PATIENT-CENTERED OUTCOMES RESEARCH INSTITUTE
FINAL RESEARCH REPORT

Evaluating Therapies to Prevent Future Stroke in Patients with Patent Foramen Ovale-Related Strokes — The SCOPE Study

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To cite this document, please use: Kent DM, Saver JL, Kasner SE, et al. (2023). *Evaluating Therapies to Prevent Future Stroke in Patients with Patent Foramen Ovale–Related Strokes — The SCOPE Study.* Patient-Centered Outcomes Research Institute (PCORI). https://doi.org/10.25302/04.2023.RS.SCOPE2019001

Article Information

Institution Receiving Award: Tufts Medical Center
PCORI ID: RS-SCOPE-2019-001
HSRProj ID: HSRP20202813

Date submitted:
Date accepted:
Original posting date:
Date revised:
Reason for revision:

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Note: *Some material in this paper comes from Kent DM, Saver JL, Kasner SE, et al. Heterogeneity of treatment effects in an analysis of pooled individual patient data from randomized trials of device closure of patent foramen ovale after stroke.* JAMA. *2021;326(22):2277-2286. doi:10.1001/jama.2021.20956*

ABSTRACT

Note: *The material presented in this section previously appeared in the following peer-reviewed publication: Kent DM, Saver JL, Kasner SE, et al. Heterogeneity of treatment effects in an analysis of pooled individual patient data from randomized trials of device closure of patent foramen ovale after stroke.* JAMA. *2021;326(22):2277-2286. doi:10.1001/jama.2021.20956*

Background: Patent foramen ovale (PFO)-associated strokes comprise approximately 10% of ischemic strokes in adults aged 18 to 60 years. Despite the overall beneficial effects of closure device placement in patients with a first PFO-associated cerebral ischemic event, the best treatment option for any individual patient encountered in routine clinical practice is often quite unclear.

Objective: The objective of this study was to evaluate the heterogeneity of treatment effect of PFO closure on stroke recurrence based on previously developed scoring systems.

Methods: Individual patient data were pooled from 6 randomized clinical trials that compared PFO closure plus medical therapy vs medical therapy alone in patients with PFO-associated stroke, which involved a total of 3740 participants. The trials were conducted worldwide from 2000 to 2017. Comparisons were made between PFO closure plus medical therapy vs medical therapy alone. Subgroup analyses used the Risk of Paradoxical Embolism (RoPE) score (a 10-point score in which higher scores reflect younger age and the absence of vascular risk factors) and the PFO-Associated Stroke Causal Likelihood (PASCAL) algorithm, which combines the RoPE score with high-risk PFO features (either an atrial septal aneurysm or a large shunt) to classify patients into 3 categories of causal relatedness: “unlikely,” “possible,” and “probable.” The main outcome was ischemic stroke.

Results: Over a median follow-up of 57 months (interquartile range, 24-64 months), 121 outcomes occurred in 3740 patients. The annualized incidence of stroke with medical therapy was 1.09% (95% CI, 0.88%-1.36%) and with device closure was 0.47% (95% CI, 0.35%-0.65%); the adjusted hazard ratio (HR) was 0.41 (95% CI, 0.27-0.60). Subgroup analyses showed statistically significant interaction effects. Patients with low vs high RoPE score had HRs of 0.61 (95% CI, 0.37-1.00) and 0.21 (95% CI, 0.11-0.42), respectively (*P* for interaction = .02). Patients classified under PASCAL as unlikely, possible, and probable had HRs of 1.14 (95% CI, 0.53-2.46), 0.38 (95% CI, 0.22-0.65), and 0.10 (95% CI, 0.03-0.35), respectively (*P* for interaction = .003). The 2-year absolute risk reduction was −0.7% (95% CI, −4.0% to 2.6%), 2.1% (95% CI, 0.6%-3.6%), and 2.1% (95% CI, 0.9%-3.4%) in the unlikely, possible, and probable PASCAL categories, respectively. Device-associated adverse events were generally higher among patients classified as unlikely; the absolute risk increases in atrial fibrillation beyond day 45 postrandomization with device were 4.41% (95% CI, 1.02%-7.80%), 1.53% (95% CI, 0.33%-2.72%), 0.65% (95% CI, −0.41% to 1.71%) in the unlikely, possible, and probable PASCAL categories, respectively.

Conclusions: Among patients aged 18 to 60 years with PFO-associated stroke, risk reduction for recurrent stroke with device closure varied across groups classified by their probabilities that the stroke was causally related to the PFO. Application of these classification systems has the potential to guide individualized decisions regarding the selection of device closure vs medical therapy, supporting patient-centered decision-making for patients with PFO-associated cerebral ischemic events.

Limitations: Some limitations of the study were the following: data were missing with respect to functional outcomes with recurrent stroke; trials had heterogenous definitions of key variables; the original PASCAL classification could not be evaluated; and several questions remain unaddressed, such as the best type of antithrombotic therapy, the role of new PFO devices, and the role of closure for patients older than 60 years.

BACKGROUND

Note: *Much of the material presented in this section previously appeared in the following peer-reviewed publication: Kent DM, Saver JL, Kasner SE, et al. Heterogeneity of treatment effects in an analysis of pooled individual patient data from randomized trials of device closure of patent foramen ovale after stroke.* JAMA. *2021;326(22):2277-2286. doi:10.1001/jama.2021.20956*[1]

Each year, approximately 700 000 ischemic strokes occur in the United States,[2] and 7.63 million occur globally.[3] Among the more-than-100 sources of ischemic stroke, patent foramen ovale (PFO)-associated strokes are the third most common, surpassed only by large- and small-artery atherosclerosis and by atrial fibrillation (AF).[4,5] Both in the United States and globally, PFOs have been estimated to cause approximately 5% of all ischemic strokes and 10% of ischemic strokes in adults aged 18 to 60 years.[6] Patients who have had a first PFO-associated cerebral ischemic event (PFO-associated ischemic stroke or PFO-associated transient ischemic attack [TIA]) are at high risk for recurrent stroke. In the medical arms of randomized treatment trials, the frequency of recurrent stroke during first 5 years after an index PFO-associated cerebral ischemic event was 6%, indicating that 1 of every 17 patients had a recurrent stroke.[6] Because PFO-associated strokes often occur in young and middle-aged individuals who have postindex event life expectancies of many decades, the lifetime risk of recurrent stroke after an index PFO-associated cerebral ischemic event is certainly much higher than seen in the relatively brief time horizon of the trials.

To prevent recurrent stroke among patients with a first PFO-associated ischemic stroke or TIA, different therapeutic strategies have received some support through randomized controlled trials (RCTs). These include chronic antithrombotic therapy (with either antiplatelet or anticoagulant agents) or closure of the PFO with a percutaneous device. Each is endorsed as a treatment option in national practice guidelines.[7-9] Six RCTs comparing device closure with medical therapy have been completed to date: CLOSURE I (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), Clinical Trial Comparing Percutaneous Closure of Patent Foramen Ovale Using the Amplatzer PFO Occluder with Medical Treatment in

Patients with Cryptogenic Embolism (PC) Trial, Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment (RESPECT), REDUCE (GORE® Septal Occluder Device for Patent Foramen Ovale (PFO) Closure in Stroke Patients), CLOSE (Patent Foramen Ovale Closure or Anticoagulants Versus Antiplatelet Therapy to Prevent Stroke Recurrence), and Device Closure Versus Medical Therapy for Cryptogenic Stroke Patients With High-Risk Patent Foramen Ovale (DEFENSE-PFO).[10-16] The 6 randomized trials were conducted over an 18-year period from 2000 to 2017. Overall with regard to clinical efficacy, study-level meta-analyses have demonstrated a beneficial reduction in recurrent ischemic stroke with PFO device closure plus long-term medical antithrombotic (primarily antiplatelet) therapy compared with that with long-term medical antithrombotic therapy (antiplatelet or anticoagulant) alone.[6,17,18] In the only study-level meta-analysis that accounted for the differential length of patient follow-up in the different trials, device closure compared with medical therapy alone reduced the rate of recurrent ischemic stroke (hazard ratio [HR], 0.30 [95% CI, 0.13-0.68]; *P* = .004).[6] However, absolute risks of stroke recurrence remain very low for some of these patients, even with medical therapy, and device closure is not without harms, including AF and procedural complications such as access site or retroperitoneal hemorrhage (1.01%), cardiac tamponade (0.17%), and cardiac perforation (0.06%).[6]

Clinical Uncertainty and Questions to Be Addressed

Despite the overall beneficial effects of closure device placement in patients with a first PFO-associated cerebral ischemic event, the best treatment option for any individual patient encountered in routine clinical practice is often quite unclear. When a patient has a stroke with an unclear cause (called a *cryptogenic stroke*), an echocardiogram may be performed to see if the patient has a PFO. Patent foramen ovale is present in ~25% of the general population, and patients with a PFO can either have a stroke through a PFO-related mechanism (eg, a paradoxical embolism) or through any other occult mechanism (eg, paroxysmal AF or minimally stenosing cervicocerebral atherosclerotic plaque). Patent foramen ovale closure is highly unlikely to reduce recurrence risk in patients whose index event has a cause unrelated to PFO, but it is typically impossible to know with certainty the cause in any individual with a PFO and

cryptogenic stroke. Studies to date have not been able to address this individual patient–level clinical uncertainty.

Study-level analysis of RCTs generally only bring forward for guidance the broad reference class of all patients qualifying for a trial. In study-level data subgroup analyses, several different patient characteristics modified or tended to modify the magnitude and even the presence of benefit of 1 therapy over another. Conventional (1-variable-at-a-time) subgroup analysis as reported in trials is frequently used to explore heterogeneity of treatment effects (HTE), but these have well-known issues both with regard to credibility and applicability to individuals, because patients differ in many ways simultaneously.[19-21] In the case of PFO-associated stroke, individuals may differ from one another in the probability that a PFO was causally related to the index event[22] and in the likelihood of a recurrent event. The coarse information so far reported from the 6 previous RCTs as well as from study-level meta-analyses of these RCTs is insufficient to fully inform the best treatment choice for each individual patient.[19-21]

To address these limitations and to optimize individual decision-making for patients with PFO-associated stroke, the trialists who conducted all 6 completed RCTs of secondary prevention therapies for PFO-associated stroke have joined in this study to pool the data sets from all studies and to perform an individual patient data (IPD) meta-analysis.

Scoring Systems That Predict the Causal Relationship of PFO to Stroke

To evaluate the HTE of PFO closure on stroke recurrence, we use previously developed scoring systems that help estimate the probability that a PFO discovered in the setting of a cryptogenic stroke is likely to be causally related to the stroke. The first system is the Risk of Paradoxical Embolism (RoPE) score,[22] and the second is the PFO-Associated Stroke Causal Likelihood (PASCAL) classification system.[5]

The RoPE Score

The RoPE scoring system is depicted in Table 1 and explicated in Appendix A2. Briefly, the RoPE score provides an estimate of the probability that a PFO discovered in the setting of

an otherwise-cryptogenic ischemic stroke is the cause of the stroke rather than an incidental finding, with a higher RoPE score corresponding to a higher probability. The RoPE score is based on 2 insights: (1) the prevalence of a PFO among patients with cryptogenic stroke (compared with its prevalence in the general population) can be used, via Bayes' theorem, to estimate an average *attributable fraction* (ie, the proportion of PFOs that are pathogenic rather than incidental), and (2) the presence or absence of a PFO in a patient with a cryptogenic stroke is predictable based on patient characteristics—so that a "patient-specific" attributable fraction can be estimated based on the probability of discovering a PFO conditional on patient characteristics. Intuitively, a PFO-related stroke is more likely in younger patients, in the absence of vascular risk factors, and in the presence of a superficial infarct on neuroimaging. In theory, because closure would reliably prevent strokes caused by paradoxical embolism and only strokes caused by PFO, the attributable fraction would be assumed to correspond to the relative risk reduction (RRR) of closure in preventing a future stroke.[23]

Table 1. The RoPE Score and PASCAL Classifications

RoPE score calculator[a]		
Characteristic		**Points**
No history of hypertension		1
No history of diabetes		1
No history of stroke or transient ischemic attack		1
Nonsmoker		1
Cortical infarct on imaging		1
Age, y		
18-29		5
30-39		4
40-49		3
50-59		2
60-69		1
≥70		0
Total RoPE score (sum of individual points) = _____		
PASCAL classification system[b]		
High RoPE score (≥7)	**High-risk PFO feature (LS and/or ASA)**[c]	**PFO-related stroke**
Absent	Absent	Unlikely
Absent	Present	Possible
Present	Absent	
Present	Present	Probable

Abbreviations: ASA, atrial septal aneurysm; LS, large shunt; PASCAL, PFO-Associated Stroke Causal Likelihood; PFO, patent foramen ovale; RoPE, Risk of Paradoxical Embolism.

[a]The RoPE score assesses the probability that a PFO discovered in the setting of an otherwise-cryptogenic stroke was pathogenically related to the stroke rather than an incidental finding. The RoPE score ranges from 0 to 10, with scores of 0 to 3 indicating a negligible likelihood that the stroke is attributable to the PFO and a score of 10 indicating an approximately 90% probability that the stroke is attributable to the PFO.

[b]PASCAL combines the RoPE score with the presence or absence of high-risk PFO features to determine the likelihood that the PFO was causally related to the index stroke. See Appendix A2 for details on RoPE and Appendix A3 for details on PASCAL.

[c]ASA is defined as ≥10 mm of excursion from midline. Large shunt size was defined in our database as >20 bubbles in the left atrium on transesophageal echocardiogram.

The ROPE score was developed for use on 9 different databases[22]; although some of these data were from Europe and thus not fully representative of ethnically and racially diverse American population, we note that the score performed consistently across all 9 databases, including those with more diverse samples (eg, Northern Manhattan Stroke Study [NOMASS]).[24]

The RoPE score has been externally validated to predict the presence of a PFO in the cryptogenic stroke population.[25,26] However, the RoPE score has 2 important limitations: (1) the methods to derive the RoPE score did not permit the inclusion of high-risk features of the PFO, and (2) patients with higher RoPE scores have lower stroke recurrence rates. Thus, the RoPE score may not provide comprehensive information for patient selection.[5,8]

The PASCAL Classification System

The PASCAL classification system, described in Table 1 and explicated in Appendix A3, addresses these limitations by integrating the information of the RoPE score with PFO functional and structural features physiologically expected and epidemiologically confirmed to potentiate PFO stroke risk—namely, large shunt size and the presence of an atrial septal aneurysm (ASA).[27-29] Based on these factors, this system algorithmically assigns a likelihood of causal relationship (Table 1).[30]

Overview of Study Goals and Specific Aims

This research encompasses an updated, pooled, IPD meta-analysis (IPDMA) by a collaboration of the trialists of all 6 completed RCTs comparing PFO closure with percutaneous devices plus medical therapy vs medical therapy alone,[31-33] and examines factors that influence which therapy is best for whom. We test the influence of a wide range of patient demographic, clinical, and cardiac (eg, size of right-to-left shunt, presence of ASA) features on the effects of device closure vs medical therapy. In addition, we assess the incremental added value for effect modification modeling of 2 existing multivariable scales/algorithms to grade the causal relationship between a PFO and an index cerebral ischemic event: the RoPE score and the PASCAL classification grade. This IPD pooled analysis was undertaken, motivated by new methods proposed for predictive HTE analyses, combining many covariates, to narrow the reference class for each individual to more granular, deeply similar patients.[19,20] Individual patient data meta-analysis has several advantages over study-level meta-analysis,[34] including standardization of analyses across studies, better handling of missing data via appropriate statistical methods, the ability to estimate conditional treatment effects (often with greater statistical power for tests of the null hypothesis than with unadjusted analyses of time-to-event

outcomes[6,12,14]), and the opportunity to assess HTE across subgroups of interest—the main goal of this study. In particular, IPDMA is an ideal substrate for risk modeling approaches to HTE analysis because it is better powered than individual trials and there is typically a greater degree of patient-level risk heterogeneity than in any given trial[35,36]:

- **Specific aim 1.** Perform an IPDMA comparing the broad strategy of placement of a PFO closure device plus best medical therapy with the broad strategy of best medical therapy alone for the prevention of recurrent stroke, including an exploration of clinically relevant subgroups.

- **Specific aim 2.** Examine whether (a) the RoPE score modifies the relative effect of device closure vs medical therapy for the prevention of recurrent stroke and (b) whether the RoPE-estimated attributable fraction correlates with the RRR associated with closure across levels of the RoPE score.

- **Specific aim 3.** Assess whether the PASCAL classification grade (which integrates the RoPE score with high-risk PFO features) modifies the relative effects of device closure and compare the net clinical benefit (ie, value of a model to improve decision-making) of applying the RoPE score and the PASCAL classification grade for treatment selection against a default “treat-all” strategy.

PARTICIPATION OF PATIENTS AND OTHER STAKEHOLDERS

No patient engagement occurred in this study. We closely engaged with trialists as stakeholders in planning analyses, discussing results, and reviewing manuscripts and other publications. Trialists were instrumental in facilitating primary data collection, particularly from neuroimages and echocardiograms of the REDUCE trial, where several key variables were not in the database. The trialists provided invaluable feedback for manuscripts by email, answered queries regarding missing data, and helped harmonize data across trial databases. Although not all were retained, many of these edits were incorporated into the final submitted versions of the manuscripts. The trialists were also co-authors on the 2 abstracts submitted to International Stroke Conference 2022 and Scientific Sessions 2021—2 conferences with excellent reputations and large platforms for disseminating project results. All the trialists are authors on both the Systematic, Collaborative, PFO closure Evaluation (SCOPE) protocol, which was submitted for publication to *Systematic Reviews* in February 2021, and the main SCOPE results paper, which was recently published in the *Journal of the American Medical Association* (*JAMA*).

Engaging with the trialists as stakeholders included improved scientific rigor and the credibility and potential for increased dissemination of research findings. The trialists are well-recognized leaders in PFO, based in different countries (including 3 American teams, 2 European teams, and 1 Asian team), and so their collaboration and input greatly improved the quality of the study and lent greater credibility to the findings. In addition, we anticipate that the trialists will continue to aid in dissemination of the results to the scientific community. The trialists have also helped to refine the study to ensure its usefulness in clinical decision-making. Through this project, the team was able to build valuable relationships with experts in PFO closure and form the SCOPE Consortium and PFO Data Consortium, both of which will continue beyond this project.

METHODS

Note: *Much of the material presented in this section previously appeared in the following peer-reviewed publication: Kent DM, Saver JL, Kasner SE, et al. Heterogeneity of treatment effects in an analysis of pooled individual patient data from randomized trials of device closure of patent foramen ovale after stroke.* JAMA. *2021;326(22):2277-2286. doi:10.1001/jama.2021.20956*[1]

Study Overview

We performed a pooled IPDMA through a collaboration of the trialists of all 6 completed RCTs comparing PFO closure with percutaneous devices plus medical therapy vs medical therapy alone[31-33] and examined factors that influence which therapy is best for whom. We tested the influence of a wide range of patient demographic, clinical, and cardiac features on the effects of device closure vs medical therapy. In addition, we assessed the incremental added value for effect modification modeling of 2 existing multivariable scales/algorithms to grade the causal relationship between a PFO and an index cerebral ischemic event: the RoPE score and the PASCAL classification grade.

Study Setting/Participants

The study investigators established the SCOPE Consortium to undertake meta-analysis of pooled IPD. Study methods adhered to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) IPD guidelines, and the protocol was registered on the international prospective register of systematic reviews, PROSPERO (CRD42020186537).[37] The collaboration included all randomized phase 3 trials comparing PFO closure with medical therapy for recurrent stroke prevention published by September 2021. Trial methodology was assessed using the Risk of Bias 2.0 tool. Investigators were contacted, and data were collected and harmonized (for details, see Appendix A1 and Kent et al[38]). The data were harmonized and analyzed by 2 statisticians at the Predictive Analytics and Comparative Effectiveness (PACE) Center and Tufts Medical Center to ensure they accurately matched the values reported by the trials. Appendix Table 1 in Appendix A1 lists the variables that were harmonized across trials. Though many variables were defined consistently between trials, Appendix A5 describes

variables that required harmonizing, including ASA and shunt size. When disagreement arose or database definitions were inconsistent, 2 clinicians adjudicated the variables. Some key variables were not present in certain databases; thus, harmonization also required rereading of REDUCE echocardiograms and MRIs, which was performed by our team blinded to treatment assignment and outcome. The PC Trial was missing a key RoPE variable (superficial infarct on neuroimaging), and neuroimages from this trial could not be obtained. The following 6 trials are included in this IPDMA: the CLOSE trial,[10] The CLOSURE I trial,[11] DEFENSE-PFO trial,[12] the PC Trial[13] the REDUCE trial,[14] and the RESPECT trial[15,16] (Appendix Table 5). All trials compared the broad strategy of PFO closure device plus best medical therapy with the broad strategy of best medical therapy alone to prevent stroke recurrence in patients with PFO-associated cerebral ischemia. Some heterogeneity in the risk of bias is anticipated because of trial design differences and data missingness.[39-41] Typical of device or operative trials, all studies had Prospective Randomized Open Blinded End-point (PROBE) designs, with the exception of the DEFENSE-PFO study, which did not have blinded adjudication of outcome. Th details of these trials are described briefly in Appendix B2 and in the sections below.

Based on a systematic search performed of Medline and Embase through September 2021, these studies represent the totality of available randomized evidence on the use of percutaneous implanted devices for PFO closure vs medical therapy in patients with PFO-associated cerebral ischemic events (Appendix A1). All contributing RCTs were asked to provide the individual patient–level study data shown in Appendix Table 1. Data entered into the central SCOPE database were a limited data set, with all high-level patient identifiers removed. All data were collected under the aegis and supervision of the SCOPE steering committee, and were integrated and stored at the PACE Center at Tufts Medical Center in Boston, Massachusetts.

Interventions and Comparators or Controls

All trials compared PFO closure with standard medical therapy. Treatment assignment was randomized by computer-generated, pseudorandom numbers. Patent foramen ovale closure was attempted with various devices, specifically detailed below:

- ***CLOSE*** used a wide variety of devices including, but not limited to, Amplatzer PFO Occluder (AGA Medical), Intrasept PFO occluder (Cardia), Premere Patent Foramen Ovale Closure System (St Jude Medical), STARFlex septal occlusion system (NMT Medical Inc), Amplatzer Cribriform Occluder (AGA Medical), and Figulla Flex II PFO Occluder (Occlutech, Inc). All patients who underwent PFO closure received dual-antiplatelet therapy (75 mg of aspirin plus 75 mg of clopidogrel daily) for 3 months, followed by single-antiplatelet therapy.

- ***CLOSURE I*** used the STARFlex septal closure system. After closure, all patients were given a standard antiplatelet regimen of clopidogrel 75 mg daily for 6 months and aspirin 81 or 325 mg daily for 2 years.

- ***DEFENSE-PFO*** used a single device (Amplatzer PFO Occluder, St Jude) for closure. Patients who underwent PFO closure were generally recommended to start a dual-antiplatelet regimen (aspirin 100 mg daily plus clopidogrel 75 mg daily) for at least 6 months after the procedure. However, the local investigator or attending neurologists could choose to continue either antiplatelet therapy or anticoagulation based on the individual's risk/benefit ratio.

- The ***PC Trial*** used the Amplatzer PFO Occluder For patients randomized to closure, antithrombotic treatment was recommended, including acetylsalicylic acid at a dose of 100 to 325 mg per day for at least 5 to 6 months, as well as ticlopidine at a dose of 250 to 500 mg per day or clopidogrel at a dose of 75 to 150 mg per day for 1 to 6 months. For patients with intolerance to acetylsalicylic acid, ticlopidine or clopidogrel alone was recommended.

- ***REDUCE*** used either the Helex septal occluder (HELEX; W.L. Gore and Associates) device (implanted through late 2012) or the Cardioform Septal Occluder (GSO; W.L. Gore and Associates). All patients received antiplatelet therapy chosen by the local investigator. Patients in the PFO closure group were treated with 1 dose of clopidogrel (300 mg) before or immediately after the procedure, if they were not already receiving clopidogrel, followed by 75 mg daily for 3 days, and then resumed or started the chosen antiplatelet therapy option.

- ***RESPECT*** used the Amplatzer PFO Occluder. Patients assigned to closure also received 81 to 325 mg of aspirin and clopidogrel for 1 month after placement of the device, followed by aspirin monotherapy for 5 months. Subsequently, antiplatelet therapy was administered at the discretion of the site investigator.

The control groups received the following treatments:

- ***CLOSE*** used oral anticoagulants with vitamin K antagonists (with a target international normalized ratio [INR] of 2-3) or with direct oral anticoagulants (for patients assigned to oral anticoagulants). Patients assigned to antiplatelet therapy alone could receive aspirin, clopidogrel, or aspirin combined with extended-release dipyridamole.

- ***CLOSURE I*** used 1 of the following: warfarin with a target INR of 2 to 3 with an ideal target of 2.5; aspirin 325 mg daily; aspirin 81 mg daily only, allowed for documented gastrointestinal intolerance; or aspirin 81 mg daily with warfarin. Clopidogrel, ticlopidine, and aspirin plus extended-release dipyridamole were not allowed in the medical arm.

- For ***DEFENSE-PFO***, all patients received either antiplatelet therapy or anticoagulation chosen by the local investigator. Antiplatelet therapy included aspirin, aspirin plus clopidogrel (75 mg per day), or aspirin plus cilostazol (200 mg per day). Warfarin was used to maintain the target INR of 2 to 3.

- For the ***PC Trial***, antithrombotic treatment in the medical group was left at the discretion of the treating physician, which could include antiplatelet or oral anticoagulation.

- For ***REDUCE***, all patients received antiplatelet therapy chosen by the local investigator. Antiplatelet therapy could consist of aspirin alone (75-325 mg once daily), a combination of aspirin (50-100 mg daily) and dipyridamole (225-400 mg daily), or clopidogrel (75 mg once daily). Other combinations of antiplatelet drugs and anticoagulants were not permitted. The chosen antiplatelet therapy could be initiated immediately after randomization.

- ***RESPECT*** used 1 of the following: aspirin, warfarin, clopidogrel, or aspirin combined with extended-release dipyridamole. Aspirin with clopidogrel was also originally permitted but was eliminated in 2006 to conform to a change in secondary stroke prevention guidelines.[42]

The populations and treatment comparisons evaluated across these 6 trials were judged to be similar enough to justify making quantitative pooled analyses of their data sets.

Study Outcomes

The primary efficacy end point was recurrent ischemic stroke: an acute neurological deficit, presumed to be caused by focal ischemia, and either symptoms persisting for at least 24 hours or symptoms persisting less than 24 hours but associated with neuroimaging findings of a new, neuroanatomically relevant infarct.[43,44] This definition is the preferred definition for clinical care and for research trial stroke end points, as per national recommendations from the American Heart/Stroke Association, the National Institutes of Health,[43] and the US Food and Drug Administration.[44]

The secondary efficacy outcomes were (1) recurrent PFO-associated ischemic stroke (recurrent ischemic strokes adjudicated as not being attributable to another mechanism by investigators of the individual trials); (2) the composite of recurrent ischemic stroke or early (periprocedural or equivalent medical therapy time frame) all-cause mortality; (3) the composite of recurrent ischemic stroke, early all-cause mortality, or any vascular death; (4) the composite of recurrent ischemic stroke, TIA, or vascular death; (5) disability-worsening recurrent ischemic stroke; and (6) any recurrent stroke, ischemic or hemorrhagic.

Disability-worsening stroke was defined as a new stroke associated with any increase in the modified Rankin score at day 30 or longer poststroke. For subgroup analysis, in addition to the primary end point, only the secondary end point with the greatest number of events was examined: the composite of recurrent ischemic stroke, TIA, or vascular death.

For technical efficacy outcomes, we report effective PFO closure at 6 to 18 months (latest observation time point), defined as no or only trace residual shunting as the lead technical efficacy outcome. We also report complete PFO closure at 6 to 18 months (latest observation time point), defined as no residual shunting.

Five safety outcomes were examined, as defined in the primary trials: all serious adverse events (SAEs); major vascular procedural complication; AF; major bleeding episode; and venous thromboembolism (VTE; deep venous thrombosis/pulmonary embolism). Atrial fibrillation was analyzed in 2 ways: (1) any AF and (2) AF present any time beyond the first 45 days

postrandomization (to exclude transient periprocedural events). The following components of procedure-related adverse events are also reported: access site hemorrhage, retroperitoneal hemorrhage, cardiac tamponade, and cardiac perforation.

Sample-Size Calculations and Power

No sample-size calculations were performed for the primary analysis comparing a closure device with medical therapy because we had no control over the design of the studies included in our analyses, the studies represent the totality of available randomized evidence on PFO closure, and each study was planned based on separate prospective power calculations.

Analytical and Statistical Approaches

All analyses were performed on the pooled data. The primary analyses for efficacy outcomes assessed patients according to the treatment group to which they were randomized (ie, intention to treat [ITT]). Three additional analyses were conducted in (1) patients according to the treatment they actually received if any crossover occurred (ie, "as-treated," defined in Appendix A4), (2) patients without major protocol deviations (ie, "per-protocol," defined in Appendix A4), and (3) analysis of the ITT population, using instrumental variable analysis to further control for potential pre- and postrandomization sources of bias in estimating treatment effects (ie, "contamination-adjusted ITT analysis").[45] These analyses were adjusted for prerandomization covariates.[46] Safety outcomes were analyzed in the as-treated population only.

The secondary efficacy outcomes were analyzed using sequential gatekeeping[47] in the following order: (1) recurrent PFO-associated ischemic stroke; (2) the composite of recurrent ischemic stroke or early all-cause mortality; (3) the composite of recurrent ischemic stroke, early all-cause mortality, or any vascular death; (4) the composite of recurrent ischemic stroke, TIA, or vascular death; (5) disability-worsening recurrent ischemic stroke; and (6) any recurrent stroke, ischemic or hemorrhagic. The sequential gatekeeping strategy tests a prespecified hierarchy of outcomes and stops when an outcome test is not statistically significant, to control for multiplicity. Secondary efficacy outcomes that were unavailable uniformly across all trials

were to be removed from the gatekeeper hierarchy and examined in exploratory analyses where available.

For all time-to-event outcomes, the equality of the survivor functions was assessed using a stratified (by trial) log-rank test.[22,25] Kaplan-Meier estimates were obtained at 6, 12, 24, and 60 months for each treatment group. After confirming no violation of proportional hazards assumptions (see Appendix A1), effects were estimated using Cox proportional hazards regression with a study-specific random effect.[48] In this 1-stage analysis, a study-specific random effect was used to account for within-study homogeneity in outcomes and a fixed treatment effect.[49] The CLOSE trial, in which some patients were randomized to antiplatelet vs device and others to anticoagulant vs device, was treated as 2 trials. The Breslow method was used for tied survival times.[48] Safety analyses were based on comparisons of event proportions between treatment groups, using the Cochran-Mantel-Haenszel test (stratified by trial).[50,51] For all hypothesis-testing analyses, a 2-sided significance threshold of $P = .05$ was used, without adjustments for multiple testing.[52] All analyses were conducted using SAS (version 9.4) and R (version 4.0.2).

The primary efficacy analysis was adjusted for the following covariates: age, sex, prior myocardial infarction, diabetes, hypertension, hyperlipidemia, prior stroke or TIA, smoking status, index event (stroke vs TIA), ASA (≥10 mm of excursion from midline; definition in Appendix A5), PFO shunt size (large vs small; definition in Appendix A5), and presence vs absence of a visible superficial infarction on neuroimaging. This analysis yields a conditional average treatment effect, which is felt to be more appropriate for individual patient decisions.[53] As a stability analysis, the unadjusted effect estimate is also reported. Additional details of the statistical analysis are provided in Appendix A1.

Missing Data

In the primary analysis, patients who exited the trials early were assumed to have outcome events that were noninformative under the missing-at-random (MAR) assumption and were censored at last follow-up. Two sensitivity analyses were performed: a multiple-

imputation analysis (see Appendix A1) with covariate adjustment[54] and a tipping-point analysis.[55,56] For the conditional (adjusted) analysis and for subgroup analyses, multiple imputation to impute missing covariates was used as needed.[57] We presented missingness by study for each variable of interest.

Subgroup and Interaction Analyses

We assessed whether treatment was associated with differential effects across participant subgroups. A primary HTE analysis was based on the RoPE score. We tested the significance of effect modification using the RoPE score as a continuous variable and dichotomized the RoPE score into high (≥7) and low (<7) groups for presentation. This dichotomization was based on the distribution of scores in the original RoPE database population and consideration of the attributable fraction across scores. Because the PC Trial was missing a key RoPE variable (superficial infarct on neuroimaging), multiple imputation was used in the main analysis to include all trials, but we performed 2 stability analyses: 1 using a reduced 9-point RoPE score, excluding the imaging variable; and a 5-trial analysis excluding the PC Trial. An additional primary HTE analysis was based on the 3 levels of the PASCAL classification system: "unlikely," "possible," and "probable." We conducted sensitivity analyses of the primary HTE analysis that included only the 5 trials that predominantly tested the double-disk device class, which is the class that is currently commercially available (ie, the CLOSURE trial of an umbrella-clamshell device will be excluded).

We also report the correlation between the RoPE-estimated attributable fraction and the RRR with PFO closure using a Spearman correlation coefficient. We hypothesized that the RoPE-estimated attributable fraction would strongly correlate with the RRR with closure across RoPE strata, with higher relative effects in higher-RoPE-score groups. To include trials that might be missing a RoPE variable (eg, the PC Trial is missing the neuroradiology variable), we performed the above-described analysis using reduced 9-point RoPE score.

Secondary (exploratory) subgroup analyses were performed across each of the following 9 variables: sex (male vs female), age (≥45 vs <45 years), ASA (present vs absent [see

Appendix A5 for details]), shunt size (approximately ≤20 bubbles in the left atrium within 3 cardiac cycles, depending on classifications in individual studies [see Appendix A5 for details]), visible superficial infarction on neuroimaging (vs no visible superficial infarction), history of hypertension (vs no history of hypertension), history of diabetes (vs no history of diabetes), prior stroke or TIA (vs no prior stroke or TIA), and current smoking at study entry (vs no current smoking). Although these analyses are considered exploratory, we report *descriptive* P *values.* We assessed effect modification by including appropriate product terms for each variable and randomization assignment in Cox regression models. We used likelihood ratio tests to compare the models including such terms with models not including them. We also perform interaction analyses to assess treatment effect modification by age (in years).

Stability Analyses

To assess the robustness of our findings, we performed leave-one-out analyses: the main analyses were repeated after excluding each trial in turn, with particular interest in the analysis omitting the CLOSURE trial that tested an umbrella-clamshell device class no longer used in clinical practice. We also performed a 2-stage meta-analysis of the 6 studies using the inverse variance method and restricted maximum likelihood estimator (ie, a study-level meta-analysis). We performed separate unadjusted Cox regression analyses for each trial, followed by a 2-stage meta-analysis of the 6 studies using the inverse variance method and restricted maximum likelihood estimator.

Measures of Discrimination for Treatment Selection Markers

To examine whether the PASCAL classification system modifies the relative effect of device closure, we used 2 recently developed, threshold-free global measures of discrimination for treatment selection markers: the concordance statistic (C statistic) for benefit and the concentration of benefit index (Cb).[58] For these analyses, the base-case analysis includes only the 5 trials that predominantly tested the double-disk device class, which is the class that is currently commercially available (ie, the CLOSURE trial of an umbrella-clamshell device is excluded); a sensitivity analysis including the CLOSURE trial was also performed. We repeated

the comparison of the analysis of the PASCAL classification with the same analysis based only on the RoPE score.

The C-for-benefit examines discrimination by matching patients discordant on treatment assignment based on their scores (PASCAL or RoPE) and classifying these pairs of patients into 3 observed-benefit categories according to their outcomes: benefit (treatment 0, control 1), neutral (treatment 1, control 1 or treatment 0, control 0), or harm (treatment 1, control 0). A C statistic can then be calculated for this trinary outcome (ie, observed benefit), representing the probability that from 2 randomly selected pairs of matched individuals with unequal observed benefit, the pair with higher observed benefit also has a higher score. Matching was performed within each trial. Although benchmarks have not yet been firmly established, a Cb of 0.5 is consistent with a useless covariate-informed selection tool, whereas—based on our experiences thus far—a Cb of 0.6 is very good. A 95% CI is calculated based on bootstrapping with 1000 resampling procedures.

The Cb is based on the ratio between the number of outcomes that would be prevented if only patients above a certain treatment threshold are treated compared with population-wide therapy vs the proportion of total patients falling above the threshold, integrated across all thresholds. The function is directly analogous to a Lorenz function for outcome prediction,[59,60] and the Cb is directly analogous to the Gini coefficient, a summary measure of the skewness of this function (ie, often used as a measure of income or wealth inequality across a population). We adapted the function, used for individual patient–level predicted benefit, for varying levels of risk corresponding to the categorical classification of the PASCAL and RoPE scores. The Cb is interpretable: (1 − concentration for benefit) is the ratio of the average benefit of treatment when given to patients at random vs when given to patients with a score above threshold, integrated across all thresholds. When the Cb is 0, everyone is expected to get the same benefit (and the tool is useless); when Cb is 100, the threshold perfectly divides those who benefit from those who do not.

Net Benefit of Treatment Selection

Whether improvements in statistical performance are likely to lead to improvements in decision-making can be difficult to infer from measures of calibration and discrimination alone. Thus, we examined the net benefit of treatment selection of the 2 tools (RoPE and PASCAL) compared with population-wide treat-all and treat-none strategies across a range of decision thresholds (ie, examining the net benefit of closing only PFOs in patients above a given decision threshold). For these analyses, the base-case analysis includes only the 5 trials that predominantly tested the double-disk device class, which is the class that is currently commercially available (ie, the CLOSURE trial of an umbrella-clamshell device is excluded); a sensitivity analysis including the CLOSURE trial is also performed.

The risk difference in the primary outcome (ischemic stroke) is reported across each threshold of the RoPE score and the PASCAL classification grade. The outcome rates and risk differences in serious adverse events (and of each of the 3 major component safety outcomes: AF beyond 45 days, serious bleeding, or periprocedural complication) are reported across each threshold.[61]

We also assessed the net benefit of treatment selection using a model-based strategy vs both a treat-all strategy and a treat-none strategy using decision curve analysis.[62,63] Briefly, the net benefit is defined as the tradeoff between treatment benefits and potential harms, where harms can be expressed as the number of patients a doctor is willing to treat (NWT) to prevent 1 event. Decision thresholds from 0.5% to 5% (corresponding to NWT 200-20) were chosen for measuring the net benefit for the decrease in the 2-year event rate. This analysis yields the optimal strategy (ie, either treat all or a particular tool with the highest net benefit) for any given NWT. For example, if the preferred NWT is 100 (equal to a treatment threshold of 1%), we would decide to treat only patients with an expected treatment benefit above this threshold, and the net benefit of using the model-based strategy would be the absolute risk reduction in the treated group minus 0.01 times the proportion of patients treated.

Changes to the Original Study Protocol

The following protocol changes were made based on discussion at the February investigator meeting:

1. Classified safety outcome for AF as periprocedural vs persistent (based on presence or absence more than 45 days from randomization)
2. Made the primary analysis covariate adjusted for the prespecified variables (dependent on their uniform availability) of age, sex, coronary artery disease, diabetes, hypertension, hyperlipidemia, prior stroke, smoking status, index event (stroke vs TIA), hypermobile septum, and PFO shunt size (large vs small). This approach increases power, and the conditional average treatment effect is generally considered the estimate of interest for individual patient decision-making
3. Changed classification of large vs small shunt using a bubble cutoff of 20 instead of 10. This was largely based on availability across study databases
4. Added a dichotomous HTE analysis of the RoPE score, ≥7 vs < 7
5. Added an analysis of the correlation between the RoPE-estimated attributable fraction and the RRR. These items were added based on a recently completed analysis

The following revisions were accepted and incorporated into the protocol after receiving suggestions from investigators in the February meeting:

1. Extensive revisions of the initial background were made to be consistent with new nomenclature and paradigms reflecting a consensus group statement I (recently published in *JAMA Neurology*[5]) from the old "cryptogenic stroke with PFO" to the current "PFO-associated stroke" paradigm. The entire introduction was revised
2. Added the PASCAL grading system (also from our joint *JAMA Neurology* PFO-Associated Stroke Paper),[5] which was assessed as a risk stratification tool in the IPDMA. This tool integrates the RoPE score with high-risk anatomic features of the PFO. As a third specific aim, we assessed whether the PASCAL classification grade modifies the relative effects of device closure and compared the net clinical benefit of applying the RoPE score and the PASCAL classification grade for treatment selection against a default treat-all strategy. We added an extensive section to the analysis plan to address this aim
3. Added technical efficacy outcomes (effective PFO closure, complete PFO closure)
4. Added analysis of outcomes of interest at 60 months, in addition to 6, 12, and 24 months

5. Revised analysis for per-protocol, as-treated (ie, got the device vs did not get the device), and contaminated-adjusted ITT analyses
6. Suggested revisions to the governance structure based on template from the Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke Trials (HERMES) endovascular thrombectomy Trialist collaborative
7. Several minor corrections to the descriptions of the 6 RCTs

The following changes were made based on discussion at the trialist webinar:

1. Additional safety outcomes to be included (in addition to major vascular procedural complications, AF, and major bleeding episodes) and defined according to the definitions of the primary studies: access site hemorrhage, retroperitoneal hemorrhage, pericardial tamponade, cardiac perforation, VTE, and all SAEs

2. It was suggested that, rather than having just a single secondary clinical efficacy end point, we consider the following secondary clinical efficacy end points (after the primary efficacy end point of recurrent ischemic stroke): recurrent PFO-associated ischemic stroke; recurrent ischemic stroke or early all-cause mortality; recurrent ischemic stroke, early all-cause mortality, or any vascular death; recurrent ischemic stroke, TIA, or vascular death; disabling recurrent ischemic stroke; and any recurrent stroke, ischemic or hemorrhagic. These secondary clinical efficacy end points would be tested using the serial "gatekeeping" strategy for multiplicity control, allowing testing of multiple secondary end points with rigor and statistical power. Secondary effectiveness outcomes that were unavailable uniformly across all trials were removed from the gatekeeper analyses and examined in exploratory analyses with the trials in which they are available. We note that disabling ischemic stroke and PFO-associated stroke may not be ascertainable across all data sets and may have to be removed as secondary clinical end points

3. Different approaches were suggested for sensitivity analyses to handle missing outcome data. In the primary analysis, we assumed that patients who exited the trials early have outcome events that are noninformative under the MAR assumption and censored these patients at last follow-up. This assumes that censoring occurs independent from the possibly unobserved time to event: that is, the possibly unknown true time to the event for a patient is the same regardless of whether it is actually observed (or whether censoring occurs before it). Nevertheless, this MAR assumption may not hold, and treatment effect estimates may be sensitive to this especially when censoring is imbalanced with respect to treatment assignment. Thus, if rates of patients exiting the

trials early are substantial (ie, >10% of all the expected follow-up time), a sensitivity analysis was performed

Disabling stroke was defined as an increase in the modified Rankin Scale (mRS) score of at least 1 point from the last measured mRS score before a stroke recurrence. The worsened mRS score must have been ascertained at least 30 days from the stroke recurrence. If disabling stroke could not be ascertained across databases, it was removed as a secondary end point in the main analysis; an exploratory analysis was considered.

RESULTS

Note: *Much of the material presented in this section previously appeared in the following peer-reviewed publication: Kent DM, Saver JL, Kasner SE, et al. Heterogeneity of treatment effects in an analysis of pooled individual patient data from randomized trials of device closure of patent foramen ovale after stroke.* JAMA. *2021;326(22):2277-2286. doi:10.1001/jama.2021.20956*[1]

The systematic search identified 6 trials that had enrolled 3740 participants who had been followed for a median of 57 months (IQR, 24-64 months) (Appendix B1). The trials were conducted from 2000 to 2017. Trial details can be found in Appendix B2. All trials had some concerns for risk of bias, generally related to their PROBE design (ie, referral for blinded end point adjudication was not blinded for treatment assignment) or because of missing outcome data (Appendix B3), but none were rated as high risk of bias. Patient characteristics in the pooled cohort are shown in Table 2 (and for each study in Appendix B4).

Table 2. Baseline Patient Characteristics From 6 Pooled Trials of Device Closure vs Medical Therapy for PFO-Associated Stroke

Variable	Device (n = 1889)	Medication therapy (n = 1851)
Age, median (IQR), y	46.2 (39.0-52.7) (n = 1882)	46.0 (39.0-53.0) (n = 1846)
Sex, male, No. (%)	1024 (54.2)	1034 (55.9)
Sex, female, No. (%)	865 (45.8)	817 (44.1)
Hyperlipidemia, No. (%)	720 (38.1)	632 (34.1)
Hypertension, No. (%)	512 (27.1)	456 (24.6)
Tobacco, No./total No. (%)[a]	379/1889 (20.1)	364/1849 (19.7)
Diabetes, No. (%)	106 (5.6)	106 (5.7)
Index stroke (vs TIA[b]), No./total No. (%)	1766/1888 (93.5)	1718/1850 (92.9)
Presence of a superficial infarct, No./total No. (%)[c]	1003/1420 (70.6)	971/1432 (67.8)
Prior stroke or TIA, No. (%)	310 (16.4)	285 (15.4)
Prior stroke, No./total No. (%)	134/1888 (7.1)	105/1851 (5.7)
Large shunt, No./total No. (%)[d]	767/1787 (42.9)	815/1743 (46.8)
ASA, No./total No. (%)[e]	587/1786 (32.9)	597/1792 (33.3)

Abbreviations: ASA, atrial septal aneurysm; DEFENSE-PFO, Device Closure Versus Medical Therapy for Cryptogenic Stroke Patients With High-Risk PFO; PC, Clinical Trial Comparing Percutaneous Closure of Patent Foramen Ovale Using the Amplatzer PFO Occluder with Medical Treatment in Patients with Cryptogenic Embolism; PFO, patent foramen ovale; RESPECT, Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment; TIA, transient ischemic attack.

[a]Defined as current smoker in DEFENSE-PFO, PC Trial, RESPECT, and CLOSE; current smoker or quit within past 30 days in CLOSURE; and current smoker or quit less than 12 months ago in REDUCE.

[b]Defined as symptoms persisting less than 24 hours and not associated with neuroimaging findings of a new, neuroanatomically relevant infarct.

[c]Not reported in PC Trial.

[d]More than 20 bubbles in the left atrium on transesophageal echocardiogram for all trials except CLOSURE (>25 bubbles) and CLOSE (>30 bubbles) (see Appendix A5 for details).

[e]See Appendix A5 for details.

Primary and Secondary Efficacy Outcomes

During a median follow-up time of 57 months, a total of 121 primary end point ischemic stroke events occurred in the pooled study population. Treatment with PFO closure was associated with reduced incidence of recurrent ischemic stroke (Table 3, Figure 1). The annualized incidence of stroke with medical therapy was 1.09% (95% CI, 0.88%-1.36%), and that

with device closure was 0.47% (95% CI, 0.35%-0.65%) (adjusted HR, 0.41 [95% CI, 0.27-0.60]; *P* < .001). Secondary outcomes showed results that were consistent with the primary outcome (Table 3), except for disability-worsening stroke, which was limited because of missingness.

Table 3. Primary and Secondary Efficacy Outcomes

	Overall outcome rate events/100 person-years (95% CI) (No. of events/n)		2-y absolute difference,[a] %	HR (95% CI)		*P* value
	Device	Medical therapy	ARR (95% CI)	Unadjusted HR	Adjusted HR[b]	
Primary efficacy outcome						
Recurrent ischemic stroke[c]	0.47 (0.35-0.65) (39/1889)	1.09 (0.88-1.36) (82/1851)	1.72 **(0.73-2.72)**	0.42 (0.29-0.62)	0.41 (0.28-0.60)	<.001
Secondary efficacy outcomes (in hierarchical order)						
1. PFO-associated recurrent ischemic stroke[d]	0.24 (0.15-0.40) (16/1238)	0.90 (0.69-1.18) (53/1179)	2.21 (1.08-3.34)	0.25 (0.14-0.45)	0.24 (0.14-0.43)	<.001
2. Recurrent ischemic stroke or early all-cause mortality	0.47 (0.35-0.65) (39/1889)	1.09 (0.88-1.36) (82/1851)	1.72 (0.73-2.72)	0.42 (0.29-0.62)	0.41 (0.28-0.60)	<.001
3. Recurrent ischemic stroke, early all-cause mortality, or vascular death	0.55 (0.41-0.73) (45/1889)	1.15 (0.93-1.42) (86/1851)	1.62 (0.60-2.64)	0.45 (0.32-0.65)	0.44 (0.31-0.64)	<.001
4. Recurrent ischemic stroke, TIA, or vascular death	1.08 (0.88-1.34) (88/1889)	1.72 (1.44-2.04) (127/1851)	1.61 (0.27-2.96)	0.61 (0.46-0.80)	0.60 (0.45-0.79)	<.001
5. Disability-worsening recurrent ischemic stroke[e]	0.16 (0.09-0.27) (13/1685)	0.27 (0.17-0.41) (20/1641)	0.18 (−0.39 to 0.75)	0.62 (0.31-1.25)	0.59 (0.37-1.22)	.14

Abbreviations: ARR, absolute risk reduction (medical therapy − device); ASA, atrial septal aneurysm; HR, hazard ratio; PC, Clinical Trial Comparing Percutaneous Closure of Patent Foramen Ovale Using the Amplatzer PFO Occluder with Medical Treatment in Patients with Cryptogenic Embolism; PFO, patent foramen ovale; TIA, transient ischemic attack.

[a]Absolute difference calculated as differences in Kaplan-Meier event rates at 2 years.

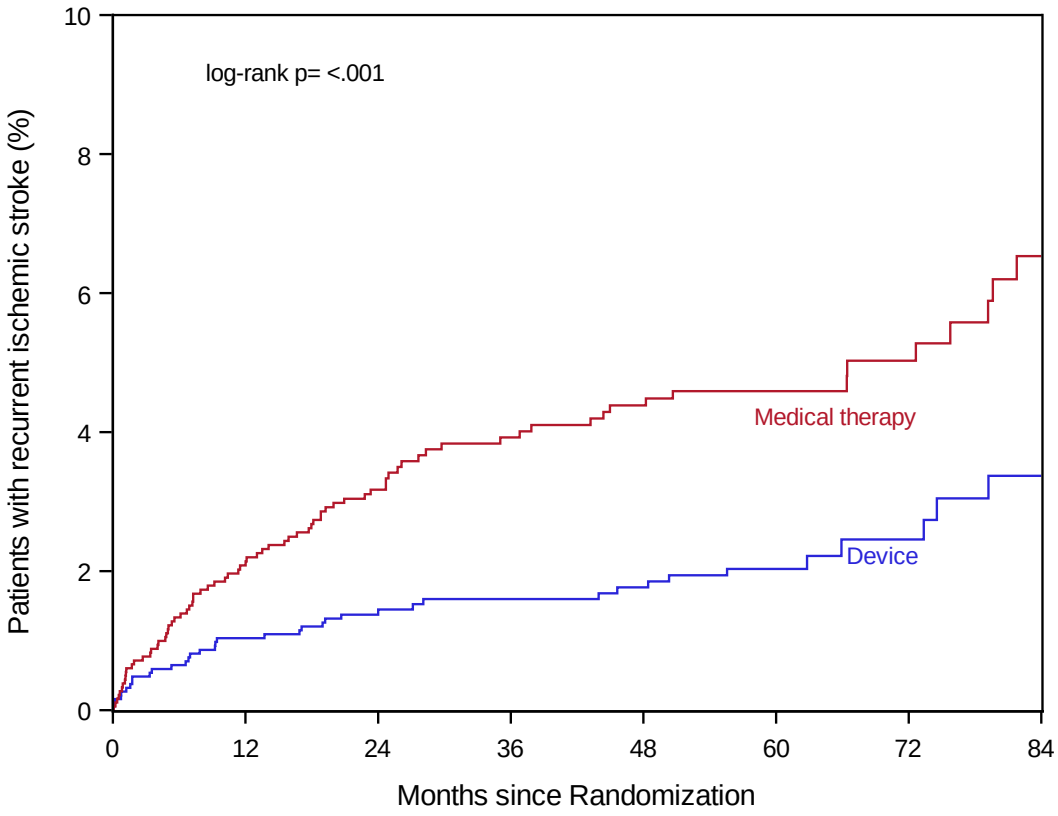
[b]Accounting for age, sex, prior myocardial infarction, diabetes, hypertension, hyperlipidemia, prior stroke or TIA, smoking status, index event (stroke vs TIA), ASA, PFO shunt size (large vs small, definition in Appendix A5), and superficial infarction on neuroimaging (present vs absent).

[b]The median time to the primary outcome of recurrent ischemic stroke was 13.7 months (interquartile range, 4.8-29.7 months; n = 121).

[d]No data for PC Trial and CLOSURE trial.

[e]Assume missing outcome is not disabling (no data for PC Trial).

Figure 1. Recurrent Ischemic Stroke Kaplan-Meier Curve



No. at Risk								
Device	1889	1771	1338	1245	1155	854	365	262
Medical therapy	1851	1668	1194	1094	971	699	390	253

The median time to the primary outcome of recurrent ischemic stroke was 13.7 months (IQR, 4.8-29.7 months; n = 121).

Stability of the Main Results

The main results for the primary outcome were robust to alternative analytic approaches. Hazard ratios were similar for the unadjusted (Table 3), per-protocol (HR, 0.37 [95% CI, 0.24-0.57]), and as-treated (0.40 [95% CI, 0.27-0.59]) analyses. Leave-one-out analyses showed that no single trial was overly influential (Appendix B5); the adjusted HR for closure ranged from 0.32 (95% CI, 0.20-0.51) without CLOSURE to 0.45 (95% CI, 0.30-0.66) without CLOSE-A (CLOSE trial randomization group 2 with contraindications to oral anticoagulants, Appendix B4). Early exiting and retained patients were largely similar (Appendix B6), although patients who had early exit from the trials posttreatment more often had prior stroke, a

superficial infarct, and a large shunt. In the multiple-imputation analysis with covariate adjustment, the HR for ischemic stroke with PFO closure vs medical therapy was 0.41 (95% CI, 0.26-0.64; *P* < .001). The tipping-point analysis showed robustness to missing data: imputed outcomes for patients not followed to the end of each trial would have to be approximately 2-fold higher in the device than in the medical group to nullify the significance of the main effect (Appendix B7). A 1-stage meta-analysis of the 6 studies using the inverse variance method and restricted maximum likelihood estimator revealed the following values: HR for fixed effects model of 0.54 (95% CI, 0.36-0.81), HR for random effects model of 0.52 (95% CI, 0.30-0.88), and test of heterogeneity *P* = .44.

Safety Outcomes

Safety analyses are shown in Table 4. Atrial fibrillation was significantly higher in the closure group (adjusted relative risk [RR], 4.54 [95% CI, 2.78-7.39]), but 46% (50/109) of the events were transient, occurring only in the first 45 days postrandomization. Beyond this periprocedural period, the rate of AF over a median follow-up of 57 months was 5.0% with device and 1.1% with medical therapy (adjusted RR, 2.60 [95% CI, 1.44-4.70]).

Table 4. Safety Outcomes

Safety outcome[a]	Overall outcome rate, % (No. of patients with event)		Risk difference, % (95% CI)[b]	Relative risk (95% CI)[b]	Cochran-Mantel-Haenszel test *P* value
As-treated population	**Device (n = 1762)**	**No device (n = 1956)[c]**			
Any SAE	28.7 (506)	26.4 (516)	1.97 (−0.89 to 4.82)	1.07 (0.97-1.19)	.18
AF (all events)	5.0 (88)	1.1 (21)	3.77 (2.65-4.89)	4.54 (2.78-7.39)	<.001
AF (present beyond 45 d)	2.4 (43)	0.8 (16)	1.38 (0.56-2.19)	2.60 (1.44-4.70)	.001
Major bleeding episode[d]	1.4 (25)	1.7 (33)	−0.31 (−1.09 to 0.47)	0.80 (0.47-1.40)	.45
VTE	1.4 (25)	0.5 (10)	0.87 (0.22-1.51)	2.59 (1.26-5.36)	.007
Intent-to-treat population	**Device (n = 1889)**	**Medical therapy (n = 1851)**			
Any SAE	28.1 (530)	27.1 (501)	1.13 (−1.72 to 3.98)	1.04 (0.94-1.16)	.44
AF (all events)	5.0 (94)	1.0 (18)	3.86 (2.77-4.94)	4.92 (2.95-8.21)	<.001
AF (present beyond 45 d)	2.4 (45)	0.8 (15)	1.31 (0.52-2.11)	2.54 (1.39-4.64)	.001
Major bleeding episode	1.5 (29)	1.6 (30)	−0.15 (−0.93 to 0.64)	0.91 (0.53-1.56)	.72
VTE	1.5 (28)	0.4 (8)	1.04 (0.40-1.68)	3.25 (1.51-7.01)	.002

Abbreviations: AF, atrial fibrillation; SAE, serious adverse event; VTE, venous thromboembolism.

[a]Raw counts of procedure-related adverse events: access site hemorrhage, 10; retroperitoneal hemorrhage, 2; cardiac tamponade, 4; and cardiac perforation, 1.

[b]Stratified by study using Cochran-Mantel-Haenszel tests.

[c]Data from 105 patients who were assigned to device but did not receive device were analyzed in the medical group. The median follow-up times from randomization for patients receiving device and not receiving device were 58.7 (IQR, 23.8-64.0) and 50.0 (23.8-63.6) months, respectively.

[d]Major bleeding episode was derived from SAE reporting in each of the trials.

RoPE Score, PASCAL Grade, and HTE

As described above, we hypothesized that the RoPE score would stratify the population by their attributable fraction and their likelihood of benefit from PFO closure. The RoPE score × treatment interaction was significant ($P < .01$), using the full 10-point RoPE score with the neuroimaging variable imputed for the PC Trial. Results stratified by RoPE scores of ≥7 vs <7 are shown in Figure 2, indicating a strong interaction ($P = .02$) on the HR scale (Figure 2A); patients with low vs high RoPE scores had HRs of 0.61 (95% CI, 0.37-1.00) and 0.21 (95% CI, 0.11-0.42), respectively. The rates for risk of stroke in the first 2 years for patients with a low RoPE score were 4.0% (95% CI, 2.5%-5.5%) and 2.9% (95% CI, 1.6-4.2) (absolute risk reduction [ARR], 1.1% [95% CI, −0.9% to 3.1%]) for the medical therapy and device groups, respectively, and 2.6% (95% CI, 1.7%-3.6%) and 0.6% (95% CI, 0.1%-1.0%) (ARR, 2.1% [95% CI, 1.0%-3.1%]) for patients with a high RoPE score (Figure 2B). The results were consistent in stability analyses excluding the PC Trial or employing a 9-point (neuroimaging-free) RoPE score (Appendix Figure 3), and with the lead secondary outcome of recurrent ischemic stroke, TIA, or vascular death (Appendix Figure 4). Interaction with age was not significant ($P = .9$). In the sensitivity analyses that included only the 5 trials that predominantly tested the double-disk device class, the interaction effects were as strong as in the primary analyses (Appendix Figure 5).

Figure 2. Recurrent Ischemic Stroke HTE Analyses for RoPE and PASCAL

Panel A

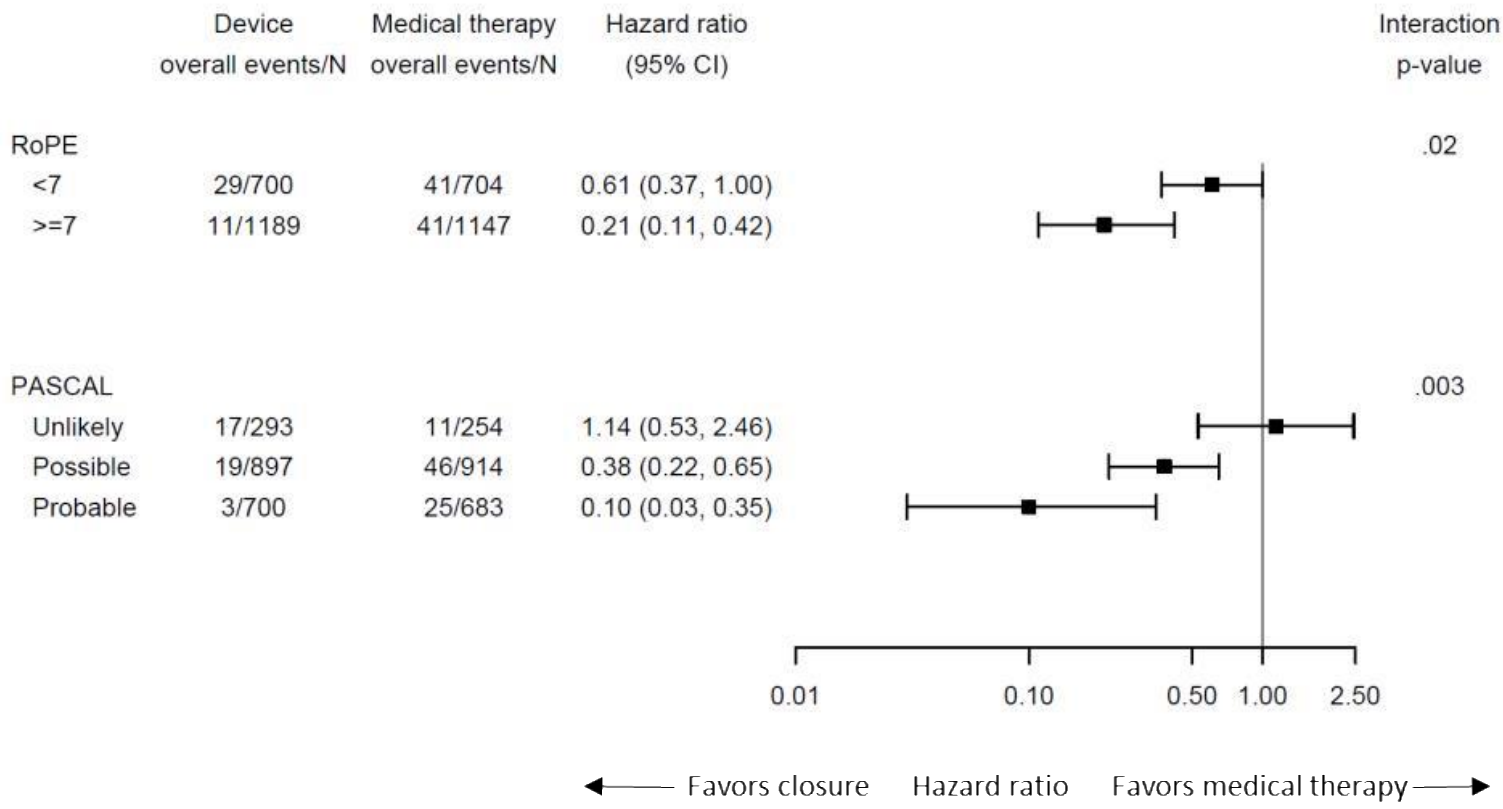
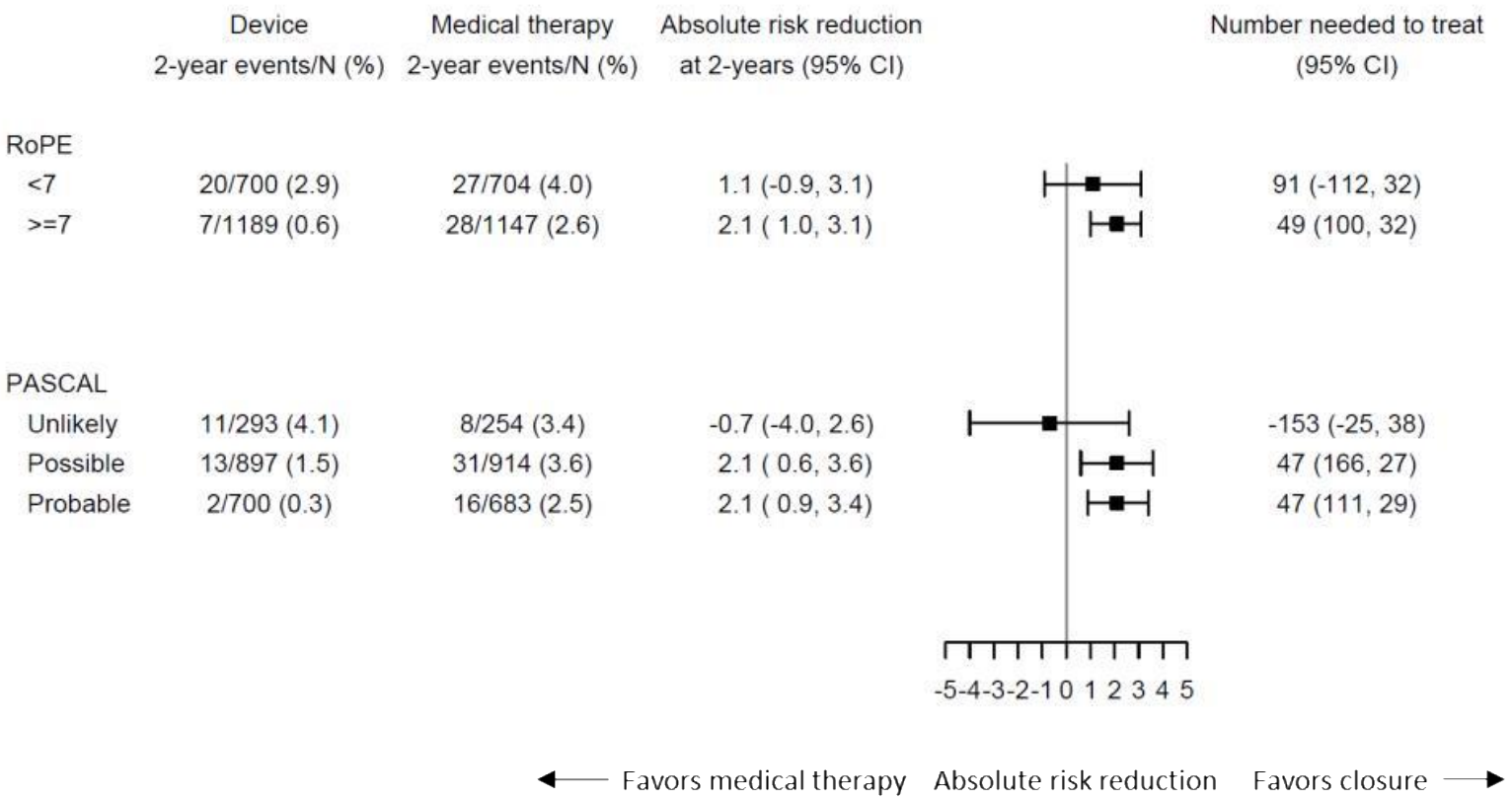


Figure 2. Recurrent Ischemic Stroke HTE Analyses for RoPE and PASCAL (cont'd)

Panel B



Abbreviations: ARR, absolute risk reduction; HR, hazard ratio; HTE, heterogeneity of treatment effects; NNT, number needed to treat; PASCAL, PFO-Associated Stroke Causal Likelihood; PFO, patent foramen ovale; RoPE, Risk of Paradoxical Embolism; TIA, transient ischemic attack.
Primary outcome of recurrent ischemic stroke with HRs (A) and ARR (B). The definition for RoPE is provided in Table 1. HRs accounted for age, sex, prior myocardial infarction, diabetes, hypertension, hyperlipidemia, prior stroke or TIA, smoking status, index event (stroke vs TIA), atrial septal aneurysm on transesophageal echocardiography (definition in Appendix A5), PFO shunt size (large vs small, definition in Appendix A5), and superficial infarction on neuroimaging (present vs absent). The 2-year ARR was calculated as differences in Kaplan-Meier event rates at 2 years. The median time to the primary outcome of recurrent ischemic stroke was 13.7 months (IQR, 4.8-29.7 months; n = 121).

Subgroup analyses based on PASCAL grading showed strong effect modification across the 3 levels of the PASCAL classification on the relative scale; patients with PASCAL classification as unlikely, possible, and probable had HRs of 1.14 (95% CI, 0.53-2.46), 0.38 (95% CI, 0.22-0.65), and 0.10 (95% CI, 0.03-0.35), respectively (*P* = .003) (Figure 2A), and clinically meaningful differences on the absolute scale at 2 years (Figure 2B). The rates for absolute risk of stroke in the first 2 years for patients with PASCAL classification of unlikely were 3.4% (95% CI, 1.1%-5.7%) and 4.1% (95% CI, 1.7%-6.4%) for the medical therapy and device groups, respectively (ARR, −0.7% [95% CI, −4.0% to 2.6%]). For patients classified as PASCAL possible, the absolute 2-year risks of ischemic stroke was 3.6% (95% CI, 2.4%-4.9%) and 1.5% (95% CI, 0.7%-2.3%) for the medical therapy and device groups, respectively (ARR, 2.1% [95% CI, 0.6%-3.6%]); for patients classified as PASCAL probable, the rates for 2-year stroke risk were 2.5% (95% CI, 1.3%-3.7%) and 0.3% (95% CI, −0.1% to 0.8%) for the medical therapy and device groups, respectively (ARR, 2.1% [95% CI, 0.9%-3.4%]). Again, the results were consistent in stability analyses excluding the PC Trial or employing a 9-point (neuroimaging-free) RoPE score (Appendix Figure 3), and with the lead secondary outcome of recurrent ischemic stroke, TIA, or vascular death (Appendix Figure 4).

The difference in the rates of safety outcomes between the device and medical groups was also consistently higher in the PASCAL unlikely group than in the probable or possible groups (Table 5). For example, the absolute risk increases of postperiprocedural (occurring greater than 45 days after randomization) AF with device were 4.41% (95% CI, 1.02%-7.80%), 1.53% (95% CI, 0.33%-2.72%), and 0.65% (95% CI, −0.41% to 1.71%) in the unlikely, possible, and probable PASCAL categories, respectively, over the full follow-up period. For comparability with 2-year ARR in ischemic stroke, 2-year differences in AF were calculated (Appendix Table 17).

Table 5. Safety Outcomes by PASCAL Classification

Safety outcome (as-treated population) by PASCAL classification[a]	Overall outcome rate, % (No. of patients with event/n)		% (95% CI)	
	Device	No device	Absolute risk difference	Relative risk
Any serious adverse event				
Unlikely	33.1 (86/260)	24.4 (69/282)	8.65 (0.56-16.74)	1.35 (1.02-1.80)
Possible	27.7 (231/835)	26.7 (258/965)	0.98 (−3.19 to 5.16)	1.04 (0.89-1.21)
Probable	28.3 (189/667)	26.8 (190/709)	1.59 (−3.15 to 6.34)	1.06 (0.89-1.26)
AF (all events)				
Unlikely	9.4 (25/260)	2.0 (6/282)	7.44 (3.39-11.50)	4.75 (1.87-12.08)
Possible	4.7 (39/835)	1.1 (11/965)	3.56 (1.94-5.17)	4.12 (2.09-8.12)
Probable	3.6 (24/667)	0.6 (4/709)	3.02 (1.47-4.58)	5.91 (2.08-16.81)
AF (present beyond 45 d)				
Unlikely	6.0 (16/260)	1.6 (5/282)	4.41 (1.02-7.80)	3.71 (1.27-10.80)
Possible	2.3 (19/835)	0.7 (7/965)	1.53 (0.33-2.72)	3.11 (1.26-7.69)
Probable	1.3 (9/667)	0.6 (4/709)	0.65 (−0.41 to 1.71)	2.06 (0.63-6.78)
Major bleeding episode				
Unlikely	1.9 (5/260)	0.7 (2/282)	1.21 (−0.74 to 3.16)	2.84 (0.48-16.62)
Possible	1.1 (9/835)	1.5 (14/965)	−0.37 (−1.41 to 0.67)	0.75 (0.32-1.72)
Probable	1.6 (11/667)	2.4 (17/709)	−0.75 (−2.23 to 0.74)	0.69 (0.32-1.46)
VTE				
Unlikely	1.3 (4/260)	0.4 (1/282)	0.95 (−0.67 to 2.58)	3.50 (0.38-32.29)
Possible	1.4 (12/835)	0.6 (6/965)	0.77 (−0.17 to 1.71)	2.25 (0.83-6.11)
Probable	1.5 (10/667)	0.4 (3/709)	1.08 (0.04-2.12)	3.54 (0.98-12.83)

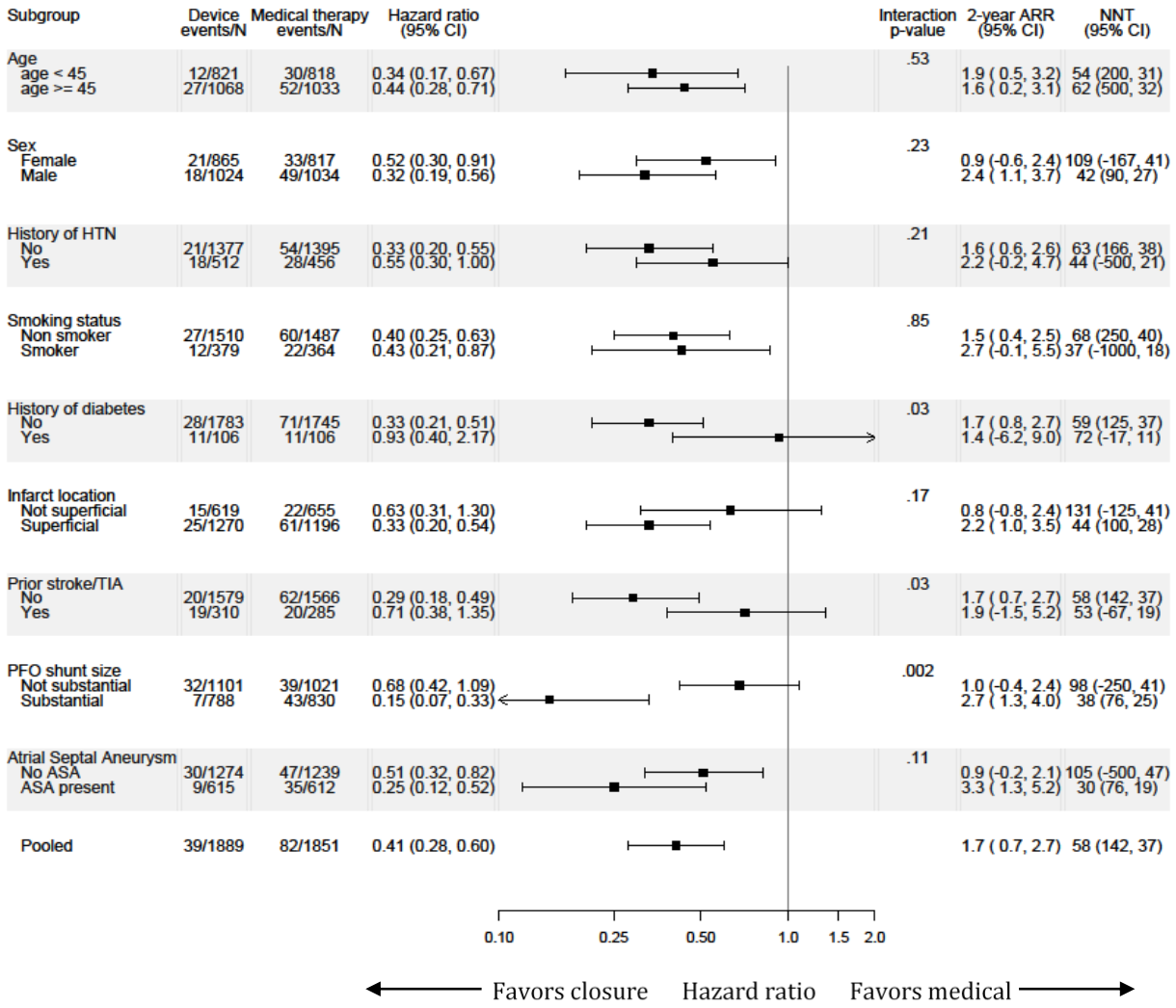
Abbreviations: AF, atrial fibrillation; PASCAL, PFO-Associated Stroke Causal Likelihood; VTE, venous thromboembolism.

[a]Safety outcomes among the as-treated population are reported over the full period of patient follow-up (median, 56.9 months [25th-75th percentile, 23.8-63.9 months]).

Exploratory Subgroup Analysis

Exploratory single-parameter subgroup analyses (Figure 3) showed nominally stronger RRRs in strata defined by variables postulated to be associated with PFO-related stroke mechanisms (ie, in the theory-anticipated direction), but evidence of effect modification was generally modest. Exploratory subgroup analyses based on the main secondary outcome showed largely similar patterns (Appendix Figure 6).

Figure 3. Recurrent Ischemic Stroke Exploratory Subgroup Analyses



Abbreviations: ARR, absolute risk reduction; ASA, atrial septal aneurysm; HR, hazard ratio; HTN, hypertension; NNT, number needed to treat; PFO, patent foramen ovale; TIA, transient ischemic attack.
Primary outcome recurrent ischemic stroke. HRs account for age, sex, prior myocardial infarction, diabetes, HTN, hyperlipidemia, prior stroke or TIA, smoking status, index event (stroke vs TIA), ASA on transesophageal echocardiography (definition in Appendix A5), PFO shunt size (large vs small, definition in Appendix A5), and superficial infarction on neuroimaging (present vs absent). Two-year ARRs were calculated as differences in Kaplan-Meier event rates at 2 years. The median time to the primary outcome of recurrent ischemic stroke was 13.7 months (IQR, 4.8-29.7 months; n = 121). Note that *P* values from exploratory analyses are provided for descriptive purposes.

Technical Efficacy Analysis

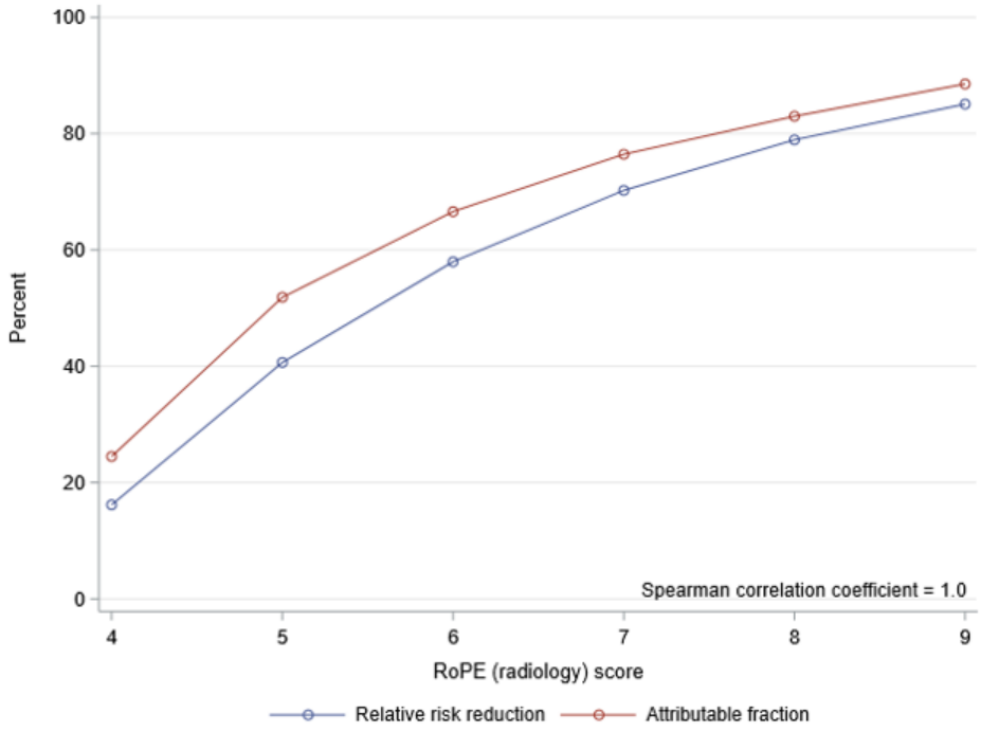
The presence of residual shunting (ie, incomplete closure) was assessed in 1475 patients who received the device (287 patients had missing values for residual shunt status). Complete closure was observed in 89.9% of the assessed patients. The primary outcome of recurrent

ischemic stroke occurred in 30 (2.3% [95% CI, 1.5%-3.2%]) patients with complete closure, compared with 4 (2.7% [95% CI, 0.7%-6.7%]) patients with incomplete closure (*P* = .74). The secondary end point of recurrent ischemic stroke, TIA, or vascular death occurred in 66 (5.0% [95% CI, 3.9%-6.3%]) patients with complete closure compared with 9 (6.0% [95% CI, 2.8%-11.2%]) patients with incomplete closure (*P* = .58).

RoPE Attributable Fraction Analysis

Using a rate of 25% as the expected prevalence of PFO in the general population, we calculated the attributable fraction (ie, the proportion of patients in which the PFO is causally related to the index event rather than just an incidental finding) across the range of RoPE (radiology) 10-point scores. The correlation between the estimated RRR for the primary outcome and the attributable fraction was 0.997 (Figure 4; *P* < 0.001). A similar correlation was observed with the nonradiology RoPE 9-point score.

Figure 4. Correlation Between Estimated RRR for Primary Outcome and Attributable Fraction



Abbreviation: RoPE, Risk of Paradoxical Embolism; RRR, relative risk reduction.
The definition of RoPE is provided in Table 1. A higher RoPE score corresponds to a higher attributable fraction (ie, a stronger causal relationship).

Concentration of Benefit

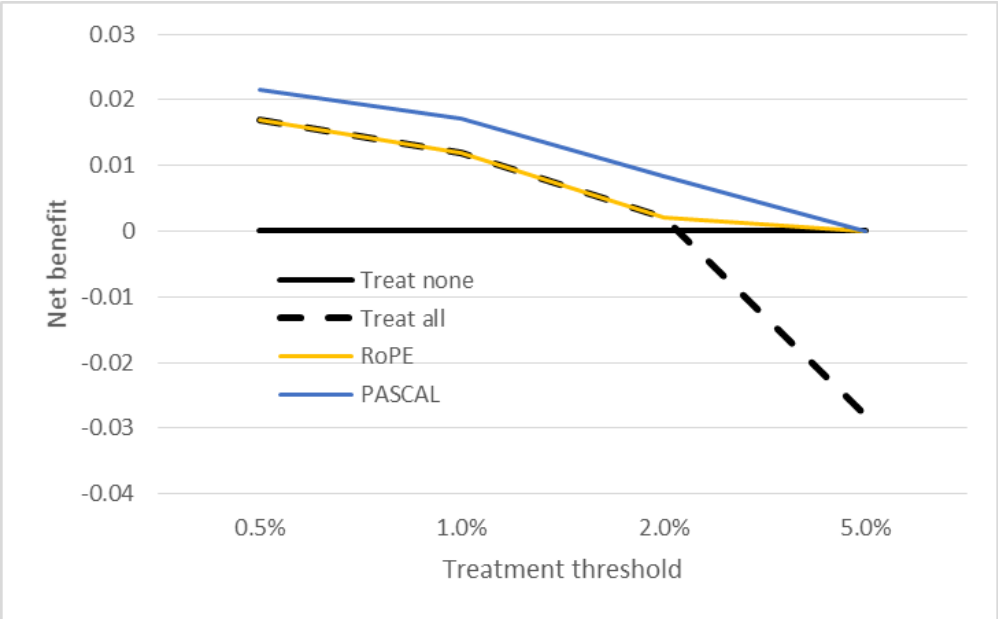
The concentration of benefit was assessed across categories of the PASCAL score. The decrease in the 2-year stroke rate (ARR) for possible and probable PASCAL categories was similar, at 2.1%, whereas in the unlikely group, there was observed harm of 0.7%. By treating only patients in the probable group (37%), we estimate that 46% of 2-year events could be avoided. By treating patients in both the possible and probable groups (85%), we estimate that 106% of events could be avoided (since the potential harm of treating the unlikely group is avoided); these results correspond to a Cb of 20%. In leaving out the CLOSURE trial by treating only patients in the probable group (41%), we estimate that 41% of 2-year events could be avoided. By treating patients in both the possible and probable groups (88%), we estimate that 100% of events could be avoided (Cb, 12%).

We also assessed the concentration of benefit across the dichotomized radiology RoPE 10-point score (<7 vs ≥7 points). The decrease in the 2-year event rate for patients with a RoPE score of at least 7 was 2.1%. We estimate by treating only patients in this group (63%) that 76% of 2-year events could be avoided (Cb, 18%). In leaving out the CLOSURE trial, we estimate by treating only patients in RoPE ≥7 group (64%) that 65% of 2-year events could be avoided (Cb, 2%).

Net Benefit of Treatment Selection

We assessed the net benefit of using model-based strategies compared with population-wide strategies of treat all and treat none for patients across a range of decision thresholds. Decision thresholds, corresponding to the number willing to treat to prevent 1 event from 0.5 to 5% (NWT, 200-20) were chosen for measuring the net benefit for the decrease in the 2-year event rate. Among the 5 trials that predominantly tested the double-disk device class, the net benefit of using PASCAL was always greater than both population-wide strategies (Figure 5). Similarly, the radiology RoPE 10-point score was never worse than (and slightly better at high decision thresholds) either population-wide strategy. Net benefit results for the model-based strategies using all 6 trials were similar.

Figure 5. Net Benefit of Treatment Selection Using 5 Trials That Tested the Double-Disk Device Class Across Decision Thresholds



Abbreviations: NWT, number of patients a doctor is willing to treat; PASCAL, PFO-Associated Stroke Causal Likelihood; RoPE, Risk of Paradoxical Embolism.

Decision thresholds from 0.5 to 5% (NWT, 200-20) were chosen for measuring the net benefit for the decrease in the 2-year event rate. The net benefit of using PASCAL was always greater than both population-wide strategies. The RoPE score was never worse than either population-wide strategy. The definition of RoPE is provided in Table 1.

DISCUSSION

Note: *Much of the material presented in this section previously appeared in the following peer-reviewed publication: Kent DM, Saver JL, Kasner SE, et al. Heterogeneity of treatment effects in an analysis of pooled individual patient data from randomized trials of device closure of patent foramen ovale after stroke.* JAMA. *2021;326(22):2277-2286. doi:10.1001/jama.2021.20956*[1]

Summary of Results

This IPDMA indicates that PFO closure in patients with otherwise cryptogenic stroke was associated with a strong RRR for recurrent stroke. The annualized risk of a future stroke for patients assigned to medical therapy was approximately 1%, which accumulates over time; this risk was reduced by device closure by approximately 60%. The benefits associated with device closure were slightly larger when analysis was confined to the 5 trials testing double-disk class closure devices currently used in clinical practice. Overall, PFO closure appeared to be relatively safe. Atrial fibrillation was somewhat more frequent with device closure. However, most AF was transient and did not cause any permanent harm; postperiprocedural AF was increased by only slightly more than 1% on the absolute scale compared with medical therapy.

Subgroup Analyses and HTE

Although the benefits associated with device closure were robust on average, treatment effects varied substantially across strata classified by the probability that the index stroke was PFO related. Device closure did not appear to be associated with any benefit for the 15% of PASCAL unlikely patients who lacked a high-risk PFO (either ASA or large shunt) and had vascular risk factors (ie, RoPE score <7), even with the exclusion of patients with defined stroke mechanisms from these trials. Conversely, device closure was associated with approximately a 90% RRR for patients with a PASCAL probable grade, who had both high-risk PFO characteristics and a high RoPE score. Device closure was associated with intermediate relative effects in the PASCAL possible category. Although relative-effect estimates differed between the probable and possible PASCAL subgroups, the 2-year absolute risk difference among patients in these patients was approximately 2%, for a 2-year number needed to treat of approximately 50, a

comparable effect magnitude to that of the 3 mainstays of medical therapy for secondary stroke prevention: antihypertensive therapy, antiplatelet therapy, and statin therapy.

Moreover, the patients who were likely to receive greater benefit also appeared to be at lower risk for device-associated adverse events such as AF, making the harm-benefit trade-offs of device closure more clearly favorable in the possible and probable groups. The lower risk of adverse events in the patients with potential high benefit is consonant with evidence showing a higher risk of incident AF in patients with lower RoPE scores,[26] who are older, and who have more vascular risk factors. This increased risk may reflect occult AF being a more likely mechanism for the index stroke in these patients and reflect a greater susceptibility to arrhythmogenic effects of device-tissue contact.

The results illustrate several core concepts of HTE analyses. Even in this pooled analysis of 6 clinical trials, most of the conventional 1-variable-at-a-time subgroup analysis did not generally have estimated effects that would be considered clinically or statistically significant, even though estimated effects were consistently in the theorized direction (eg, attenuated effects for each subgroup with a vascular risk factor). Combining variables creates greater contrast in effects between patients for whom treatment is favorable or not and could help personalize decision-making by more comprehensively describing individuals. The clinical reasoning incorporated into the PASCAL classification system was developed over decades, including the RoPE score, which was derived on an observational database independent from this study.

Lessons Learned

These results also underscore the importance of performing HTE analyses on both relative and absolute scales. Clinically important HTE is variation in the absolute risk difference that spans a clinically important decision threshold,[19,20,64] such as the difference in the treatment effect observed in the PASCAL unlikely strata (where results were null) vs that observed in other strata. Variation on the relative scale may provide mechanistic information, but even strong and statistically significant interaction effects may be clinically unimportant if all groups benefit (as with the RoPE score, when used alone).

Generalizability

Individual participant data meta-analysis has several advantages over study-level meta-analysis,[34] including the standardization of analyses across studies, better handling of missing data, the ability to estimate both absolute effects at various time points and conditional treatment effects,[6,12,14] and the opportunity to assess HTE. This study also used a novel approach to predict the patients who are most likely to respond using multiple variables combined, providing new information to inform decisions about which patients should be treated with PFO closure.

Study Limitations

This study has several limitations. First, the magnitude of the benefit associated with device closure with respect to preventing disabling stroke remains uncertain, because substantial data about functional outcomes associated with recurrent stroke were missing. Second, definitions of several key variables, such as large shunt or the presence of an ASA, differed across trials. Nevertheless, this variation across trials did not preclude robust results from pooling data across studies. Third, although the analysis validates both the RoPE score as an indicator of the stroke mechanism (ie, attributable fraction) and the assessed PASCAL system, the original, extended PASCAL classification (Appendix A3, Appendix Figure 1) could not be evaluated because the study did not identify patients in the uncommon extremely high-risk categories (eg, thrombus straddling PFO; patients with concomitant deep vein thrombosis). Fourth, despite the comprehensiveness of this analysis, several important clinical questions remain unaddressed, including the best antithrombotic therapy (eg, anticoagulation vs antiplatelet therapy) with or without closure, the role of new PFO devices, and the role of closure for patients over age 60 years. Fifth, the racial composition was nonrepresentative of US populations. Although race data were collected in only 2 trials (CLOSURE [89.3% White] and REDUCE [92.6% White]), 2 of the remaining databases were European (presumably almost exclusively White) and 1 was South Korean (almost exclusively Asian). Thus, African American patients are underrepresented in this IPDMA, which may influence the generalizability of the results.

Results in Context

To our knowledge, this IPDMA includes the totality of randomized evidence comparing the broad strategy of PFO-closure with medical therapy for patients with PFO-associated cerebral ischemic events. The analyses described provide the most definitive evidence, to our knowledge, to guide management decisions regarding selection of device closure vs medical therapy, addressing key scientific controversies and supporting patient-centered decision-making for patients with PFO-associated cerebral ischemic events. This collaboration and data set also form an ongoing resource to address additional questions related to PFO-associated cerebral ischemic events not directly addressed in the current aims.

Future Research

Although this study focused on understanding who benefits from device closure vs medical therapy, the pooling of these trials can also support future research comparing different medical therapies for PFO-associated stroke (in particular anticoagulation vs antiplatelet therapy)[64] as well as the potential differential effects and risks of different devices (in particular, double-disk vs umbrella-clamshell devices).[6]

Additional questions for future study include whether selected patients older than 60 years might benefit from closure (including those with high-risk PFO anatomical features/favorable PASCAL classifications) and the potential benefits of new closure devices, including bioabsorbable devices and suture devices.

CONCLUSIONS

We present an IPDMA of 6 trials showing that risk reduction for recurrent stroke with device closure varied across subgroups classified by their probabilities that the stroke was causally related to the PFO, among patients aged 18 to 60 years. These causal classification systems are based on easily obtained variables, help determine the benefit of device closure, and have the potential to guide individualized decision-making.

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- Kent DM, Saver JL, Ruthazer R, et al. Risk of Paradoxical Embolism (RoPE)-estimated attributable fraction correlates with the benefit of patent foramen ovale closure: an analysis of 3 trials. *Stroke*. 2020;51(10):3119-3123. doi:10.1161/STROKEAHA.120.029350

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ACKNOWLEDGMENTS

The authors would like to thank Rebecca E.H. Maunder, BSc, from the PACE Center (Tufts Medical Center) for her help with manuscript preparation, who was partially supported through the PCORI grant. Robin Ruthazer, MPH, provided statistical consultation during the preparation of the protocol. The authors would also like to thank Abbott U.S. and W.L. Gore (who received no compensation) for facilitating data access.

APPENDICES

Appendix A. Supplementary Methods

Appendix A: Supplementary Methods

Appendix A1. Analysis Details

This analysis includes all trials that were identified for a systematic review of studies looking at recurrent stroke with patent foramen ovale (PFO). The SCOPE PI (Kent) was part of the team that performed this systematic review, which was updated in August 2019 for guideline development by the American Academy of Neurology (AAN). And subsequently updated to September 2021 for this article. Based on this systematic search performed of Medline and Embase, these studies represent the *totality of available randomized evidence on the use of percutaneous implanted devices for PFO closure versus medical therapy in patients with PFO-associated cerebral ischemic events*. Complete information about the search strategy and systematic review can be found in the original guidance.[1] **Appendix B1** shows a PRISMA flowchart of all studies identified.

All RCTs identified in the systematic review provided individual patient-level study data. Data entered into the central SCOPE database were a limited dataset (LDS), with all high-level patient identifiers removed. All data were collected under the aegis and supervision of the SCOPE Steering Committee, and integrated and stored at the Predictive Analytics and Comparative Effectiveness (PACE) Center at Tufts Medical Center, Boston, MA. The data were harmonized and analyzed by two statisticians at the PACE Center, Tufts Medical Center to ensure they accurately matched the values reported by the trials. **Appendix A5** describes variables that were harmonized, including ASA and shunt size. There were no issues identified in checking IPD.

The PI of this study (Kent) developed an initial list of variables based on variables used in a prior 3-trial individual patient meta-analysis[2] and variables that make up the Risk of Paradoxical Embolism (RoPE) Score[3,4]. The list was further expanded and refined at an investigator meeting in February 2020. **Appendix Table 1** displays the variables collected.

Appendix B4 provides the patient-level characteristics for each study, and note where data was missing.

All analyses were conducted using SAS (Version 9.4) and R (Version 4.0.2).

Examination of proportional hazards assumption

Proportional hazards assumptions were assessed using graphical and statistical test-based methods. Visual assessment of the log-log survival curve for each treatment group in each trial was used to detect violations of proportionality. Time-dependent covariates — interactions between the predictors and log(time) — were included to assess proportionality for each predictor. Additionally, tests of proportional hazards assumption was based on scaled Schoenfeld residuals for each predictor and overall (global test).[5] No visual or statistical violation of proportional hazards was observed.

Handling of missing data

Missing values for covariates were imputed using fully conditional specification methods (predictive mean matching for continuous variables and discriminant function method for all dichotomous variables) to generate 10 complete data sets.[6] The imputation model for each variable with missing values included all pre-specified covariates and the outcome. Analyses were conducted in each of the 10 compete data sets separately and pooled using Rubin's Rules.

Random effects Cox proportional hazards regression

Study-specific random effects were modeled using SAS PROC PHREG procedure using the RANDOM statement to fit a shared frailty model for clustered data.[7] The log-normal distribution of shared frailty was used and the common variance parameter (covariance estimate = 0.13; asymptotic standard error = 0.12) was estimated using residual maximum likelihood.

Assessment of linear assumption

The functional form of continuous variables (age and RoPE Score) was assessed for linearity using higher order polynomial terms (i.e., quadratic). These higher order terms were tested for statistical significance and model fit was assessed by differences in likelihood ratio compared to models with a linear relationship. We found no evidence of statistically significant non-linear associations with the treatment effect.

Appendix Table 1. Variables of Interest.

Category	Variable
Clinical Variables	Age (at time of stroke)
	Sex
	Coronary artery disease
	Diabetes
	Hypertension
	Hyperlipidemia
	Prior spells: number, date(s), event(s)
	Smoking status: current
	Body Mass Index
	Index event: stroke or TIA
	Index event: date
	Medication at index event: statin, antiplatelet, anticoagulant, CP/HRT
Echocardiographic Variables	Mobility of septum: normal, hypermobile
	PFO size: large, not large
	Shunt at rest: yes, no
Neuroradiology Variables	Index stroke seen: yes, no

	Location: superficial, deep
	Size: large, small/not seen
	Multiple: yes, no (not seen = single)
	Prior stroke: yes, no
Treatment Variables	Warfarin (anticoagulant, Coumadin)
	Antiplatelets
Follow-Up Variables	Date of last follow-up
	Duration of follow-up
	Recurrent stroke
	Recurrent TIA
	Date of recurrent event
	Death
	Date of death
	Cause of death
	PFO closure (treatment)
	Atrial Fibrillation, all and after 45 days (safety)
	Major Bleeding (safety)
	Procedural complication (safety)
Cohort Designation and Randomization	Intent-to-treat group (closure vs. medical therapy)
	Per-protocol group (closure vs. medical therapy vs. excluded)
	As-treated group (closure vs. medical therapy vs. excluded)

CP, contraceptive pill; HRT, hormone replacement therapy; PFO, patent foramen ovale; TIA indicates transient ischemic attack.

Appendix A2. RoPE Score Detail

Patent foramen ovale (PFO) are randomly distributed in the general population in about 25% of adults, and not associated with other vascular risk factors. However, among patients with cryptogenic stroke (CS), the presence of a PFO is highly associated with the absence of conventional vascular risk factors and the presence of specific neuroimaging findings (a superficial cortical infarct). This negative association arises from index event (or "collider") bias;[8] that is, it is induced because vascular risk factors and PFO are causes of the same outcome (i.e., cryptogenic stroke).

Based on this observation, we developed a model to predict the presence of PFO in patients with otherwise cryptogenic stroke and transformed this probability, using Bayes Theorem, into a "patient-specific" attributable fraction — i.e., the fraction of cryptogenic strokes that are attributable to PFO in a group of patients sharing a Risk of Paradoxical Embolism (RoPE) Score, according to the following equation:

$$\text{PFO Attributable Fraction} = 1 - \left(\frac{\text{Prevalence of PFO in controls} \times [1 - \text{Prevalence of PFO in CS cases}]}{\text{Prevalence of PFO in CS cases} \times [1 - \text{Prevalence of PFO in controls}]}\right)$$

We found that easily obtainable clinical characteristics can identify CS patients who vary markedly in the prevalence of PFO, reflecting substantial and clinically important variation in the probability that a discovered PFO is likely to be causally related to the stroke rather than an incidental present (**Appendix Table 2**). For example, a PFO is discovered in just 23% of cryptogenic stroke patients in the lowest RoPE Score strata, which is approximately the same as the general population—indicating that PFOs in these patients are almost always an incidental finding. Conversely, PFOs are found in greater than 70% of cryptogenic stroke patients with a RoPE Score of 9-10, indicating almost a 90% probability that the stroke can be attributed to the presence of the PFO.

Appendix Table 2. PFO-Attributable Fraction by RoPE Score.[4] Cryptogenic stroke n=3023.

RoPE Score	Patients, N (n=3023)	Prevalence of PFO % (95% CI)	PFO-Attributable Fraction[a] % (95% CI)	Estimated 2-yr stroke/TIA recurrence rate (among those with PFO, n=1324)[4]
0-3	613	23% (19% to 26%)	0% (0% to 4%)	20 (12-28)
4	511	35% (31% to 39%)	38% (25% to 48%)	12 (6-18)
5	516	34% (30% to 38%)	34% (21% to 45%)	7 (3-11)
6	482	47% (42% to 51%)	62% (54% to 68%)	8 (4-12)
7	434	54% (49% to 59%)	72% (66% to 76%)	6 (2-10)
8	287	67% (62% to 73%)	84% (79% to 87%)	6 (2-10)
9-10	180	73% (66% to 79%)	88% (83% to 91%)	2 (0-4)

[a]Based on the observed prevalence of PFO, rather than the predicted, and assumes a population prevalence of PFO of 25%.
CI, confidence interval; PFO indicates patent foramen ovale; TIA, transient ischemic attack.

The RoPE Score has been externally validated by independent teams to predict the presence of a PFO in the CS population[9,10] and it is widely used in shared decision making. However, it is not intended to be used in isolation. The premise of the RoPE Study was that mechanical closure will benefit patients with a high *attributable recurrence risk*, which can be thought of as the product of the attributable fraction (predicted by the RoPE Score) and the stroke recurrence risk. A higher RoPE Score, however, is associated with a lower recurrence risk. In the RoPE study the 2 year risk of stroke/transient ischemic attack (TIA) recurrence of patients with a RoPE Score of 0 to 3 was ~20 but was only ~2% in those with a RoPE Score of 9 to 10.[4]

Further, the methods used to develop the RoPE Score (prediction of the presence of a PFO in cryptogenic stroke patients) did not permit high risk anatomic features of the PFO itself (such as the size of the left-to-right shunt and the presence of an atrial septal aneurysm) to be incorporated into

the Score. For these reasons, recent consensus documents suggest that the RoPE Score should be part of a broader evaluation to help determine those patients whose PFO is most likely to be caused by a PFO-related mechanism who might benefit from closure.[11-13]

Appendix A3. PASCAL Score Detail

To further improve the identification of ischemic strokes due to patent foramen ovale, an international consensus group recently proposed the PFO-Associated Stroke Causal Likelihood (PASCAL) Classification System (**Appendix Figure 1**). This is different from the other three and directly germane to the current study. Among patients with no major defined cause of ischemic stroke, the PASCAL classification system integrates information regarding: 1) presence of features that increase likelihood of PFO-stroke mechanisms (high risk PFO physiologic and structural features of large shunt or atrial septal aneurysm), and 2) absence of features that increase likelihood of an occult non-PFO stroke mechanisms (older age, vascular risk factors, and stroke topography features) as quantified in the RoPE score. Based on this combination of factors, the original, extended PASCAL Classification System algorithmically assigns a likelihood of causal relationship among five levels: Definite, Highly Probable, Probable, Possible, and Unlikely.[16] The PASCAL algorithm was developed using a mixed methods approach incorporating expert judgement, physiologic and epidemiologic data, and the validated RoPE Score. The original, extended PASCAL Classification system is shown in **Appendix Figure 1**.

Appendix Figure 1. The Extended PFO-Associated Stroke Causal Likelihood (PASCAL) Classification System.

Risk Grade	Features	Casual Relatedness	
		Low RoPE Score[a]	High RoPE Score[a]
Very high risk	PFO + straddling thrombus	Definite	Definite
High risk	BOTH of: 1A. PFO + ASA, *or* 1B. Large shunt PFO, *AND* 2. PE or DVT preceding index infarct	Probable	Highly Probable
Medium risk	ANY of: 1. PFO + ASA 2. Large shunt PFO	Possible	Probable
Low risk	Small shunt PFO without ASA	Unlikely	Possible

[a]The RoPE Score includes points for 5 age categories, cortical infarct, absence of hypertension, diabetes, prior stroke or transient ischemic attack, and smoking. A higher RoPE score (≥ 7 points) increases probability of causal association.
ASA, atrial septal aneurysm; DVT, deep vein thrombosis; PE, pulmonary embolism; PFO indicates patent foramen ovale; RoPE, Risk of Paradoxical Embolism.

While data regarding many of the patient features used in the extended PASCAL Classification system were collected in the RCTs analyzed in the SCOPE project, two were not: 1) the presence of a thrombus straddling the PFO opening (supporting Definite causal relatedness), and 2) the occurrence of a PE or DVT shortly before or concurrent with the index ischemic stroke (supporting Highly Probable or Probable causal relatedness). Accordingly, for the current pooled analysis a simpler PASCAL classification system was developed by censoring those two uncollected patients' features and using the collected patient features to algorithmically assign patients to three levels of likelihood of causal relationship: Probable, Possible, and Unlikely (main manuscript Table 1B). The SCOPE protocol prespecified as one of its primary aims testing for heterogeneity of treatment effect in the pooled RCT data based on patient PASCAL Probable, Possible, and Unlikely grades.

Appendix A4. Definitions of "Per-protocol" and "As-treated" Populations

Systematic, Collaborative, PFO closure Evaluation (SCOPE)	**Per-Protocol population (if possible to identify across trials): all patients who: i) received the randomly assigned treatment, ii) adhered at least moderately to the trial-mandated long-term medical treatment specific to their allocated treatment group (including long-term antithrombotic therapy in the medical therapy-only treatment group and long-term post-device antithrombotic therapy in the closure device plus medical therapy group, iii) did not have a major inclusion or exclusion violation, classified according to the treatment group to which they were randomly assigned and iv) patients who are NOT lost to follow up, when these patients are able to be identified (special considerations for PC and RESPECT trials)**
CLOSE	*An additional analysis was performed in the per-protocol cohort, which included patients who received the randomly assigned treatment, adhered to the protocol-mandated medical treatment **until the end of the trial**, and did not have a major protocol violation.*
PC Trial	*In a per-protocol analysis, we restricted the analysis to data from patients in the closure group in whom implantation of a device was attempted and patients in the medical-therapy group who received treatment as assigned at the time of randomization; if patients in the medical-therapy group crossed over to the closure group, the data were censored at the time of crossover.* **Special consideration:** • PC Trial censored people who crossed over at the time of crossover in their PP analysis. We decided we would not do this, and instead exclude patients who crossed over. • In their publication, they used the **LTFU at 3 years** to identify and report. Using the 3 year variable would hopefully be consistent with their publication and make their definition closer to the other trials.
CLOSURE	*Defined as all randomized patients who received the treatment to which they were randomized, who had no major inclusion/exclusion criteria violations, and **who had a follow-up of at least 22 months.***
RESPECT	*The per-protocol cohort included patients who received the randomly assigned treatment, adhered to the protocol-mandated medical treatment, and did not have a major inclusion or exclusion violation.* **Special consideration:** • Respect did not exclude patients who were lost to follow up in their per protocol analysis. In their short-term publication, they identified *119* patients who "discontinued prior to primary endpoint", and in their long-term follow-up publication, they identified *264* patients who "discontinued prior to primary endpoint." • In the data they provided, they provided information about *226* patients who discontinued, these patients have been excluded from the SCOPE per-protocol analysis.

REDUCE	*For per-protocol (PP) analysis, only subjects who were randomized and treated according to critical protocol requirements were analyzed, according to treatment assigned at randomization. Specifically, subjects randomized to the closure group who received antiplatelet medical therapy and PFO closure with a study device within 90 days post-randomization, and subjects randomized to medical therapy who received antiplatelet medical therapy and no PFO closure by any means at any time, were included in the PP analysis. The PP population excludes subjects who violated key eligibility criteria, did not receive the therapy to which they were randomized, or did not comply with one of the protocol required medical regimens.*
DEFENSE	*Included patients who received the randomly assigned treatment, adhered to the protocol-mandated medical treatment until the end of the trial, and did not have a major protocol violation.*

SCOPE "As treated" population definition:

All the patients in the study classified according to the treatment actually received (i.e., this analysis will compare patients who "got device" versus those that did not). Patients randomized to medication but got device are censored at time of crossover to the device arm.

Special consideration: PC trial did not provide device procedure dates for all patients.

Appendix A5. Description of Atrial Septal Aneurysm and Shunt Size Variables

Appendix Table 3. Variable Definition for ASA Class.

SCOPE Excursion Class	Systematic, Collaborative, PFO closure Evaluation (SCOPE)	defined as ≥10 mm of excursion from midline
TOTAL	CLOSURE	*mobility of septum of 10 mm or greater total excursion of the septum*
midline	PC Trial	*protrusion of the interatrial septum, or part of it, of more or equal to 15mm beyond the plane of the interatrial septum and the diameter of the aneurysm base measured at least 15mm.*
TOTAL	RESPECT	*defined as ≥10 mm septum primum excursion*
TOTAL	REDUCE	*defined as the movement of the septum primum into either atrium for a total excursion of at least 10 mm (from an imaginary midline).*
midline	DEFENSE	*ASA based on Defense defined asa or hypermobile septum, where ASA=atrial septal aneurysm (protrusion of the dilated segment of the septum at least 15 mm beyond the level surface of the atrial septum), hypermobility (phasic septal excursion into either atrium ≥10 mm)*
TOTAL	CLOSE	septum primum excursion greater than 10mm as identified on TEE

PFO indicates patent foramen ovale; TEE, transesophageal echocardiogram.

Appendix Table 4. Variable Definition for Large Shunt Size.

Systematic, Collaborative, PFO closure Evaluation (SCOPE)	Target: Large shunt size was defined in our database as >20+ bubbles (values below in BLUE coded as 'large' in our database)
CLOSURE	*Small: (1) None; (2): Trace, 1~10 bubbles, (3) Moderate, ~10-25 bubbles*, ***Large: (4) Substantial, ~25 or more bubbles***

PC Trial	*Small: grade 0 = none; grade 1 = minimal (1-5 bubbles), grade 2 = moderate (6 to 20 bubbles),* ***Large: grade 3 = severe (>20 bubbles)***
RESPECT	*Small: Grade 0 (none), Grade 1 = 1-9 bubbles; Grade 2 = 10 to 20 bubbles;* ***Large: Grade 3 = over 20 bubbles***
REDUCE	*PENN RE-READ FROM TEE (IF MISSING (~20% of time), USED ORIGINAL DATA FROM GORE):* *Small :(0)Grade 0[no bubbles], (1)Grade 1 [1-9 bubbles], (2)Grade 2 [10-20] bubbles,* ***Large: (3)Grade3 [>20 bubbles]***
DEFENSE	*Small: (≤20 Microbubbles),* ***Large (>20 microbubbles)***
CLOSE	*Small : ≤30 Bubbles on TTE or TEE,* ***Large: >30 microbubbles on TTE or TEE***

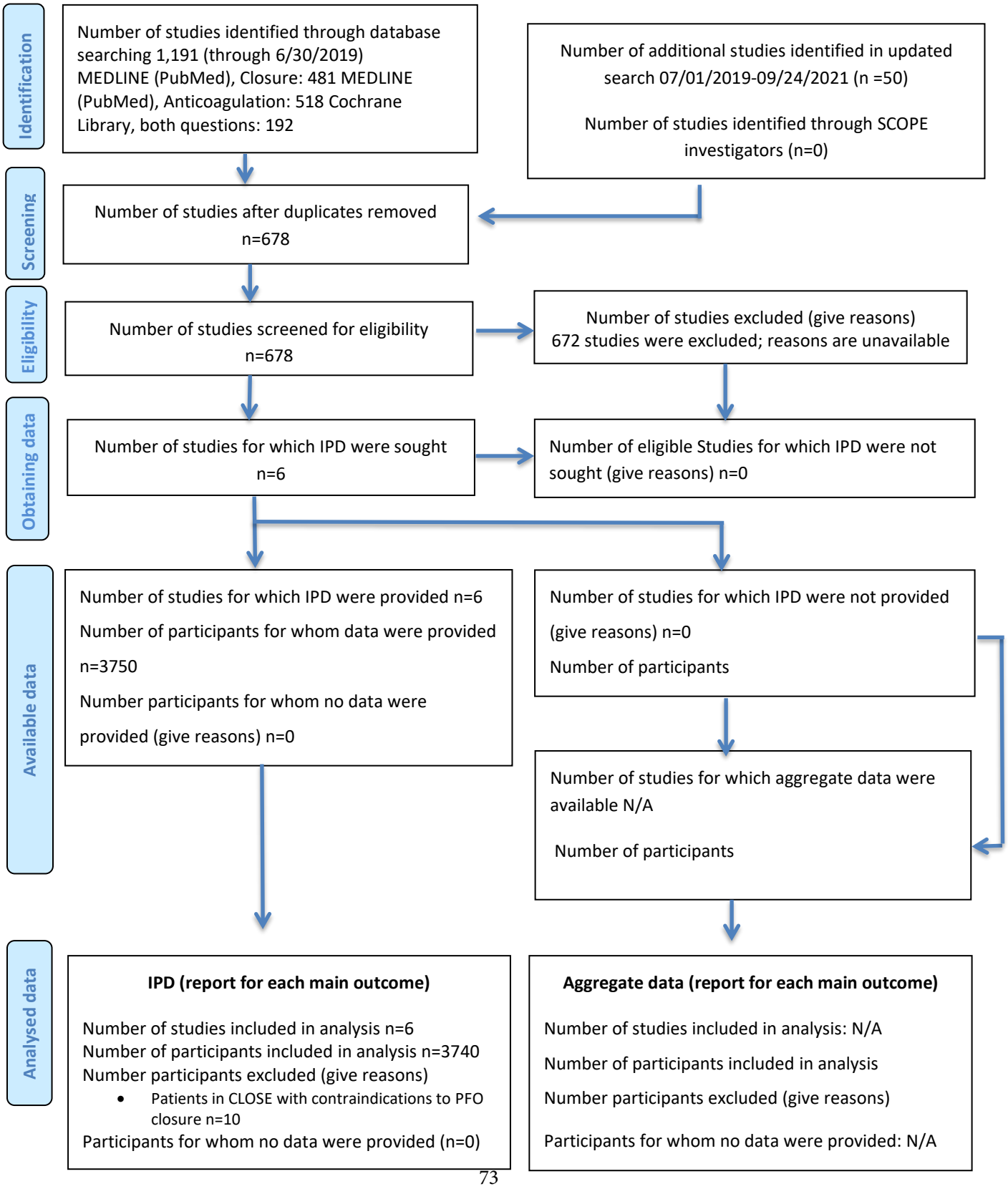
PFO indicates patent foramen ovale; TEE, transesophageal echocardiogram; TTE, transthoracic echocardiogram;

Appendix B. Supplementary Results

Appendix B: Supplementary Results

Appendix B1. PRISMA IPD Flow Diagram

Appendix Figure 2. PRISMA IPD Flow Diagram.



Appendix B2. Descriptions of Trials

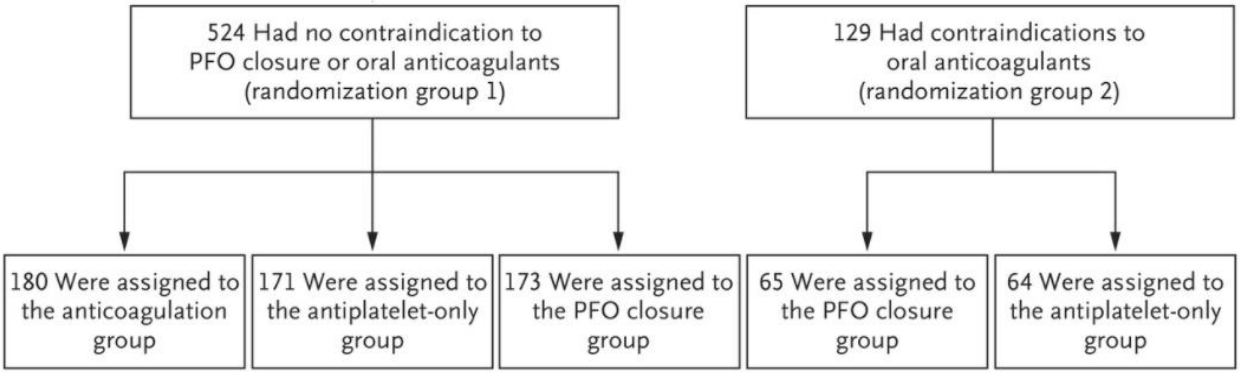
Appendix Table 5. Features of Patent Foramen Ovale Closure Device Trials.

Trial	Year of Publication	Enrollment/ Follow-up	Geography	Type of Device	Inclusion Criteria			Patient Number	Follow-Up Years (mean)/ Patient-years	Ratio of Follow-Up Dev/Med[a]
					Event Type	Timing	Age			
CLOSURE	2012	E: 2003-2008 F: 2003-2010	United States, Canada	STARflex (NMT Medical)	Cryptogenic IS or TIA	≤ 6 mo	18-60	909	1.7/1555	1.06
PC Trial	2013	E: 2003-2009 F: 2000-2012	Europe, Canada, Brazil, Australia	Amplatzer	Cryptogenic IS or periph embolism	No restriction	<60	414	4.1/1681	1.04
RESPECT	2013/2017	E: 2003-2011 F: 2003-2016	United States, Canada	Amplatzer	Cryptogenic IS (Tissue-Def)	≤ 9 mo	18-60	980	5.8/5688	1.14
CLOSE	2017	E: 2007-2014 F: 2007-2016	France, Germany	Multiple[d]	Cryptogenic IS (Tissue-Def)	≤ 6 mo	16-60	473 (653)[b]	5.3/2507	1.04
REDUCE	2017	E: 2008-2015 F: 2008-2016	Europe, Canada, United States	Helex or Cardioform (Gore)	Cryptogenic IS (Tissue-Def)	≤ 6 mo	18-59	664	3.4/2232	1.10
DEFENSE-PFO	2018	E: 2011-2017 F: 2011-2017	South Korea	Amplatzer	Cryptogenic IS (Tissue-Def)	≤ 6 mo	18-80	120	1.6[c]/≈187	1.03

[a]Mean duration of follow-up among device patients/mean duration of follow-up among medical patients. Longer follow-up among device patients occurred because of (1) more end point events in medical patients, ending study participation, and (2) more dropouts in medical patients, in part to pursue device placement outside of the trials.
[b]Full results reported for 473 patients randomized to closure and medical antiplatelet therapy groups, pending for 180 randomized to the medical anticoagulation therapy group.
[c]For DEFENSE-PFO, only follow-up years estimated from the Kaplan–Meier curve of the fully-reported time period—the first 2 years after enrollment.
[d]Devices included Amplatzer PFO occluder (121), Intrasept PFO occluder (31), Premere (22), Starflex septal occluder system (21), Amplatzer cribriform occluder (15), Figulla Flex II PFO occluder (15), Atriasept II occluder (3), Amplatzer ASD occluder (2), Figulla Flex II UNI occluder (2), Gore septal occluder (2), Figulla Flex II ASD occluder (1).
CLOSE indicates Patent Foramen Ovale Closure or Anticoagulants Versus Antiplatelet Therapy to Prevent Stroke Recurrence; CLOSURE, 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; DEFENSE-PFO, Device Closure Versus Medical Therapy for Cryptogenic Stroke Patients With High-Risk Patent Foramen Ovale; IS, ischemic stroke; PC Trial, Clinical Trial Comparing Percutaneous Closure of Patent Foramen Ovale Using the Amplatzer PFO Occluder With Medical Treatment in Patients With Cryptogenic Embolism; REDUCE, Gore REDUCE Clinical Study; RESPECT, Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment; and TIA, transient ischemic attack.

Appendix B: Supplementary Results

The ***CLOSE (Patent Foramen Ovale Closure or Anticoagulants versus Antiplatelet Therapy to Prevent Stroke Recurrence) Trial***[17], conducted between 2008 and 2016, randomized patients 16 to 60 years of age with a recent cryptogenic, tissue-defined, ischemic stroke of embolic or single small deep topography and a high-risk PFO [with associated atrial septal aneurysm (ASA) or large interatrial shunt], to one of three treatments: PFO closure (predominantly with double-disk PFO occluder devices) plus long-term antiplatelet therapy (238 patients); antiplatelet therapy alone (235 patients); or oral anticoagulation (187 patients). The primary end point was recurrent, tissue-defined, ischemic or hemorrhagic stroke. The mean duration of follow-up was 5.4 ± 1.9 years in the PFO closure group, 5.3 ± 2.0 years in the anti-platelet-only group, and 5.4 ± 2.0 years in the anticoagulant group. Major exclusion criteria were another cause for the index stroke as or more likely than the PFO, previous surgical or endovascular treatments of PFO or ASA, indication for long-term anticoagulant or antiplatelet therapy for another reason, and contraindication to antithrombotic therapy.



We analyzed the CLOSE trial as two distinct studies according to the randomization groups below. For randomization group 1 we combined the anticoagulant and antiplatelet groups into a single medical therapy arm.

Appendix B: Supplementary Results

The ***CLOSURE I (Evaluation of the STARFlex Closure System in Patients with a Stroke and/or Transient Ischemic Attack due to Presumed Paradoxical Embolism Through a Patent Foramen Ovale) Trial***[18], conducted between 2003 and 2008, randomized patients aged 18 to 60 years with a PFO and cryptogenic, tissue-defined, ischemic stroke or high-likelihood, tissue-defined, TIA to receive PFO closure with umbrella-clamshell occluder devices plus antiplatelet therapy (447 patients) versus antithrombotic therapy (either warfarin anticoagulation or aspirin antiplatelet therapy) alone (462 patients). The primary endpoint was a composite of recurrent, tissue-defined, ischemic or hemorrhagic stroke or high-likelihood, tissue-defined, TIA during 2 years of follow-up, death from any cause during the first 30 days, or death from neurologic causes between 31 days and 2 years. Major exclusion criteria were a potential source of TIA or ischemic stroke other than PFO, including atherosclerosis and other cardiac disease; hypercoagulability requiring treatment with warfarin; and known hypersensitivity or contraindication to antithrombotic therapy.

The ***DEFENSE-PFO (Device Closure Versus Medical Therapy for Cryptogenic Stroke Patients With High-Risk Patent Foramen Ovale) Trial***[19] randomized patients with cryptogenic, tissue-defined, embolic topography, ischemic stroke and high-risk PFO (associated ASA, septal hypermobility, or large PFO size) between 2011 and 2017 to undergo either PFO closure with a double-disk occlude device (n=60) or medical therapy with antiplatelet agents or anticoagulants alone (n=60). The primary endpoint was a composite of tissue-defined, ischemic and hemorrhagic stroke, vascular death, or Thrombolysis in Myocardial Infarction (TIMI)-defined major bleeding during 2 years of follow-up. Major exclusions were another cause for the index stroke as or more likely than the PFO, history of myocardial infarction or unstable angina, and contraindications to antiplatelet therapy.

The ***PC (Percutaneous Closure) Trial***[20], between 2000 and 2009, randomized patients younger than 60 years old with a PFO and cryptogenic, tissue-defined, ischemic stroke or a peripheral thromboembolic event to receive PFO closure with a double-disk device plus medical therapy (204

patients) versus medical therapy with antiplatelet agents or anticoagulants alone (210 patients). The primary endpoint was a composite of time-defined ischemic or hemorrhagic stroke, time-defined transient ischemic attack, peripheral embolism, or all-cause death. The mean follow-up duration was 4.1 and 4.0 years in the closure and medical therapy groups, respectively. Reasons for patient exclusion included the following: any identifiable cause for the thromboembolic event other than PFO; contraindication for chronic antiplatelet or anticoagulant therapy; requirement for chronic anticoagulant therapy for another disease entity, and previous surgical or percutaneous PFO closure.

The ***REDUCE Trial (GORE® Septal Occluder Device for Patent Foramen Ovale (PFO) Closure in Stroke Patients)***[21]*,* between 2008 and 2015, randomized patients aged 18 to 59 with a PFO who had had a tissue-defined, embolic topography, ischemic stroke to undergo PFO closure with a double-disk device plus antiplatelet therapy (n=441) or to receive antiplatelet therapy alone (n=223). The co-primary endpoints were recurrent, tissue-defined, ischemic stroke through at least 24 months and the incidence of any new brain infarction, symptomatic or asymptomatic, on 24 month MRI. Among reasons for patient exclusions were any identifiable cause for the thromboembolic event as or more likely than PFO, uncontrolled diabetes mellitus, uncontrolled hypertension, recent alcohol or drug abuse, and a specific indication for anticoagulation.

The ***RESPECT (Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment) Trial***[22,23], between 2003 and 2016, randomized patients aged 18 to 60 with a PFO and tissue-defined, ischemic stroke of embolic or single small deep topography stroke to receive PFO closure with a double-disk device plus medical therapy (499 patients) or medical therapy alone with antiplatelet or anticoagulant agents (481 patients). The primary end point was a composite of recurrent, tissue-defined, ischemic stroke or early (within 30-45d) post-randomization all-cause death with a median follow-up of 5.9 years. Among reasons for patient exclusion were: cerebral, cardiovascular, and systemic conditions suggesting non-PFO-related

mechanisms for stroke; contraindications to aspirin or clopidogrel treatment; and anatomical contraindications to device placement.

Appendix B3. Assessment of Risk of Bias and Small Study Effect

Assessment of Risk of Bias

We slightly modified the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2). We omitted the domain for analysis since that is not relevant for this individual patient data meta-analysis, where we are not reliant on reported trial results. The table below shows scores (1= low risk; 2= some concerns; 3= high risk) for each of the domains and for the overall assessment. The '+' indicates a slightly higher level of concern for bias. Two investigators (DMK and DET) rated all items. Disagreements were resolved by consensus. The risk of bias in the overall assessment reflects the weakest domain.

Appendix Table 6. Risk of Bias Assessment.

Study	Validity Domain				
	Randomization/ Allocation Concealment	Deviations from Intended Intervention (Evidence of large/differential cross-over for 1 treatment)	Bias from Missingness of Outcome Data (<10%; non-differential)	Bias in Outcome Measurement	Overall Assessment
CLOSURE	1	1+	1	2	2
PC Trial	1	1+	2	2+	2+
RESPECT	1	1+	2+	1+	2+
REDUCE	1	1	2	2	2
CLOSE	1	1+	1	2	2
DEFENSE	1	1+	1	2+	2+

Deviations from intended intervention were scored higher when there was large/differential crossover that might reflect patient preference these studies, which were not blinded. Five out of six trials were based on a prospective randomized open blinded end-point (PROBE) design. Since these trials have risk from 'referral bias' for endpoint adjudication, trials were generally scored a 2 in this domain. Of these

trials, only the RESPECT Trial specified the use of a validated symptom-detection questionnaires and automatic referral to mitigate referral bias, and therefore received a 1+.

Beyond these risks from a PROBE design, 3 trials had more serious concerns:

1. RESPECT had a substantial and differential drop out (albeit over a longer follow up time).

The dropout rate was 33.3% in the medical-therapy group and 20.8% in the PFO closure group, resulting in a significant between-group difference in the median duration of safety follow-up (2669 patient-years in the medical-therapy group vs. 3141 patient-years in the PFO closure group, p<.001). Higher risk patients appeared to drop out from the medical arm, potentially biasing toward the null.

2. The PC Trial had relatively high rates of drop out and also had some evidence of referral bias for endpoint adjudication.

Among 414 patients, 7 patients in the closure group and 11 in the medical-therapy group withdrew from the study; 24 and 31 others, respectively, were lost to follow-up.

There was a relatively low rate of referral for adjudication and differential rate of non-events (7 for medical therapy versus 2 for device) suggesting the possibility of less sensitive referral in the device arm.

3. The DEFENSE Trial did not have blinded outcome adjudication.

Small Study Effect

An assessment of small study effects by assessing funnel plot asymmetry. Trial sample sizes ranged from 120 (DEFENSE) to 980 (RESPECT). Visual inspection of the funnel plot for the six trials (where the CLOSE trial is treated as a single trial) did not suggest asymmetry. In addition, two formal tests for asymmetry were conducted. The test of asymmetry using the arcsin transformation for binary outcomes[24] was not statistically significant (p-value = 0.11). A similar linear regression test of asymmetry based on the log(hazard ratio) and standard error was also not significant (p-value = 0.59). These tests are generally

not recommended for meta-analyses with fewer than 10 studies and should be interpreted accordingly[25]. In two of the six trials included in our analysis there were no observed recurrent ischemic strokes in the device arm leading to unstable with-in trial estimated hazard ratios and standard errors. In an analysis excluding these trials (DEFENSE, CLOSE) the HR was 0.52 (95% CI, 0.35-0.78). These effect estimates reveal stability in our analysis of the primary outcome.

Appendix B4. Patient Characteristics in Each Study

Appendix Table 7. CLOSURE.

Variable	N	Full Sample	Device	Medication Therapy
Recurrent ischemic strokes (primary outcome), events/N		25/909	12/447	13/462
			HR (95% CI) = 0.93 (0.43, 2.05)	
Age in years, mean (sd)	909	45.47 (9.34)	45.75 (9.63)	45.19 (9.06)
Male Gender	909	471 (51.8%)	233 (52.1%)	238 (51.5%)
White Race	909	812 (89.3%)	398 (89.0%)	414 (89.6%)
Smoke	907	138 (15.2%)	69 (15.4%)	69 (15.0%)
Diabetes	909	71 (7.8%)	41 (9.2%)	30 (6.5%)
High Cholesterol	909	401 (44.1%)	212 (47.4%)	189 (40.9%)
Hypertension	909	282 (31.0%)	151 (33.8%)	131 (28.4%)
Prior Stroke	909	51 (5.6%)	26 (5.8%)	25 (5.4%)
Prior Stroke or TIA	909	114 (12.5%)	55 (12.3%)	59 (12.8%)
Atrial Septal Aneurysm	873	311 (35.6%)	153 (35.8%)	158 (35.4%)
Large Sized Shunt[a]	777	154 (19.8%)	88 (22.9%)	66 (16.8%)
Presence of a Superficial Infarct[b]	556	289 (52.0%)	127 (49.2%)	162 (54.4%)
Index Stroke (vs. TIA)	907	653 (72.0%)	324 (72.6%)	329 (71.4%)

[a]>20 bubbles for all trials except CLOSURE (>25) and CLOSE (>30).
[b]Not reported in PC Trial.
HR indicates hazard ratio comparing device to medication therapy; SD, standard deviation; TIA indicates transient ischemic attack.

Appendix Table 8. PC Trial.

Variable	N	Full Sample	Device	Medication Therapy
Recurrent ischemic strokes (primary outcome), events/N		8/414	1/204	7/210
			HR (95% CI) = 0.14 (0.02, 1.15)	
Age in years, mean (sd)	414	44.48 (10.17)	44.32 (10.23)	44.63 (10.13)
Male Gender	414	206 (49.8%)	92 (45.1%)	114 (54.3%)
White Race	NR			
Smoke	414	99 (23.9%)	52 (25.5%)	47 (22.4%)
Diabetes	414	11 (2.7%)	5 (2.5%)	6 (2.9%)
High Cholesterol	414	112 (27.1%)	50 (24.5%)	62 (29.5%)
Hypertension	414	107 (25.8%)	49 (24.0%)	58 (27.6%)
Prior Stroke	NR			
Prior Stroke or TIA	414	155 (37.4%)	76 (37.3%)	79 (37.6%)
Atrial Septal Aneurysm	414	98 (23.7%)	47 (23.0%)	51 (24.3%)

Large Sized Shunt[a]	369	80 (21.7%)	43 (23.2%)	37 (20.1%)
Presence of a Superficial Infarct[b]	NR			
Index Stroke (vs. TIA)	414	414 (100%)	204 (100%)	210 (100%)

[a]>20 bubbles for all trials except CLOSURE (>25) and CLOSE (>30).
[b]Not reported in PC Trial.
NR, not reported; SD, standard deviation; TIA indicates transient ischemic attack.

Appendix Table 9. RESPECT.

Variable	N	Full Sample	Device	Medication Therapy
Recurrent ischemic strokes (primary outcome), events/N		46/980	18/499	28/481
			HR (95% CI) = 0.55 (0.31, 1.00)	
Age in years , mean (sd)	968	45.44 (9.84)	45.24 (9.67)	45.65 (10.01)
Male Gender	980	536 (54.7%)	268 (53.7%)	268 (55.7%)
White Race	NR			
Smoke	980	130 (13.3%)	75 (15.0%)	55 (11.4%)
Diabetes	980	74 (7.6%)	33 (6.6%)	41 (8.5%)
High Cholesterol	980	391 (39.9%)	196 (39.3%)	195 (40.5%)
Hypertension	980	313 (31.9%)	160 (32.1%)	153 (31.8%)
Prior Stroke	979	104 (10.6%)	53 (10.6%)	51 (10.6%)
Prior Stroke or TIA	980	182 (18.6%)	93 (18.6%)	89 (18.5%)
Atrial Septal Aneurysm	980	349 (35.6%)	179 (35.9%)	170 (35.3%)
Large Sized Shunt[a]	969	478 (49.3%)	247 (50.0%)	231 (48.6%)
Presence of a Superficial Infarct[b]	897	706 (78.7%)	357 (80.0%)	349 (77.4%)
Index Stroke (vs. TIA)	980	980 (100%)	499 (100%)	481 (100%)

[a]>20 bubbles for all trials except CLOSURE (>25) and CLOSE (>30).
[b]Not reported in PC Trial.
NR, not reported; SD, standard deviation; TIA indicates transient ischemic attack.

Appendix Table 10. REDUCE.

Variable	N	Full Sample	Device	Medication Therapy
Recurrent ischemic strokes (primary outcome), events/N		20/664	8/441	12/223
			HR (95% CI) = 0.31 (0.13, 0.76)	
Age in years, mean (sd)	664	45.22 (9.36)	45.42 (9.26)	44.83 (9.56)
Male Gender	664	399 (60.1%)	261 (59.2%)	138 (61.9%)
White Race	664	615 (92.6%)	412 (93.4%)	203 (91.0%)
Smoke	664	161 (24.2%)	105 (23.8%)	56 (25.1%)
Diabetes	664	28 (4.2%)	18 (4.1%)	10 (4.5%)
High Cholesterol	664	317 (47.7%)	214 (48.5%)	103 (46.2%)
Hypertension	664	171 (25.8%)	113 (25.6%)	58 (26.0%)

Prior Stroke	664	55 (8.3%)	42 (9.5%)	13 (5.8%)
Prior Stroke or TIA	664	85 (12.8%)	62 (14.1%)	23 (10.3%)
Atrial Septal Aneurysm	538	143 (26.6%)	98 (27.4%)	45 (25.0%)
Large Sized Shunt[a]	642	168 (26.2%)	123 (28.9%)	45 (20.8%)
Presence of a Superficial Infarct[b]	626	449 (71.7%)	304 (72.7%)	145 (69.7%)
Index Stroke (vs. TIA)	664	664 (100%)	441 (100%)	223 (100%)

[a]>20 bubbles for all trials except CLOSURE (>25) and CLOSE (>30).
[b]Not reported in PC Trial.
SD, standard deviation; TIA indicates transient ischemic attack.

Appendix Table 11. DEFENSE.

Variable	N	Full Sample	Device	Medication Therapy
Recurrent ischemic strokes (primary outcome), events/N		5/120	0/60	5/60
Age in years , mean (sd)	120	51.75 (13.78)	49.27 (14.74)	54.23 (12.37)
Male Gender	120	67 (55.8%)	33 (55.0%)	34 (56.7%)
White Race	NR			
Smoke	120	26 (21.7%)	10 (16.7%)	16 (26.7%)
Diabetes	120	14 (11.7%)	6 (10.0%)	8 (13.3%)
High Cholesterol	120	43 (35.8%)	18 (30.0%)	25 (41.7%)
Hypertension	120	29 (24.2%)	12 (20.0%)	17 (28.3%)
Prior Stroke	120	6 (5.0%)	3 (5.0%)	3 (5.0%)
Prior Stroke or TIA	120	10 (8.3%)	4 (6.7%)	6 (10.0%)
Atrial Septal Aneurysm	120	58 (48.3%)	29 (48.3%)	29 (48.3%)
Large Sized Shunt[a]	120	96 (80.0%)	50 (83.3%)	46 (76.7%)
Presence of a Superficial Infarct[b]	120	104 (86.7%)	56 (93.3%)	48 (80.0%)
Index Stroke (vs. TIA)	120	120 (100%)	60 (100%)	60 (100%)

[a]>20 bubbles for all trials except CLOSURE (>25) and CLOSE (>30).
[b]Not reported in PC Trial.
NR, not reported; SD, standard deviation; TIA indicates transient ischemic attack.

Appendix Table 12. CLOSE-A (randomization group 2: had contraindications to oral anticoagulants).

Variable	N	Full Sample	Device	Medication Therapy
Recurrent ischemic strokes (primary outcome), events/N		7/129	0/65	7/64
Age in years, mean (sd)	129	40.61 (11.18)	39.59 (11.89)	41.65 (10.40)
Male Gender	129	84 (65.1%)	41 (63.1%)	43 (67.2%)
White Race	NR			

Smoke	129	36 (27.9%)	16 (24.6%)	20 (31.3%)
Diabetes	129	3 (2.3%)	1 (1.5%)	2 (3.1%)
High Cholesterol	129	22 (17.1%)	10 (15.4%)	12 (18.8%)
Hypertension	129	10 (7.8%)	5 (7.7%)	5 (7.8%)
Prior Stroke	129	4 (3.1%)	2 (3.1%)	2 (3.1%)
Prior Stroke or TIA	129	12 (9.3%)	5 (7.7%)	7 (10.9%)
Atrial Septal Aneurysm	129	53 (41.1%)	28 (43.1%)	25 (39.1%)
Large Sized Shunt[a]	129	120 (93.0%)	60 (92.3%)	60 (93.8%)
Presence of a Superficial Infarct[b]	129	85 (65.9%)	41 (63.1%)	44 (68.8%)
Index Stroke (vs. TIA)	129	129 (100%)	65 (100%)	64 (100%)

[a]>20 bubbles for all trials except CLOSURE (>25) and CLOSE (>30).
[b]Not reported in PC Trial.
NR, not reported; SD, standard deviation; TIA indicates transient ischemic attack.

Appendix Table 13. CLOSE-B (randomization group 1: had no contraindications to PFO closure or oral anticoagulants).

Variable	N	Full Sample	Device	Medication Therapy
Recurrent ischemic strokes (primary outcome), events/N		10/524	0/173	10/351
Age in years , mean (sd)	524	44.25 (9.66)	44.13 (9.08)	44.31 (9.95)
Male Gender	524	295 (56.3%)	96 (55.5%)	199 (56.7%)
White Race	NR			
Smoke	524	153 (29.2%)	52 (30.1%)	101 (28.8%)
Diabetes	524	11 (2.1%)	2 (1.2%)	9 (2.6%)
High Cholesterol	524	66 (12.6%)	20 (11.6%)	46 (13.1%)
Hypertension	524	56 (10.7%)	22 (12.7%)	34 (9.7%)
Prior Stroke	524	19 (3.6%)	8 (4.6%)	11 (3.1%)
Prior Stroke or TIA	524	37 (7.1%)	15 (8.7%)	22 (6.3%)
Atrial Septal Aneurysm	524	172 (32.8%)	53 (30.6%)	119 (33.9%)
Large Sized Shunt[a]	524	486 (92.7%)	156 (90.2%)	330 (94.0%)
Presence of a Superficial Infarct[b]	524	341 (65.1%)	118 (68.2%)	223 (63.5%)
Index Stroke (vs. TIA)	524	524 (100%)	173 (100%)	351 (100%)

[a]>20 bubbles for all trials except CLOSURE (>25) and CLOSE (>30)..
[b]Not reported in PC Trial.
NR, not reported; SD, standard deviation; TIA indicates transient ischemic attack.

Appendix B5. Leave-one-out Stability Analyses

Appendix Table 14. Leave-one-out Stability Analyses.

	Adjusted Cox regression[a]
Trial left-out…	HR (95% CI)
CLOSE-A (randomization group 2)	0.439 (0.296, 0.651)
CLOSE-B (randomization group 1)	0.429 (0.289, 0.636)
CLOSURE	0.321 (0.204, 0.505)
DEFENSE	0.420 (0.284, 0.622)
PC Trial	0.425 (0.286, 0.633)
REDUCE	0.436 (0.285, 0.668)
RESPECT	0.335 (0.135, 0.549)

[a]Adjusted for: age, sex, coronary artery disease, diabetes, hypertension, hyperlipidemia, prior stroke or TIA, smoking status, index event (stroke versus TIA), hypermobile septum, PFO shunt size (large versus small) and infract location (superficial versus deep).
CI, confidence interval; HR indicates hazard ratio.

Appendix B6. Patient Characteristics of Early Exiting Patients

We compared baseline characteristics for patients with observed length of follow-up that was less than half of expected follow-up (with-in trial maximum follow up time) compared to those with greater follow-up.

Appendix Table 15. Patient Characteristics of Early Exiting Patients.

	N	Not early N=2774	Early exit (follow up less than half of expected) N=966	Not early vs. early p-value	Early exit (follow up less than half of expected) N=966			
					N	Device N=433	Medical therapy N=533	Device vs. Medical therapy p-value
Age in years , mean (sd)	3728	45.36 (9.82)	44.62 (10.34)	.046	954	44.08 (10.61)	45.05 (10.10)	0.15
Male Gender	3740	1525 (55.0%)	533 (55.2%)	.91	966	239 (55.2%)	294 (55.2%)	0.99
White Race	1573	1286 (91.3%)	141 (85.5%)	.01	165	56 (77.8%)	85 (91.4%)	0.01
Smoke	3738	536 (19.3%)	207 (21.5%)	.15	965	85 (19.6%)	122 (22.9%)	0.21
Diabetes	3740	146 (5.3%)	66 (6.8%)	.07	966	29 (6.7%)	37 (6.9%)	0.88
High Cholesterol	3740	1024 (36.9%)	328 (34.0%)	.10	966	154 (35.6%)	174 (32.6%)	0.34
Hypertension	3740	724 (26.1%)	244 (25.3%)	.61	966	123 (28.4%)	121 (22.7%)	0.04
Prior Stroke	3739	157 (5.7%)	82 (8.5%)	.002	965	40 (9.3%)	42 (7.9%)	0.44
Prior Stroke/TIA	3740	438 (15.8%)	157 (16.3%)	.73	966	72 (16.6%)	85 (15.9%)	0.78
Atrial Septal Aneurysm	3578	867 (32.9%)	317 (33.6%)	.69	943	146 (34.6%)	171 (32.8%)	0.57
Large Sized Shunt	3530	1082 (41.5%)	500 (54.2%)	<.001	922	223 (53.5%)	277 (54.9%)	0.68
Presence of a Superficial Infarct	2852	1370 (66.7%)	604 (75.6%)	<.001	799	282 (80.1%)	322 (72.0%)	0.008
Index Stroke (vs. TIA)	3738	2549 (91.9%)	935 (97.0%)	<.001	964	420 (97.2%)	515 (96.8%)	0.71

SD indicates standard deviation; TIA, transient ischemic attack.

Appendix B7. Tipping Point Analysis

We imputed missing event times for patients if their observed length of follow-up was less than half or less than three quarters of expected follow-up (with-in trial maximum follow up time). This sensitivity analysis suggests that all subjects randomized to the device arm censored prior to the end of follow-up (trial-specific maximum) would need to have a **twofold** increase in event hazard (recurrent ischemic stroke) compared with patients randomized to the medical therapy arm for the statistically significant result in favor of the device versus medical therapy to be nullified (the 'tipping point').

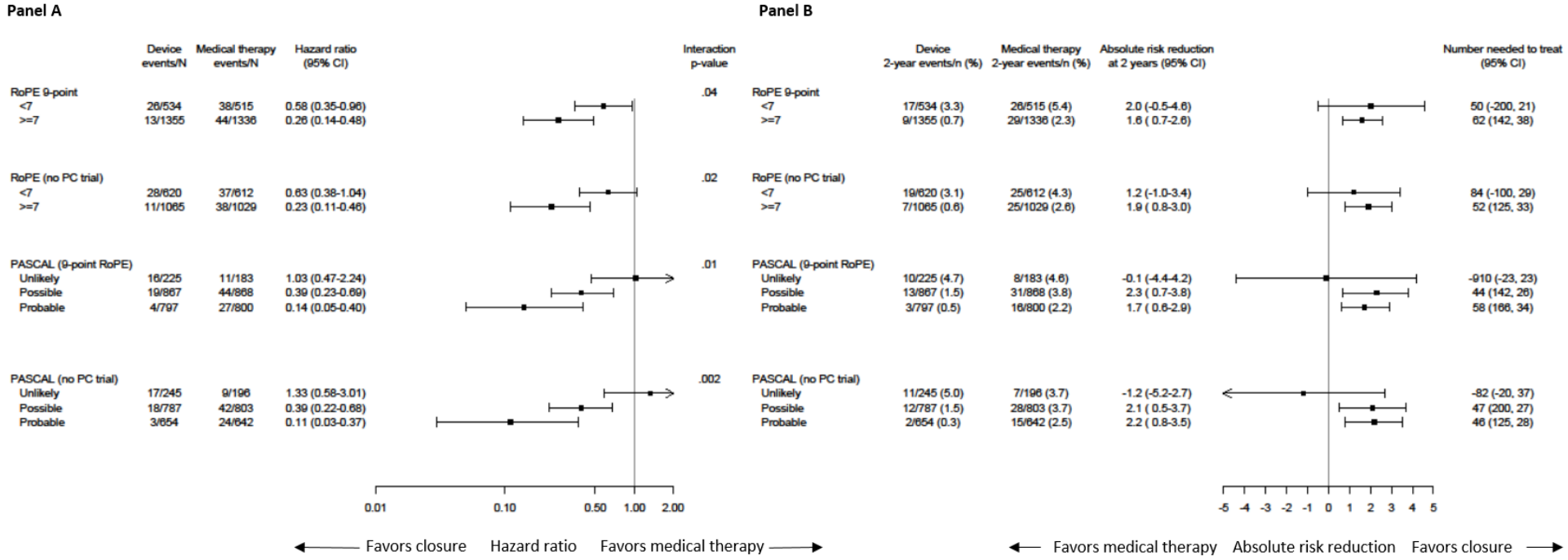
Appendix Table 16. Tipping Point Analysis of Primary Outcome.

Impute missing event time if observed follow-up < half of expected follow-up						
Medical therapy	**Impute missing event time**	**N**		**Device delta hazard**	**HR**	**Upper 95% CL**
	No	1318		1.0 (censored at random)	0.410	0.638
	Yes	**533**		1.5	0.508	0.766
Device				2	0.594	0.938
	No	1456		2.5 (tipping point)	0.681	1.170
	Yes	**433**				
Impute missing event time if observed follow-up < three quarters of expected follow-up						
Medical therapy	**Impute missing event time**	**N**		**Device delta hazard**	**HR**	**Upper 95% CL**
	No	955		1.0 (censored at random)	0.405	0.639
	Yes	**896**		1.5	0.524	0.798
Device				2 (tipping point)	0.641	1.051
	No	1122				
	Yes	**767**				

CL, confidence limit; HR indicates hazard ratio.

Appendix B8. RoPE and PASCAL Analyses

Appendix Figure 3. Recurrent Ischemic Stroke Heterogeneous Treatment Effects (HTE) Stability Analyses for RoPE and PASCAL.



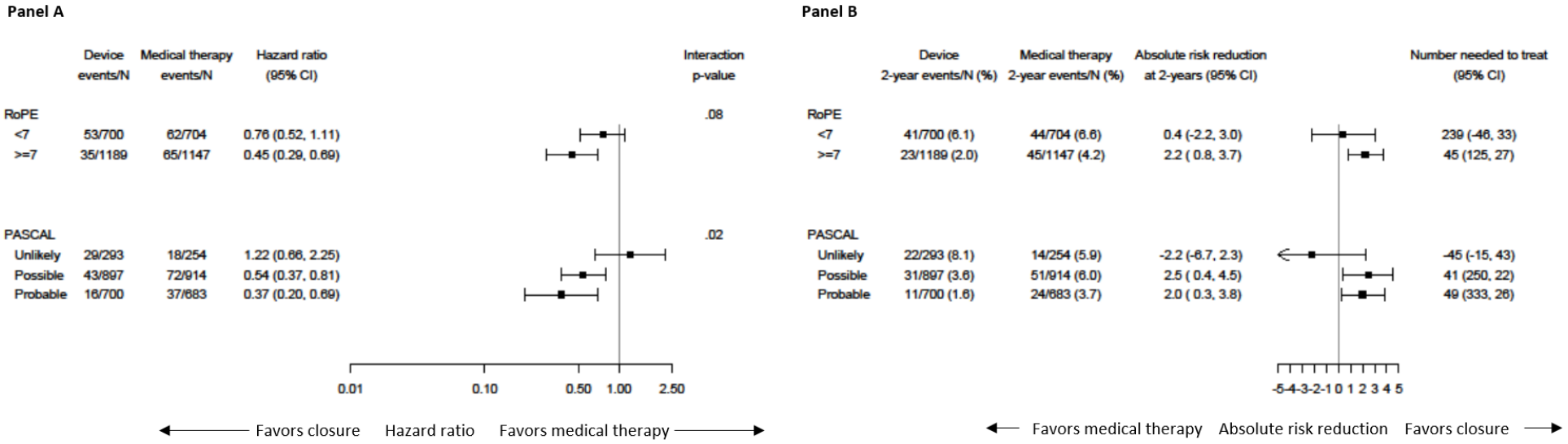
Legend:

Primary outcome of recurrent ischemic stroke**. Panel A: Hazard ratios. Panel B: Absolute risk reduction.** HR accounting for: age, sex, prior myocardial infarction, diabetes, hypertension, hyperlipidemia, prior stroke or TIA, smoking status, index event (stroke versus TIA), atrial septal aneurysm on trans-esophageal echocardiography (definition in Appendix A5), PFO shunt size (large versus small, definition in Appendix A5) and superficial infarction on neuroimaging (present versus absent). 2-year ARR calculated as differences in Kaplan Meier event rates at two years. Median time to the primary outcome of recurrent ischemic stroke was 13.7 months (n=121; interquartile range 4.8 to 29.7).

ARR, absolute risk reduction; CI, confidence interval; HR, hazard ratio; HTE, heterogeneous treatment effect; NNT, number-needed-to-treat; PASCAL, PFO-Associated Stroke Causal Likelihood; RoPE indicates Risk of Paradoxical Embolism.

Appendix B: Supplementary Results

Appendix Figure 4. Secondary Outcome RoPE and PASCAL Heterogeneous Treatment Effects (HTE) Analyses.



Legend:

Secondary outcome of recurrent ischemic stroke, TIA, or vascular death. **Panel A: Hazard ratios. Panel B: Absolute risk reduction.** HR accounting for: age, sex, prior myocardial infarction, diabetes, hypertension, hyperlipidemia, prior stroke or TIA, smoking status, index event (stroke versus TIA), atrial septal aneurysm on trans-esophageal echocardiography (definition in Appendix A5), PFO shunt size (large versus small, definition in Appendix A5) and superficial infarction on neuroimaging (present versus absent). 2-year ARR calculated as differences in Kaplan Meier event rates at two years.

ARR, absolute risk reduction; CI, confidence interval; HR, hazard ratio; HTE, heterogeneous treatment effect; NNT, number-needed-to-treat; PASCAL, PFO-Associated Stroke Causal Likelihood; RoPE indicates Risk of Paradoxical Embolism.

Appendix B9. Safety Outcomes by PASCAL Classification

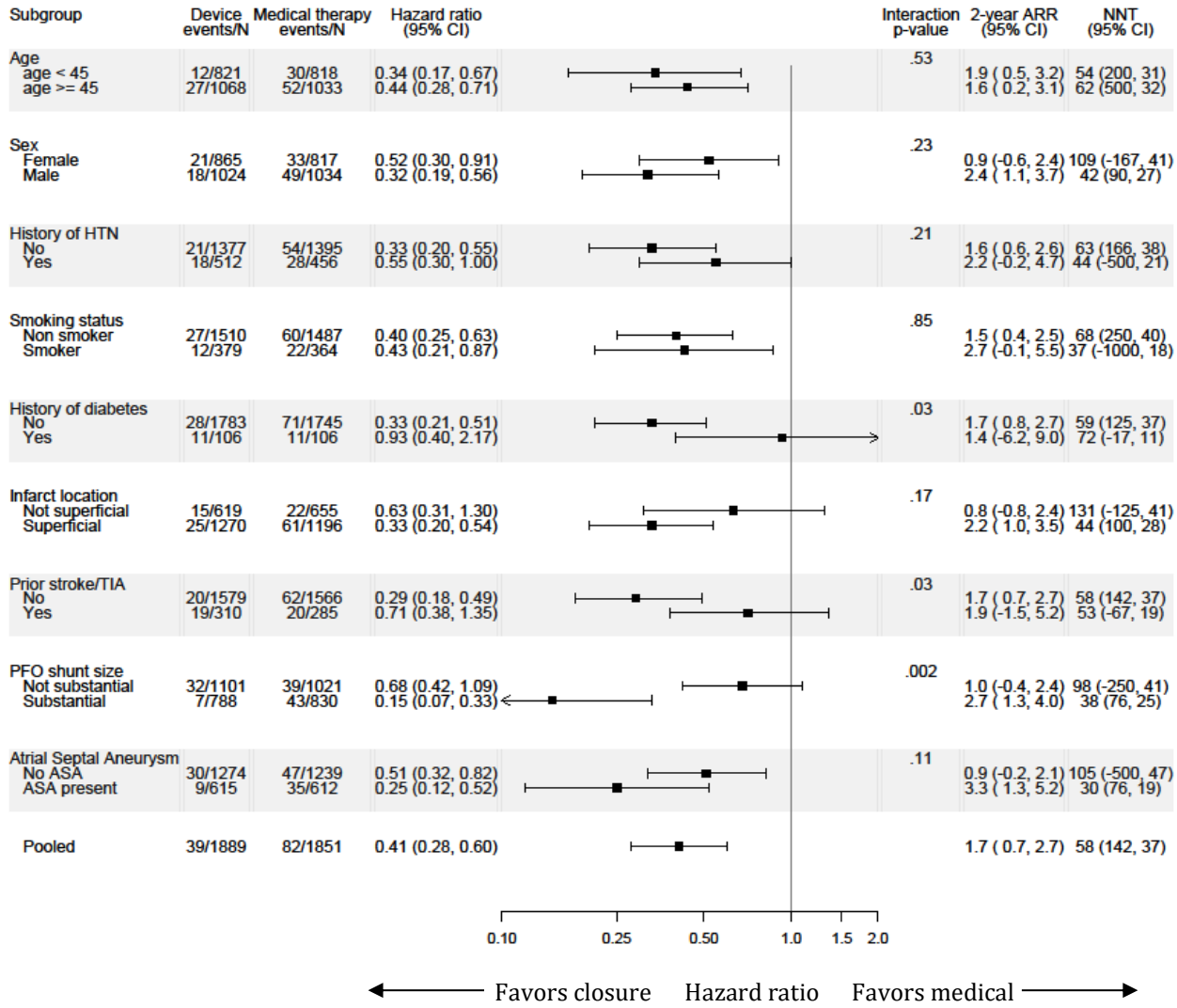
Appendix Table 17. Safety Outcomes by PASCAL Classification with 2 year Atrial Fibrillation Rates.

	Kaplan Meier 2-year rate % (patients with event/n)		Absolute Risk Difference % (95% CI)
Safety outcome (as-treated population)	**Device**	**No device**	
PASCAL Classification			
Atrial fibrillation (all events)			
Unlikely	7.6 (20/260)	1.8 (5/282)	5.8 (2.2, 9.4)
Possible	3.8 (31/835)	0.3 (3/965)	3.5 (2.1, 4.8)
Probable	2.5 (16/667)	0.5 (3/709)	2.0 (0.6, 3.3)
Atrial fibrillation (present beyond 45 days)			
Unlikely	4.2 (11/260)	1.5 (4/282)	2.7 (-0.2, 5.6)
Possible	1.7 (14/835)	0.3 (3/965)	1.4 (0.4, 2.3)
Probable	1.1 (8/667)	0.5 (3/709)	0.6 (-0.4, 1.6)
Leave out CLOSURE trial			
Atrial fibrillation (all events)			
Unlikely	8.1 (13/159)	1.3 (2/165)	6.8 (2.2, 11.4)
Possible	3.0 (19/640)	0.2 (1/695)	2.8 (1.5, 4.2)
Probable	2.4 (14/564)	0.6 (3/587)	1.9 (0.5, 3.3)
Atrial fibrillation (present beyond 45 days)			
Unlikely	4.4 (7/159)	1.4 (2/165)	3.0 (-0.7, 6.8)
Possible	1.4 (9/640)	0.2 (1/695)	1.2 (0.3, 2.2)
Probable	1.2 (7/564)	0.6 (3/587)	0.6 (-0.5, 1.7)

CI, confidence interval; PASCAL indicates PFO-Associated Stroke Causal Likelihood.

Appendix B10. Outcome Exploratory Subgroup Analyses

Appendix Figure 5. Recurrent Ischemic Stroke Exploratory Subgroup Analyses.

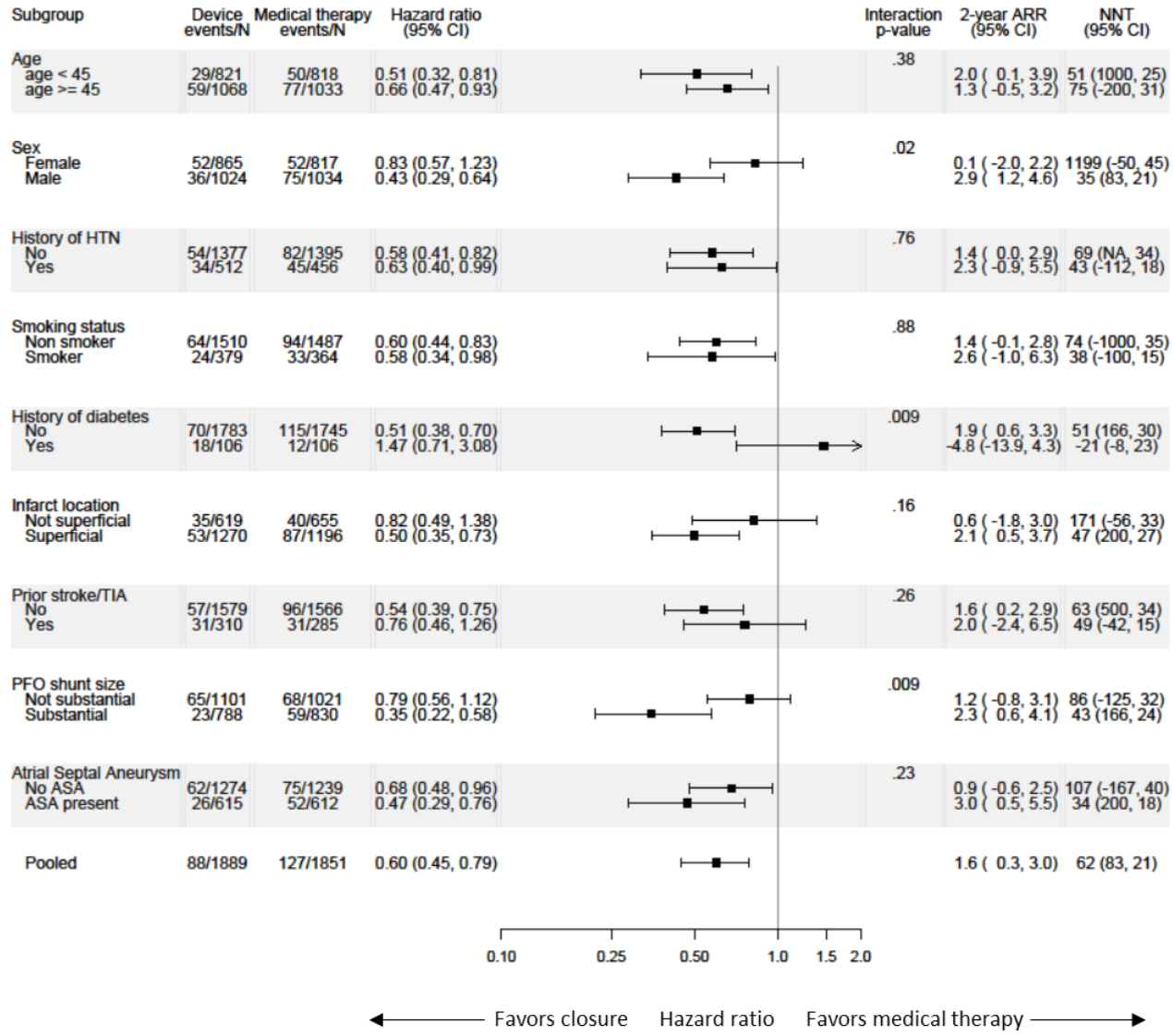


Legend:

Primary outcome recurrent ischemic stroke. HR accounting for: age, sex, prior myocardial infarction, diabetes, hypertension, hyperlipidemia, prior stroke or TIA, smoking status, index event (stroke versus TIA), atrial septal aneurysm on trans-esophageal echocardiography (definition in Appendix A5), PFO shunt size (large versus small, definition in Appendix A5) and superficial infarction on neuroimaging (present versus absent). 2-year ARR calculated as differences in Kaplan Meier event rates at two years. Median time to the primary outcome of recurrent ischemic stroke was 13.7 months (n=121; interquartile range 4.8 to 29.7). Note: p-values from exploratory analyses are provided for descriptive purposes.

ARR, absolute risk reduction; CI, confidence interval; HR, hazard ratio; NNT, number-needed-to-treat.

Appendix Figure 6. Secondary Outcome Exploratory Subgroup Analyses.



Legend:

Secondary outcome recurrent ischemic stroke, TIA, or vascular death. HR accounting for: age, sex, prior myocardial infarction, diabetes, hypertension, hyperlipidemia, prior stroke or TIA, smoking status, index event (stroke versus TIA), atrial septal aneurysm on trans-esophageal echocardiography (definition in Appendix A5), PFO shunt size (large versus small, definition in Appendix A5) and superficial infarction on neuroimaging (present versus absent). 2-year ARR calculated as differences in Kaplan Meier event rates at two years. Note: p-values from exploratory analyses are provided for descriptive purposes.

ARR, absolute risk reduction; CI, confidence interval; HR, hazard ratio; NNT, number-needed-to-treat.

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Acknowledgment:
Research reported in this report was funded through a Patient-Centered Outcomes Research Institute® (PCORI®) Award (RS-SCOPE-2019-001).
Further information available at: https://www.pcori.org/research-results/2019/evaluating-therapies-prevent-future-stroke-patients-patent-foramen-ovale-related-strokes-scope-study