Suppl Table 1. Characteristics of the five trials included in this meta-analysis.

Trial name	Device used for PFO closure	Definition of medical therapy	Primary Endpoint	PFO closure group total no.	PFO closure group no. of males	PFO closure group age (yrs)	Medical therapy group total no.	Medical therapy group no. of males	Medical therapy group age (yrs)	Follow-up (months)	Ref
CLOSURE I	STARFlex Septal Closure System	Aspirin, warfarin, or both	Stroke, TIA, 30-day mortality, neurology-related death	447	223	46.3	462	328	45.7	24	[1]
PC	Amplatzer PFO Occluder	Aspirin, thienopyridine, oral anticoagulation, heparin	Stroke, TIA, death, peripheral embolism	204	92	44.3	210	114	44.6	49	[2]
CLOSE	Amplatzer PFO Occluder, Intrasept PFO occluder, Premere, Starflex septal occluder system, Amplatzer cribriform occluder, Figulla Flex II PFO	Aspirin and clopidogrel for 3 months followed by single antiplatelet therapy	Fatal or non-fatal stroke	238	137	42.9	596	248	44.1	64	[3]

	occluder, Atriasept II occluder, Amplatzer ASD occluder, Figulla Flex II UNI occluder, Gore septal occluder, Figulla Flex II ASD occlude										
RESPECT	Amplatzer PFO Occluder	Aspirin, warfarin, clopidogrel, and aspirin combined with extended-release dipyridamole	Non-fatal ischemic stroke, fatal ischemic stroke, or early death after randomization	499	268	45.7	481	268	46.2	71	[4]
REDUCE	Helex Septal Occluder, Cardioform Septal Occluder	Aspirin, aspirin and dipyridamole, or clopidogrel	Co-primary endpoint: 1) ischemic stroke, 2) new ischemic stroke or silent brain infarction	441	261	45.4	223	138	44.8	34	[5]

Suppl Table 2. Definitions of stroke and TIA of the five trials.

Trial name	Stroke definition	TIA definition	Ref
CLOSURE I	Acute focal neurological event that is MR imaging positive, regardless of duration of clinical symptoms, or if imaging cannot be performed for confirmation, it was defined as a persistent focal neurological deficit lasting longer than 24 hours	The patient must have experienced a sudden focal neurological event lasting at least 10 minutes without evidence of acute ischemic brain injury on DWMR imaging, with symptoms consisting of hemiplegia / paresis, monoplegia / paresis, quadriplegia / paresis, language disturbance other than isolated slurred speech, blindness in one or both eyes, or significant difficulty walking. Dysarthria, vertigo, sensory symptoms, confusion, memory loss, syncope, lightheadedness, or diplopia in isolation will not be accepted as sufficient for the diagnosis; such symptoms must be accompanied by focal weakness or combinations of multiple symptoms localizable to the anterior or posterior circulation to be accepted as TIAs. Atypical symptoms such as a marching evolution, positive phenomena such as visual scintillations, or prominent unilateral throbbing headache suggesting migraine will be characterized as “transient neurological events of unknown etiology” and will NOT be called TIAs.	[1]

PC	Any neurologic deficit lasting for >24 hours typically with documentation in magnet resonance imaging (MRI) or computer tomography (CT)	Temporary neurologic deficit presumably due to reduced blood flow in a particular cerebral artery lasting for ⩽24 hours with complete resolution of the neurologic deficit.	[2]
CLOSE	sudden onset of focal neurological symptoms with the presence of cerebral infarction in the appropriate territory on brain imaging (CT or MRI), regardless of the duration of the symptoms (less than or greater than 24 hours)	Sudden onset of neurological symptoms, presumed to be ischemic, resolving in less than 24 hours, clearly attributable to focal involvement of the central nervous system (or of the eye) with no signs of a corresponding recent cerebral infarction on brain imaging. The diagnosis of TIA will be confirmed by a neurologist, in light of clinical data and brain imaging (MRI with diffusion sequence is recommended). Symptoms or signs compatible with this diagnosis and the territory of the TIA will be based on standard guidelines.	[3]
RESPECT	Ischemic stroke was defined as an acute focal neurologic deficit, which was presumed to be due to focal ischemia, and either symptoms that persisted for 24 hours or longer or symptoms that persisted for less than 24 hours but were associated with findings of a new, neuroanatomically relevant, cerebral infarct on magnetic resonance imaging (MRI) or computed tomography (CT)	ACAS TIA/stroke algorithm	[4]
REDUCE	an acute focal neurologic deficit, presumably due to ischemia, that either resulted in clinical symptoms lasting 24 hours or more or was associated with evidence of relevant infarction on magnetic resonance imaging (MRI) or — if MRI could not be performed — computed tomography (CT) of the brain	Clinical symptoms persisting <24 hours	[5]

Suppl Table 3. Events for stroke and TIA of the five trials.

Trial name	PFO closure person-years	Medical therapy person-years	PFO closure primary endpoint	Medical therapy primary endpoint	PFO closure stroke	Medical therapy stroke	PFO closure TIA	Medical therapy TIA	Ref
CLOSURE I	820	847	23	29	12	13	13	17	[1]
PC	836	840	7	11	1	5	5	7	[2]
CLOSE	1285	3099	0	24	8	44	8	19	[3]
RESPECT	3141	2669	18	28	18	28	17	23	[4]
REDUCE	1529	703	22	20	6	12	1	1	[5]

Suppl Table 4. Events for total AF, short-term and long-term AF of the five trials.

Trial name	PFO closure person-years	Medical therapy person-years	PFO closure total AF	Medical therapy total AF	PFO closure short-term AF	Medical therapy short-term AF	PFO closure long-term AF	Medical therapy long-term AF	Ref
CLOSURE I	820	847	23	3	17	0	6	3	[1]
PC	836	840	6	2	4	0	2	2	[2]
CLOSE	1285	3099	11	19	11	2	0	0	[3]
RESPECT	3141	2669	7	4	3	2	6	2	[4]
REDUCE	1529	703	29	9	19	0	10	1	[5]

Suppl Table 5. Events for bleeding events and gastrointestinal complications of the five trials.

Trial name	PFO closure person-years	Medical therapy person-years	PFO closure bleeding	Medical therapy bleeding	PFO closure gastrointestinal complications	Medical therapy gastrointestinal complications	Ref
CLOSURE I	820	847	10	4	-	-	[1]
PC	836	840	8	12	-	-	[2]
CLOSE	1285	3099	2	19	0	3	[3]
RESPECT	3141	2669	11	6	6	4	[4]
REDUCE	1529	703	8	6	1	1	[5]

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