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

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-analysis[2] and variables that make up the Risk of Paradoxical Embolism (RoPE) Score[3,4]. The list was further expanded and refined at an investigator meeting in February 2020. **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 compete data sets separately and pooled using Rubin's Rules.

Random effects Cox proportional hazards regression

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

Assessment of linear assumption

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

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	Mobility of septum: normal, hypermobile
	PFO size: large, not large
	Shunt at rest: yes, no
Neuroradiology Variables	Index stroke seen: yes, no
	Location: superficial, deep

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

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:

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

We found that easily obtainable clinical characteristics can identify CS patients who vary markedly in the prevalence of PFO, reflecting substantial and clinically important variation in the probability that a discovered PFO is likely to be causally related to the stroke rather than an incidental present (**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, *or* 1B. Large shunt PFO, *AND* 2. PE or DVT preceding index infarct	Probable	Highly Probable
Medium risk	ANY of: 1. PFO + ASA 2. Large shunt PFO	Possible	Probable
Low risk	Small shunt PFO without ASA	Unlikely	Possible

[a]The RoPE Score includes points for 5 age categories, cortical infarct, absence of hypertension, diabetes, prior stroke or transient ischemic attack, and smoking. A higher RoPE score (≥ 7 points) increases probability of causal association.
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

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

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

SCOPE "As treated" population definition:

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

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

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

PFO indicates patent foramen ovale; TEE, transesophageal echocardiogram.

eTable 4. Variable Definition for Large Shunt Size.

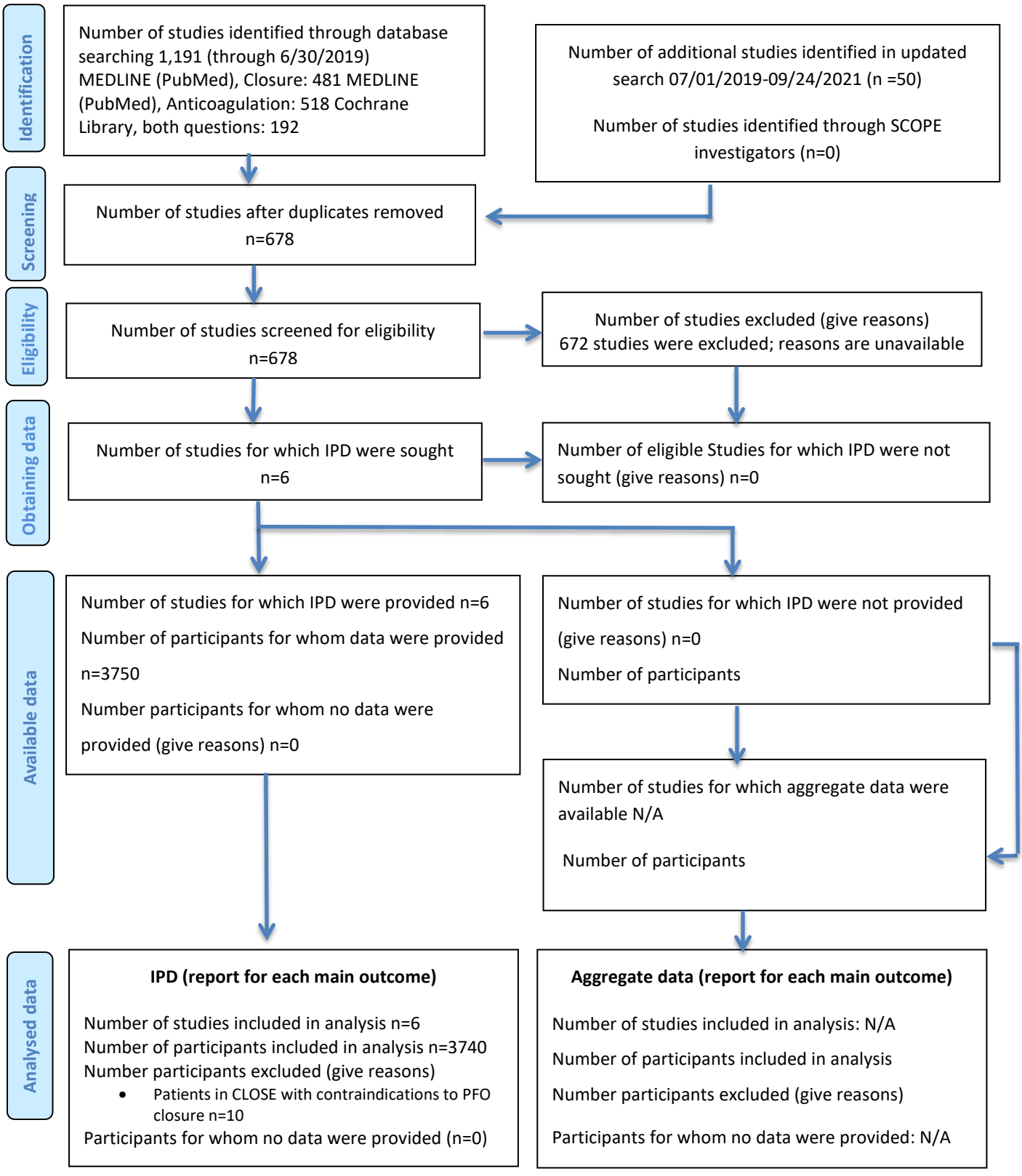
Systematic, Collaborative, PFO closure Evaluation (SCOPE)	Target: Large shunt size was defined in our database as >20+ bubbles (values below in BLUE coded as 'large' in our database)
CLOSURE	*Small: (1) None; (2): Trace, 1~10 bubbles, (3) Moderate, ~10-25 bubbles,* ***Large: (4) Substantial, ~25 or more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

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

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

eAppendix 6. PRISMA IPD Flow Diagram

eFigure 2. PRISMA IPD Flow Diagram.



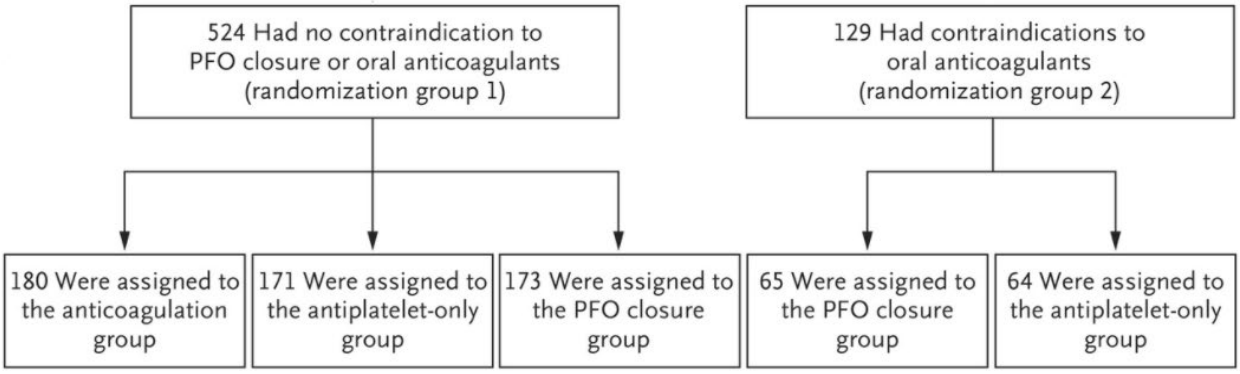
eAppendix 7. Descriptions of Trials

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

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

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



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

The ***CLOSURE I (Evaluation of the STARFlex Closure System in Patients with a Stroke and/or Transient Ischemic Attack due to Presumed Paradoxical Embolism Through a Patent***

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

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

The ***PC (Percutaneous Closure) Trial***[20], between 2000 and 2009, randomized patients younger than 60 years old with a PFO and cryptogenic, tissue-defined, ischemic stroke or a peripheral thromboembolic event to receive PFO closure with a double-disk device plus medical therapy (204 patients) versus medical therapy with antiplatelet agents or anticoagulants alone (210 patients). The primary endpoint was a composite of time-defined ischemic or hemorrhagic

stroke, time-defined transient ischemic attack, peripheral embolism, or all-cause death. The mean follow-up duration was 4.1 and 4.0 years in the closure and medical therapy groups, respectively. Reasons for patient exclusion included the following: any identifiable cause for the thromboembolic event other than PFO; contraindication for chronic antiplatelet or anticoagulant therapy; requirement for chronic anticoagulant therapy for another disease entity, and previous surgical or percutaneous PFO closure.

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

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

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 outcomes[24] was not statistically significant (p-value = 0.11). A similar linear regression

test of asymmetry based on the log(hazard ratio) and standard error was also not significant (p-value = 0.59). These tests are generally not recommended for meta-analyses with fewer than 10 studies and should be interpreted accordingly[25]. In two of the six trials included in our analysis there were no observed recurrent ischemic strokes in the device arm leading to unstable with-in trial estimated hazard ratios and standard errors. In an analysis excluding these trials (DEFENSE, CLOSE) the HR was 0.52 (95% CI, 0.35-0.78). These effect estimates reveal stability in our analysis of the primary outcome.

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).
[b]Not 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).
[b]Not 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).
[b]Not 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).
[b]Not 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).
[b]Not 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).
[b]Not 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)..
[b]Not 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]
Trial left-out…	HR (95% CI)
CLOSE-A (randomization group 2)	0.439 (0.296, 0.651)
CLOSE-B (randomization group 1)	0.429 (0.289, 0.636)
CLOSURE	0.321 (0.204, 0.505)
DEFENSE	0.420 (0.284, 0.622)
PC Trial	0.425 (0.286, 0.633)
REDUCE	0.436 (0.285, 0.668)
RESPECT	0.335 (0.135, 0.549)

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

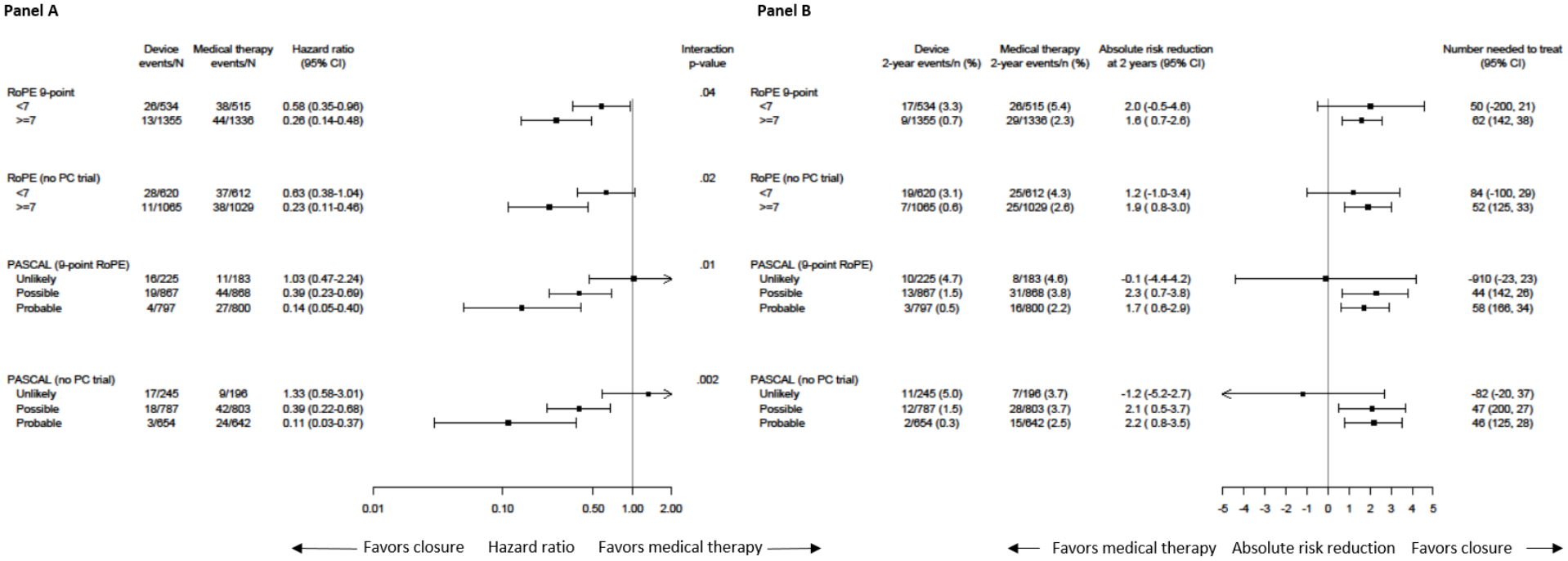
eTable 16. Tipping Point Analysis of Primary Outcome.

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

HR indicates hazard ratio; CL, confidence limit.

eAppendix 13. RoPE and PASCAL Analyses

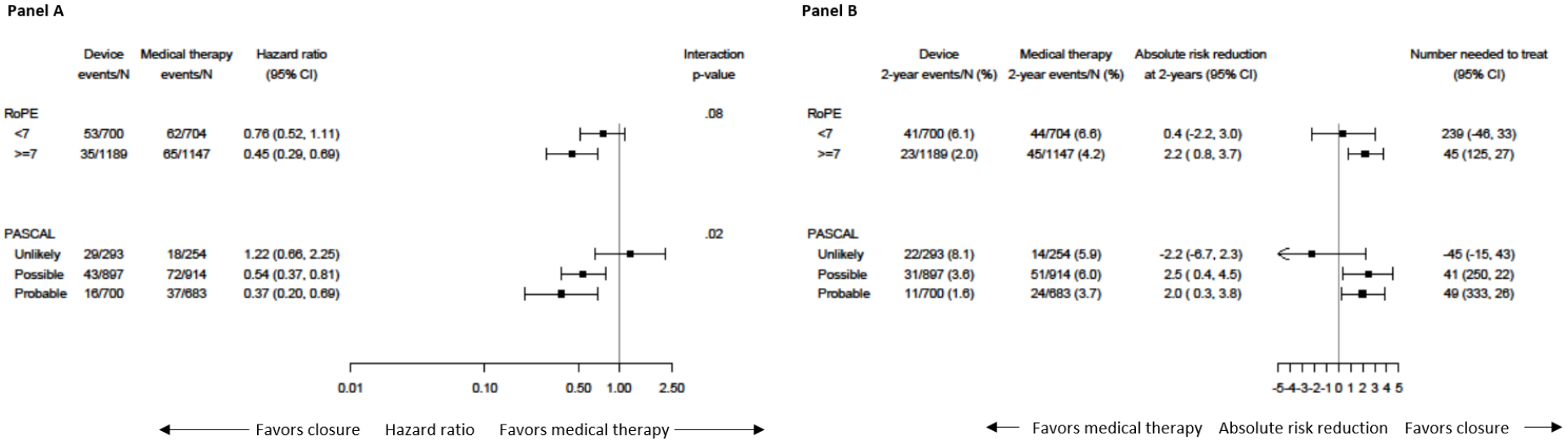
eFigure 3. Recurrent Ischemic Stroke Heterogeneous Treatment Effects (HTE) Stability Analyses for RoPE and PASCAL.



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)

[a]Safety 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.

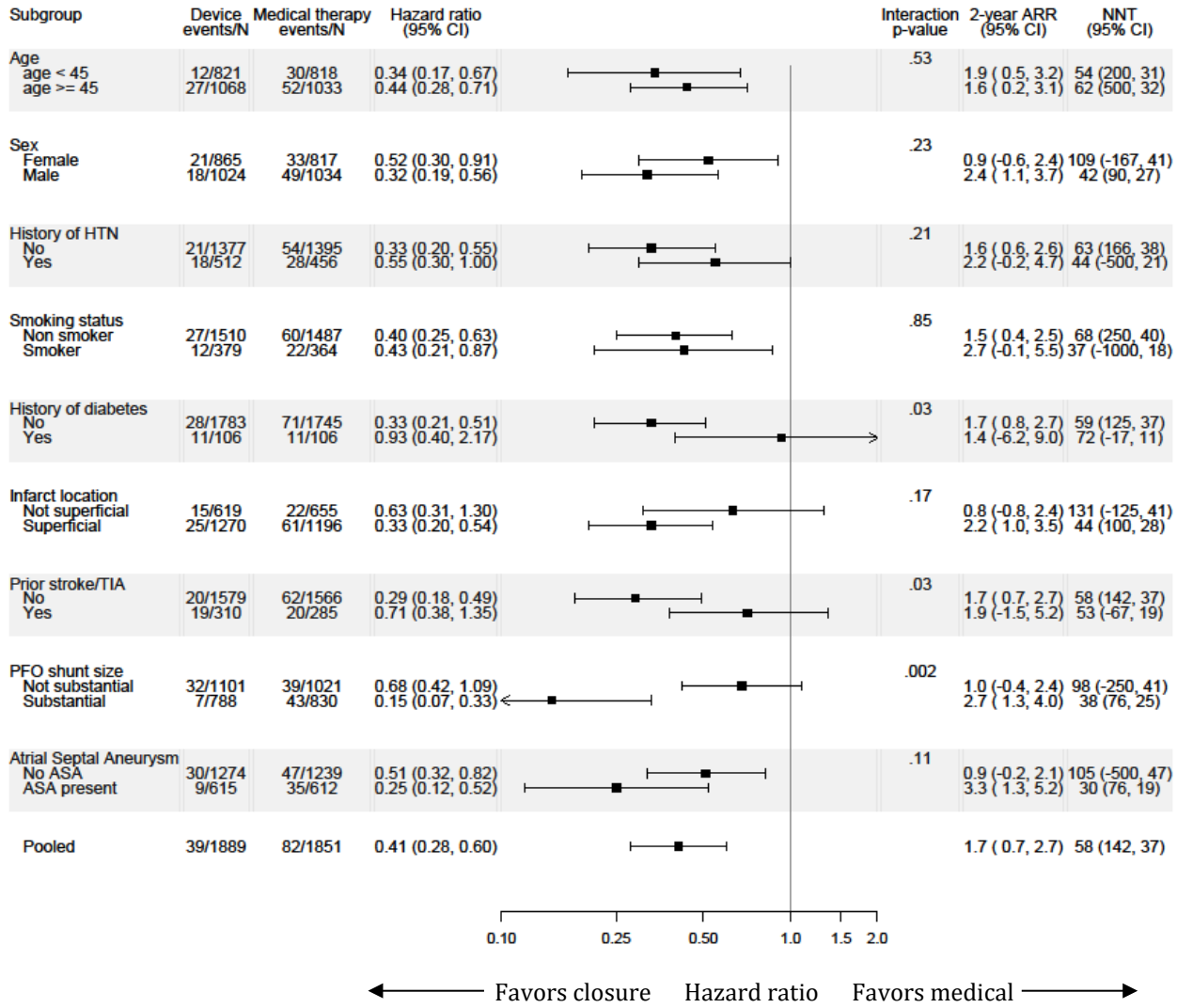
eTable 18. Safety Outcomes by PASCAL Classification with 2 year Atrial Fibrillation Rates.

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

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

eAppendix 15. Outcome Exploratory Subgroup Analyses

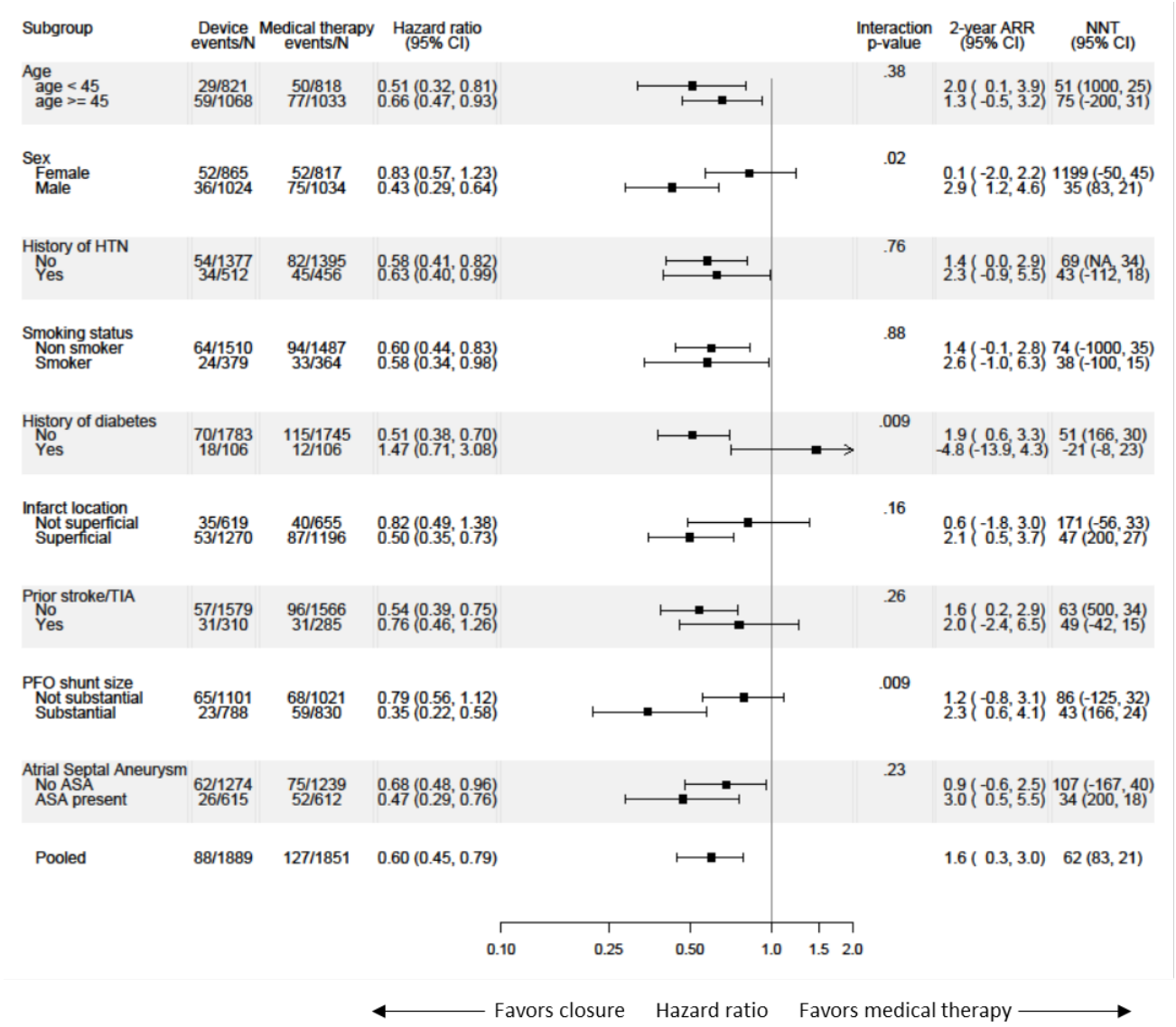
eFigure 5. Recurrent Ischemic Stroke Exploratory Subgroup Analyses.



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 trans-esophageal 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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