequence generation and allocation concealment was limited. Although these two methodologic aspects were likely performed as in the other trials, it was not possible to assess them due to missing information. Four trials[5-7,13] received significant support from the manufacturer of the device implanted for tPFOc, sometimes contributing to the design, other times providing the statistical analyses, thus implying a minimum risk

of bias. In the CLOSURE I trial[5], however, even though only the STARFlex occluder was implanted, the impact of the sponsor might be considered less influential after review of the results. In the same trial, the original sample size (n=1,600) was reduced to 800 patients (March 2007) due to slow enrolment and later (June 2007) increased to 900 patients to obtain the minimum number of subjects evaluable (n=752). The CLOSURE I, PC, RESPECT, Gore REDUCE and DEFENSE-PFO trials[5-7,13,14] were powered for composite endpoints and observed incidences of stroke were lower than expected. In the Gore REDUCE trial[13], the original primary endpoint of stroke was modified at interim analysis to a composite of stroke or brain imaging lesion. The CLOSE trial[12] was investigator-initiated and supported by a government institution, but data were presented as a 2x2 design though the randomisation ratio was 1:1:1. In this trial[12], the original sample size (n=900) was not reached due to insufficient budget and investigation was terminated early. The DEFENSE-PFO trial[14] was investigator-initiated and supported by a scientific research foundation, but terminated early and characterised by lower than expected incidences of events. In the same trial, blinding of outcome assessment is unclear, while some important secondary safety outcomes, such as atrial fibrillation or major bleeding, are not considered.

Supplementary Table 1. PRISMA checklist.

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6-7, Supplementary Appendix
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6, Supplementary Appendix
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6, Supplementary Appendix
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary Appendix
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6, Flow Diagram, Supplementary Appendix
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6, Supplementary

			Appendix
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6, Supplementary Appendix
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	10, Supplementary Appendix
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7-9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7-8
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7-9, Supplementary Appendix
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8-9, Supplementary Appendix
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	10, Flow Diagram, Table 1, Tables S3-S7, Supplementary Appendix
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10, Flow Diagram, Table 1, Tables S3-S8, Supplementary Appendix
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	13, Figure S5, Table S10,

			Supplementary Appendix
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	10-13, Figures 1, Supplementary Appendix
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10-13, Figures 1-9, Supplementary Appendix
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	13, Supplementary Appendix
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	10-13, Figures 2-7, Figure S2, Figure S3 Supplementary Appendix
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13-17
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	13-18
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13-19
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Supplementary Appendix

Supplementary Table 2. Literature search.

Database	Keywords	Results (n)
PubMed	("patent foramen ovale"[All Fields] OR "PFO"[All Fields] OR "atrial septal aneurysm"[All Fields] OR "interatrial shunt"[All Fields] OR "right-to-left shunt"[All Fields]) AND ("closure"[All Fields] OR "transcatheter"[All Fields]) AND ("stroke"[All Fields] OR "transient ischemic attack"[All Fields] OR "TIA"[All Fields] OR "infarction"[All Fields] OR "embolism"[All Fields])	1,084
Scopus	TITLE-ABS-KEY (patent AND foramen AND ovale) OR TITLE-ABS-KEY (pfo) OR TITLE-ABS-KEY (atrial AND septal AND aneurysm) OR (interatrial AND shunt) AND TITLE-ABS-KEY (stroke) OR TITLE-ABS-KEY (transient AND ischemic AND attack) OR TITLE-ABS-KEY (tia) OR TITLE-ABS-KEY (infarction) OR TITLE-ABS-KEY (embolism) AND (LIMIT-TO (SUBJAREA , "MEDI"))	4,919
Web of Science	(((TS=(patent foramen ovale OR PFO OR atrial septal aneurysm OR interatrial shunt OR right to left shunt) AND TS=(closure OR transcatheter) AND TS=(stroke OR TIA OR transient ischemic attack OR TIA OR infarction OR	1,320

	embolism)))) AND DOCUMENT TYPES: (Article OR Abstract of Published Item OR Bibliography OR Book OR Book Chapter OR Database Review OR Letter OR Meeting Abstract OR Proceedings Paper OR Review)	
ScienceDirect	"patent foramen ovale" OR PFO OR "atrial septal aneurysm" OR "interatrial shunt" AND closure OR transcatheter AND stroke OR "transient ischemic attack" OR TIA OR infarction OR embolism All Sources(Medicine and Dentistry)	3,918
Ovid	(patent foramen ovale or PFO or atrial septal aneurysm or interatrial shunt).af. and (closure or transcatheter).af. and (stroke or transient ischemic attack or TIA or infarction or embolism).af.	4,652

Supplementary Table 3. Key eligibility criteria across the included trials.

Trial	Inclusion criteria	Exclusion criteria
CLOSURE I	• Age 18-60 years old • Positive bubble test by TEE demonstrating right-to-left shunting through PFO during Valsalva manoeuvre • Stroke <6 months not related to a previously documented PFO or other identifiable cause • TIA associated with acute brain infarct at DW-MRI or transient lateralising motor weakness, speech difficulty, amaurosis fugax or blindness <6 months before not related to a previously documented PFO or other identifiable cause • Vascular access from the femoral vein expected to accommodate the 10 Fr delivery system • Critical cardiac structures not expected to come in contact with the device with approximately 1 mm of margin • The size of the PFO must be amenable to selection of a STARFlex device • Acquisition of the informed consent	• No right-to-left shunting through a PFO • Potential source of embolic stroke or TIA other than PFO (carotid artery stenosis >50% or ulcerated plaque or association with thrombus; >50% intracranial stenosis appropriate to patient's symptoms; complex aortic arch atheroma exhibiting high-risk features for embolism; aortic arch, carotid artery, or vertebral artery dissection; mitral or aortic valve stenosis; mitral or aortic valve vegetations; mitral or aortic valve calcified annulus; prosthetic heart valves; left ventricular ejection fraction of <30%; left ventricular aneurysm; recent anterior wall myocardial infarction <3 months before the neurological event; chronic atrial fibrillation; >2 atrial fibrillation or flutter episodes lasting >30 seconds not related to a reversible cause) • Large, redundant atrial septal aneurysm which cannot be covered by the STARFlex device without interference with other intracardiac structures • Congenital cardiac defects not repaired prior to enrolment (atrial septal defect, ventricular septal defect, coarctation of the aorta, patent ductus arteriosus) • Thrombus or lumen occlusion between the femoral vein access site and the right atrium • Previously implanted atrial septal device • Echocardiographic evidence of an intra-atrial or ventricular thrombus • Current or <6 months intravenous drug abuse

	• Known active endocarditis or documented bacteraemia • Active infections requiring current antibiotic therapy • Serum creatinine >2.0 mg/dL • Women with suspected or known pregnancy • Known hypersensitivity or contraindication to warfarin, aspirin, heparin, and clopidogrel • Sensitivity to contrast media, which cannot be adequately pre-medicated • Any medical condition other than index stroke requiring anticoagulation with warfarin • White blood count of <3,000 cells/mm^3 • Platelet count <100,000 cells/mm^3 or >700,000 cells/mm^3 • Any disorder of platelet function • Any coagulopathy • Moderate or high positive titer of antiphospholipid antibodies • Known vasculitis or neurologic disorder • Inability to perform a satisfactory Valsalva manoeuvre • Contraindication to TEE • Active peptic ulcer or upper gastro-intestinal bleeding <6 months • Current participation to another investigation that has not completed the primary endpoint or that clinically interferes with the current study endpoints • Permanent pacemaker • Inferior vena cava filter • Right ventricle muscle failure • Pulmonary hypertension • Severe tricuspid regurgitation • Cirrhosis or portal hypertension

		• Pulmonary arteriovenous malformations • Life expectancy <24 months
PC	• Age <60 years old • Documentation of PFO with or without atrial septal aneurysm and right-to-left shunting at TEE by positive bubble test and/or colour Doppler flow imaging, either spontaneously or with a Valsalva or cough manoeuvre • Ischaemic stroke verified clinically and neuroradiologically by MRI, CT or angiography in the absence of another identifiable cause • Symptoms of TIA and neuroradiologically identified intracranial ischaemic lesion in the absence of another identifiable cause • Clinically and radiologically verified extracranial peripheral thromboembolism in the absence of another identifiable cause • Sufficient recovery from the thromboembolic index event to allow independent daily activities • Exclusive implantation of an AMPLATZER PFO Occluder device	• Any identifiable cause for the thromboembolic event other than PFO • Chronic anticoagulant therapy for reason other than paradoxical embolism • Mural thrombus • Dilated cardiomyopathy • Prosthetic heart valve • Mitral stenosis • Bacterial and non-bacterial endocarditis • Cardiac myxoma • Stherosclerosis of the aorta • Chronic or paroxysmal atrial fibrillation • Significant atherosclerosis or dissection of the aorta • Clinically relevant atherosclerosis and/or dissection of the intra- and extracranial arteries • Any pre-existing neurological disorder or significant intracranial disease • Severe central nervous disease • Significant collagen vascular disease • Giant cell arteritis • Vasculitis or systemic necrotising vasculitis • Hyperviscosity syndromes • Hypercoagulable states • Contraindication for chronic oral anticoagulant or antiplatelet therapy • Severe bleeding disorder <3 months prior to randomisation • Known coagulopathy

		• Platelet disorder • Significant retinopathy • Significant intracranial disease • Previous intracranial haemorrhage • Previous surgical or percutaneous PFO closure • Drug and/or alcohol abuse <48 hours prior to the thromboembolic index event • Septicaemia or severe localised infection • Follow-up over the next 5 years not possible • Inability to obtain the informed consent
RESPECT	• Age 18-60 years old • Documentation PFO at TEE by positive bubble test at rest and/or during Valsalva manoeuvre • Stroke <270 days without explanation other than paradoxical embolism, with symptoms persisting ≥24 hours or symptoms persisting <24 hours but cerebral infarct at MRI or CT	• Stenosis >50% of the intracranial and extracranial vessels supplying the involved lesion • Intracardiac thrombus or tumour • Acute or recent (<6 months) myocardial infarction or unstable angina • Left ventricular aneurysm or akinesis • Mitral valve stenosis or severe mitral regurgitation irrespective of aetiology • Aortic valve stenosis with gradient >40 mmHg or severe aortic valve regurgitation • Mitral or aortic valve vegetation or prosthesis • Aortic arch plaques protruding >4 mm into the lumen • Left ventricular dilated cardiomyopathy with LVEF <35% • Other source of right-to-left shunt (atrial septal defect and/or fenestrated septum, chronic or intermittent atrial fibrillation/atrial flutter) • Active endocarditis or other untreated infections • Kidney, liver or lung failure

		• Sustained elevated systemic blood pressure to >160/90 mmHg despite medications • Sustained glucose levels >200 mg/dL and presence of glucose in the urine despite administration of insulin • Lacunar infarct probably due to intrinsic small vessel as qualifying event • Arterial dissection as qualifying event • Signs of progressive neurological dysfunction • Hypercoagulable state • Contraindication to aspirin or clopidogrel • Pregnancy or desire to become pregnant within the next year • Interference between AMPLATZER PFO Occluder and intracardiac or intravascular structures • Malignancy or other illness with life expectancy <2 years • No availability for follow-up for the duration of the trial • Inability to obtain the informed consent
CLOSE	• Age 16-60 years old • Documented PFO with large shunt >30 microbubbles on TTE or TEE, either spontaneous or during provocation manoeuvres, and/or atrial septal aneurysm on TEE with base of aneurysm ≥15 mm and excursion >10 mm • Stroke ≤6 months or initial or recurrent retinal ischaemia confirmed by cerebral imaging • Modified Rankin score ≤3 • Absence of another identifiable cause of stroke or retinal ischaemia on a thorough aetiological work	• Index stroke with possible cause other than PFO • Atrial septal defect isolated or associated with PFO and significant left-to-right shunt requiring closure • Previous surgical or endovascular treatments of PFO or atrial septal aneurysm • Very large or multiperforated atrial septal aneurysm • Indication for long-term anticoagulant or antiplatelet therapy for another reason • Contraindication to both antiplatelet drugs and oral anticoagulants • Presence of thrombus or occlusion between the femoral venous access and the right atrium

		• Inferior vena cava filter • Severe pulmonary artery hypertension • Severe liver failure • Active peptic ulcer • Proliferative diabetic retinopathy • History of severe bleeding • History of bleeding or coagulopathy related to endovascular treatment • Active infection • Follow-up impossible or expected poor compliance • Presence of other medical problems that would either lead to inability to complete the study or interfere with the assessment of outcomes • Known or suspected pregnancy • Breastfeeding • Participation in another study • Inability to obtain the informed consent
Gore REDUCE	• Age 18-60 years old • Documented PFO and right-to left shunting, either spontaneous or during Valsalva manoeuvre, by positive bubble test at TEE • Ischaemic stroke <180 days, verified by a neurologist, without identifiable cause other than PFO • TIA associated with new brain infarct at imaging <180 days, verified by a neurologist, without identifiable cause other than PFO • Absence of an identifiable source of thromboembolism in the systemic arterial circulation • Vascular imaging that rules out other potential sources of cerebral thromboembolism (dissection of the aorta or	• Presence of other potential source of cardio-embolism (atrial fibrillation or atrial flutter, prosthetic heart valve, severe native valve disease, left ventricular ejection fraction <40%, akinesia or severe hypokinesia of ventricular wall motion, intracardiac thrombus, mitral valve stenosis, prior cardiac surgery, other major congenital cardiac abnormality) • Anatomic criteria identified during the screening evaluation and/or the screening TEE that are unfavourable for successful placement of the GORE® HELEX Septal Occluder / GORE CARDIOFORM Septal Occluder or contraindications for any device placement (inability to accommodate a 10 Fr delivery catheter, need for trans-septal puncture, requirement for

	neck vessels, carotid stenosis >50% and/or presence of ulcerated plaques, or intracranial stenosis >50%) • No evidence of hypercoagulable state requiring anticoagulation • Willingness and capability of complying with the study protocol requirements, including the specified follow-up period • Acquisition of the informed consent	placement of more than one device, estimated size of PFO too large for successful device placement, likelihood that device would impinge on cardiac structures, likelihood that anatomy would prevent discs from apposing the septal tissue) • Neurological deficits not due to stroke that may affect the patient's neurologic assessments • Lacunar stroke syndrome • Intracranial pathology that makes the patient inappropriate for study participation (brain tumour other than meningioma, arteriovenous malformation, cerebral haemorrhage, cerebral venous sinus thrombosis on CT or MRI, cerebral aneurysm >7 mm) • Contraindication to study medications • Chronic anticoagulation therapy that cannot be discontinued • Known sensitivity to contrast media that cannot be controlled adequately with pre-medication • Prior myocardial infarction • Uncontrolled systemic hypertension • Uncontrolled diabetes mellitus • Pulmonary hypertension (mean pulmonary artery pressure >25 mmHg) • Active autoimmune disease • Active infection • Abuse of alcohol and/or drugs • Pregnancy, lactation or intent on becoming pregnant through next 24 months • Modified Rankin Scale score ≥3 • Life expectancy of <1 year • Major surgical procedure <30 days before randomisation

		• Major elective surgical procedure <30 days after randomisation or PFO closure • Current participation in another investigation that has not completed its primary endpoint or that will clinically confound the study endpoints or does not permit subject to participate in other study • Anatomic or comorbid conditions that could limit the patient's ability to participate in the study or to comply with follow-up requirements, or impact on the scientific soundness of the results • Need for any concomitant procedure, based on the results of the screening evaluations, during the PFO closure procedure that may confound detection of device-related adverse events
DEFENSE-PFO	• Age 18-80 years old • Documented PFO and right-to-left shunting, either spontaneous or during Valsalva manoeuvre, by positive bubble test at TEE and evidence of high-risk features defined as presence of atrial septal aneurysm (dilated segmentary septum protrusion ≥15 mm) or septum hypermobility (phasic septal excursion ≥10 mm) or PFO size ≥2 mm during Valsalva manoeuvre. • Ischaemic stroke <180 days, with symptoms lasting 24 hours or more or was associated with evidence of relevant infarction on magnetic resonance imaging of the brain and exclusion of significant large-artery atherosclerotic disease, established cardioembolic source, small-vessel occlusive disease, hypercoagulable disorder requiring anticoagulation, or arterial dissection. • Willingness to participate in follow-up visits	• Other source of right-to-left shunt including atrial septal defect and fenestrated septum • Previous ischaemic stroke due to small-vessel occlusive disease • Chronic or intermittent atrial fibrillation or flutter • History of myocardial infarction or unstable angina • History of intracranial bleeding, confirmed arteriovenous malformation, aneurysm or uncontrolled coagulopathy • Pre-existing neurological disorder • Left ventricular systolic dysfunction with aneurysm of akinesia • Contraindications to TEE • Contraindications to antiplatelet therapy • Underlying malignancy • Pregnancy or desire to become pregnant

CT: computed tomography; MRI: magnetic resonance imaging; PFO: patent foramen ovale; TEE: transoesophageal echocardiography; TTE: transthoracic echocardiography

Supplementary Table 4. Main clinical and anatomic characteristics by group.

	Total (n=3,560)	tPFOc (n=1,889)	ATA (n=1,671)	*p*
Age	45.3±9.9	45.3±9.9	45.4±9.9	0.764
Male	55.0 (1,958)	54.2 (1,024)	55.9 (934)	0.313
Diabetes	5.9 (209)	5.6 (106)	6.2 (103)	0.484
Smoking	17.4 (618)	17.8 (337)	16.8 (281)	0.421
Hypertension	26.6 (947)	26.9 (509)	26.2 (438)	0.621
Hypercholesterolaemia	34.8 (1,009)[a]	34.8 (504)[a]	34.8 (505)[a]	0.933
Index event of stroke	92.8 (3,304)	93.5 (1,766)	92.0 (1,538)	0.095
Large PFO	61.7 (1,992)[b]	62.0 (1,070)[b]	61.3 (922)[b]	0.705
Septal aneurysm	32.0 (926)[c]	32.2 (466)[c]	31.7 (460)[c]	0.791

Data are presented as percentage (number) or mean (standard deviation).

[a] Rates of hypercholesterolaemia are not disclosed/collected in the Gore REDUCE trial[13], therefore data from this study are not included.

[b] Available from 93.8% (3,227), 94.3% (1,726), and 93.3% (1,503) of patients, respectively. Not reported in the DEFENSE-PFO[14].

[c] In the Gore REDUCE trial[13], rates of septal aneurysm were collected only for the PFO closure group, therefore data from this study are not included.

Supplementary Table 5. Main clinical and anatomic characteristics by trial.

	Total (n=3,560)	CLOSURE I (n=909)	PC (n=414)	RESPECT (n=980)	CLOSE (n=473)	Gore REDUCE (n=664)	DEFENSE-PFO (n=120)	*p*
Age	45.2±9.8	45.5±9.3	44.5±10.2	45.4±9.8	43.3±10.3	45.2±9.4	51.2±13.5	<0.001
Male	55.0 (1,958)	51.8 (471)	49.8 (206)	54.7 (536)	59.0 (279)	60.1 (399)	55.8 (67)	0.003
Diabetes	5.9 (209)	7.8 (71)	2.7 (11)	7.5 (73)	2.5 (12)	4.2 (28)	11.7 (14)	<0.001
Smoking	17.4 (618)	15.2 (138)	23.9 (99)	13.3 (130)	29.0 (137)	13.3 (88)	21.7 (26)	<0.001
Hypertension	26.7 (918)	31.0 (282)	25.8 (107)	31.4 (308)	10.8 (51)	25.6 (170)	24.2 (29)	<0.001
Hypercholesterolaemia	34.8 (1,009)	44.1 (401)	27.1 (112)	39.5 (387)	14.0 (66)	—	35.8 (43)	<0.001
Index event of stroke	92.8 (3,304)	72.0 (653)	100 (414)	100 (980)	100 (473)	100 (664)	100 (120)	<0.001
Large PFO	61.7 (1,992)	61.1 (475)	21.7 (80)	76.1 (737)	92.8 (439)	40.7 (261)	—	<0.001
Septal aneurysm	26.0 (926)	35.6 (311)	23.7 (98)	35.6 (349)	32.8 (155)	20.4 (86)	10.8 (13)	<0.001

Data are presented as percentage (number) or mean (standard deviation).

Supplementary Table 6. Antiplatelet and anticoagulant medications in patients assigned to tPFOc and ATA across the included trials.

	CLOSURE I	PC	RESPECT	CLOSE	Gore REDUCE	DEFENSE-PFO
Medications in the tPFOc group	Acetylsalicylic acid 81-325 mg daily for 2 years and clopidogrel 75 mg daily for 6 months [6-month DAPT]	Acetylsalicylic acid 100-325 mg daily for 5-6 months and clopidogrel 75-150 mg daily for 1-6 months or ticlopidine 250-500 mg daily for 1-6 months [1- to 6-month DAPT]	Acetylsalicylic acid 81-325 mg daily for 6 months + clopidogrel 75 mg daily for 1 month [1-month DAPT]	Acetylsalicylic acid 75 mg daily for 3 months + clopidogrel 75 mg daily for 3 months [3-month DAPT] followed by acetylsalicylic acid or clopidogrel or acetylsalicylic acid + extended-release dipyridamole	• Acetylsalicylic acid 75-325 mg daily or • Clopidogrel 75 mg daily or • Acetylsalicylic acid 50-100 mg daily + dipyridamole 225-400 mg daily Patients were expected to continue antiplatelet therapy for the duration of the follow-up [≥2 years of DAPT]	• Acetylsalicylic acid 100 mg daily + clopidogrel 75 mg daily for at least 6 months [≥6-month DAPT] At physician's discretion, patients either stopped antiplatelet therapy or took acetylsalicylic acid, or acetylsalicylic acid and clopidogrel, or aspirin and cilostazol or • Warfarin After 6 months, at physician's discretion, patients either stopped the therapy or continued oral anticoagulation.
Medications in the ATA group	• Acetylsalicylic acid 81-325 mg daily or • Clopidogrel 75 mg daily or • Acetylsalicylic acid 81-325 mg daily + clopidogrel 75 mg daily	• Antiplatelet therapy • Anticoagulation	• Acetylsalicylic acid • Warfarin • Clopidogrel • Acetylsalicylic acid + extended-release dipyridamole • Acetylsalicylic acid + clopidogrel	Acetylsalicylic acid 75 mg daily for 3 months + clopidogrel 75 mg daily for 3 months followed by acetylsalicylic acid or clopidogrel or acetylsalicylic acid +	• Acetylsalicylic acid 75-325 mg daily or • Clopidogrel 75 mg daily or • Acetylsalicylic acid 50-100 mg daily + dipyridamole 225-400 mg daily	• Acetylsalicylic acid 100 mg daily + clopidogrel 75 mg daily for at least 6 months [≥6-month DAPT] At physician's discretion, patients either stopped antiplatelet therapy or took acetylsalicylic acid, or

		extended-release dipyridamole	acetylsalicylic acid and clopidogrel, or aspirin and cilostazol or • Warfarin After 6 months, at physician's discretion, patients either stopped the therapy or continued oral anticoagulation.

DAPT: dual antiplatelet therapy

Supplementary Table 7. Primary endpoints and definitions of stroke across the included trials.

	CLOSURE I	PC	RESPECT	CLOSE	Gore REDUCE	DEFENSE-PFO
Primary endpoint	TIA or ischaemic stroke <180 days	TIA with brain infarct at imaging or ischaemic stroke or extra-cranial embolism	Ischaemic stroke <270 days	Ischaemic stroke <180 days	TIA with new brain infarct at imaging or ischaemic stroke <180 days	Ischaemic stroke <180 days
Definition of stroke	Acute focal neurological event that is MRI positive, regardless of duration of clinical symptoms.	Any neurologic deficit lasting for >24 hours. Whenever possible a head CT/MRI scan is performed to differentiate ischaemic stroke from haemorrhage.	Acute focal neurological deficit presumed to be due to focal ischaemia and either symptoms persisting ≥24 hours or symptoms persisting <24 hours but associated with MRI or CT findings of a new, neuroanatomically relevant, cerebral infarct.	Sudden onset of focal neurological symptoms either lasting >24 hours with no apparent cause other than cerebral ischaemia or associated with the presence of cerebral infarction in the appropriate territory on brain imaging (CT or MRI), regardless of the duration of symptoms.	Clinical symptoms lasting ≥24 hours associated with evidence of brain infarction on MRI or CT	Clinical symptoms lasting ≥24 hours or evidence of brain infarction on MRI

CT: computed tomography; MRI: magnetic resonance imaging

Supplementary Table 8. Ischaemic stroke across trials and follow-up time points.

	Events		Events / 100 person-years		Kaplan-Meier estimates (%)	
	tPFOc	ATA	tPFOc	ATA	tPFOc	ATA
CLOSURE I						
• **2 Years**	12	13	1.43	1.60	2.9	3.1
PC						
• **2 Years**	• 1	• 4	• 0.26	• 1.05	• 0.5	• 2.1
• **5 Years/Longest Follow-Up**	• 1	• 7	• 0.12	• 0.86	• 0.5	• 4.1
RESPECT						
• **2 Years**	• 8	• 14	• 0.84	• 1.61	• 1.6	• 3.1
• **5 Years**	• 12	• 21	• 0.54	• 1.08	• 2.6	• 4.9
• **Longest Follow-Up**	• 18	• 28	• 0.58	• 1.07	• 4.9	• 11.6
CLOSE						
• **2 Years**	• 0	• 8	• 0	• 1.75	• 0	• 3.4
• **5 Years**	• 0	• 11	• 0	• 1.11	• 0	• 4.9
• **Longest Follow-Up**	• 0	• 14	• 0	• 1.13	• 0	• 8.1
Gore REDUCE						
• **2 Years**	• 5	• 10	• 0.60	• 2.55	• 1.2	• 4.7
• **5 Years/Longest Follow-Up**	• 6	• 12	• 0.39	• 1.71	• 1.6	• 5.9
DEFENSE-PFO						
• **2 Years**	0	5	0	5.38	0	10.5
Total						
• **2 Years**	• 26	• 54	• 0.73	• 1.84	• 1.4	• 3.5
• **5 Years**	• 31	• 69	• 0.47	• 1.31	• 2.0	• 5.2
• **Longest Follow-Up**	• 37	• 79	• 0.48	• 1.26	• 3.6	• 12.0

All trials were included.

Supplementary Table 9. Main adverse cardiovascular events other than atrial fibrillation and major bleeding across the included trials.

tPFOc vs. ATA	CLOSURE I	PC	RESPECT	CLOSE	Gore REDUCE	DEFENSE-PFO
Procedural complications	–	1.5 (3)	2.4 (12)	5.9 (14)	2.5 (11)	–
Device-related complications	–	0	2.6 (13)	–	1.4 (6)	–
Erosion of cardiac structures	–	–	–	–	0	–
Vascular complications	3.2 (13)	1.0 (2)	0.6 (3)	0.8 (2) / 0	1.0 (4)	–
Any adverse event	–	34.8 (71) / 29.5 (62)	–	–	–	–
Any serious adverse event	16.9 (68) / 16.6 (76)	21.1 (43) / 17.6 (37)	40.3 (201) / 36.0 (173)	35.7 (85) / 33.2 (78)	23.1 (102) / 27.8 (62)	–
Any minor adverse event	–	19.6 (40) / 20.0 (42)	–	–	–	–
Death	0.5 (2) / 0.9 (4)	1.0 (2) / 0	1.4 (7) / 2.3 (11)	0 vs 0	2 (0.5) / 0	–
Any bleeding	–	3.0 (8) / 5.7 (12)	2.2 (11) / 1.0 (5)	–	–	–
Syncope	0 / 0.5 (2)	1.0 (2) / 0.5 (1)	0.6 (3) / 1.0 (5)	0 / 0	–	–
Dyspnoea	–	0 / 1.9 (4)	0.6 (3) / 0.2 (1)	0.4 (1) / 0	–	–
Chest pain/discomfort	–	1.5 (3) / 1.9 (4)	3.6 (18) / 3.1 (15)	0.8 (2) / 0	0.4 (2) / 0	–
Pulmonary embolism	–	–	2.4 (12) / 0.6 (3)	0.4 (1) / 0	0.5 (2) / 0.4 (1)	–
Coronary embolism	–	–	–	0.8 (2) / 0	–	–
Systemic embolism	–	0 vs. 0	–	–	0 / 0	–

Values are reported as percentage (number). Non-procedure- and device-related events are listed as tPFOc group / ATA group. Data are illustrated according to the longest available follow-up.

Supplementary Table 10. Evaluation according to GRADE of the overall reliability of the conclusions provided.

Quality assessment						Overall quality
Trials	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	
Stroke						
6	Randomised trials	Not serious	Serious	Not serious	Not serious	⊕⊕⊕◯ MODERATE
TIA						
6	Randomised trials	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕⊕ HIGH
Atrial fibrillation						
5	Randomised trials	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕⊕ HIGH
Major bleeding						
5	Randomised trials	Not serious	Not serious	Not serious	Not serious	⊕⊕⊕⊕ HIGH
Migraine						
5	Randomised trials	Serious	Not serious	Serious	Not serious	⊕⊕◯◯ LOW

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