

Appendices Legend:

Appendix 1: Summary of search and strategies

Appendix 2: Tables

- eTable 1: Characteristics of eligible studies

Appendix 3: Figures

- eFigure 1: Risk of bias of included randomised controlled trials

Appendix 4: PFO closure vs antiplatelet forest plots (Direct evidence only)

- eFigure 1: Ischaemic stroke
- eFigure 2: TIA
- eFigure 3: Systemic emboli
- eFigure 4: Death
- eFigure 5: Major bleeding
- eFigure 6: Pulmonary embolism

Appendix 5: PFO closure vs anticoagulation forest plots (Direct evidence only)

- eFigure 1: Ischaemic stroke
- eFigure 2: TIA
- eFigure 3: Systemic emboli
- eFigure 4: Pulmonary emboli
- eFigure 5: Major bleeding

Appendix 6: Complications of PFO closure vs medical therapy forest plots (Direct evidence only)

- eFigure 1: All atrial fibrillation
- eFigure 2: Persistent atrial fibrillation
- eFigure 3: Transient atrial fibrillation
- eFigure 4: Serious device or procedure related

Appendix 7: Anticoagulation vs antiplatelet forest plots (Direct evidence only)

- eFigure 1: Stroke
- eFigure 2: TIA
- eFigure 3: Major bleeding
- eFigure 4: Death

Appendix 8: Meta-regression and NMA Figures

- eFigure 1: Meta-regression evaluating the effect of moderate or higher shunt size on the effectiveness of PFO closure versus medical therapy
- eFigure 2: Meta-regression evaluating the proportion of patients on anticoagulation compared to those with moderate or higher shunt size
- eFigure 3: Network of included RCTs with available direct comparisons for ischaemic stroke.

Appendix 9: NMA Table

- eTable 1: Direct and indirect estimates of effects for the network meta-analysis

Appendix 1: Summary of search and strategies

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
Search Strategy:

-
- 1 cerebrovascular disorders/ or basal ganglia cerebrovascular disease/ or exp brain ischemia/ or carotid artery diseases/ or carotid artery thrombosis/ or intracranial arterial diseases/ or cerebral arterial diseases/ or exp "intracranial embolism and thrombosis"/ or exp stroke/ (237544)
 - 2 (isch?emi\$ adj6 (stroke\$ or apoplex\$ or cerebral vasc\$ or cerebrovasc\$ or cva or attack\$)).tw. (62463)
 - 3 ((brain or cerebr\$ or cerebell\$ or vertebrobasil\$ or hemispher\$ or intracran\$ or intracerebral or infratentorial or supratentorial or middle cerebr\$ or mca\$ or anterior circulation) adj5 (isch?emi\$ or infarct\$ or thrombo\$ or emboli\$ or occlus\$ or hypoxi\$)).tw. (105788)
 - 4 (TIA or TIAs).mp. (8376)
 - 5 Embolism, Paradoxical/ (914)
 - 6 heart atria/ and (embolism/ or thromboembolism/) (648)
 - 7 ((paradoxic\$ or crossed) adj5 embolism\$).tw. (1585)
 - 8 (cryptogenic adj5 stroke).tw. (1168)
 - 9 or/1-8 (293081)

Annotation: population part 1: stroke or cryptogenic stroke

- 10 heart septal defects, atrial/ or foramen ovale, patent/ (14696)
- 11 heart septum/ or atrial septum/ or foramen ovale/ (10405)
- 12 (patent foramen ovale or PFO).tw. (5125)
- 13 (atrial sept\$ adj5 defect\$).tw. (10211)
- 14 ((right to left or R-L or venous to arterial or venous-arterial or V-A) adj3 shunt).tw. (2212)
- 15 or/10-14 (30798)

Annotation: population part 2: PFO

- 16 9 and 15 (3491)

Annotation: population Stroke and PFO

- 17 limit 16 to yr="2012 -Current" (1094)

Annotation: since last review

- 18 limit 17 to ("therapy (maximizes sensitivity)" or "therapy (maximizes specificity)" or "therapy (best balance of sensitivity and specificity)") (429)
- 19 randomised controlled trial.pt. (496904)
- 20 controlled clinical trial.pt. (99253)
- 21 randomised.ab. (433409)
- 22 placebo.ab. (202740)
- 23 drug therapy.fs. (2114500)
- 24 randomly.ab. (298737)
- 25 trial.ab. (457112)
- 26 groups.ab. (1845391)
- 27 or/19-26 (4369043)
- 28 exp animals/ not humans.sh. (4677556)
- 29 27 not 28 (3778961)
- 30 17 and 29 (274)
- 31 18 or 30 (485)

Annotation: Population stroke and PFO limit to since 2012 and RCTs

- 32 "prostheses and implants"/ or septal occluder device/ (47787)
- 33 Wound Closure Techniques/ (1141)

- 34 (close or closure or septal occluder).tw. (384980)
- 35 (cardioseal or gore helex or amplatzer or starflex or cardia or intrasept or premere).tw. (9507)
- 36 su.fs. (1918373)
- 37 or/32-36 (2271562)

Annotation: Septal occluder device as per Liu 2015 CDSR

- 38 exp Anticoagulants/ (212306)
- 39 anticoagulant\$.tw. (55364)
- 40 (acenocoumarol\$ or dicoumarol\$ or ethyl biscoumacetate\$ or phenprocoumon\$ or warfarin\$ or ancrod\$ or citric acid\$ or coumarin\$ or chromonar\$ or coumestro\$ or esculi\$ or ochratoxin\$ or umbelliferone\$ or dermatan?sul\$ or dextran\$ or edetic acid\$ or enoxaparin\$ or gabexate\$ or heparin\$ or lmwh\$ or nadroparin\$ or pentosan sulfuric polyester\$ or phenindione\$ or protein c or protein s or tedelparin\$).tw. (192083)
- 41 (argatroban or tinzaparin or parnaparin or reviparin or danaparoid or lomoparan or org 10172 or mesoglycan or polysaccharide sulphate\$ or sp54 or sp-54 or md805 or md-805 or cy222 or cy-222 or cy216 or cy-216).tw. (2862)
- 42 (Marevan or Fragmin\$ or Fraxiparin\$ or Klexane).tw. (638)
- 43 exp Pipecolic acids/ae, tu (3633)
- 44 exp Vitamin K/ai (2564)
- 45 Vitamin K antagonist\$.tw. (4641)
- 46 exp Antithrombins/ae, pd, de, tu (6778)
- 47 exp Blood coagulation factors/ai, de (16900)
- 48 exp Blood coagulation/de (19187)
- 49 (anticoagulat\$ or antithromb\$).tw. (67390)
- 50 or/38-49 (376368)

Annotation: anticoagulants as per Berge 2002 CDSR

- 51 Factor Xa Inhibitors/ (3589)
- 52 Dabigatran/ (2442)
- 53 Rivaroxaban/ (2106)
- 54 (dabigatran or rivaroxaban or apixaban or edoxaban).mp. (7012)
- 55 anti-factor Xa.mp. (893)
- 56 (factor Xa adj2 (antag* or inhibit*)).mp. (5256)
- 57 novel oral anticoagulant*.mp. (1068)
- 58 noac.mp. (829)
- 59 noacs.mp. (1129)
- 60 pradax.mp. (8)
- 61 pradaxa.mp. (127)
- 62 BIBR-953.mp. (8)
- 63 BIBR-953ZW.mp. (2)
- 64 xarelto.mp. (114)
- 65 BAY 59-7939.mp. (27)
- 66 BMS-562247.mp. (6)
- 67 eliquis.mp. (43)
- 68 lixiana.mp. (13)
- 69 DU-176.mp. (1)
- 70 DU-176b.mp. (27)
- 71 non-vitamin K.mp. (828)
- 72 or/51-71 (11701)
- 73 direct oral anticoagulant*.mp. (1161)
- 74 DOAC.mp. (449)
- 75 DOACs.mp. (570)

76 TSOAC.mp. (25)
77 TSOACs.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (40)
78 oral anticoagulant.mp. (4604)
79 (new or novel or direct or direct-acting or target-specific or targeted or non-vitamin K).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (3920515)
80 78 and 79 (1801)
81 72 or 73 or 74 or 75 or 80 (12741)
Annotation: NOACs or DOACs from 2016 Canadian Cardiac Society GL search RC
82 exp Platelet aggregation inhibitors/ (106651)
83 (antiplatelet\$ or anti-platelet\$ or antiaggreg\$ or anti-aggreg\$ or (platelet\$ adj5 inhibit\$) or (thrombocyt\$ adj5 inhibit\$)).tw. (50701)
84 (alprostadi\$ or aspirin\$ or dipyridamol\$ or disintegrin\$ or epoprostenol\$ or iloprost\$ or ketanserin\$ or ketorolac tromethamine\$ or milrinone\$ or mopidamol\$ or pentoxifyllin\$ or procainamide\$ or ticlopidine\$ or thiophen\$ or trapidil\$).tw. (85938)
85 (acetyl salicylic acid\$ or acetyl?salicylic acid or clopidogrel\$ or picotamide\$ or ligustrazine\$ or levamisol\$ or suloctidil\$ or ozagrel\$ or oky046 or oky-046 or defibrotide\$ or cilostazol or satigrel or sarpolgrelate or kbt3022 or kbt-3022 or isbogrel or cv4151 or cv-4151 or triflusal).tw. (27863)
86 (Dispril or Albyl\$ or Ticlid\$ or Persantin\$ or Plavix).tw. (707)
87 exp Platelet glycoprotein gpiib-iii complex/ai, de (3381)
88 (((glycoprotein iib\$ or gp iib\$) adj5 (antagonist\$ or inhibitor\$)) or GR144053 or GR-144053 or abciximab\$ or tirofiban\$ or eftifibatid\$).tw. (5389)
89 (ReoPro or Integrilin\$ or Aggrastat).tw. (468)
90 exp Platelet activation/de (26939)
91 exp Blood platelets/de (19928)
92 or/82-91 (202643)
Annotation: antiplatelets as per Berge 2002 CDSR
93 37 or 50 or 81 or 92 (2776671)
Annotation: Intervention block
94 31 and 93 (366)
95 remove duplicates from 94 (326)

Central

Date Run: 16/10/17 21:33:56.134

Description:

ID	Search Hits
#1	MeSH descriptor: [Stroke] explode all trees 7179
#2	MeSH descriptor: [Cerebrovascular Disorders] explode all trees 12133
#3	(isch*emi* near/6 (stroke* or apoplex* or cerebral next vasc* or cerebrovasc* or cva or attack*)) 10210
#4	((brain or cerebr* or cerebell* or vertebrobasil* or hemispher* or intracran* or intracerebral or infratentorial or supratentorial or middle next cerebr* or mca* or "anterior circulation") near/5 (isch*emi* or infarct* or thrombo* or emboli* or occlus* or hypoxi*)) 11401
#5	(tia or tias) 1201
#6	MeSH descriptor: [Embolism, Paradoxical] explode all trees15

#7	((paradoxic* or crossed) near/5 embolism*)	49
#8	(cryptogenic near/5 stroke)	143
#9	MeSH descriptor: [Heart Atria] explode all trees	565
#10	MeSH descriptor: [Embolism and Thrombosis] explode all trees	6758
#11	#9 and #10	49
#12	atria* near/3 (emboli* or thromboemboli*)	206
#13	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #11 or #12	24313
#14	MeSH descriptor: [Heart Septal Defects, Atrial] explode all trees	187
#15	"patent foramen ovale" or PFO	277
#16	atrial sept* near/5 defect*	290
#17	((("right to left" or "R-L" or "venous to arterial" or "venous-arterial" or "V-A") near/3 shunt)	71
#18	#14 or #15 or #16 or #17	567
#19	#13 and #18 Publication Year from 2012 to 2017	81

Appendix 2: Tables

eTable 1: Characteristics of eligible studies

PFO closure plus antiplatelet vs antiplatelet therapy								
Study, year	Intervention	Medical therapy	Withdrawn or loss to follow-up		Crossover from med therapy to PFO closure (%)	Crossover from PFO closure to med therapy	Percent PFO closure performed /patients in PFO cohort	Percent technical success/PFO closure attempt
			PFO (%)	Medical therapy (%)				
Furlan, 2012	STARFlex Device. Clopidogrel for 6 months and ASA for 2 years	ASA 325mg daily (56%)	1.8	0.65	1.73	8.72	90.6	89.4
Mas, 2017	PFO closure (Amplatzer 51.5% ^x) plus ASA 75mg daily and clopidogrel 75mg daily x 3 months then aspirin or clopidogrel or aspirin plus ER dipyridamole	Aspirin or clopidogrel or aspirin plus ER dipyridamole	8.8	5.1	4.25	8.82	99.6	88.6
Meier, 2013	Amplatzer occluder. ASA 5-6 months. clopidogrel or ticlopidine 1-6 months	Antiplatelet (67%) or anticoagulation (31%)	15.2	19.5	13.3	6.4	96.1	97.4
Saver, 2017	Amplatzer occluder 100%. ASA 81-325mg daily plus clopidogrel 75mg daily x 1 months then ASA x 5 months	ASA, warfarin, clopidogrel (25%), or ASA plus dipyridamole (75%)	20.8	33.3	3.95	2.8	93.6	99.6
Sondergaard, 2017	PFO Closure (Cardoiform Septal occluder 61%, Gore helex Septal occluder 39%) plus antiplatelet (ASA 75-325mg daily, aggrenox, or clopidogrel. Clopidogrel 300mg x 1 then 75 daily x 3 days for everyone	Antiplatelet (ASA 75-325mg daily, ASA plus dipyridamole, or clopidogrel. (100%)	8.3	14.7	6.3	7.3	96.1	97.4
Lee, 2018	PFO Closure (100% Amplatzer PFO occluder). Suggested DAPT for 6 months with ASA 100mg and clopidogrel 75mg daily. However, up to treating physician. Could even use anticoagulation	Antiplatelet with ASA or ASA and Clopidogrel 75mg daily, or ASA and Cilostazol 200mg daily. Could anticoagulate with warfarin (INR 2.0-3.0)	0	0	0	11.7	88.3	100
PFO closure plus antiplatelet vs anticoagulation								
Study, year	Intervention	Control	Withdrawn or loss to follow-up		Crossover from antiplatelet to	Crossover from anticoagulation	Percent technical success/PFO	Percent technical success/PFO

					anticoagulation (%)	to antiplatelet (%)	closure attempts	closure attempts
			PFO Closure plus antiplatelet	Anticoagulation				
Mas 2017	PFO closure (Amplatzer 51.5%†) plus ASA 75mg daily and clopidogrel 75mg daily x 3 months then aspirin or clopidogrel or aspirin plus ER dipyridamole	Warfarin with target INR 2-3 (93%) or direct oral anticoagulant (7%)	NA	NA	NA	NA	NA	NA

Anticoagulation vs antiplatelet therapy

Study, year	Intervention	Control	Withdrawn or loss to follow-up		Crossover from antiplatelet to anticoagulation (%)	Crossover from anticoagulation to antiplatelet (%)
			Anticoagulation (%)	Antiplatelet (%)		
Mas 2017	Warfarin with target INR 2-3 (93%) or direct oral anticoagulant (7%)	Aspirin or clopidogrel or aspirin plus ER dipyridamole	23.5	5.7	5.17	20.3
Shariat, 2013	Warfarin 2.5mg po daily (INR 2-3)	Aspirin 80mg po tid (100%)	8.7	4.2	0	0
Homma (PICSS, 2002)	Warfarin (INR 1.4-2.8) F/U 24 months	Aspirin 325mg po od	6.4	2.8	NA	NA

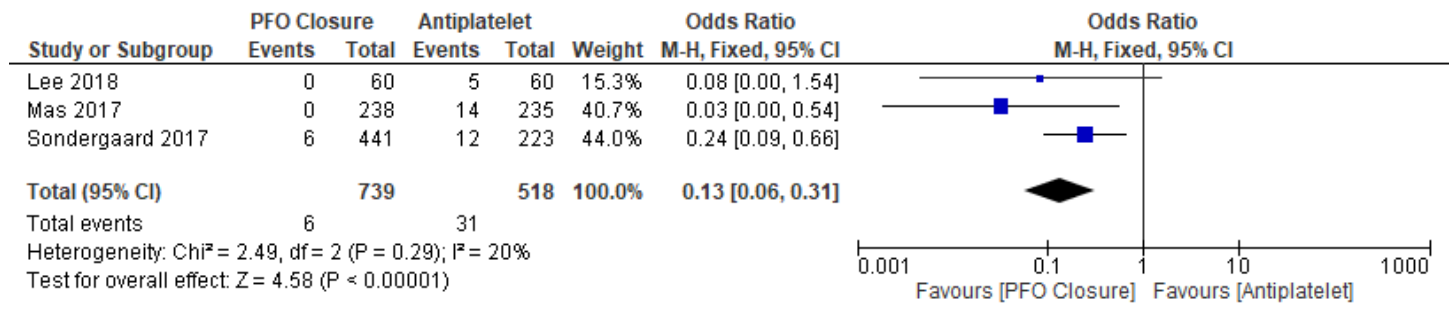
† 13% Intrasept PFO occluder, 9% STARFlex Septal Closure System, 9% Premere, 6% Amplatzer cribriform occluder, 6% Figulla Flex II PFO occluder, 1% Atriasept II occluder, 1% Gore Helex septal occluder, 1% Amplatzer AS occluder, 1% Figulla Flex II UNI occluder, 1% Figulla Flex II ASD occluder
 NA = Not available

Appendix 3: Figures

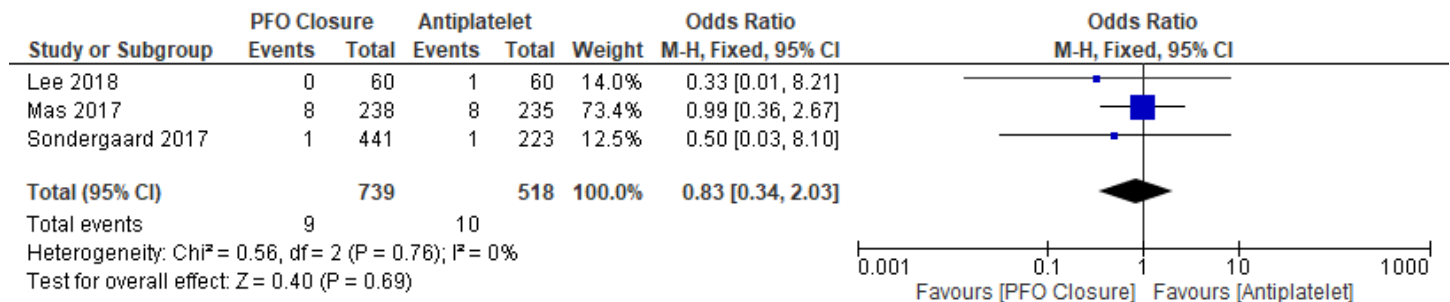
	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Furlan 2012	+	+	-	+	+	+
Homma 2002	+	+	+	+	+	+
Lee 2018	+	+	-	+	+	+
Mas 2017	+	+	-	+	+	+
Meier 2013	+	+	-	+	-	+
Saver 2017	+	+	-	+	-	+
Shariat 2013	+	+	-	-	-	+
Sondergaard 2017	+	+	-	+	-	+

eFigure 1: Risk of bias of included randomised controlled trials

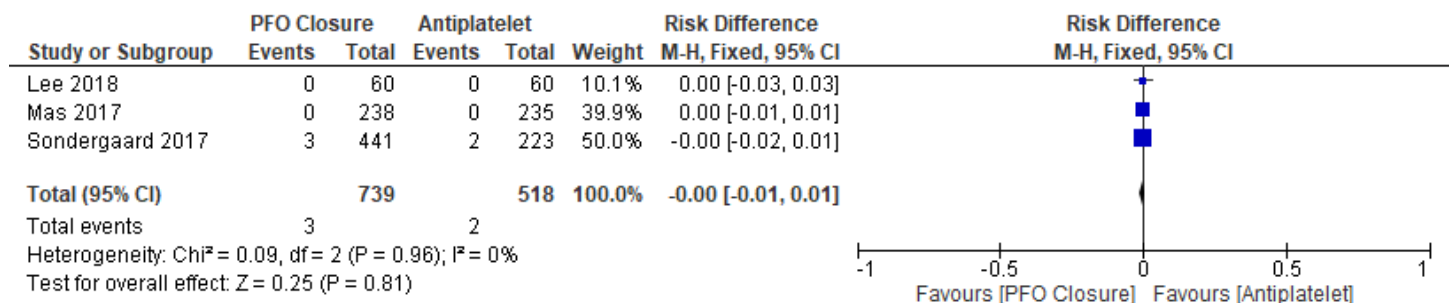
Appendix 4: PFO closure vs antiplatelet therapy forest plots (Direct evidence only)



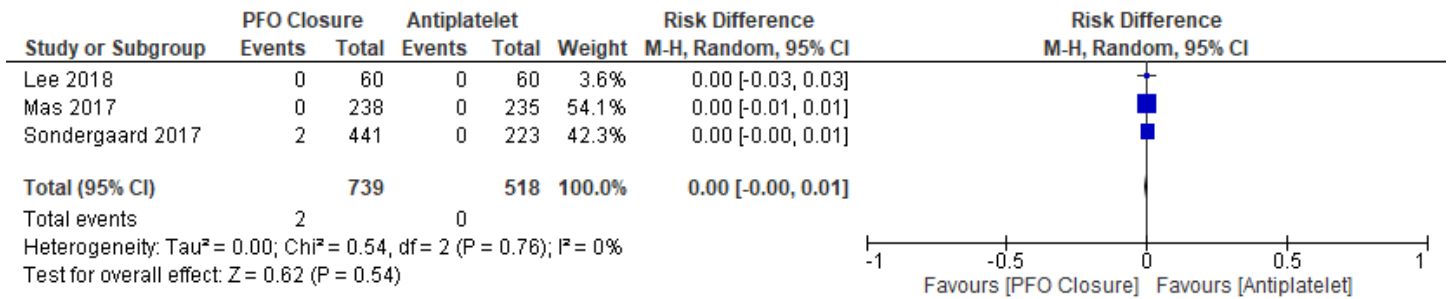
eFigure 1: Ischaemic stroke



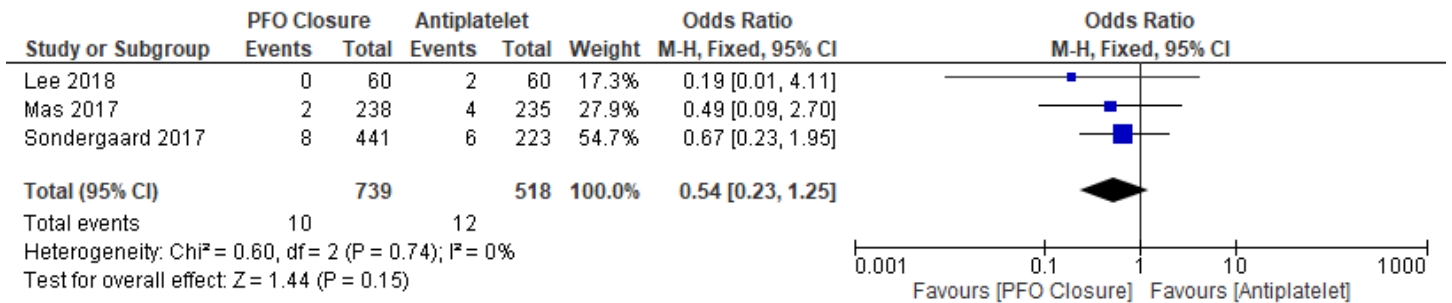
eFigure 2: TIA



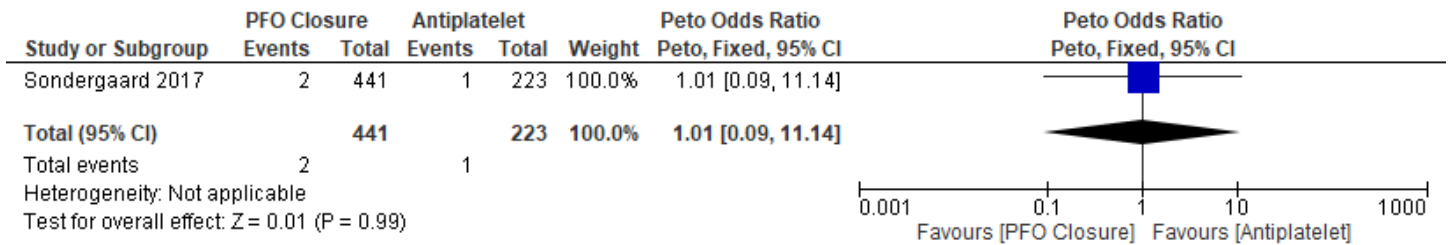
eFigure 3: Systemic embolism



eFigure 4: Death

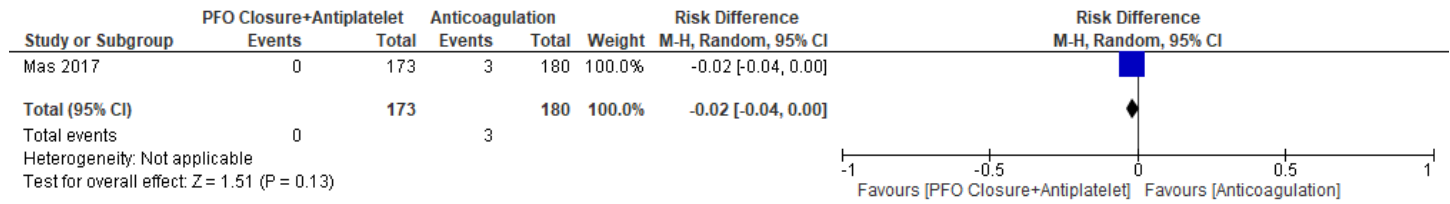


eFigure 5: Major bleeding

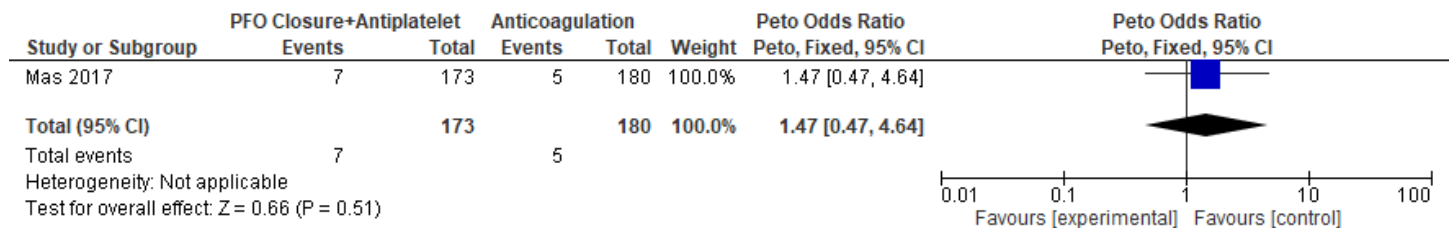


eFigure 6: Pulmonary embolism

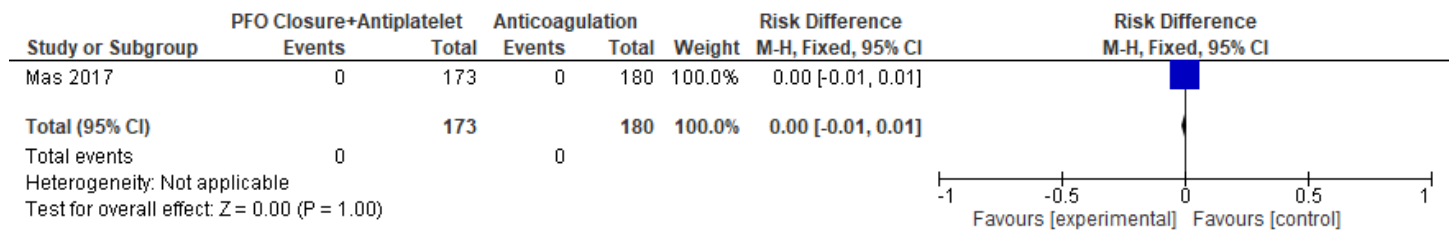
Appendix 5: PFO closure vs Anticoagulation forest plots (Direct evidence only)



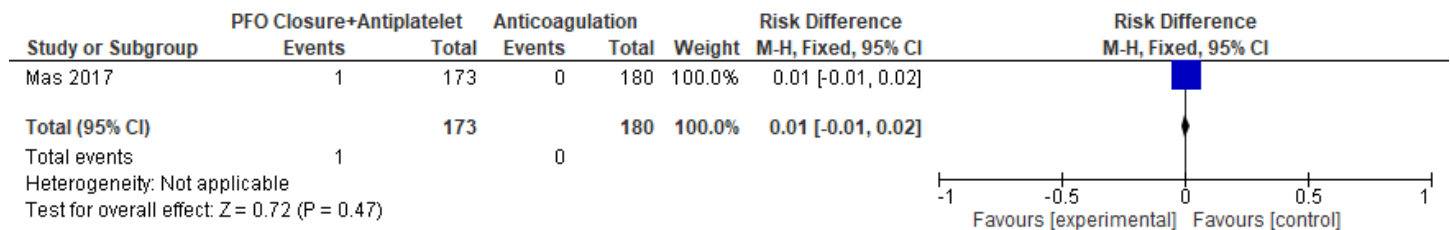
eFigure 1: Ischaemic stroke



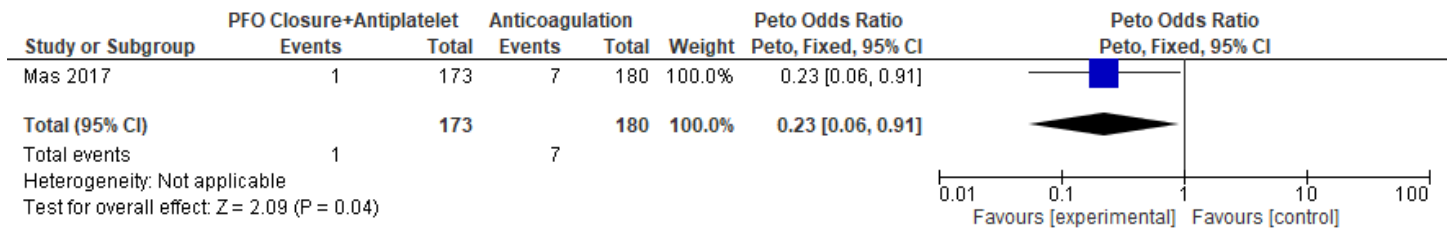
eFigure 2: TIA



eFigure 3: Systemic embolism

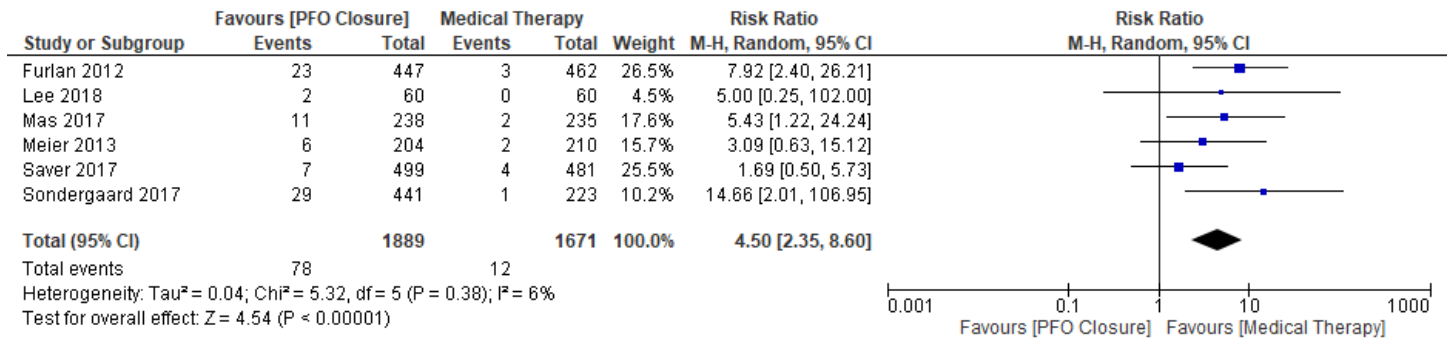


eFigure 4: Pulmonary embolism

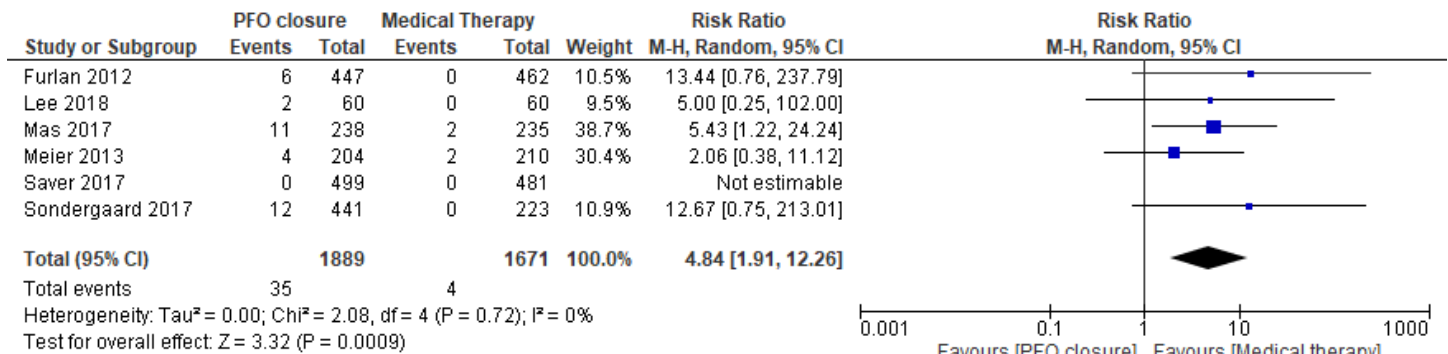


eFigure 5: Major bleeding

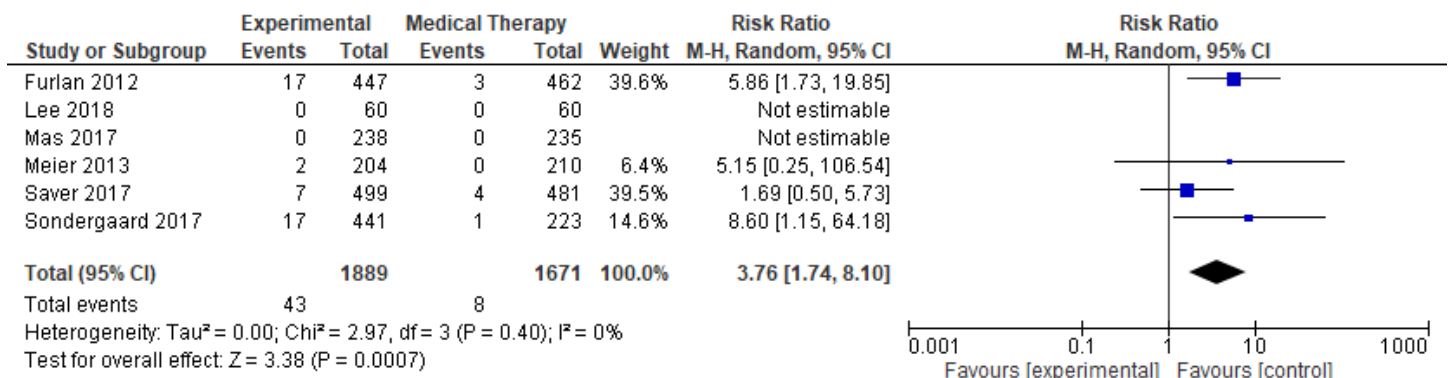
Appendix 6: Complications of PFO closure vs medical therapy forest plots (Direct evidence only)



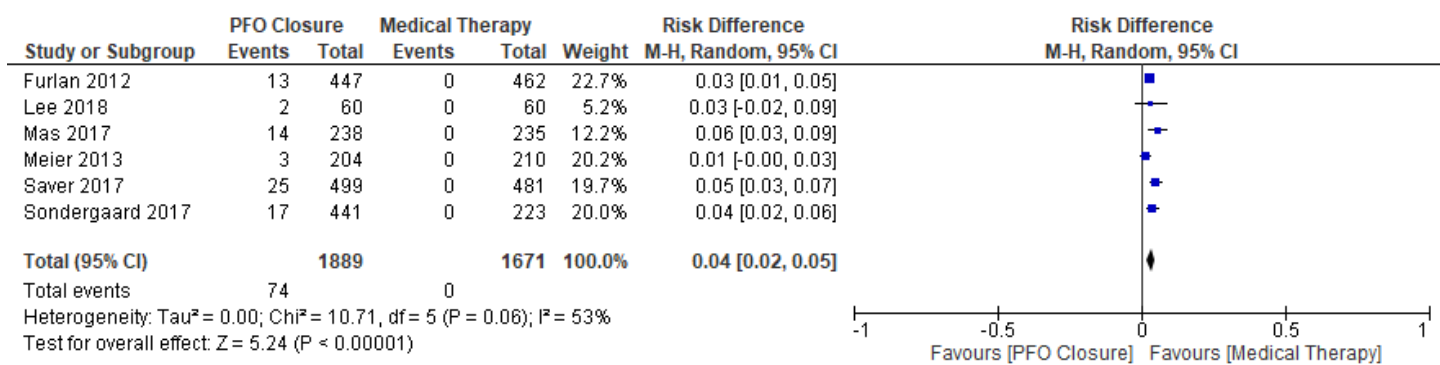
eFigure 1: All atrial fibrillation



eFigure 2: Persistent atrial fibrillation

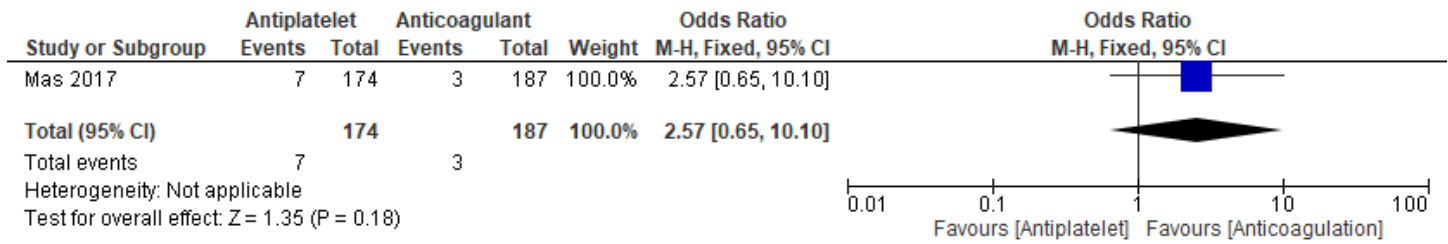


eFigure 3: Transient atrial fibrillation

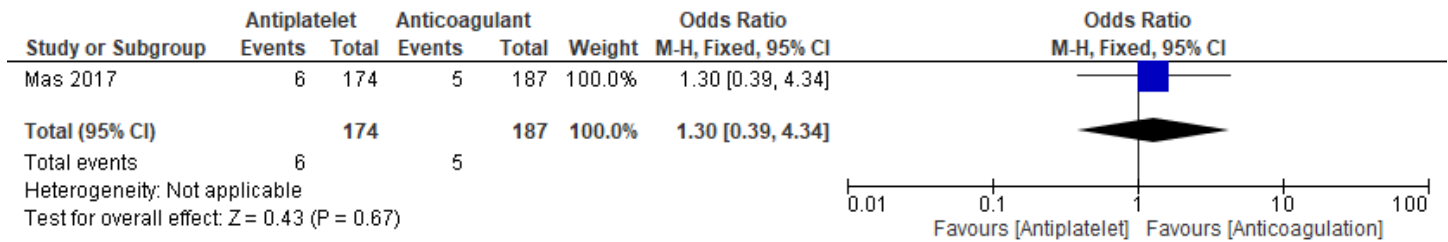


eFigure 4: Device or procedure related adverse events

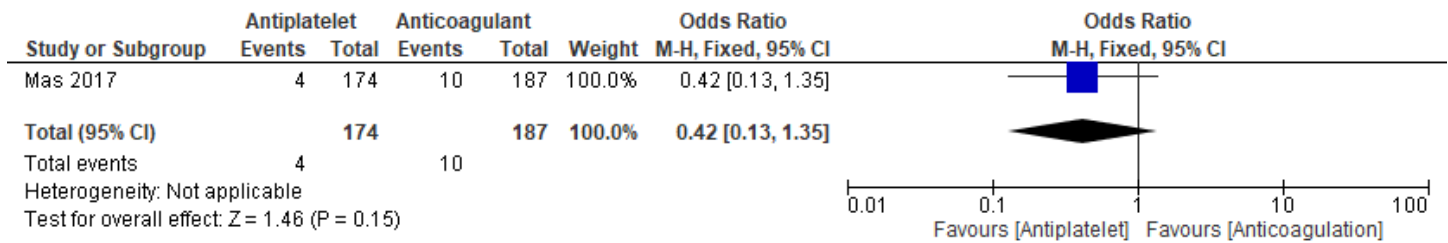
Appendix 7: Anticoagulation vs antiplatelet therapy forest plots (Direct evidence only)



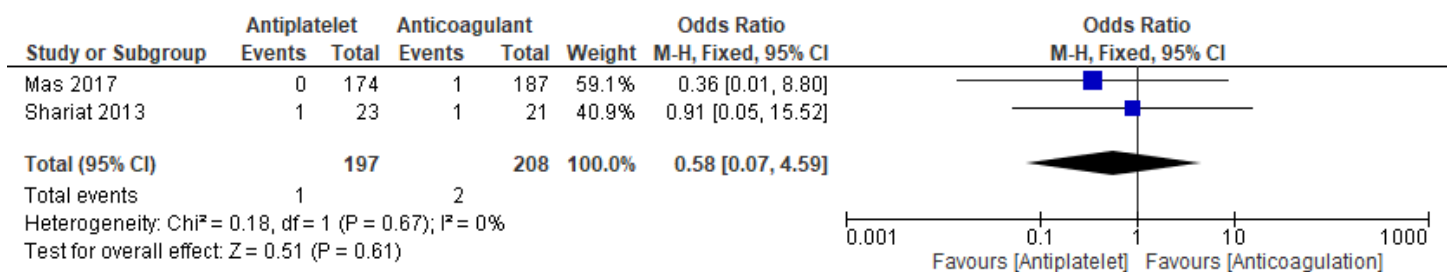
eFigure 1: Ischaemic stroke



eFigure 2: TIA

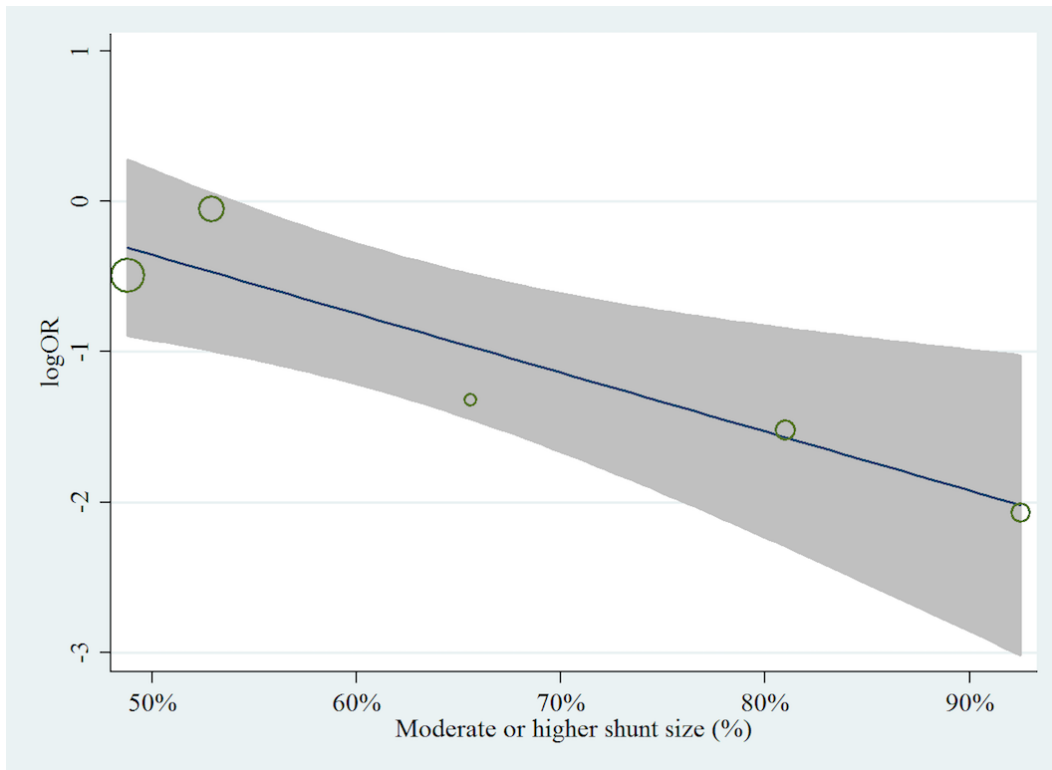


eFigure 3: Major bleeding

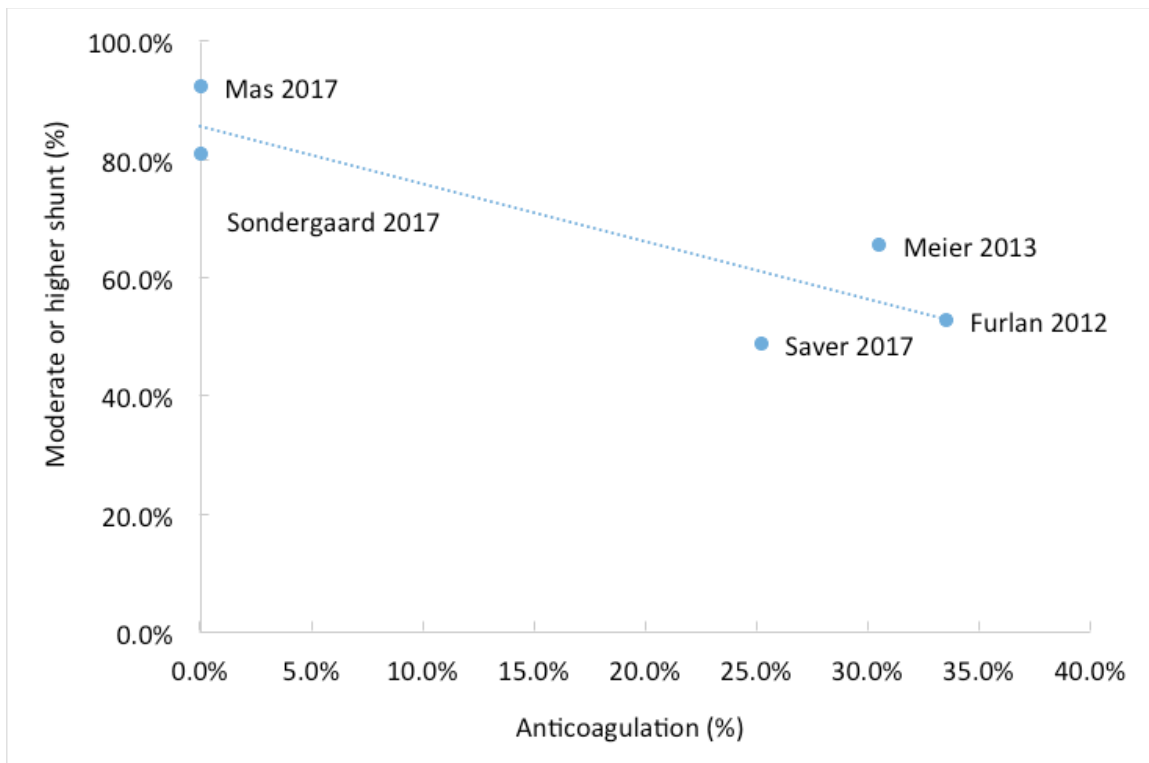


eFigure 4: Death

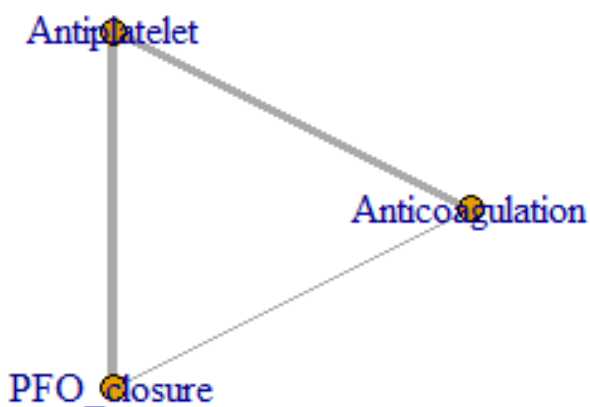
Appendix 8: Meta-regression and NMA Figures



eFigure 1: Meta-regression evaluating the effect of the proportion of participants with a moderate or higher shunt size on the effectiveness of PFO closure versus medical therapy in patients with a PFO and cryptogenic stroke. PFO closure was more effective in RCTs that had a higher proportion of patients with moderate or higher PFO shunts, $p=0.047$. Note, the shunt size was not reported in the DEFENSE-PFO Trial and thus it was not included in the analysis.



eFigure 2: Scatter plot of randomised trials of PFO closure in patients with cryptogenic stroke showing an inverse relationship between the proportion of participants with a moderate or higher shunt and proportion of patients prescribed anticoagulation in the medical therapy arm. Note, the shunt size was not reported in the DEFENSE-PFO Trial and thus it was not included in the analysis.



eFigure 3: Network of included RCTs with available direct comparisons for ischaemic stroke.

Note: The thickness of the lines (edges) is proportional to the number of RCTs evaluating each treatment and direct comparison.

Appendix 9: NMA Table

eTable 1: Direct and indirect estimates of effects

Outcomes	Comparisons	Direct [OR,95%CrI]	Indirect [OR,95%CrI]§	NMA [OR,95%CrI]
Ischemic stroke	PFO+antiplatelet vs. antiplatelet	0.14 (0.05, 0.34)	Not estimable*	0.12 (0.04, 0.27)
	PFO+antiplatelet vs. anticoagulation	9.6e-16 (2.0e-47, 6.3e+16)	0.45 (0.06, 3.18)	0.44 (0.08, 3.76)
	Antiplatelet vs. anticoagulation	4.67 (0.80, 26.95)	Not estimable*	3.73 (0.84, 28.11)
Death	PFO+antiplatelet vs. antiplatelet	3.1e+14 (4.32, 8.5e+62)	Not estimable*	2.48 (0.16, 99.11)
	PFO+antiplatelet vs. anticoagulation	3.4e-06 (1.5e-14, 728.3)	0.97 (0.02, 47.77)	0.59 (0.01, 22.76)
	Antiplatelet vs. anticoagulation	0.72 (0.01, 21.93)	Not estimable*	0.23 (0.01, 3.44)
Major bleeding	PFO+antiplatelet vs. antiplatelet	0.54 (0.21, 1.40)	Not estimable*	0.48 (0.20, 1.10)
	PFO+antiplatelet vs. anticoagulation	0.09 (0.00, 2.15)	0.30 (0.08, 1.12)	0.25 (0.07, 0.82)
	Antiplatelet vs. anticoagulation	0.60 (0.19, 1.80)	Not estimable*	0.53 (0.18, 1.47)
Recurrent TIA	PFO+antiplatelet vs. antiplatelet	0.75 (0.26, 2.13)	Not estimable*	0.82 (0.31, 2.09)
	PFO+antiplatelet vs. anticoagulation	1.51 (0.34, 6.72)	0.88 (0.11, 6.85)	1.25 (0.39, 4.38)
	Antiplatelet vs. anticoagulation	1.28 (0.26, 6.32)	Not estimable*	1.53 (0.50, 5.21)
Systemic embolism	PFO+antiplatelet vs. antiplatelet	0.79 (0.12, 6.76)	Not estimable*	0.73 (0.12, 5.52)
	PFO+antiplatelet vs. anticoagulation	0.01 (1.4e-10, 1.0e+06)	0.06 (5.7e-09, 6.0e+05)	0.03 (4.0e-08, 1280.0)
	Antiplatelet vs. anticoagulation	0.01 (1.4e-10, 4.0e+05)	Not estimable*	0.04 (5.4e-08, 1616.0)

§ Indirect results were from back-calculated

* Cannot be estimated because the intervention was not connected in a loop in the evidence network