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Heterogeneity of Treatment Effects in an Analysis of Pooled Individual Patient Data From Randomized Trials of Device Closure of Patent Foramen Ovale After Stroke

David M. Kent, MD, MS; Jeffrey L. Saver, MD; Scott E. Kasner, MD; Jason Nelson, MS; John D. Carroll, MD; Gilles Chatellier, MD; Geneviève Derumeaux, MD; Anthony J. Furlan, MD; Howard C. Herrmann, MD; Peter Jüni, MD; Jong S. Kim, MD; Benjamin Koethe, MS; Pil Hyung Lee, MD; Benedicte Lefebvre, MD; Heinrich P. Mattle, MD; Bernhard Meier, MD; Mark Reisman, MD; Richard W. Smalling, MD, PhD; Lars Soendergaard, MD; Jae-Kwan Song, MD; Jean-Louis Mas, MD; David E. Thaler, MD, PhD

IMPORTANCE Patent foramen ovale (PFO)-associated strokes comprise approximately 10% of ischemic strokes in adults aged 18 to 60 years. While device closure decreases stroke recurrence risk overall, the best treatment for any individual is often unclear.

OBJECTIVE To evaluate heterogeneity of treatment effect of PFO closure on stroke recurrence based on previously developed scoring systems.

DESIGN, SETTING, AND PARTICIPANTS Investigators for the Systematic, Collaborative, PFO Closure Evaluation (SCOPE) Consortium pooled individual patient data from all 6 randomized clinical trials that compared PFO closure plus medical therapy vs medical therapy alone in patients with PFO-associated stroke, and included a total of 3740 participants. The trials were conducted worldwide from 2000 to 2017.

EXPOSURES PFO closure plus medical therapy vs medical therapy alone. Subgroup analyses used the Risk of Paradoxical Embolism (RoPE) Score (a 10-point scoring system in which higher scores reflect younger age and the absence of vascular risk factors) and the PFO-Associated Stroke Causal Likelihood (PASCAL) Classification System, which combines the RoPE Score with high-risk PFO features (either an atrial septal aneurysm or a large-sized shunt) to classify patients into 3 categories of causal relatedness: unlikely, possible, and probable.

MAIN OUTCOMES AND MEASURES Ischemic stroke.

RESULTS Over a median follow-up of 57 months (IQR, 24-64), 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%) (adjusted hazard ratio [HR], 0.41 [95% CI, 0.28-0.60]). The 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 as unlikely, possible, and probable using the PASCAL Classification System 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 after randomization with a device were 4.41% (95% CI, 1.02% to 7.80%), 1.53% (95% CI, 0.33% to 2.72%), and 0.65% (95% CI, -0.41% to 1.71%) in the unlikely, possible, and probable PASCAL categories, respectively.

CONCLUSIONS AND RELEVANCE 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 this classification system has the potential to guide individualized decision-making.

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Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: David M. Kent, MD, MS, Predictive Analytics and Comparative Effectiveness Center, Institute for Clinical Research and Health Policy Studies, Tufts Medical Center, 800 Washington St, PO Box 63, Boston, MA 02111 (dkent1@tuftsmedicalcenter.org).

Patent foramen ovale (PFO)-associated strokes comprise 10% of ischemic strokes in young and middle-aged adults aged 18 to 60 years.¹ Therapeutic strategies to prevent recurrent stroke among patients with a PFO-associated ischemic stroke include antithrombotic therapy or percutaneous device closure of the PFO, each of which is endorsed in practice guidelines.²⁻⁴

Six randomized clinical trials that compared device closure and medical therapy vs medical therapy alone have been completed.⁵⁻¹¹ Study-level meta-analyses^{1,12} have shown that closure was associated with a lower rate of recurrent ischemic stroke.¹² However, absolute risks of stroke recurrence remain very low for some patients with medical therapy, and device closure has associated risks and adverse effects.¹ Recent guidelines stressed the importance of informed shared decision-making evaluating the individual probability of benefit and the risks of a lifelong device.²⁻⁴

However, study-level analysis of randomized clinical trials generally only provides results for the broad reference class of all patients qualifying for a trial. Yet individual patients differ from one another in many ways that can affect the potential for benefit. Conventional, one-variable-at-a-time subgroup analyses explore heterogeneity of treatment effect (HTE) in a limited manner but have well-known issues with both credibility from multiplicity and applicability to individuals because patients vary in many different potentially important ways simultaneously.¹³⁻¹⁵

This individual participant data 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.^{13,14}

Methods

Institutional Review Board and Patient Consent

The Tufts Health Sciences institutional review board approved this study. Patient consent was not required for this secondary data analysis.

Study Design and Inclusion Criteria

The study investigators established the Systematic, Collaborative, PFO Closure Evaluation (SCOPE) Consortium to undertake meta-analysis of pooled individual participant data. Study methods adhered to the Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data guidelines and the protocol was registered on PROSPERO (CRD42020186537).¹⁶ The collaboration included all randomized phase 3 trials comparing PFO closure vs medical therapy for recurrent stroke prevention published by September 2021. Trial methodology was assessed with the Risk of Bias 2.0 tool (Cochrane Methods). Investigators were contacted and data were collected and harmonized (for details see eAppendix 1 and eTable 1 in the Supplement).

The 3 prespecified study aims were to (1) assess overall efficacy and safety of PFO device closure plus medical therapy

Key Points

Question Which patients with patent foramen ovale (PFO)-associated stroke might benefit from PFO closure?

Findings In this individual participant data meta-analysis that included 6 randomized clinical trials with 3740 patients with otherwise cryptogenic stroke and PFO, PFO closure plus medical therapy, compared with medical therapy alone, was associated with varying risk reduction for recurrent stroke among subgroups with different probabilities that the stroke was causally related to the PFO. For patients classified as unlikely (ie, with vascular risk factors and without high-risk PFO features), the hazard ratio (HR) was 1.14 but was not statistically significant; for those classified as possible or probable, the HRs were 0.38 and 0.10, respectively, both statistically significant.

Meaning Application of a multivariable causal classification system to randomized trial results distinguished subgroups who may benefit from PFO closure from those unlikely to receive benefit.

vs medical therapy alone for the prevention of recurrent stroke; (2) examine whether the Risk of Paradoxical Embolism (RoPE) Score¹⁷ is associated with differential treatment effect; and (3) examine whether the PFO-Associated Stroke Causal Likelihood (PASCAL) Classification System¹⁸ is associated with differential treatment effect.

The RoPE Score and the PASCAL Classification System

RoPE is depicted in Table 1 and explicated in eAppendix 2 and eTable 2 in the Supplement. 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. Because PFOs are present in approximately 25% of the general population, patients with PFO can have a stroke either through a PFO-related mechanism (eg, a paradoxical embolism) or through another occult mechanism (eg, paroxysmal atrial fibrillation or minimally stenosing cervicocerebral atherosclerotic plaque). The RoPE Score is based on 2 insights: (1) the prevalence of a PFO among patients with cryptogenic stroke (compared with that in the general population) can be used, via the 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 prevent only strokes caused by paradoxical embolism, the attributable fraction would be assumed to correspond to the relative risk reduction of closure in preventing a future stroke.¹⁹

The RoPE Score has been externally validated to predict the presence of a PFO in the cryptogenic stroke population.^{20,21}

However, the RoPE Score has 2 important limitations: the methods to derive the RoPE Score did not permit inclusion of high-risk features of the PFO and patients with higher RoPE Scores have lower stroke recurrence rates. Thus, the RoPE Score may not provide comprehensive information for patient selection.^{3,18}

The PASCAL Classification System depicted in Table 1 and explicated in eAppendix 3 and eFigure 1 in the [Supplement](#) 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, shunt size and the presence of an atrial septal aneurysm.²²⁻²⁴ Based on these factors, this system algorithmically assigns a likelihood of causal relationship (Table 1).²⁵

Outcomes

The primary efficacy end point was recurrent ischemic stroke: an acute neurologic deficit, presumed to be due to focal ischemia, and either symptoms persisting 24 hours or longer or symptoms persisting less than 24 hours but associated with neuroimaging findings of a new neuroanatomically relevant infarct.^{26,27}

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, transient ischemic attack (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 at day 30 or longer after the stroke in the modified Rankin Scale. 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.

Five safety outcomes were examined, as defined in the primary trials: all serious adverse events; major vascular procedural complication; atrial fibrillation; major bleeding episode; and venous thromboembolism (deep venous thrombosis/pulmonary embolism). Both all atrial fibrillation and atrial fibrillation present any time beyond the first 45 days after randomization (to exclude transient periprocedural events) were analyzed separately.

Statistical Analysis

The primary analyses for efficacy outcomes assessed patients according to the treatment group to which they were randomized. Two additional analyses were conducted in (1) patients according to the treatment they actually received if any crossover occurred (ie, as treated, defined in eAppendix 4 in the [Supplement](#)) and (2) patients without major protocol deviations (ie, per protocol, defined in eAppendix 4 in the [Supplement](#)). These analyses were adjusted for prerandomization

Table 1. Risk of Paradoxical Embolism (RoPE) Score and PFO-Associated Stroke Causal Likelihood (PASCAL) Classification System

Characteristic	Points	
RoPE Score calculator^a		
No history of		
Hypertension	1	
Diabetes	1	
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)	PFO-related stroke
Absent	Absent	Unlikely
Absent	Present	Possible
Present	Absent	Possible
Present	Present	Probable

Abbreviations: ASA, atrial septal aneurysm; LS, large shunt; PFO, patent foramen ovale.

^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 9 or 10 indicating an approximately 90% probability that the stroke is attributable to the PFO. See eAppendix 2 and eTable 2 in the [Supplement](#) for details.

^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 eAppendix 3 and eFigure 1 in the [Supplement](#) for details. Large shunt size was defined in the database as >20 bubbles in the left atrium on transesophageal echo; ASA was defined as ≥10 mm of excursion from midline.

covariates. Safety outcomes were analyzed in the as-treated population only.

The secondary efficacy outcomes were analyzed using sequential gatekeeping²⁸ 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.^{17,20} Kaplan-Meier estimates were obtained at

Table 2. Baseline Patient Characteristics From 6 Pooled Trials of Device Closure vs Medical Therapy for Patent Foramen Ovale–Associated Stroke

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

Abbreviation: TIA, transient ischemic attack.

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

^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 the PC Trial.

^d More than 20 bubbles in the left atrium on transesophageal echo for all trials except the CLOSURE (>25) and CLOSE (>30) Trials (see eAppendix 5 and eTables 3 and 4 in the Supplement for details).

^e See eAppendix 5 and eTables 3 and 4 in the Supplement for details.

6, 12, 24, and 60 months for each treatment group. After confirming no violation of proportional hazards assumptions (eAppendix 1 and eTable 1 in the Supplement), effects were estimated using Cox proportional hazards regression with a study-specific random effect.²⁹ 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.³⁰ 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.²⁹ Safety analyses were based on comparisons of event proportions between treatment groups, using the Cochran-Mantel-Haenszel test (stratified by trial).^{31,32} For all hypothesis-testing analyses, a 2-sided *P* value significance threshold of .05 was used, without adjustments for multiple testing.³³ All analyses were conducted using SAS (version 9.4; SAS Institute) and R (version 4.0.2; The R Foundation).

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), atrial septal aneurysm (≥ 10 mm of excursion from midline, definition in eAppendix 5 and eTables 3 and 4 in the Supplement), PFO shunt size (large vs small, definition in eAppendix 5 and eTables 3 and 4 in the Supplement), and presence vs absence of a visible superficial infarction on neuroimaging. As a stability analysis, the unadjusted effect estimate is also reported. Additional details of the statistical analysis are provided in eAppendix 1 and eTable 1 in the Supplement.

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 assumption and were censored at last follow-up. Two sensitivity analyses were performed: a multiple imputation analysis (eAppendix 1 and eTable 1 in the

Supplement) with covariate adjustment³⁴ and a tipping-point analysis.^{35,36}

For the conditional (adjusted) analysis and for subgroup analyses, multiple imputation to impute missing covariates was used as needed.³⁷

Subgroup and Interaction Analyses

We assessed whether treatment was associated with differential effects across 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. 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 (2) 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.

Secondary (exploratory) subgroup analyses were performed across each of the following 9 variables: sex (male vs female); age (≥ 45 vs < 45 years); atrial septal aneurysm (present vs absent; defined as ≥ 10 mm excursion from midline, depending on study [see eAppendix 5 and eTables 3 and 4 in the Supplement for details]); shunt size (approximately ≥ 20 bubbles in the left atrium within 3 cardiac cycles, depending on classifications in individual studies [see eAppendix 5 and eTables 3 and 4 in the Supplement for details]); visible superficial infarction on neuroimaging; history of hypertension; history of diabetes; prior stroke or TIA; and current smoking at study entry. Though 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.

Table 3. Primary and Secondary Efficacy Outcomes

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

Abbreviations: ARR, absolute risk reduction (medical therapy - device); HR, hazard ratio; 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), atrial septal aneurysm, PFO shunt size (large vs small, definition in

eAppendix 5 and eTables 3 and 4 in the Supplement), and superficial infarction on neuroimaging (present vs absent).

^c No data for the PC and CLOSURE Trials.

^d Assume missing outcome is not disabling (no data for PC Trial). Median time to the primary outcome of recurrent ischemic stroke was 13.7 months (IQR, 4.8-29.7; n = 121).

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.

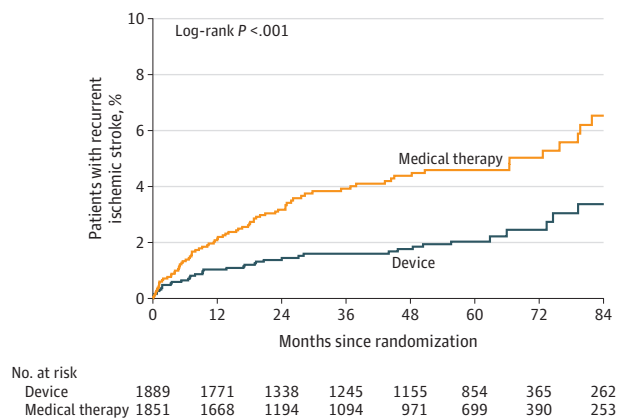
Results

The systematic search identified 6 trials that had enrolled 3740 participants who had been followed up for a median of 57 months (IQR, 24-64) (eAppendix 6 and eFigure 2 in the Supplement). The trials were conducted from 2000 to 2017. Trial details can be found in eAppendix 7 and eTable 5 in the Supplement. All trials had some concerns for risk of bias, generally related to their randomized open-blinded end point (PROBE) design or due to missing outcome data (eAppendix 8 and eTable 6 in the Supplement), 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 eAppendix 9 and eTables 7-13 in the Supplement).

Primary and Secondary Efficacy Outcomes

During a median follow-up of 57 months, a total of 121 primary end point ischemic stroke events occurred in the pooled study population. Treatment with PFO closure was associ-

Figure 1. Kaplan-Meier Curve of Recurrent Ischemic Stroke



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

ated 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 with device closure was 0.47% (95% CI, 0.35%-0.65%) (adjusted hazard ratio [HR], 0.41 [95% CI, 0.28-0.60]; P < .001). Secondary outcomes showed results that were consistent with the primary outcome (Table 3), with the exception of disability-worsening stroke, which was limited due to missingness.

Table 4. Safety Outcomes

Safety outcome (as-treated population)	Overall outcome rate, patients with event/No. of patients (%)		Risk (95% CI) ^a		Mantel-Haenszel test P value
	Device	No device ^b	Difference, %	Relative	
Any serious adverse event	506/1762 (28.7)	516/1956 (26.4)	1.97 (−0.89 to 4.82)	1.07 (0.97 to 1.19)	.18
Atrial fibrillation					
All events	88/1762 (5.0)	21/1956 (1.1)	3.77 (2.65 to 4.89)	4.54 (2.78 to 7.39)	<.001
Present beyond 45 d	43/1762 (2.4)	16/1956 (0.8)	1.38 (0.56 to 2.19)	2.60 (1.44 to 4.70)	.001
Major bleeding episode ^c	25/1762 (1.4)	33/1956 (1.7)	−0.31 (−1.09 to 0.47)	0.80 (0.47 to 1.40)	.45
Venous thromboembolism	25/1762 (1.4)	10/1956 (0.5)	0.87 (0.22 to 1.51)	2.59 (1.26 to 5.36)	.007

^a Stratified by study using Cochran-Mantel-Haenszel tests.

^b Data from 105 patients who were assigned to device but did not receive device were analyzed in the medical therapy group. The median follow-up times from randomization for patients receiving device and not receiving

device were 58.7 months (IQR, 23.8-64.0) and 50.0 months (23.8-63.6), respectively.

^c Major bleeding episode was derived from serious adverse event reporting in each of the individual trials.

Stability of the Main Results

The main results for the primary outcome were robust to alternative analytic approaches. HRs were similar for the unadjusted (Table 3), per-protocol (HR, 0.37 [95% CI, 0.24-0.57]), and as-treated (HR, 0.40 [95% CI, 0.27-0.59]) analyses. Leave-one-out analyses showed that no single trial was overly influential (eAppendix 10 and eTable 14 in the [Supplement](#)); the adjusted HR for closure ranged from 0.32 (95% CI, 0.20-0.51) (without the CLOSURE Trial) to 0.45 (95% CI, 0.30-0.66) (without the CLOSE-A Trial). Early exiting and retained patients were largely similar (eAppendix 11 and eTable 15 in the [Supplement](#)), although patients who had early exit from the trials 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 up to the end of each trial would have to be approximately 2-fold higher in the device compared with the medical therapy group to nullify the significance of the main effect (eAppendix 12 and eTable 16 in the [Supplement](#)).

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 after randomization. Beyond this periprocedural period, the rate of atrial fibrillation 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]).

RoPE Score, PASCAL Classification, and Treatment Effect Heterogeneity

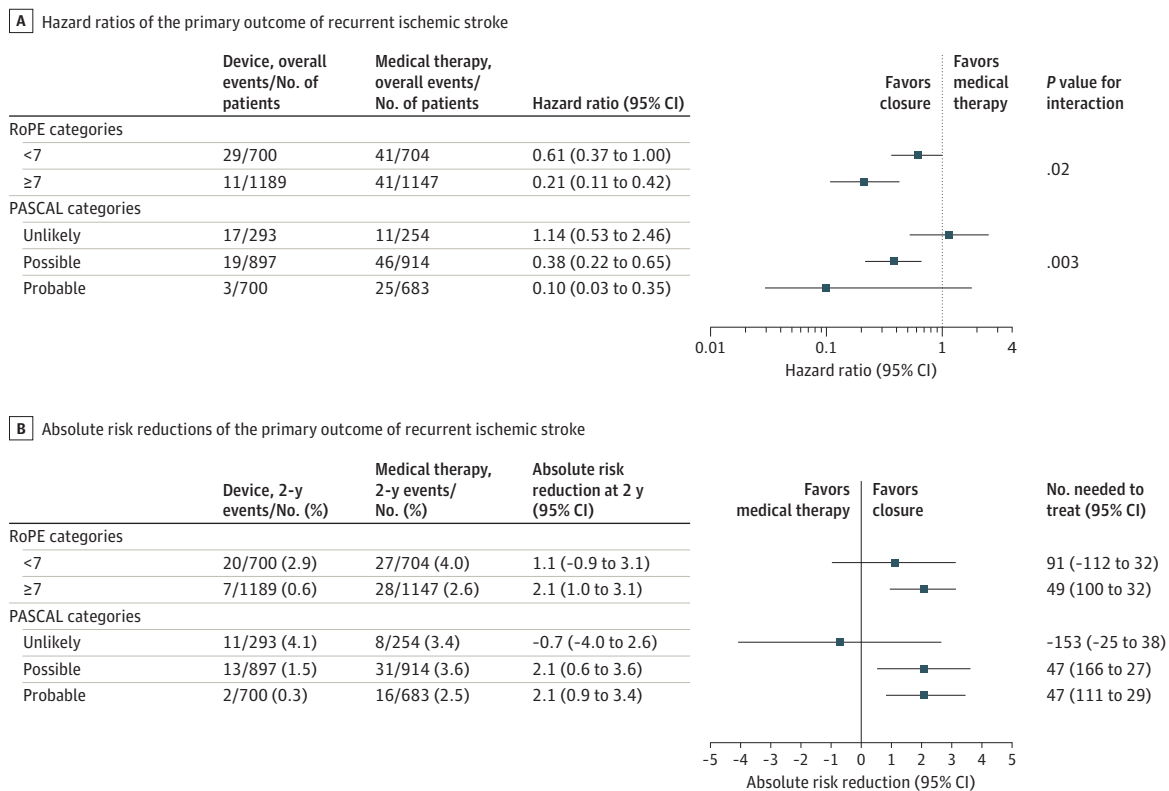
The RoPE Score-by-treatment interaction was significant ($P < .01$), using the full 10-point RoPE Score with the neuroimaging variable imputed for the PC Trial. Results were stratified by RoPE Score as 7 or greater vs less than 7 and are shown in [Figure 2](#), indicating a strong interaction ($P = .02$) on the HR scale ([Figure 2A](#)); patients with low vs high RoPE Scores had HRs of 0.61 (95% CI, 0.37 to 1.00) and 0.21 (95% CI, 0.11 to 0.42), respectively. The risks of stroke in the first 2 years for pa-

tients with a low RoPE Score were 4.0% (95% CI, 2.5% to 5.5%) and 2.9% (95% CI, 1.6% to 4.2%) (absolute risk reduction [ARR], 1.1% [95% CI, −0.9% to 3.1%]) for the medical therapy and device groups, respectively, and for patients with a high RoPE Score were 2.6% (95% CI, 1.7% to 3.6%) and 0.6% (95% CI, 0.1% to 1.0%) (ARR, 2.1% [95% CI, 1.0% to 3.1%]) for the medical therapy and device groups, respectively ([Figure 2B](#)). Results were consistent in stability analyses excluding the PC Trial, or using a 9-point (neuroimaging-free) RoPE Score ([eFigure 3 in the Supplement](#)), and with the lead secondary outcome of recurrent ischemic stroke, TIA, or vascular death ([eFigure 4 in the Supplement](#)) ([eAppendix 13 in the Supplement](#)).

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

The difference in the rates of safety outcomes between the device and medical therapy groups was also consistently higher in the unlikely group than in the probable or possible groups of the PASCAL Classification System ([eTable 17 in the Supplement](#)). For example, the absolute risk increase of postperiprocedural (occurring >45 days after randomization) atrial fibrillation with a device was 4.41% (95% CI, 1.02% to

Figure 2. Recurrent Ischemic Stroke Heterogeneity of Treatment Effect (HTE) Analyses for RoPE and PASCAL



The hazard ratios account for age, sex, prior myocardial infarction, diabetes, hypertension, hyperlipidemia, prior stroke or transient ischemic attack, smoking status, index event (stroke vs transient ischemic attack), atrial septal aneurysm on transesophageal echocardiography (definition in eAppendix 5 and eTables 3 and 4 in the Supplement), patent foramen ovale shunt size (large vs small, definition in eAppendix 5 and eTables 3 and 4 in the

Supplement), and superficial infarction on neuroimaging (present vs absent). Two-year absolute risk reductions calculated as differences in Kaplan-Meier event rates at 2 years. Median time to the primary outcome of recurrent ischemic stroke was 13.7 months (IQR, 4.8-29.7; n = 121). RoPE indicates Risk of Paradoxical Embolism (definition provided in Table 1); PASCAL, PFO-Associated Stroke Causal Likelihood.

7.80%), 1.53% (95% CI, 0.33% to 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 absolute risk reduction in ischemic stroke, 2-year differences in atrial fibrillation were calculated (eTable 18 in the Supplement) (eAppendix 14 in the Supplement).

Exploratory Subgroup Analysis

Exploratory single-parameter subgroup analyses (eFigure 5 in the Supplement) showed nominally stronger relative risk reductions 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 (eFigure 6 in the Supplement) (eAppendix 15 in the Supplement).

Discussion

This individual patient data meta-analysis indicates that PFO closure in patients with otherwise cryptogenic stroke was

associated with a strong relative reduction in the risk of 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 trials testing double-disk class closure devices currently used in clinical practice. Overall, PFO closure appeared relatively safe. Atrial fibrillation was somewhat more frequent with device closure. However, most atrial fibrillation was transient and did not cause any permanent harm; postprocedural atrial fibrillation was increased by only slightly more than 1% on the absolute scale compared with medical therapy.

While 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 patients in the PASCAL unlikely classification who lacked a high-risk PFO (either atrial septal aneurysm or large shunt) and also had vascular risk factors (ie, RoPE Score <7), even with the careful exclusion of patients with defined stroke mechanisms from

these trials. Conversely, device closure was associated with approximately a 90% relative risk reduction for patients with a PASCAL probable classification 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. While relative effect estimates differed between the probable and possible PASCAL subgroups, the 2-year absolute risk difference among 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 likely to receive greater benefit also appeared to be at lower risk for device-associated adverse events such as atrial fibrillation, 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 prior evidence showing a higher risk of incident atrial fibrillation in patients with lower RoPE Scores,²¹ who are older and have more vascular risk factors. This increased risk may reflect occult atrial fibrillation being a more likely mechanism for the index stroke in these patients and may also 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 conventional one-variable-at-a-time subgroup analysis did not generally have estimated effects that would be considered clinically or statistically significant, even while 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 treatment-favorable and -unfavorable patients, 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.

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,^{13,14,38} 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 pro-

vide 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).

Individual participant data meta-analysis has several advantages over study-level meta-analysis,³⁹ 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,^{1,7,11} and the opportunity to assess HTE. This study also used a novel approach to predict patients most likely to respond using multiple variables combined, providing new information to inform decisions about which patients should be treated with PFO closure.

Limitations

This study has several limitations. First, the magnitude of the benefit associated with device closure with respect to preventing disabling stroke remains uncertain, as substantial data were missing with respect to functional outcomes with recurrent stroke. Second, definitions of several key variables, such as large shunt or the presence of an atrial septal aneurysm, were nonidentical across trials. Nevertheless, this variation across trials did not preclude robust results from pooling data across studies. Third, while 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 3 and eFigure 1 in the Supplement) could not be evaluated because patients in the uncommon extremely high-risk categories (eg, thrombus straddling PFO; patients with concomitant deep venous thrombosis) were not identified in the study. 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 older than 60 years.

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 this classification system has the potential to guide individualized decision-making.

ARTICLE INFORMATION

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Author Affiliations: Predictive Analytics and Comparative Effectiveness Center, Tufts Medical Center/Tufts University School of Medicine, Boston, Massachusetts (Kent, Nelson, Koethe); Comprehensive Stroke Center and Department of Neurology, David Geffen School of Medicine, University of California, Los Angeles (Saver); Comprehensive Stroke Center, Department of

Neurology, University of Pennsylvania Medical Center, Philadelphia (Kasner); Division of Cardiology, Department of Medicine, University of Colorado Denver, Aurora (Carroll); Centre d'Investigations Cliniques, Unité de Recherche Clinique, Hôpital Européen Georges-Pompidou, Assistance Publique-Hôpitaux de Paris, Paris, France (Chatellier); Département de Physiologie, Hôpital Henri Mondro, Assistance Publique-Hôpitaux de Paris, Créteil, France (Derumeaux);

Department of Neurology, Case Western Reserve University, Cleveland, Ohio (Furlan); Division of Cardiovascular Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia (Herrmann, Lefebvre); Applied Health Research Centre, Li Ka Shing Knowledge Institute of St Michael's Hospital, University of Toronto, Ontario, Canada (Jüni); Department of Neurology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea (Kim); Department of

Cardiology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea (Lee, Song); Department of Neurology, Bern University Hospital, Bern, Switzerland (Mattle); Department of Cardiology, Bern University Hospital, Bern, Switzerland (Meier); Division of Cardiology, University of Washington Medical Center, Seattle (Reisman); Division of Cardiology, Department of Medicine, UTHealth/McGovern Medical School, Houston, Texas (Smalling); Department of Cardiology, University of Copenhagen Hospital Rigshospitalet, Copenhagen, Denmark (Soendergaard); GHU Paris Psychiatrie et Neurosciences, Hôpital Sainte-Anne, Département of Neurology, Institut de Psychiatrie et Neurosciences de Paris, Université de Paris, Paris, France (Mas); Department of Neurology, Tufts Medical Center/Tufts University School of Medicine, Boston, Massachusetts (Thaler).

Author Contributions: Dr Kent had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Kent, Saver, Kasner, Carroll, Chatellier, Herrmann, Meier, Sondergaard, Song, Thaler.

Acquisition, analysis, or interpretation of data: Kent, Saver, Kasner, Nelson, Carroll, Derumeaux, Furlan, Herrmann, Jüni, Kim, Koethe, Lee, Lefebvre, Mattle, Meier, Reisman, Smalling, Mas, Thaler.

Drafting of the manuscript: Kent, Nelson, Koethe, Song.

Critical revision of the manuscript for important intellectual content: Kent, Saver, Kasner, Nelson, Carroll, Chatellier, Derumeaux, Furlan, Herrmann, Jüni, Kim, Lee, Lefebvre, Mattle, Meier, Reisman, Smalling, Sondergaard, Mas, Thaler.

Statistical analysis: Kent, Saver, Nelson, Chatellier, Jüni, Koethe.

Obtained funding: Kent, Mas, Thaler.

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was a member of the steering committee for the RESPECT Trial sponsored by Abbott; a local site investigator for the REDUCE Trial sponsored by Gore; a local site investigator in the TRILUMINATE, COAPT, EVEREST 2, SUMMIT, and EXPAND clinical trials; on the steering committee for the AMULET IDE project; and as chair of the data and safety monitoring board for the TENDYNE EFS project, all associated with Abbott. Dr Carroll was also a consultant for Holistick. Dr Furlan was PI of CLOSURE NMT Boston. Dr Herrmann reported receiving grants and personal fees from WL Gore Inc, grants from Abbott, and consultant fees and equity from Holistick Medical during the conduct of the study. Outside of this work, Dr Herrmann has received institutional research funding from Bayer, Boston Scientific, Edwards Lifesciences, Highlife Medical, Medtronic, and Shockwave; consultant fees from Edwards Lifesciences, Medtronic, and Shockwave; and equity in Microinterventional Devices. Dr Jüni reported serving as an unpaid member of the steering group of trials funded by Abbott Vascular, AstraZeneca, Biotronik, Biosensors, St Jude Medical, Terumo, and The Medicines Company; receiving research grants to the institution from AstraZeneca, Appili Therapeutics, Biotronik, Biosensors International, Eli Lilly, and The Medicines Company; and receiving honoraria to the institution for participation in advisory boards and/or consulting from Amgen, Ava, and Fresenius, but has not received personal payments by any pharmaceutical company or device manufacturer. Mr Koethe reported receiving grants from PCORI during the conduct of the study. Dr Mattle reported receiving grants from Abbott for the PC and PRIMA Trials during the conduct of the study and personal fees from Servier, Bayer, Medtronic, and Cerenovus outside the submitted work. Dr Meier was a co-PI for the PC and PRIMA Trials and received personal fees from Abbott during the conduct of the study. Dr Smalling was a member of the steering committee for the RESPECT Trial, sponsored by Abbott, St Jude Medical, and AGA Medical; has served as a consultant and proctor for PFO closure (Abbott); and is on the steering committee for the PFO-PAS registry for Abbott. Dr Thaler reported receiving personal fees from Abbott for serving as a steering committee member of the RESPECT and AMULET Trials during the conduct of the study. No other disclosures were reported.

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Supplemental Online Content

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*. doi:10.1001/jama.2021.20956

eAppendix 1. Analysis Details

eTable 1. Variables of Interest

eAppendix 2. RoPE Score Detail

eTable 2. PFO-Attributable Fraction by RoPE Score

eAppendix 3. PASCAL Score Details

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

eAppendix 4. Definitions of “Per-Protocol” and “As-Treated” Populations

eAppendix 5. Description of Atrial Septal Aneurysm and Shunt Size Variables

eTable 3. Variable Definition of ASA Class

eTable 4. Variable Definition for Large Shunt Size

eAppendix 6. PRISMA IPD Flow Diagram

eFigure 2. PRISMA IPD Flow Diagram

eAppendix 7. Description of Trials

eTable 5. Features of Patent Foramen Ovale Closure Device Trials

eAppendix 8. Assessment of Risk of Bias and Small Study Effect

eTable 6. Risk of Bias Assessment

eAppendix 9. Patient Characteristics in Each Study

eTable 7. CLOSURE

eTable 8. PC Trial

eTable 9. RESPECT

eTable 10. REDUCE

eTable 11. DEFENSE

eTable 12. CLOSE-A

eTable 13. CLOSE-B

eAppendix 10. Leave-One-Out Stability Analyses

eTable 14. Leave-One-Out Stability Analyses

eAppendix 11. Patient Characteristics of Early Exiting Patients

eTable 15. Patient Characteristics of Early Exiting Patients

eAppendix 12. Tipping Point Analysis

eTable 16. Tipping Point Analysis of Primary Outcome

eAppendix 13. RoPE and PASCAL Analyses

eFigure 3. Recurrent Ischemic Stroke Heterogeneous Treatment Effect Stability Analyses for RoPE and PASCAL

eFigure 4. Secondary Outcome RoPE and PASCAL Heterogeneous Treatment Effect Analyses

eAppendix 14. Safety Outcomes by PASCAL Classification

eTable 17. Safety Outcomes by PASCAL Classification

eTable 18. Safety Outcomes by PASCAL Classification With 2-Year Atrial Fibrillation Rates

eAppendix 15. Outcome Exploratory Subgroup Analyses

eFigure 5. Recurrent Ischemic Stroke Exploratory Subgroup Analyses

eFigure 6. Secondary Outcome Exploratory Subgroup Analyses

eReferences

This supplemental material has been provided by the authors to give readers additional information about their work.

eAppendix 1. 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 6** 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 5** 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-analysis² 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. **eTable 1** displays the variables collected.

eAppendix 9 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 complete 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.

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

eAppendix 2. 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:

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

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 (**eTable 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.

eTable 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* % (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)

*Based on the observed prevalence of PFO, rather than the predicted, and assumes a population prevalence of PFO of 25%.
PFO indicates patent foramen ovale; CI, confidence interval; 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

eAppendix 3. PASCAL Score Details

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 (**eFigure 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 **eFigure 1**.

eFigure 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, <i>or</i> 1B. Large shunt PFO, <i>AND</i> 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

^aThe 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.

PFO indicates patent foramen ovale; RoPE, Risk of Paradoxical Embolism; ASA, atrial septal aneurysm; PE, pulmonary embolism; DVT, deep vein thrombosis.

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.

eAppendix 4. Definitions of “Per-protocol” and “As-treated” Populations

<p>Systematic, Collaborative, PFO closure Evaluation (SCOPE)</p>	<p>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)</p>
<p>CLOSE</p>	<p><i>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.</i></p>
<p>PC Trial</p>	<p><i>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.</i></p> <p>Special consideration:</p> <ul style="list-style-type: none"> • 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.
<p>CLOSURE</p>	<p><i>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.</i></p>
<p>RESPECT</p>	<p><i>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.</i></p> <p>Special consideration:</p> <ul style="list-style-type: none"> • 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	<i>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.</i>
DEFENSE	<i>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.</i>

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.

eAppendix 5. Description of Atrial Septal Aneurysm and Shunt Size Variables

eTable 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	<i>mobility of septum of 10 mm or greater total excursion of the septum</i>
midline	PC Trial	<i>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.</i>
TOTAL	RESPECT	<i>defined as ≥ 10 mm septum primum excursion</i>
TOTAL	REDUCE	<i>defined as the movement of the septum primum into either atrium for a total excursion of at least 10 mm (from an imaginary midline).</i>
midline	DEFENSE	<i>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)</i>
TOTAL	CLOSE	septum primum excursion greater than 10mm as identified on TEE

PFO indicates patent foramen ovale; TEE, transesophageal echocardiogram.

eTable 4. Variable Definition for Large Shunt Size.

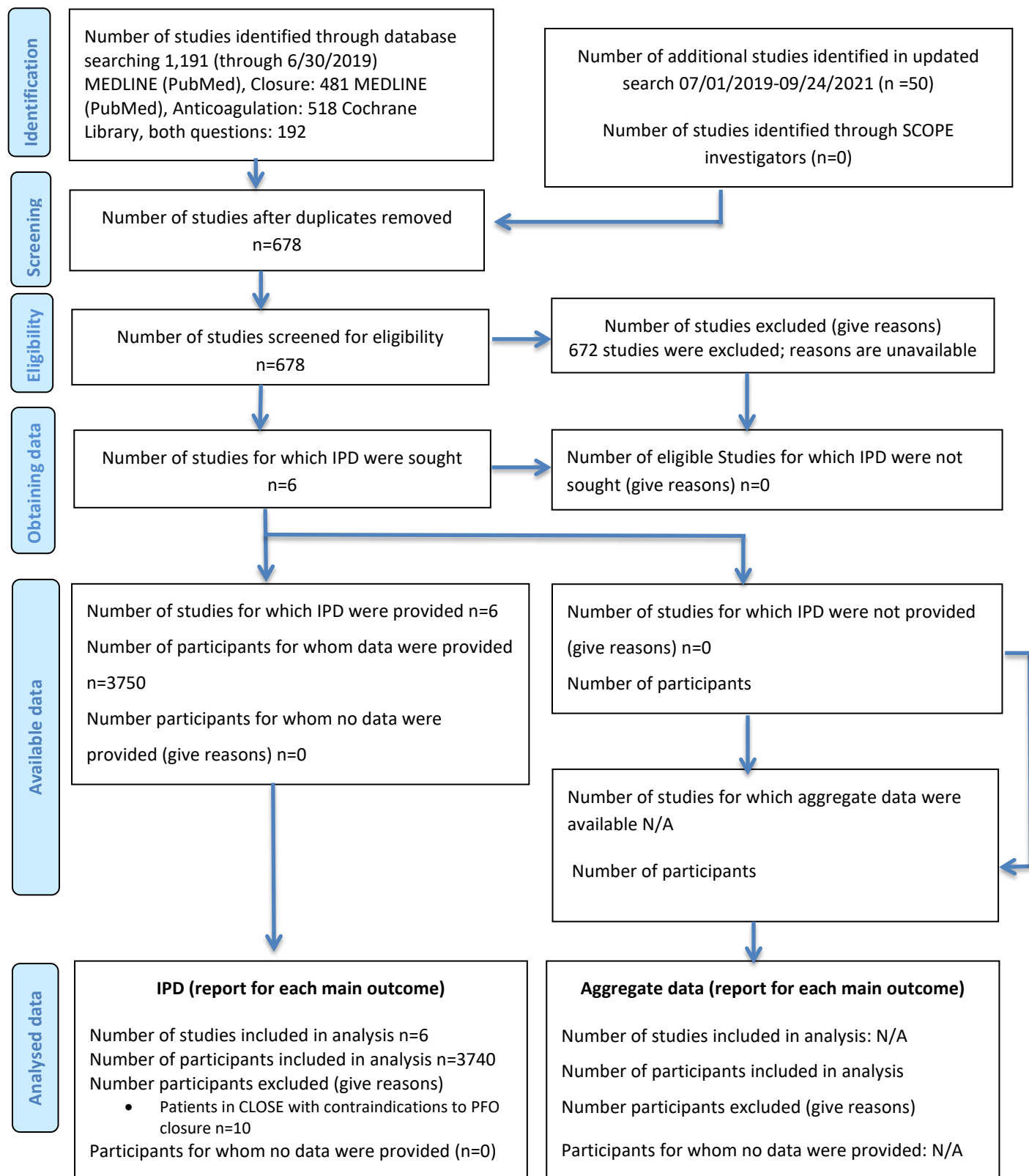
Systematic, Collaborative, PFO closure Evaluation (SCOPE)	Target: Large shunt size was defined in our database as >20+ bubbles (values below in BLUE coded as 'large' in our database)
CLOSURE	<i>Small: (1) None; (2): Trace, 1~10 bubbles, (3) Moderate, ~10-25 bubbles, Large: (4) Substantial, ~25 or more bubbles</i>
PC Trial	<i>Small: grade 0 = none; grade 1 = minimal (1-5 bubbles), grade 2 = moderate (6 to 20 bubbles), Large: grade 3 = severe (>20 bubbles)</i>

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

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

eAppendix 6. PRISMA IPD Flow Diagram

eFigure 2. PRISMA IPD Flow Diagram.



eAppendix 7. Descriptions of Trials

eTable 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	United States, Canada	STARflex (NMT Medical)	Cryptogenic IS or TIA	≤ 6 mo	18-60	909	1.7/1555	1.06
		F: 2003-2010								
PC Trial	2013	E: 2003-2009	Europe, Canada, Brazil, Australia	Amplatzer	Cryptogenic IS or periph embolism	No restriction	<60	414	4.1/1681	1.04
		F: 2000-2012								
RESPECT	2013/2017	E: 2003-2011	United States, Canada	Amplatzer	Cryptogenic IS (Tissue-Def)	≤ 9 mo	18-60	980	5.8/5688	1.14
		F: 2003-2016								
CLOSE	2017	E: 2007-2014	France, Germany	Multiple ^d	Cryptogenic IS (Tissue-Def)	≤ 6 mo	16-60	473 (653) ^b	5.3/2507	1.04
		F: 2007-2016								
REDUCE	2017	E: 2008-2015	Europe, Canada, United States	Helix or Cardioform (Gore)	Cryptogenic IS (Tissue-Def)	≤ 6 mo	18-59	664	3.4/2232	1.10
		F: 2008-2016								
DEFENSE-PFO	2018	E: 2011-2017	South Korea	Amplatzer	Cryptogenic IS (Tissue-Def)	≤ 6 mo	18-80	120	1.6 ^c /≈187	1.03
		F: 2011-2017								

^aMean 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.

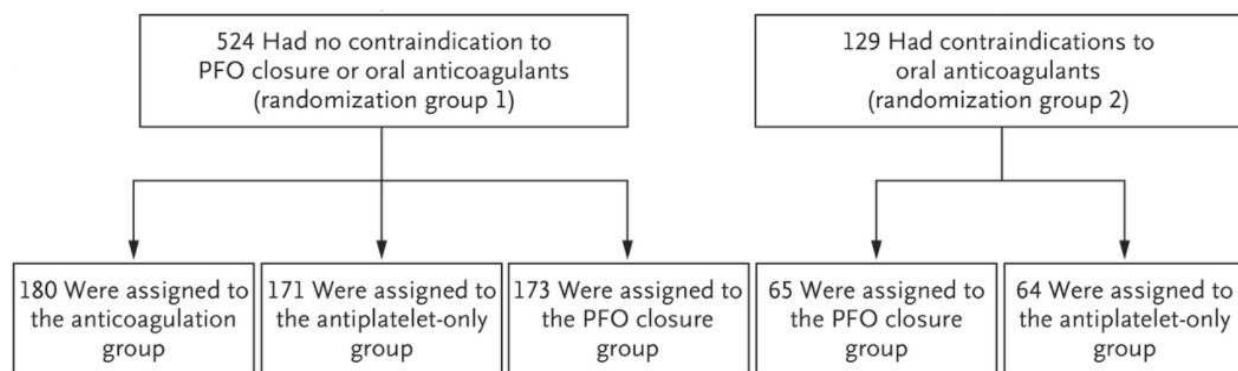
^bFull results reported for 473 patients randomized to closure and medical antiplatelet therapy groups, pending for 180 randomized to the medical anticoagulation therapy group.

^cFor DEFENSE-PFO, only follow-up years estimated from the Kaplan–Meier curve of the fully-reported time period—the first 2 years after enrollment.

^dDevices 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.

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 CLOSURE 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.

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) Trial¹⁸, 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) Trial¹⁹** 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) Trial²⁰**, 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.

eAppendix 8. 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.

eTable 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 outcomes²⁴ 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 accordingly²⁵. In two of the six trials included in our analysis there were no observed recurrent ischemic strokes in the device arm leading to unstable within-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.

eAppendix 9. Patient Characteristics in Each Study

eTable 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).

^bNot reported in PC Trial.

TIA indicates transient ischemic attack. HR indicates hazard ratio comparing device to medication therapy.

eTable 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).

^bNot reported in PC Trial.

TIA indicates transient ischemic attack; NR, not reported.

eTable 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).

^bNot reported in PC Trial.

TIA indicates transient ischemic attack; NR, not reported.

eTable 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).

^bNot reported in PC Trial.

TIA indicates transient ischemic attack.

eTable 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).

^bNot reported in PC Trial.

TIA indicates transient ischemic attack; NR, not reported.

eTable 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).

^bNot reported in PC Trial.

TIA indicates transient ischemic attack; NR, not reported.

eTable 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)..

^bNot reported in PC Trial.

TIA indicates transient ischemic attack; NR, not reported.

eAppendix 10. Leave-one-out Stability Analyses

eTable 14. Leave-one-out Stability Analyses.

	Adjusted Cox regression^a
<i>Trial left-out...</i>	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)

^aAdjusted 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).
HR indicates hazard ratio; CI, confidence interval.

eAppendix 11. 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.

eTable 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.

eAppendix 12. 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').

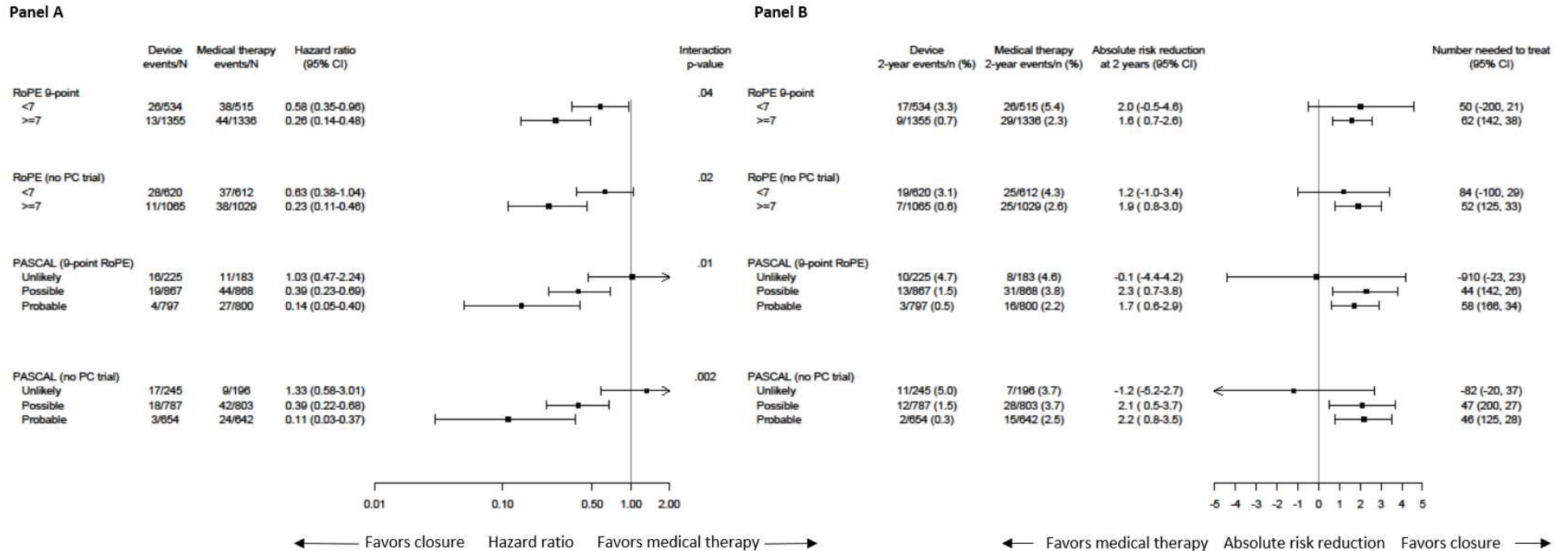
eTable 16. Tipping Point Analysis of Primary Outcome.

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

HR indicates hazard ratio; CL, confidence limit.

eAppendix 13. RoPE and PASCAL Analyses

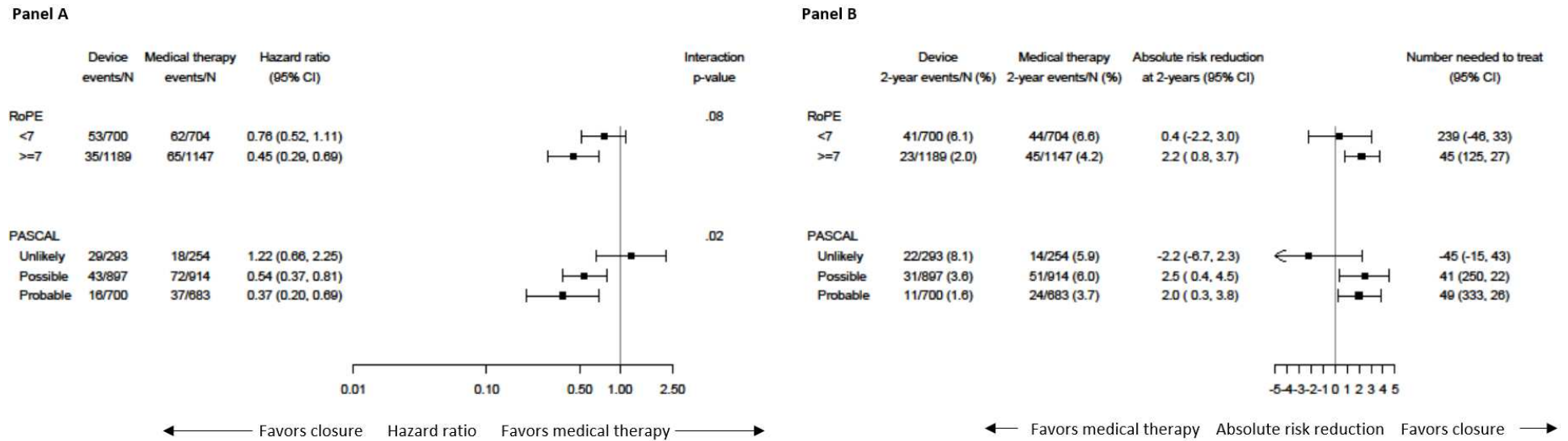
eFigure 3. Recurrent Ischemic Stroke Heterogeneous Treatment Effects (HTE) Stability Analyses for RoPE and PASCAL.



Legend:

Primary outcome of recurrent ischemic stroke. **Panel A: Hazard ratios.** **Panel B: Absolute risk reduction.** RoPE indicates Risk of Paradoxical Embolism; HTE, heterogeneous treatment effect; PASCAL, PFO-Associated Stroke Causal Likelihood; HR, hazard ratio; CI, confidence interval; ARR, absolute risk reduction; NNT, number-needed-to-treat. 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).

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

eAppendix 14. Safety Outcomes by PASCAL Classification

eTable 17. Safety Outcomes by PASCAL Classification.

Safety outcome (as-treated population) ^a	Overall outcome rate % (patients with event/n)		Absolute Risk Difference % (95% CI)	Relative Risk % (95% CI)
	Device	No device		
PASCAL Classification				
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, 5.16)	1.04 (0.89, 1.21)
Probable	28.3 (189/667)	26.8 (190/709)	1.59 (-3.15, 6.34)	1.06 (0.89, 1.26)
Atrial fibrillation (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)
Atrial fibrillation (present beyond 45 days)				
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, 1.71)	2.06 (0.63, 6.78)
Major bleeding episode				
Unlikely	1.9 (5/260)	0.7 (2/282)	1.21 (-0.74, 3.16)	2.84 (0.48, 16.62)
Possible	1.1 (9/835)	1.5 (14/965)	-0.37 (-1.41, 0.67)	0.75 (0.32, 1.72)
Probable	1.6 (11/667)	2.4 (17/709)	-0.75 (-2.23, 0.74)	0.69 (0.32, 1.46)
Venous thromboembolism				
Unlikely	1.3 (4/260)	0.4 (1/282)	0.95 (-0.67, 2.58)	3.50 (0.38, 32.29)
Possible	1.4 (12/835)	0.6 (6/965)	0.77 (-0.17, 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)

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

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

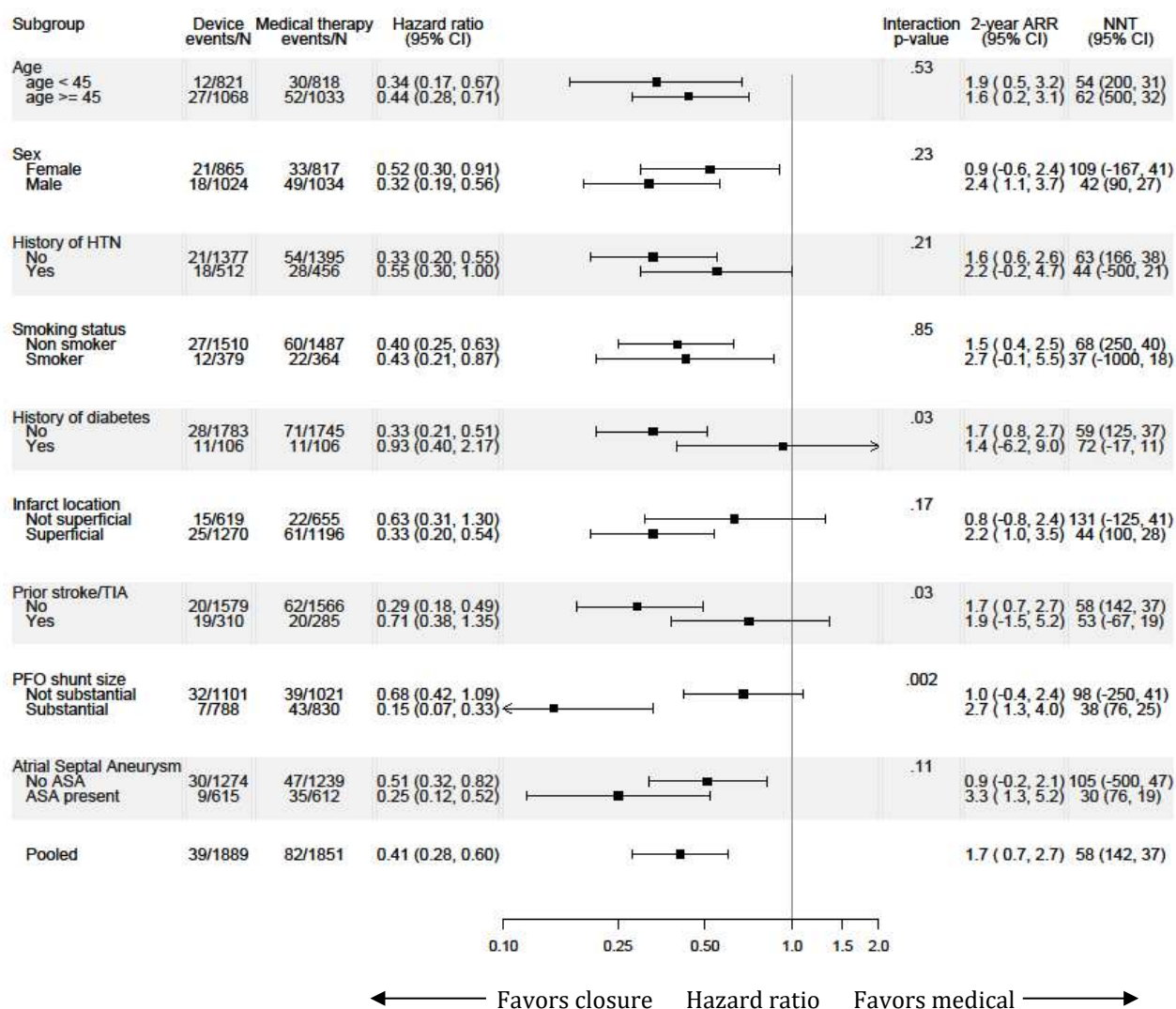
eTable 18. Safety Outcomes by PASCAL Classification with 2 year Atrial Fibrillation Rates.

Safety outcome (as-treated population)	Kaplan Meier 2-year rate % (patients with event/n)		Absolute Risk Difference % (95% CI)
	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)

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

eAppendix 15. Outcome Exploratory Subgroup Analyses

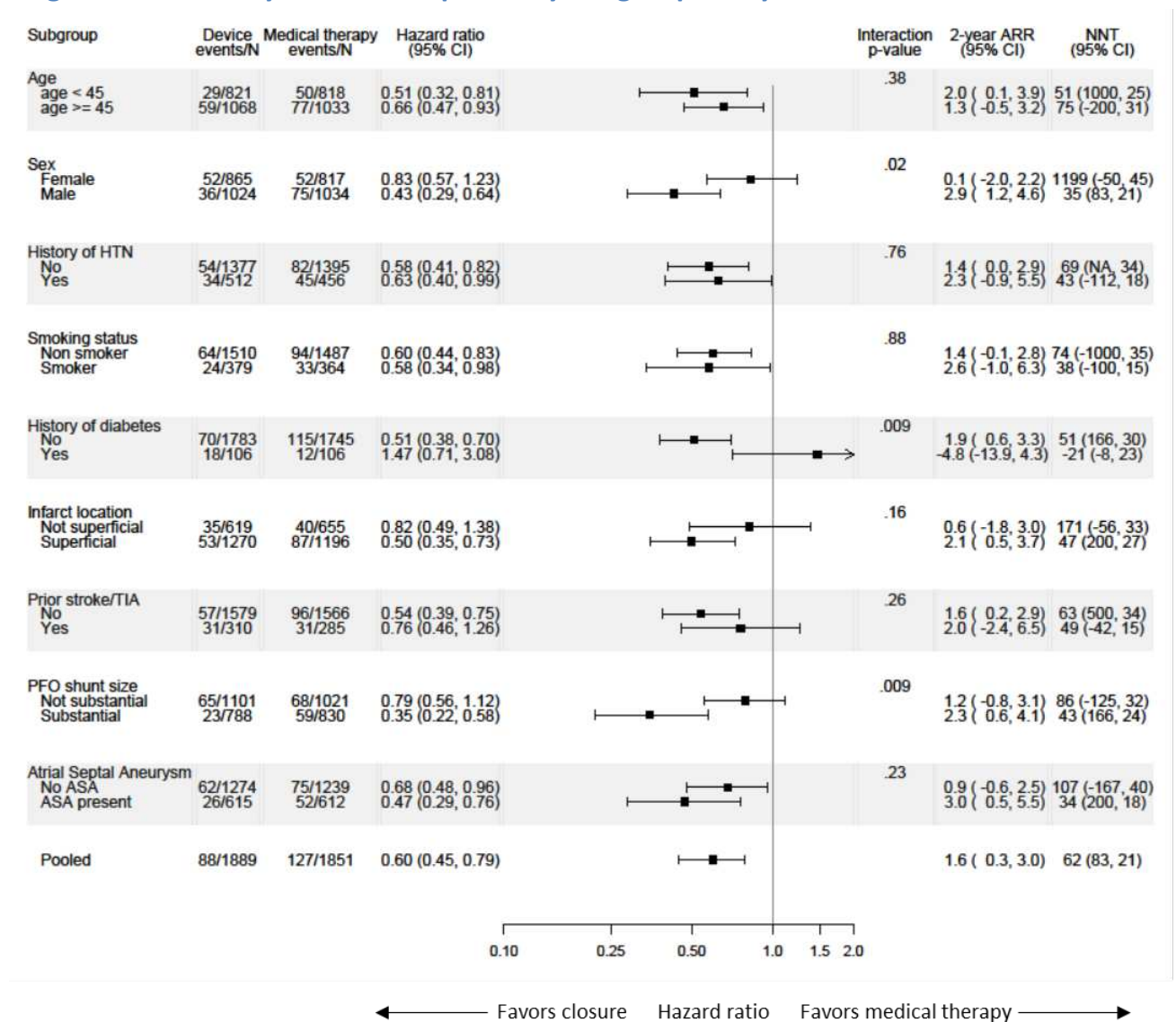
Figure 5. Recurrent Ischemic Stroke Exploratory Subgroup Analyses.



Legend:

Primary outcome recurrent ischemic stroke. HR, hazard ratio; CI, confidence interval; ARR, absolute risk reduction; NNT, number-needed-to-treat. 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 transesophageal echocardiography (definition in Appendix 5), PFO shunt size (large versus small, definition in Appendix 5) 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.

eFigure 6. Secondary Outcome Exploratory Subgroup Analyses.



Legend:

Secondary outcome recurrent ischemic stroke, TIA, or vascular death. HR, hazard ratio; CI, confidence interval; ARR, absolute risk reduction; NNT, number-needed-to-treat. 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 eAppendix 5), PFO shunt size (large versus small, definition in eAppendix 5) 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.

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