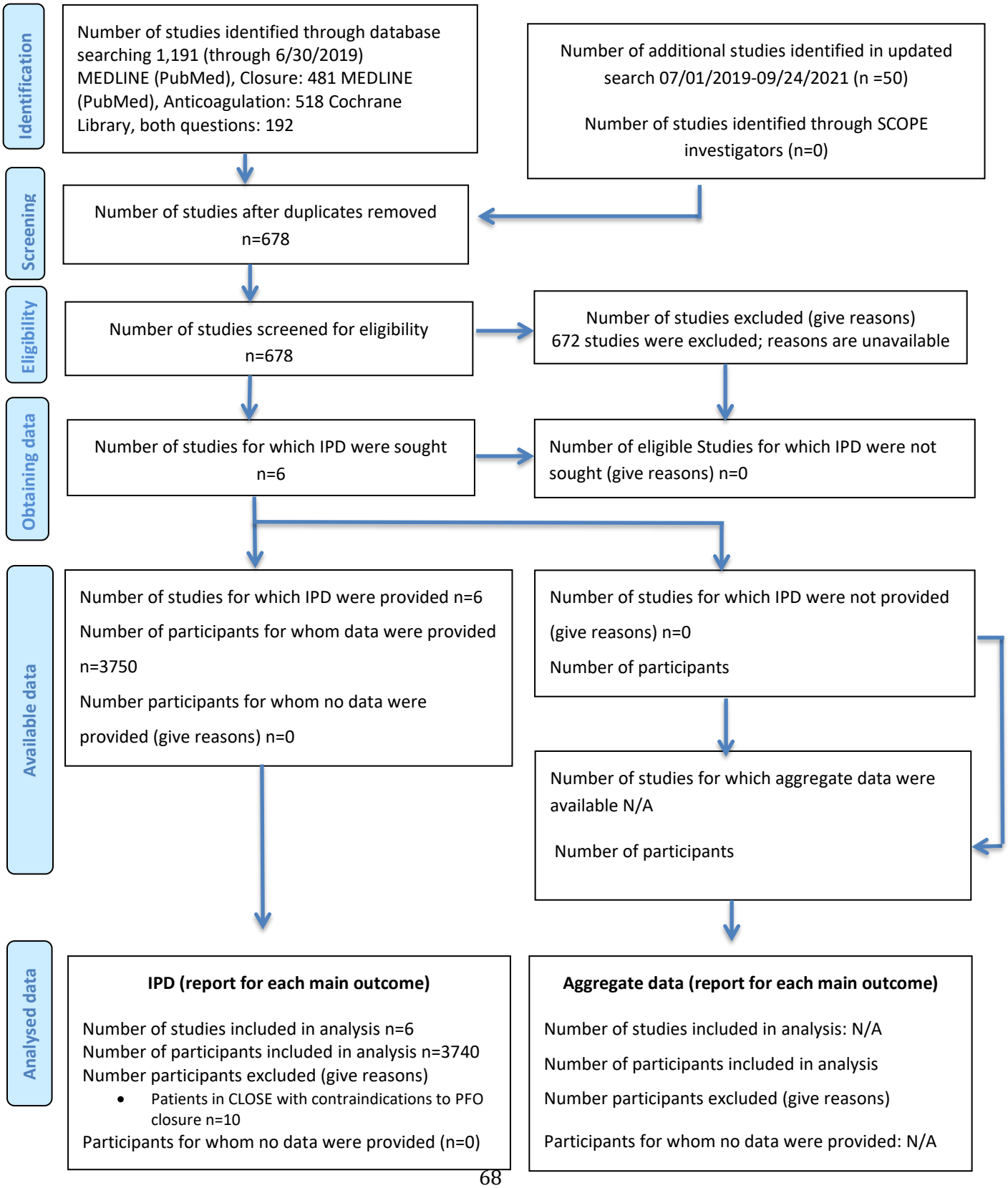
Appendix B: Supplementary Results

Appendix B1. PRISMA IPD Flow Diagram

Appendix Figure 2. PRISMA IPD Flow Diagram.



Appendix B2. Descriptions of Trials

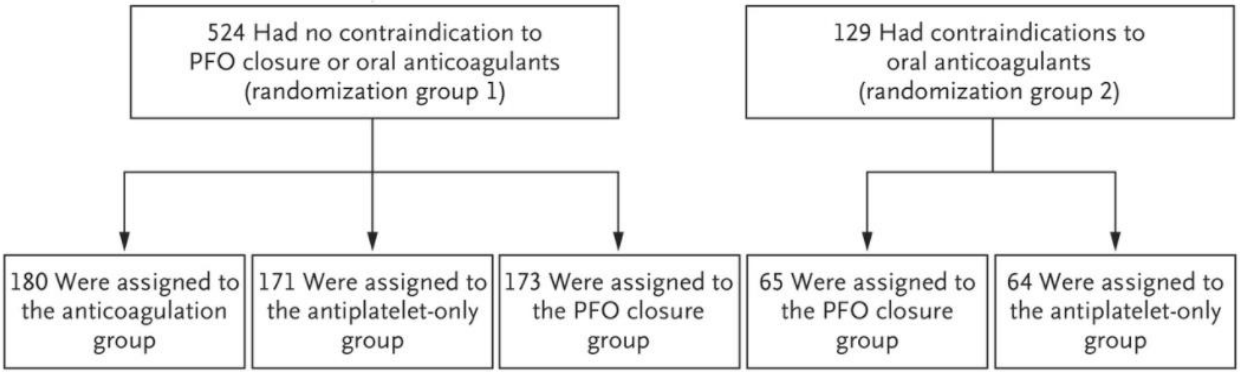
Appendix Table 5. Features of Patent Foramen Ovale Closure Device Trials.

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

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

Appendix B: Supplementary Results

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



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

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

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

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

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

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

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

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

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

Assessment of Risk of Bias

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

Appendix Table 6. Risk of Bias Assessment.

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

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

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

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

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

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

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

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

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

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

Small Study Effect

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

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

Appendix B4. Patient Characteristics in Each Study

Appendix Table 7. CLOSURE.

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

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

Appendix Table 8. PC Trial.

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

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

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

Appendix Table 9. RESPECT.

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

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

Appendix Table 10. REDUCE.

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

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

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

Appendix Table 11. DEFENSE.

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

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

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

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

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

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

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

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

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

Appendix B5. Leave-one-out Stability Analyses

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

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

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

Appendix B6. Patient Characteristics of Early Exiting Patients

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

Appendix Table 15. Patient Characteristics of Early Exiting Patients.

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

SD indicates standard deviation; TIA, transient ischemic attack.

Appendix B7. Tipping Point Analysis

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

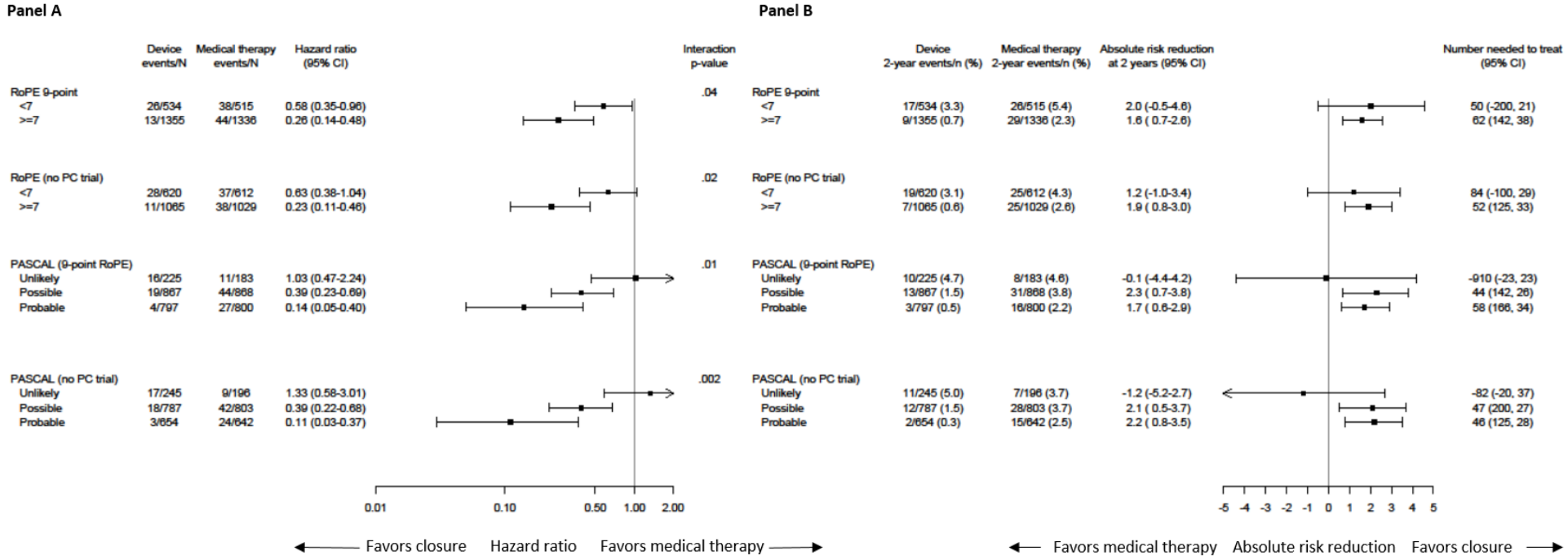
Appendix Table 16. Tipping Point Analysis of Primary Outcome.

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

CL, confidence limit; HR indicates hazard ratio.

Appendix B8. RoPE and PASCAL Analyses

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



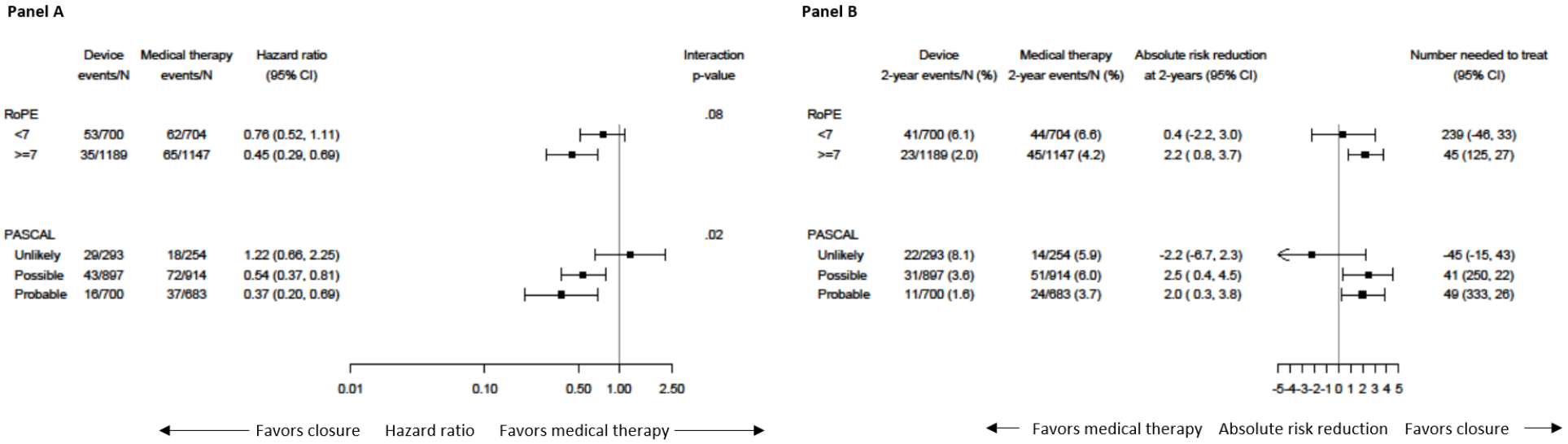
Legend:

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

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

Appendix B: Supplementary Results

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



Legend:

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

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

Appendix B9. Safety Outcomes by PASCAL Classification

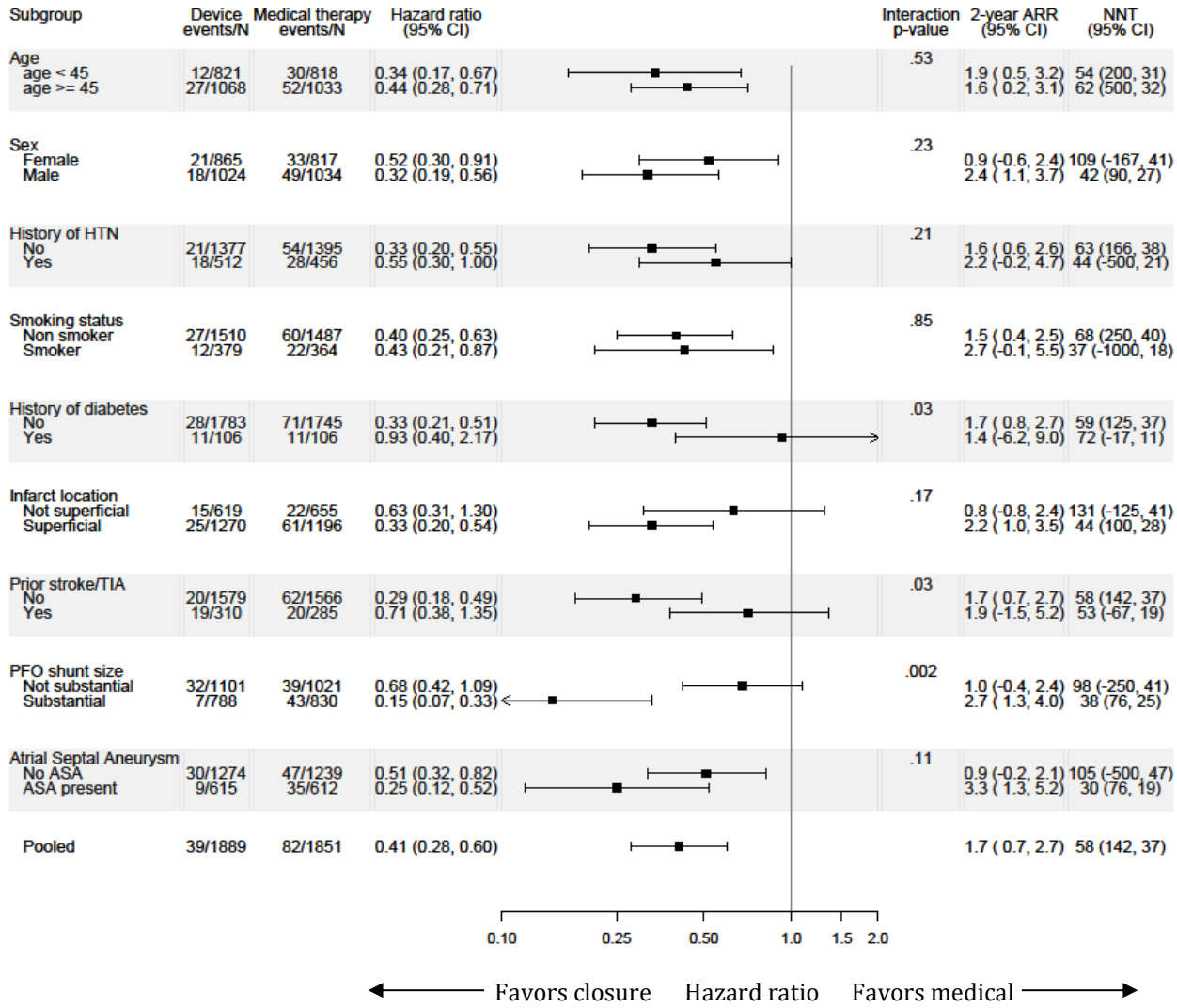
Appendix Table 17. Safety Outcomes by PASCAL Classification with 2 year Atrial Fibrillation Rates.

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

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

Appendix B10. Outcome Exploratory Subgroup Analyses

Appendix Figure 5. Recurrent Ischemic Stroke Exploratory Subgroup Analyses.

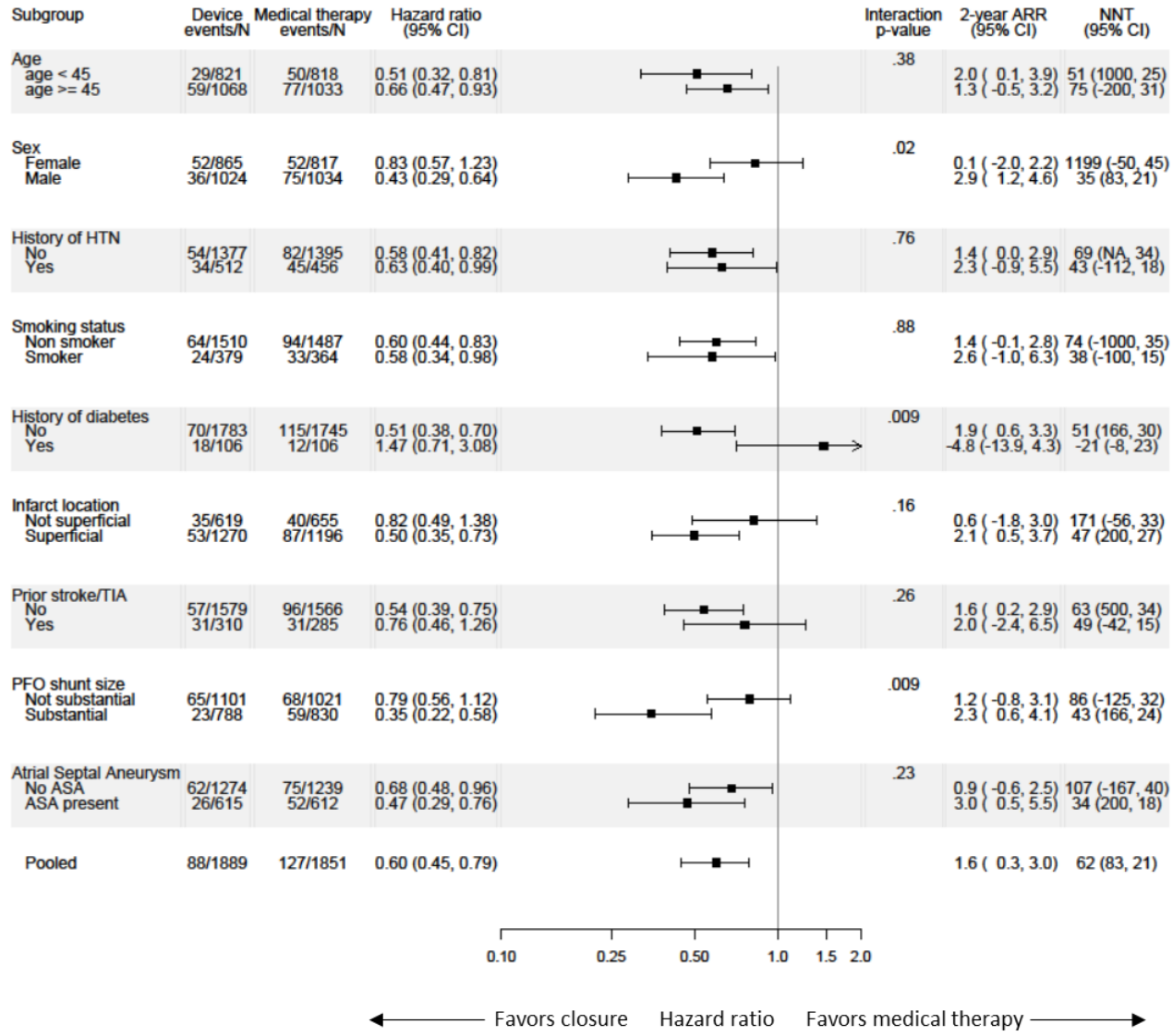


Legend:

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

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

Appendix Figure 6. Secondary Outcome Exploratory Subgroup Analyses.



Legend:

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

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

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