Appendix B2. Descriptions of Trials

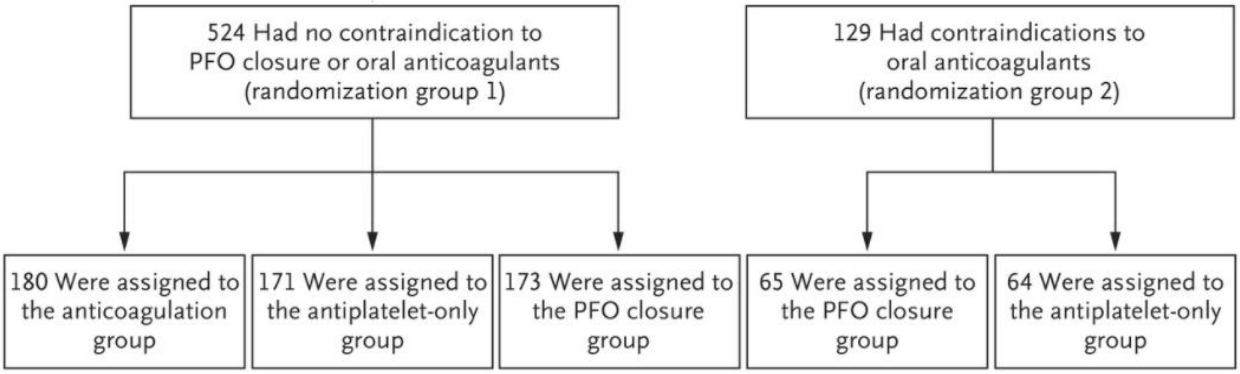
Appendix Table 5. Features of Patent Foramen Ovale Closure Device Trials.

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.