Question 16 evidence tables

Question 16: What is the best method to prevent recurrent stroke in patients with patent foramen ovale?

NB Any discrepancies between reviewers in evidence quality and comment were discussed at the corresponding evidence review meeting

PFO = patent foramen ovale, PFOC = patent foramen ovale closure, MT = medical therapy, BMT = best medical therapy, NNT = number needed to treat, NNH = number needed to harm, TSA = trial sequential analysis, AF = atrial fibrillation, AFL = atrial flutter, GI = gastrointestinal, AP = antiplatelet, OAC = oral anticoagulation, ITT analysis = intention to treat analysis, AE = adverse event, DVT = deep vein thrombosis, PE = pulmonary embolism, ASA = acetylsalicylic acid (aspirin), SR = systematic review, MA = meta-analysis, RCT = randomised controlled trial, IPDMA = individual patient data meta-analysis, MDT = multidisciplinary team, PICO = patient/population, intervention, comparison and outcomes, OR = odds ratio, CI = confidence interval, QoL = quality of life, ADL = activities of daily living, OR = odds ratio, RR = relative risk, aOR = adjusted odds ratio, cOR = crude odds ratio, CI = confidence interval, RoB = risk of bias, I2 = heterogeneity statistic.

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
644	P. Agasthi et al. 2019. Are we there yet with patent foramen ovale closure for secondary prevention in cryptogenic stroke? A systematic review and meta-analysis of randomized trials. SAGE Open Medicine 7	Meta analysis evaluate the benefit of patent foramen ovale closure in stroke prevention assessing the incidence of recurrent stroke after patent foramen ovale closure when compared to medical therapy five studies with a total of 3440 patients 5 studies	Patent foramen ovale closure when compared to medical therapy in patient with previous cryptogenic stroke	recurrent stroke, transient ischemic attack and composite end point of stroke + transient ischemic attack + peripheral embolism	Patent foramen ovale closure versus medical therapy group were 0.4 (95% confidence interval 0.25–0.63, I2 = 57.5%), 0.93 (95% confidence interval 0.61–1.42, I2 = 0%), and 0.6 (95% confidence interval 0.44–0.82, I2 = 0%)	++ High Moderate heterogeneity
644	P. Agasthi et al. 2019. Are we there yet with patent foramen ovale closure for secondary prevention in cryptogenic stroke? A systematic review and	RCTs >18y 5 RCTs	Closure v MT in stroke or TIA	OR. Stroke, also TIA and composite stroke/TIA/Peripheral embolism	PFO closure plus MT reduced the risk of recurrent stroke by 33% when compared to MT alone (pooled OR = 0.38, 95% CI = 0.17–0.88, p = 0.02, I2 = 57.5%) . NNT with PFO closure to prevent 1 recurrent stroke is 42. No sig reduction in TIA	++ Appears well conducted and presented.

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
	meta-analysis of randomized trials. SAGE Open Medicine 7				More AF OR 4.89. The NNH to cause one atrial fibrillation with PFO closure is 39. No difference bleeding Subgroup: >45 non-sig reduction, sig <45, non-sig in female, sig in males, Mod/large shunt sig reduction, not small. ASA no difference	
645	Y. Ahmad et al. 2018. Patent foramen ovale closure vs. medical therapy for cryptogenic stroke: a meta-analysis of randomized controlled trials. European Heart Journal 39: 1638-1649	meta-analysis of randomized controlled trials (RCTs) comparing device closure with medical therapy to prevent recurrent stroke for patients with PFO. 5 studies	PFO closure	primary efficacy endpoint was recurrent stroke	PFO closure was superior to medical therapy for prevention of stroke [hazard ratio (HR) 0.32, 95% confidence interval (95% CI) 0.13–0.82; P = 0.018, I2 = 73.4%]. The risk of AF was significantly increased with device closure [risk ratio (RR) 4.68, 95% CI 2.19–10.00, P<0.001, heterogeneity I2 = 27.5%)]. large shunts, PFO closure was associated with a significant reduction in stroke (HR 0.33, 95% CI 0.16–0.72; P = 0.005), whilst there was no significant reduction in stroke in patients with a small shunt (HR 0.90, 95% CI 0.50–1.60; P = 0.712)	**++** High But significant heterogeneity
645	Y. Ahmad et al. 2018. Patent foramen ovale closure vs. medical therapy for cryptogenic stroke: a	Meta-analysis 5 RCTs	of closure vs BMT (described) 3 RCTs for shunt size	High risk (HR) of recurrent stroke	Reduce HR HR 0.32 95% CI 0.13–0.82; P= 0.018 Increased risk AF risk	**++** High

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
	meta-analysis of randomized controlled trials. European Heart Journal 39: 1638-1649				ratio (RR) 4.68, 95% CI 2.19–10.00, P<0.001, heterogeneity I2= 27.5% significant p value for interaction between shunt category and the risk of recurrent stroke	
646	A. K. Akobeng et al. 2018. Patent foramen ovale (PFO) closure versus medical therapy for prevention of recurrent stroke in patients with prior cryptogenic stroke: A systematic review and meta-analysis of randomized controlled trials. Catheterization & Cardiovascular Interventions 92: 165-173	Effect of closure of a patent foramen ovale (PFO) compared with medical therapy for the prevention of stroke in patients with prior cryptogenic stroke	PFO closure	occurrence of stroke. Secondary outcomes of interest were transient ischemic attacks (TIAs), atrial fibrillation/flutter, serious adverse events, and all-cause mortality.	Patients treated with PFO closure had a lower risk of stroke (RR 0.39, 95% CI 0.18–0.88, I2557%, P50.02) compared with those treated with medical therapy PFO closure on a composite outcome of cerebrovascular events is more pronounced in patients with a large PFO shunt (RR 0.25, 95% CI 0.12–0.54, I250%, P50.0004), male patients (RR 0.34, 95% CI 0.15–0.75, I2536%, P50.07), and those aged _45 years (RR 0.35, 95% CI 0.15–0.79, I250%, P50.01). PFO closure had a higher risk of atrial fibrillation/ flutter compared with those who received medical therapy (RR 4.73, 95% CI 2.09–10.70, I2531%, P50.0002)	**++** High Mild to moderate heterogeneity
646	A. K. Akobeng et al. 2018. Patent foramen ovale (PFO) closure versus medical therapy for	RCT Nov 17	Closure v BMT	The primary outcome of interest for this study was the occurrence of Stroke Risk ratios. Secondary outcomes of	1.5% (28/1,829) of patients who had PFO closure compared to 3.7% (60/1,611) of patients who received	**++** High

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
	prevention of recurrent stroke in patients with prior cryptogenic stroke: A systematic review and meta-analysis of randomized controlled trials. Catheterization & Cardiovascular Interventions 92: 165-173			interest were transient ischemic attacks (TIAs), atrial fibrillation/flutter, serious adverse events, and all-cause mortality	medical therapy (RR 0.39, 95% CI 0.18–0.88, I2557%, P50.002) NNT 28-69 Grade low or moderate for the 5 RCTs due to risk of bias and imprecision large right to left shunt (RR 0.25, 95% CI 012–0.54, I250%, P50.0004); age _45 years (RR 0.35, 95% CI 0.15–0.79, I250%, P50.01); and male gender (RR 0.34, 95% CI 0.15–0.75, I2536%, P50.007) were associated with significant reductions	
647	T. Ando et al. 2018. Meta-Analysis Comparing Patent Foramen Ovale Closure Versus Medical Therapy to Prevent Recurrent Cryptogenic Stroke. American Journal of Cardiology 21: 649-655	meta-analysis of randomized controlled trials that compared PFO closure plus MT with MT alone in patients with cryptogenic stroke	PFO closure vs medical therapy	Stroke TIA Mortality Major bleeding Atrial fibrillation	Five randomized controlled trials (3,440 patients) were included. Mean follow-up was 4.1 years. PFO closure reduced the risk of recurrent stroke by 58% (RR 0.42, 95% CI 0.20 to 0.91, p = 0.03) PFO closure did not reduce the risk of transient ischemia attack (RR 0.78, 95% CI 0.53 to 1.15, p = 0.21), mortality (RR 0.74, 95% CI 0.35 to 1.60, p = 0.45), or major bleeding (RR 0.96, 95% CI 0.42 to 2.20, p = 0.93) increase the risk of atrial fibrillation (RR 4.69, 95% CI 2.17 to 10.12, p <0.0001)	**+** Acceptable

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
647	T. Ando et al. 2018. Meta-Analysis Comparing Patent Foramen Ovale Closure Versus Medical Therapy to Prevent Recurrent Cryptogenic Stroke. American Journal of Cardiology 21: 649-655	Metaanalysis and 'Trial Sequential Analysis' Including sd later 2 and longterm respect TSA to as risk of type 1 error	RCT and TSA. 5 studies	RR Stroke, Also TIA, Mortality, bleeding, AF Large PFO	The pooled rate of stroke in the patients was 2.0% in the patients who received PFO closure plus MT and 4.5% in the patients who received MT alone. PFO closure plus MT reduced the risk of recurrent stroke by 58% compared with MT alone (RR 0.42, 95% CI 0.20 to 0.91, p=0.03 The TSA: Trial sequential analysis showed that the cumulative Z-score crossed the conventional boundary (p = 0.05), and reached the trial sequential boundary (Figure 3). This suggests that there is likely adequate evidence to conclude that PFO closure plus MT reduces the rate of recurrent stroke by at least 60% com- pared with MT alone. (These were prespecified in the methods section). PFO closure plus MT significantly increased the risk of newly detected AF by more than 4 times compared with the MT alone (RR 4.69, 95% CI 2.17 to 10.12, p <0.001, I2 = 29%, p for heterogeneity 0.23	**++** High
648	G. Chatellier et al. 2018. Closure, anticoagulation, or	Systematic review and meta-analysis of randomized controlled trials (RCTs) comparing patent foramen ovale (PFO) closure,	PFO closure versus antithrombotic	Primary end point was fatal or nonfatal recurrent stroke. Secondary end points were occurrence of	PFO closure was associated with a lower risk of recurrent stroke compared with antithrombotic therapy	**+** Acceptable

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
	antiplatelet therapy for cryptogenic stroke with patent foramen ovale: Systematic review of randomized trials, sequential meta-analysis, and new insights from the CLOSE study. Journal of the American Heart Association 7(12) (no pagination)	anticoagulation, and antiplatelet therapy to prevent stroke recurrence in patients with PFO-associated cryptogenic stroke. 6 trials 3560 patients	therapy (antiplatelet therapy or anticoagulation), PFO closure versus antiplatelet therapy, PFO closure versus anticoagulation, and anticoagulation versus antiplatelet therapy.	a transient ischemic attack (TIA), all-cause mortality, major bleeding, major procedural complication, and new-onset atrial fibrillation.	(antiplatelet therapy or anticoagulation: 3560 patients from 6 RCTs; RR=0.36, 95% CI: 0.17–0.79; I2=59%) PFO closure on stroke recurrence was larger in patients with atrial septal aneurysm or large shunt (RR=0.27, 95% CI, 0.11–0.70; I2=42%) compared with patients without these anatomical features (RR=0.80, 95% CI, 0.43–1.47; I2=12%) New-onset atrial fibrillation was more frequent in patients randomized to PFO closure versus antithrombotic therapy (RR=4.33, 95% CI, 2.37–7.89; I2=14%)	
648	G. Chatellier et al. 2018. Closure, anticoagulation, or antiplatelet therapy for cryptogenic stroke with patent foramen ovale: Systematic review of randomized trials, sequential meta-analysis, and new insights from the CLOSE study. Journal of the American Heart Association 7(12) (no pagination)	Systematic review and meta-analysis of all randomized data allowing the direct comparison of PFO closure, anticoagulation, and antiplatelet therapy to prevent recurrent stroke in patients with cryptogenic stroke and PFO. Up to March 18 (includes DEFENCE-PFO) included published data from all RCTs and unpublished data from the 3-arm CLOSE trial "Because traditional updated meta-analyses may sometimes lead to false-positive results due to repeated significance testing,14 we performed trial sequential analyses (TSA)" No age limit	SR, MA, TSA *Upon request, the data, analytic methods, and study materials will be made available to other researchers for purposes of reproducing *but the study protocol was not registered. Compared Closure v AP, OAC, AP or OAC, and AP v OAC	Prevention of recurrent stroke in patients with stroke or TIA	*Antithrombotic* pooled RR 0.36, 95% CI, 0.17–0.79, P=0.01 zIn patients with higher-risk anatomical features, the pooled RR for PFO closure was 0.27 (95% CI, 0.11–0.70, P=0.01; I2=42%), whereas it was 0.80 (95% CI, 0.43–1.47, P=0.41; I2=12%) in patients with lower-risk anatomical features. No reduction TIA, mortality, bleeding. AF pooled RR 4.33, *Anticoagulation* On CLOSE, and head to head not pre-specified	**++/+**

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
			Our primary end point was fatal or nonfatal recurrent stroke. Secondary end points were occurrence of a transient ischemic attack (TIA),1all-cause mortality, major bleeding, major procedural complication, and new-onset atrial fibrillation.		Few event (3 v 0); HR was 0.14 (95% CI, 0.00–1.45; P=0.26 *AP v OAC* PICSS not good enough, small single centre not good enough, only CLOSE HR 0.44, 95% CI, 0.11–1.48	
649	K. Dahal et al. 2019. Who benefits from percutaneous closure of patent foramen ovale vs medical therapy for stroke prevention? In-depth and updated meta-analysis of randomized trials. World Journal of Cardiology 11: 126-136	Meta-analysis of 6 RCTs including 3560 patients (gender, age shunt size atrial septal aneurysm).	PFOC vs medical therapy	Ischemic stroke (IS), transient ischemic attack (TIA), a composite of IS, TIA and systemic embolism (SE), mortality, major bleeding, atrial fibrillation (AF) and procedural complications were the major outcomes	PFOC, compared to medical therapy reduced the risk of IS [odds ratio: 0.34; 95% confidence interval: 0.15-0.78; P = 0.01] and the composite of IS, TIA and SE [0.55 (0.32-0.93); P = 0.02] and increased the AF risk [4.79 (2.35-9.77); P < 0.0001]. No statistical difference was observed in the risk of TIA [0.86 (0.54-1.38); P = 0.54], mortality [0.74 (0.28-1.93); P = 0.53] and major bleeding [0.81 (0.42-1.56); P = 0.53] PFO closure reduced the risk of stroke in persons who were males, ≤ 45 years of age and had large shunt or atrial septal aneurysm	**++** High quality
649	K. Dahal et al. 2019.	MA of RCTs Up to Sept 18 (included DEFENCE-PFO)	Short methods section	Use OR Recurrent IS, TIA, SE, a composite of IS, TIA and	PFO closure, compared to medical therapy reduced the	**+** Possibly

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
	Who benefits from percutaneous closure of patent foramen ovale vs medical therapy for stroke prevention? In-depth and updated meta-analysis of randomized trials. World Journal of Cardiology 11: 126-136			SE, major bleeding, mortality and procedural complications including atrial fibrillation (AF) risk were the major outcomes (nor described as primary, secondary)	risk of IS (OR: 0.34; 95%CI 0.15-0.78, P = 0.01). Also reduction in compost, no reduction TIA, mortality or bleeding. Increase in AF 4.79 (2.35-9.77) Subgroup: reduction in the risk of stroke (Figure 5) in patients who were male [0.25; 0.07-0.96; P = 0.04; I2 = 61%], ≤ 45 years of age [0.37; 0.17-0.82; P = 0.01; I2 = 0%] and had large shunt [0.22; 0.11-0.47; P < 0.0001; I2 = 0%] or ASA [0.16; 0.05-0.51; P = 0.002; I2 = 0%] PFO closure showed a reduction in stroke risk in females [0.50; 0.23-1.08; P = 0.08; I2 = 0%] and patients > 45 years of age [0.32; 0.10-1.06; P = 0.06; I2 = 52%]; however, it did not reach statistical significance. In patients with small shunt, there was no statistical difference in the stroke outcomes [0.88; 0.34-2.27; P = 0.8; I2 = 11%] Large shunt, male and younger subgroup benefit, small shunt still benefit. Not proven email and over 45.	No mention respecified and Id say some others
650	F. Darmoch et al. 2018. Transcatheter Closure of Patent Foramen Ovale versus Medical	Cryptogenic stroke PFO Meta analysis 5 trials 3440 patients	PFO closure medical therapy	Recurrent stroke TIA AF/AFL Bleeding complications	Significant risk reduction in risk of recurrent stroke in the PFO closure group when compared with medical	+ Acceptable Heterogeneity of primary outcome 59%

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
	Therapy after Cryptogenic Stroke: A Meta-Analysis of Randomized Controlled Trials. Cerebrovascular Diseases 45: 162-169	Random effects model			therapy (RR 0.42; 95% CI 0.20–0.91, p = 0.03) Recurrence of TIA in the PFO closure group compared to the medical therapy-alone group (3.2 vs. 3.8%; RR 0.84, 95% CI 0.59–1.20, I2 = 0%, p = 0.35) AF: (RR 4.63, 95% CI 2.30–9.30, I2 = 16%, p < 0.0001. Bleeding: RR 0.85, 95% CI 0.37–1.95, p = 0.70	
650	F. Darmoch et al. 2018. Transcatheter Closure of Patent Foramen Ovale versus Medical Therapy after Cryptogenic Stroke: A Meta-Analysis of Randomized Controlled Trials. Cerebrovascular Diseases 45: 162-169	meta-analysis RCTs, <60Years with CS 3,440 patients (mean age 45.7 years, 55% are men) with a mean follow- up of 49 months PFO size not analysed.	Closure	summary risk ratios (RRs) Absolute risk difference and NNT for statistically significant outcomes	pooled RR for recurrent stroke [0.42, 95% CI 0.20–0.91 ARD)= –0.03 (95% CI –0.05 to –0.01) and a potential number needed to treat of 33 No difference TIA More AF in all studies (RR 4.63, 95% CI 2.30–9.30, I2 = 16%). potential number needed to harm of 33 Sub- group analysis of patients stratified by age, gender, and device type showed no statistically significant difference .	**+** (does not say preregistered)
651	S. De Rosa et al. 2018. Percutaneous Closure Versus Medical Treatment in Stroke Patients With Patent Foramen Ovale: A	Cryptogenic stroke Metanalysis 4 trials 2531 patients	PFOC vs medical therapy	Rates of stroke or transient ischemic attack (TIA) or of new-onset atrial fibrillation (AF) or atrial flutter (AFL). Mortality	PFO closure reduced the risk for the main outcome of stroke or TIA (risk difference [RD], _0.029 [95% CI, _0.050 to _0.007]) and increased the risk for new-onset AF or AFL (RD, 0.033 [CI, 0.012 to 0.054]). The beneficial effect	**++** High quality

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
	Systematic Review and Meta-analysis. Annals of Internal Medicine 168: 343-350				of PFO closure was associated with larger interatrial shunts (P = 0.034).	
651	S. De Rosa et al. 2018. Percutaneous Closure Versus Medical Treatment in Stroke Patients With Patent Foramen Ovale: A Systematic Review and Meta-analysis. Annals of Internal Medicine 168: 343-350	Meta analysis of RCTs Up to Sept 2017	Closure Included only devices commercially available (ie excluded CLOSURE 1), and only original trial as longer follow-up of RESPECT showed poor retention Subgroup and sensitivity analysis including longer FU	Primary analyses based on the composite end point of stroke or TIA, with IS and Death as secondary	Risk Difference of IS/TIA , -0.029 [95% CI, -0.050 to -0.007]; P = 0.008; I2 = 34% Stroke occurred in 1.2% of patients who received treatment with a PFO closure device, compared with 4.1% who received medical therapy (RD, -0.031 [CI, -0.051 to -0.010]; P = 0.003; I2 = 61% New-onset AF or AFL occurred in 4.1% with a PFO closure de-vice, compared with 1.0% who medical(RD, 0.033 [CI, 0.012 to 0.054]; P = 0.002; I2 = 66 progressively greater beneficial effect on ischemic stroke prevention with increasing IAS size in patients with a moderate to large shunt (P = 0.034) The heterogeneity found for the end point of ischemic stroke (I2 = 61%) decreased to below 50% (I2 = 49%) after the results of the original RESPECT trial were substituted with the prolonged follow-up analysis	**++** That STARflex/CLOSURE 1 excluded may make it more applicable. Used RD and no NNT
652	E. M. Fiorelli et al. 2018.	Cryptogenic stroke ITT meta analysis Study level	PFOC vs medical therapy (antiplatelets and anticoagulants)	Primary outcomes are stroke or transient ischemic attack (TIA) and	Lower recurrence of stroke or TIA at	**++** High quality

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
	Secondary prevention of cryptogenic stroke in patients with patent foramen ovale: a systematic review and meta-analysis. Internal & Emergency Medicine 13: 1287-1303	6 trials 3677 patients Random effects model Trial sequential analysis		all-cause mortality. Secondary outcomes are peripheral embolism, bleeding, serious adverse events, myocardial infarction and atrial dysrhythmias	a mean follow-up of 3.88 years compared to medical therapy [risk ratio (RR) 0.55, 95% CI 0.38–0.81; I2 = 40% TSA confirms this result. No difference is found in mortality (RR 0.74, 95% CI 0.35–1.60; I2 = 0%) PFO closure is associated with a higher incidence of atrial dysrhythmias (RR 4.55, 95% CI 2.16–9.60; I2 = 25%)	
652	E. M. Fiorelli et al. 2018. Secondary prevention of cryptogenic stroke in patients with patent foramen ovale: a systematic review and meta-analysis. Internal & Emergency Medicine 13: 1287-1303	systematic review and meta-analysis September 2017 Adults, CS or TIA 6 Trials (inc DEFENCE) mean age 47.3	Closure	Primary Stroke or TIA	Primary (Stroke/TIA) RR 0.55, 95% CI 0.38–0.81; p=0.002; partici-pants=3440),I2 = 40% Stroke separately: RR 0.42, 95% CI 0.20–0.91; p=0.03; par-ticipants = 3440; I2 = 59 Numerically lower RR in studies with AP as medical than AP/OAC (0.32, 0.77) *meta-regression of data from four studies [8, 10, 20, 26] reveals an inverse correlation between the overall proportion of patients treated with antiplatelet therapy in the medical treatment group, and the RR of stroke or TIA at follow-up in the PFO closure group* No difference for Age and Gender Sensitivity analysis excluding CLOSE as all large More AF across studies	**++** For the question, using Stroke/TIA is problematic. Benefit in smaller PFOs is only for this outcome. The analysis of studies using AP or both is not sufficient evidence for AP v OAC

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
					No difference in AP v OAC comparison directly (did a MA for this)	
653	A. Garg et al. 2019. Recurrent Stroke Reduction with Patent Foramen Ovale Closure versus Medical Therapy Based on Patent Foramen Ovale Characteristics: A Meta-Analysis of Randomized Controlled Trials. Cardiology 144: 40-49	Cryptogenic stroke Study level meta analysis 6 trials 3747 patients Random effects model DEFENSE PFO (2018) [11] CLOSE (2017) [9] RESPECT (2017) [8] REDUCE (2017) [10] PC (2013) [7] CLOSURE (2012) [5]	PFOC Medical therapy Anticoagulants Antiplatelet agents	Recurrent stroke. Secondary end points: transient ischemic attack, all-cause death, major bleeding, and newly detected atrial fibrillation (AF)	Significant reduction in the risk of recurrent stroke in the closure arm compared to MT (RR 0.41; 95% CI 0.20–0.83), with mild heterogeneity (I2 = 51%) Significant reduction in stroke in patients with moderate to large shunt (RR 0.35; 95% CI 0.18–0.68), while such an association was lacking in patients with small shunt (RR 0.98; 95% CI 0.56–1.73) Nonsignificant trend towards a reduction in stroke with PFO closure regardless of the presence or absence of aneurysm. No difference in TIA bleeding mortality	**+/-** Adequate
653	A. Garg et al. 2019. Recurrent Stroke Reduction with Patent Foramen Ovale Closure versus Medical Therapy Based on Patent Foramen Ovale Characteristics: A Meta-Analysis of Randomized Controlled Trials. Cardiology 144: 40-49	MA of RCTs (6) April 18	PFO Closure v MT	Primary: recurrent stroke Secondary: TIA, bleeding, death, AF Stratified by shunt size (Mod/large v small), ASA, type of medical Tx Then combined as 'high risk features'	Stroke: 2% in the PFO closure group and of 4.3% in the MT group RR 0.41; 95% CI 0.20– 0.83), with mild heterogeneity (I2 = 51% . Heterogen no longer sig after removal of closure1 RR 0.35v mod/large shunt (SS), 0.98 for small Reduction v asp, not v OAC Reduction in high risk not low risk No difference TIA, death, bleeding. Higher AF.	**+** Excluded non-published No pub bias assessment No assessment of studies bias sources

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
654	B. Kheiri et al. 2019. Patent foramen ovale closure versus medical therapy after cryptogenic stroke: An updated meta-analysis of all randomized clinical trials. Cardiology Journal 26: 47-55	SR and MA to Oct 17 CS and PFO	Closure v MT	Stroke Subgroup shunt size	Stroke: reduced HR 0.32 95% CI 0.13–0.82 With heterogeneity Low recurrence generally 0.61 v 1.17% Af increased risk ratio (RR) 4.68, 95% CI 2.19–10.00 No difference in bleeding, 3.2%V procedure related events Shunt size: reduction if lMod/large HR 0.33 not if small HR 0.9 (CLOSE excluded as all mod/large or ASA)	**++** Good assessment of bias Noted lack of stated blinded end-point adduction in CLOSE, CLOSURE, and REDUCE Therefore intermediate quality Downplays the adverse effects. Good summary first paragraph of discussion: Low risk, reduced by closure, especially if large D (not ASA) and AF increased by closure
655	B. Kheiri et al. 2020. Meta-Analysis of Secondary Prevention of Cryptogenic Stroke. Cardiovascular Revascularization Medicine 21: 1285-1290	Cryptogenic stroke or ESUS Study level metanalysis Network metanalysis 10 trials 32,143 patients primary all-cause death, or cardiovascular death), individual TIA, all-cause death, major bleeding, and intracranial bleeding.	PFOC Warfarin Antiplatelet	Outcome was recurrent ischemic stroke. Secondary outcomes included trial-reported composite of ischemic events (recurrent stroke, TIA, systemic embolism, myocardial infarction,	Significantly reduced recurrent ischemic stroke compared with antiplatelet therapy (HR = 0.66; [95% confidence interval (CI) = 0.47–0.94]). Meta-regression analysis showed significantly reduced recurrent stroke with longer duration of therapy, and significantly increased events with advanced age no significant differences with regard to the composite ischemic outcome, transient ischemic attack, any death, major bleeding, or intracranial bleeding network meta-analysis, compared to antiplatelet therapy, warfarin (HR=0.31; [95% credible interval (CrI) = 0.12–0.68]) and PFO closure (HR = 0.14; 95% CrI = 0.05–0.31]) were	- Low quality

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
					associated with significantly reduced recurrent ischemic stroke. In rank order, PF O closure was associated with the best outcome,	
655	B. Kheiri et al. 2020. Meta-Analysis of Secondary Prevention of Cryptogenic Stroke. Cardiovascular Revascularization Medicine 21: 1285-1290	MA of cryptogen with additional PFO analysis as amended protocol Network meta analysis of PFO options	Medication and closure in cryptogenic stroke	Stroke primary	Compared to antiplatelet therapy, warfarin (HR = 0.31; 95% CrI = 0.12–0.68) and PFO closure (HR = 0.14; 95% CrI =0.05–0.31) were associated with significantly reduced risk of recurrent ischemic stroke	**+** Complex, pooling of large number of studies, and PFO separately
656	J. C. L. Lai et al. 2018. Patent foramen ovale closure versus medical therapy for stroke prevention: A systematic review and meta-analysis of randomized controlled trials F1000Research 6 (no pagination)	Study level metanalysis 5 trials including long-term follow up of RESPECT REDUCE CLOSE CLOSURE I PC 1829 patients in the PFO closure arm and 1972 patients in the medical therapy arm		Primary endpoint troke TIA Bleeding AF GI complications	When compared to medical therapy, PFO closure significantly reduced primary endpoint events with a risk ratio [RR] of 0.60 (95% CI: 0.44-0.83, P < 0.0001; I2: 15%). It also reduced stroke (RR: 0.50, 95% CI: 0.35-0.73, P < 0.0001; I2: 32%) despite increasing the risk of atrial fibrillation/flutter (RR: 1.90, 95% CI: 1.23-2.93, P < 0.01; I2: 43%). However, it did not reduce transient ischemic accident events (0.75; 95% CI: 0.51-1.10, P = 0.14; I2: 0%), all-cause bleeding (RR: 0.89; 95% CI: 0.44-1.78, P = 0.74; I2: 51%) or gastrointestinal complications (RR: 0.92; 95% CI: 0.32-2.70, P = 0.88; I2: 0%)	**+/-** Adequate quality

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
656	J. C. L. Lai et al. 2018. Patent foramen ovale closure versus medical therapy for stroke prevention: A systematic review and meta-analysis of randomized controlled trials F1000Research 6 (no pagination)	SR and MA Sept 17 RCT with stroke outcomes	Closure v medical	'Primary end point' . Rate ratios	ate ratio [RR] of 0.60 (95% CI: 0.44-0.83, P < 0.0001; I2: 15. Also a HR of 0.61 Secondary looked at stroke: RR of 0.50 that was statistically significant (95% CI: 0.35-0.73, P < 0.0001; I2: 32% Increase in AF, RR: 1.90 Mostly transient or paroxysmal. Serious or permanent RR: 2.19, not SS	**+** Different end points together
657	Y. Ma et al. 2018. Patent foramen ovale closure or medical therapy for secondary prevention of cryptogenic stroke: An update meta-analysis of randomized controlled trials Medicine 97: e11965	Cryptogenic stroke patients with PFO 6 trials 3630 participants Study level meta-analysis Only ITT analysis	PFOC vs Medical therapy	Procedure related endpoints	Procedure success rate was 97% (95% CI 95.3–99.2%) whole follow-up period, procedure-related or device-related complication rate was 3.7% (95% CI 2.3–5.1%). Compared with medical therapy, closure reduced risk of recurrent stroke by 48% (RR 0.52, 95% CI 0.29–0.93) no difference in TIA between closure and medical therapy groups closure significantly increased risk of atrial fibrillation (RR 4.25, 95% CI 2.10– 8.60)	**+/-** Adequate study quality
657	Y. Ma et al. 2018.	Meta-analysis RCTs, May 2017	Clore or medical therapy (AP or OAC)	RR of recurrent stroke	Reduced stroke 48% (RR 0.52, 95% CI 0.29–0.93)	**+** Overall good.

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
	Patent foramen ovale closure or medical therapy for secondary prevention of cryptogenic stroke: An update meta-analysis of randomized controlled trials Medicine 97: e11965				More AF RR 4.25N diff bleeding, serious AEs, mortality	Pooled the heterogeneous medical arms. Said May 17, but DEFENCE PFO not published then (perhaps it was online)
658	H. Mir et al. 2018. Patent foramen ovale closure, antiplatelet therapy or anticoagulation in patients with patent foramen ovale and cryptogenic stroke: a systematic review and network meta-analysis incorporating complementary external evidence BMJ Open 8: e023761	Network meta analysis and meta regression Applied Grade approach to assess degree of certainty Study y level meta analysis 10 trials – three did not specify AP vs OAC 3 PFO +AP versus vs AP 1 PFO + AP vs OAC	PFOC Plus AP therapy AP therapy alone Anticoagulant therapy alone	Stroke Major bleeding Atrial fibrillation (Persistent) Device related adverse events	FO closure versus antiplatelet therapy probably results in substantial reduction in ischaemic stroke recurrence (risk difference per 1000 patients over 5 years (RD): −87, 95% credible interval (CrI) −100 to −33; moderate certainty). Compared with anticoagulation, PFO closure may confer little or no difference in ischaemic stroke recurrence (low certainty) but probably has a lower risk of major bleeding (RD −20, 95% CrI −27 to −2, moderate certainty). Relative to either medical therapy, PFO closure probably increases the risk of persistent atrial fibrillation (RD 18, 95% CI +5 to +56, moderate certainty) and device-related adverse events (RD +36, 95% CI +23 to +50, high certainty). Anticoagulation, compared	++ High quality

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
					with antiplatelet therapy, may reduce the risk of ischaemic stroke recurrence (RD −71, 95% CrI −100 to +17, low certainty), but probably increases the risk of major bleeding (RD +12, 95% CrI −5 to +65, moderate certainty).	
658	H. Mir et al. 2018. Patent foramen ovale closure, antiplatelet therapy or anticoagulation in patients with patent foramen ovale and cryptogenic stroke: a systematic review and network meta-analysis incorporating complementary external evidence BMJ Open 8: e023761	This systematic review is part of the BMJ Rapid Recommendations project, a collaborative effort from the MAGIC research and innovation programme (www. magicproject. org) and the BMJ. CS with PFO Extensive analysis including Network MA,	Closure v AP v OAC, and OAC v AP	Stroke	Closure v AP: NMA OR 0.12, 95% CrI 0.04 to 0.27; risk difference per 1000 patient-years followed for 5 years (RD): −87, 95% CrI −100 to −33; moderate certainty. The reduction in stroke with PFO closure decreased as the proportion of patients receiving anticoagulation in the medical therapy arm increased (p=0.036). More AF but serious Bias No significant benefit of closure v OAC, smaller numnbbers/imprecision . Additional indirect evidence added, no benefit (low certainty). Increase in transient and permanent AF (mod certainty). Increased device AEs OAC v AP: possible benefit NMA OR 0.27, 95% CrI 0.03 to	**++** Appears very high, NMA and methods I am not familiar with Most detailed analysis

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
					1.21. Complementary analysis OR 0.17, 95% CrI 0.08 to 0.36; RD −81, 95% CrI −91 to −62; low certainty. More bleeding mod certainty. Uncertainty re large shunt (more AP in studies large shunts)	
659	G. Ntaios et al. 2018. Closure of Patent Foramen Ovale Versus Medical Therapy in Patients With Cryptogenic Stroke or Transient Ischemic Attack: Updated Systematic Review and Meta-Analysis. Stroke 49: 412-418	Cryptogenic stroke or TIA Study level metanalysis 5 trials 3627 patients Rando effects model	PFOC Medical therapy	Primary outcome of this meta-analysis was recurrence of ischemic stroke Secondary end points were all-cause mortality, transient ischemic attack, new-onset atrial fibrillation, and myocardial infarction	3.7-year mean follow-up, there was significant difference in ischemic stroke recurrence (0.53 versus 1.1 per 100 patient-years, respectively; odds ratio [OR], 0.43; 95% confidence intervals (CI), 0.21–0.90; relative risk reduction, 50.5%; absolute risk reduction, 2.11%; and number needed to treat to prevent 1 event, 46.5 for 3.7 years). New-onset atrial fibrillation occurred more frequently in the PFO closure arm (1.3 versus 0.25 per 100 patient-years, respectively; OR, 5.15; 95% CI, 2.18–12.15) and resolved in 72% of cases within 45 days	**+/-** Adequate study
659	G. Ntaios et al. 2018. Closure of Patent Foramen Ovale Versus Medical Therapy in Patients With	MA Sept 17 (extension of previous 2013 search) 5 trials	Closure v MT in CS with PFO	Primary; stroke Secondary|; Mortality, AF, AF, MI, TIA	Primary: reduction; 0.53 versus 1.1 per 100 patient-years, respectively; OR, 0.43; 95% CI, 0.21–0.90; RRR, 51.5%; ARR, 2.1%; NNT, 46.5 for 3.7 years	**++** Analysis of combined high risk is unusual but explained.

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
	Cryptogenic Stroke or Transient Ischemic Attack: Updated Systematic Review and Meta-Analysis. Stroke 49: 412-418				No diff mortality, TIA, AE, MI Increase AF: 1.3 versus 0.25 per 100 patient-years, respectively; OR, 5.15; 95% CI, 2.18–12.15; relative risk increase, 403.1%; absolute risk increase, 3.8%; NNT, 26.2 for 3.7 years In the PFO occlusion arms, 56.6% of the events of atrial fibrillation were transient and 72% resolved within 30 to 45 days. Sub analysis of device, only STARRflex different High risk: different in trial, and pooled eg ASA or large shunt: No benefit low risk, benefit high risk OR, 0.39; 95% CI, 0.16–0.96; RRR, 61.0%; ARR, 3.3%; NNT, 30 for 3.7 years . I2 58%	
660	L. Palaiodimos et al. 2018. Percutaneous closure of patent foramen ovale vs. medical treatment for patients with history of cryptogenic stroke: A systematic review and meta-analysis of randomized controlled trials. Cardiovascular Revascularization Medicine 19: 852-858	Study level metanalysis 5 trials 3440 patients Radom effect model sensitivity analysis was performed for Amplatzer device	PFOC Medical therapy	New ischemic stroke	Closure devices were superior to medical therapy for prevention of recurrent ischemic strokes (HR = 0.29; CI: 0.02–0.56), but were associated with increased risk of new onset of atrial fibrillation (AF) and atrial flutter (RR=4.67; CI: 2.22–9.81).	- Low quality

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
660	L. Palaiodimos et al. 2018. Percutaneous closure of patent foramen ovale vs. medical treatment for patients with history of cryptogenic stroke: A systematic review and meta-analysis of randomized controlled trials. Cardiovascular Revascularization Medicine 19: 852-858	MA or RCTs Nov 17 Yielded 5 RCTs	Closure in cryptogenic with PFO	Efficacy ischaemic stroke. Safety AF. Secondary: TIA, mortality, bleeding, new onset of DVT or PE Or serious AE Subgroups predefined.	*Patients treated with a closure device* HR: 0.29; 95% CI: 0.02–0.56; I2 = 67.1%	**+** Unclear if intention to treat, does not specify and uses terminology in results Different shunt definitions pooled as in others.
661	R. Piccolo et al. 2018. Patent foramen ovale closure vs. medical therapy for recurrent stroke prevention: Evolution of treatment effect during follow-up. International Journal of Cardiology 255	Embolic stroke of unknown origin Random effects metanalysis 2531 patients 4 randomized trials	PFO closure vs. medical therapy among patients with embolic stroke	PFO closure was associated with a significant reduction in the risk of stroke at longest available follow-up (HR 0.18, 95%CI 0.06 to 0.59, P = 0.005) treatment effect remaining consistent (P-for-interaction =0.356) between 1- and 5-year	Insufficient information Poor quality therefore	PFO closure reduces the risk of stroke compared with medical therapy, with a significant reduction in recurrences starting already within 1-year after percutaneous PFO closure
661	R. Piccolo et al. 2018. Patent foramen ovale closure vs. medical therapy for recurrent stroke prevention: Evolution of treatment effect during follow-up.	Meta-analytic approach. RCTS With Kaplan Meier curves for primary outcome (digitised and time to event reconstructed) 4 RCTs	Closure	Stroke	Reduced stroke by PFO closure: HR 0.18, 95%CI 0.06 to 0.59, P = 0.005 Similar effect year <1, 1-5 and after 5 (smaller no, not sig >5y)	**+** Short communication paper, aspects of PRISM checklist not described. The method used of digitisation of KM is not familiar to me.

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
	International Journal of Cardiology 255					
662	B. Qiu et al. 2018. Closure versus Medical Therapy for Patent Foramen Ovale in Patients with Cryptogenic Stroke: An Updated Meta-Analysis of Randomized Controlled Trials. Journal of Stroke & Cerebrovascular Diseases 27: 3463-3472	Cryptogenic stroke Study level meta-analysis 6 trials 3560 patients	PFOC Medical therapy	Recurrent stroke Newly detected AF	The Pooled Incidence Recurrent Strokes Is 1.96% in the PFO closure group and 4.60% in the medical therapy group (Relative risk[RR].39, 95% confidence interval[CI].18-.82, P = .01). fibrillation occurredin77of1844(4.18%) patients in the PFO closure group and in 12 of 1667 (.72%) patients in the medical therapy group (RR4.56,95%CI2.21-9.41, P <.0001).	**+/-** Adequate quality
662	B. Qiu et al. 2018. Closure versus Medical Therapy for Patent Foramen Ovale in Patients with Cryptogenic Stroke: An Updated Meta-Analysis of Randomized Controlled Trials. Journal of Stroke & Cerebrovascular Diseases 27: 3463-3472	Meta analysis UP TO march 18 (includes DEFENCE) >18 years, TIA or Stroke	Closure	Primary Stroke (Risk Ration and CIs) Adverse: AF, Bleeding and Death Subgroup: Age, AF, Death	Primary: 37of1889(1.96%) v 77of1671 (4.60%) RR.39,95% CI.18-.82,P=.01) With significant heterogeneity (I2=56% No difference AEs More AF (RR 4.56), low heterogeneity Now difference death, bleeding (moderate heterogeneity) RR for large shunts lower)	**++**
663	M. Sa et al. 2018.	cryptogenic stroke Study level metanalysis Five studies	PFOC Medical therapy	stroke death major bleeding	The risk ratio (RR) for stroke in the “device closure”	**+/-** Adequate quality

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
	Closure of Patent Foramen Ovale versus Medical Therapy after Cryptogenic Stroke: Meta-Analysis of Five Randomized Controlled Trials with 3440 Patients. Brazilian Journal of Cardiovascular Surgery 33: 89-98	3440 patients Meta-regression analyses were performed to determine whether the effects of the PFO closure were modulated by prespecified factors.		atrial fibrillation	group compared with the "medical therapy" showed a statistically significant difference between the groups, favouring the "device closure" group (RR 0.400; 95% CI 0.183-0.873, P=0.021). atrial fibrillation in the "device closure group (RR 4.000; 95% CI 2.262-7.092, P<0.001). Sensitivity analysis: REDUCE trial[8] was left out of this last analysis because the presence of an atrial septal aneurysm was determined at the time of the PFO closure procedure and, therefore, it was not recorded before trial entry or among the patients in the antiplatelet-only group.	
663	M. Sa et al. 2018. Closure of Patent Foramen Ovale versus Medical Therapy after Cryptogenic Stroke: Meta-Analysis of Five Randomized Controlled Trials with 3440 Patients. Brazilian Journal of Cardiovascular Surgery 33: 89-98	RCTs , stroke or TIA with PFO. Sept 17 5 RCTs	Closure v MT	Stroke	Reduced stroke RR 0.400. mod heterogeneity. More AF RR 4.0. No significant difference mortality, bleeding. No impact ASA.	**+/++** Well conducted, recorded RCT. Combined heterogeneous MT Analysed ASA, no discussion on shunt size.
664	H. Saber et al. 2018.	Cryptogenic stroke Network metanalysis 6 trials	PFOC Antiplatelet agents	Recurrent stroke Atrial fibrillation Bleeding complications	Lower rates of recurrent stroke (odds ratio [OR] 0.30, 95% credibility	**+/-** Adequate quality

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
	Network meta-analysis of patent foramen ovale management strategies in cryptogenic stroke. Neurology 91(1)	3497 patients Direct and indirect evidence	Oral anticoagulation therapy		interval [CrI] 0.17–0.49 and OR 0.42, 95% CrI 0.22–0.78, respectively) PFO closure had the highest top rank probability of atrial fibrillation and OAT had the highest risk of bleeding complications.	
664	H. Saber et al. 2018. Network meta-analysis of patent foramen ovale management strategies in cryptogenic stroke. Neurology 91(1)	Network Meta-analysis Oct 2017 CS and PFO Includes PICSS	Closure	Primary: recurrent stroke Secondary: AF and Bleeding	with APA therapy as the reference, PFO closure and OAT (OR 0.13, 95%CrI 0.04–0.32 and OR 0.28, 95%CrI 0.09–0.81, respectively) were associated with lower rates of recurrent stroke There was no statistically significant difference in the efficacy of PFO closure and OAT (OR 0.70, 95% CrI 0.37–1.49) in ranking best outcome probability for stroke prevention, PFO closure was ranked the highest (88%) followed by OAT (61%) and APA therapy (0.001%) use of APA or OAT was associated with a significantly lower rate of incident atrial fibrillation when compared to	++

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
					PFO closure (OR 0.04, CrI 0.00–0.21 and 0.01, CrI 0.00–0.28, respectively)	
665	V. Schulze et al. 2018. Patent foramen ovale closure or medical therapy for cryptogenic ischemic stroke: an updated meta-analysis of randomized controlled trials. Clinical Research in Cardiology 107: 745-755	Cryptogenic stroke Study level meta-analysis 5 trials 3440 patients		Clinical efficacy outcomes were recurrent stroke, recurrent TIA, and their combination; safety outcomes were mortality, major bleeding, venous thromboembolism (VTE), and new-onset atrial fibrillation/flutter (NOAF).	PFO-C significantly reduced recurrent stroke [odds ratio (OR) 0.41, 95% confidence interval (CI) 0.19–0.90; p = 0.03] and the combination of recurrent stroke + TIA (OR 0.53, CI 0.36–0.80; p = 0.002) compared to MT; recurrent TIA alone showed no differences (OR 0.77; CI 0.51–1.14; p = 0.19). NOAF was significantly more frequent after PFO-C (OR 5.75, CI 3.09–10.70; p < 0.00001). Mortality (OR 0.80, CI 0.39–1.67), major bleeding (OR 0.96, CI 0.48–1.92), and VTE (OR 2.45, CI 0.75–7.99) remained neutral	
665	V. Schulze et al. 2018. Patent foramen ovale closure or medical therapy for cryptogenic ischemic stroke: an updated meta-analysis of randomized controlled trials. Clinical Research in Cardiology 107: 745-755	Metanalysis of RCTs (5 studies) Oct 17 Secondary prevention of stroke inpatients with PFO All studies were 18-60 Nearly all stroke, some TIA (PC Trial only)	Closure	Clinical: Stroke, TIA, both Safety: Mortality, bleeding, VTE, cardiac thrombi, AF Odds Ratios with CIs	Stroke: 2% in PFO-C vs. 4.5% in MT; weighted mean follow-up of 4 years; (OR) 0.41, 0.19–0.90, , I2 = 59%; No S.S. reduction TIA, reduction in combined No diff mortality, bleeding,. Non-sig trend for more VTE with closure. 7 of 8 cardiac thrombi in closure group (small nos)	++

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
					More AF, OR 5.75 with CI 3.09–10.70 not heterogeneous. Subgroup: reduced in patients ≤ 45 (OR 0.42 , I2 = 0%; p = 0.04), more heterogeneity and no significant advantage in older patients (OR 0.45 with CI 0.16–1.26	
666	A. Smer et al. 2018. Meta-analysis of Randomized Controlled Trials on Patent Foramen Ovale Closure Versus Medical Therapy for Secondary Prevention of Cryptogenic Stroke. American Journal of Cardiology 121: 1393-1399	Cryptogenic stroke Study level metanalysis 5 trials 3440 patients	PFOC Medical therapy (OAC and AP)	Recurrent stroke Atrial fibrillation Subgroup AP and OAC Shunt size	PFO closure significantly reduced the risk of stroke compared with the medical therapy (2.8% vs 5.8%; relative risk [RR] 0.48, confidence interval [CI] 0.27 to 0.87, p = 0.01, I2 = 56%). The number needed to treat for stroke prevention was 10.5. PFO closure was associated with an increased risk of atrial fibrillation compared with medical therapy (4.2% vs 0.7%; RR 4.55, CI 2.16 to 9.6, p = 0.0001, I2 = 25%). There was no significant difference in all-cause mortality (RR 1.33, CI 0.56 to 3.16, p = 0.52, I2 = 0%), as well as no difference in bleeding risk between the 2 groups (RR 0.94, CI 0.49 to 1.83, p = 0.86, I2 = 29%).	**+/-** Adequate study
666	A. Smer et al. 2018. Meta-analysis of Randomized	MA of RCTs Sept 17	Closure v MT	Stroke or TIA	Primary: 2.8% vs 5.8%; RR 0.48, CI 0.27 to 0.87, p = 0.01, I2 = 56% . NNT 10.5 More AF RR 4.55	**+** Included TIA in primary, and I think mislabeled in Forest Plot

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
	Controlled Trials on Patent Foramen Ovale Closure Versus Medical Therapy for Secondary Prevention of Cryptogenic Stroke. American Journal of Cardiology 121: 1393-1399				No difference bleeding, mortality Benefit v AP arm, uncertain v Anticoagulation arm No difference ASA. Red mod/large shunt, not small.	
667	S. Vidale et al. 2019. Patent Foramen Ovale Closure Versus Medical Therapy in Cryptogenic Strokes and Transient Ischemic Attacks: A Meta-Analysis of Randomized Trials. Angiology 70: 325-331	Cryptogenic strokes Study level metanalysis fixed- and random-effects metaanalyses. 6 trials 3560 patietns	PFOC and Medical therapies	stroke or TIA recurrence stroke recurrences. New onset AF	PFO closure was superior to medical treatment for both primary (RR: 0.39; 95% CI: 0.18-0.82; P < .02) and secondary end points (RR: 0.58; 95% CI: 0.44-0.76; P < .001). Transcatheter closure significantly increased the risk of new-onset atrial fibrillation (AF; RR: 5.74; P < .001).	**+/-** Adequate study
667	S. Vidale et al. 2019. Patent Foramen Ovale Closure Versus Medical Therapy in Cryptogenic Strokes and Transient Ischemic Attacks: A Meta-Analysis of Randomized Trials. Angiology 70: 325-331	MA of RCTs April 18 (6 studies)	Closure v MT in cryptogenic stroke	Stroke Secondary Stroke/TIA By Gender, age, shunt, qual event, ASA	Primary: RR 0.39 (95% CI: 0.18-0.82; P 1⁄4 .01 Lower RR <45 (not SS >45). Males more (sump data). Larger shunt magnitude (not clear) sig, not for 'mild-mod' (don't know how they categorised) Entry event:" sig for stroke not TIA (wide CI) More AF	**+** Generally good, variable used Stroke and TIA Unclear about pooling of shunt Most data in supp
668	D. Vukadinovic et al. 2019. Interventional closure vs. medical therapy of patent foramen ovale	Cryptoge ic stroke Study level metanalysis 6 trials 3560 patients	PFOC Medical treatment	Composite outcome [stroke/transitory ischemic attack (TIA), death, and thrombolysis in myocardial infarction—	PFO closure reduced composite outcome (RR of 0.47, 0.26–0.85, p = 0.01), stroke (RR of 0.38, 0.18–0.82,	**+/-** Adequate study

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
	for secondary prevention of stroke: updated meta-analysis. Clinical Research in Cardiology 108(2): 157-166	Included only latest follow-up of RESPECT		TIMI bleeding], stroke and stroke/TIA Shunt size Bleeding New onset AF	p = 0.01) and stroke/TIA (RR of 0.56, 0.43–0.74, p < 0.0001). Analysis had 70.5% power to detect observed reduction of RR for the primary outcome, 70.6% for stroke and 98.7% for stroke/TIA. Bleeding rates were comparable (RR of 0.91, 0.60–1.38, p = 0.66), while there was higher burden of new AF (RR of 5.54, 3–10.2, p < 0.0001) after interventional closure. Subgroup analysis revealed that patients with large shunts had substantial less recurrent strokes over patients with small shunts (p for interaction = 0.02).	
668	D. Vukadinovic et al. 2019. Interventional closure vs. medical therapy of patent foramen ovale for secondary prevention of stroke: updated meta-analysis. Clinical Research in Cardiology 108(2): 157-166	RCTs, min 100 participants and 1 year Adults, closure v medical March 18 (6 trials)	Closure v medical	Primary trial outcome, also IS and TIA Subgroup anatomy and age, and device	The RR for ischemic stroke in interventional group was 0.38 0.18–0.82, p = 0.01 Many results of combined endpoint More AF 4.2 v 0.7% No sig difference bleeding Less AF with amplatzer occluder (data in Supp). No interaction Amlplazer and primary outcome. The NNT to prevent one stroke and stroke/TIA was 37 and 27 over 3.8 years, respectively In patients with moderate/large shunts, the	**+** Using different endpoints problematic

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
					NNT for stroke was 24 compared to 221 in patients without moderate/large shunts over a 4.1 years. In patients < 45 years of age, the NNT for stroke was 29, while in those > 45 years was 31, over 4.6 years The number needed to harm (NNH) for AF was 29 over 3.8 years	
669	T. K. M. Wang et al. 2019. Patent Foramen Ovale Closure Versus Medical Therapy for Cryptogenic Stroke: Meta-Analysis of Randomised Trials. Heart Lung and Circulation 28(4): 623-631	Cryptogenic stroke Metanalysis 6 studies of 5 RCTS	PFO closure vs medical therapy for secondary stroke prevention	Composite of ischaemic stroke, transient ischaemic attack (TIA) and composite neurovascular or mortality events	Significant reduction for Stroke, but not TIA. Reduction of Composite of neurovascular events and mortality HR 0.71 (0.48-0.85 AF 4.6 times moremore	**+/-** Adequate quality
669	T. K. M. Wang et al. 2019. Patent Foramen Ovale Closure Versus Medical Therapy for Cryptogenic Stroke: Meta-Analysis of Randomised Trials. Heart Lung and Circulation 28(4): 623-631	MA of RCTs Sept 17	Stroke v MT	Stroke/TIA	Stroke outcome: lower occurrence of both stroke (2.0% versus 4.5%, OR 0.41, 95% CI: 0.19–0.90, p = 0.03, I2 = 59% No diff bleeding, mortality, AEs More AF 4.1% versus 0.7%, OR 4.62, 95% CI: 2.03–10.49, p = 0.0003, I2 = 35% Subgroup: male, <45	**+** Short Limited exploration of subgroup

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
670	H. B. Xu et al. 2018. Patent foramen ovale closure versus medical therapy for cryptogenic stroke: An updated meta-analysis. Journal of the Neurological Sciences 390: 139-149	Cryptogenic stroke with PFO Metanalysis 3440 patients 5 studies	PFOC vs MT	The two primary endpoints were stroke and transient ischemic attack (TIA). Secondary outcomes included all-cause mortality, new-onset atrial fibrillation or flutter, major bleeding and any adverse event.	PFO closure reduced the incidence of recurrent stroke in CS patients with PFO compared to medical therapy (Risk ratio (RR) 0.42, 95% confidence intervals (CI) 0.20–0.91, P=0.03; hazard ratio (HR) 0.34, 95% CI 0.15–0.78, p=0.01) No significant differences for TIA, ACM, major bleeding, adverse events. Higher risk of new-onset atrial fibrillation or flutter was found in closure group (RR 4.69, 95% CI 2.17–10.12, P < 0.0001)	**+/-** Adequate quality
670	H. B. Xu et al. 2018. Patent foramen ovale closure versus medical therapy for cryptogenic stroke: An updated meta-analysis. Journal of the Neurological Sciences 390: 139-149	Metaanalysis Sept 17 5 RCTs 2012-17	Closure v MT in CS	two primary outcomes were the incidence of recurrent stroke and TIA, separately. Risk ratio	Stroke 2% v 4% RR 0.42, 95% CI 0.20–0.9 Time to event: HR 0.34, 95% CI 0.15–0.78 Mod hetro both No diff TIA More AF 4.3 v 7% RR 4.69 No diff mortality, bleeding, AEs ignificant interaction effect of presence or absence of ASA on the preventive effect of PFO closure	**+** Nothing in paper on quality of studies (in Supp) No comment of shunt size in result, mentioned in methods. Unusual
671	X. L. Zhang et al. 2018. Percutaneous closure versus medical therapy for stroke with patent foramen Ovale: a systematic review and meta-analysis.	Cryptogenic stroke Metanalysis 2 RCTS and 15 observational studies 6961 pts	PFOC vs MT	Primary outcome: composite outcome of ischemic stroke, transient ischemic attack (TIA), or all-cause death AF	Primary outcome: lower incidence with PFOC odds ratio [OR]: 0.57; 95% confidence interval [CI]: 0.38 to 0.85; P = 0.006), mainly driven by lower incidence of stroke (OR: 0.39;	**+/-** Adequate study

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
	BMC Cardiovascular Disorders 18: 45				95% CI: 0.24 to 0.63; P < 0.001) AF increased: odds ratio [OR]: 0.57; 95% confidence interval [CI]: 0.38 to 0.85; P = 0.006), mainly driven by lower incidence of stroke (OR: 0.39; 95% CI: 0.24 to 0.63; P < 0.001)	
671	X. L. Zhang et al. 2018. Percutaneous closure versus medical therapy for stroke with patent foramen Ovale: a systematic review and meta-analysis. BMC Cardiovascular Disorders 18: 45	MA of RCT or other comparative analyses Sept 17 5 RCT and 15 observational	Closure v MT	primary outcome was the composite outcome of ischemic stroke, transient ischemic attack (TIA), or all- cause death; some studies also included peripheral embolism in this composite outcome. Secondary endpoints included recurrent ischemic stroke, TIA, all-cause death, atrial fibrillation (AF) or atrial flutter, pulmonary embolism, major bleeding and any serious adverse events	Compositive outcome: OR: 0.57; 95% CI: 0.38 to 0.85; P = 0.006. Similar if RCT only OR: 0.62 NNT 43 (?time) Stroke only: OR: 0.39 (Similar RCT and observational) No diff TIA No diff mortality In RCTs more AF OR 5.74 and PE OR 3.03 The number needed to harm was 30 and 143 respectively No diff AE, bleeding significantly lower incidence of the composite out- come only in patients with large shunt size, and lower incidence of recurrent stroke in patients with large shunt size and those present with atrial septal aneurysm, but no significant interaction was detected Significant limitation in consistence	++

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
672	P.H. Lee et al (2018). Cryptogenic Stroke and High-Risk Patent Foramen Ovale: The DEFENSE-PFO Trial. J Am Coll Cardiol. 71: 20. 2335–2342.	cryptogenic stroke and high-risk PFO (ischemic stroke within the previous 6 months with no identifiable cause other than a high risk PFO with right-to-left shunting) Randomised trial Open label morphologic characteristics of the PFO, as evaluated by transesophageal echocardiography phasic septal excursion into either atrium $10 mm), or PFO size (maximum separation of the septum primum from the secundum) $2 mm 120 patients 2.8 yearw follow-up	transcatheter PFO closure and a medication-only group. Medication either aspirin, aspiring + clopidogrel or OAC chosen by the investigator	primary endpoint was a composite of stroke, vascular death, or Thrombolysis In Myocardial Infarction–defined major bleeding during 2 years of follow-up	primary endpoint occurred exclusively in the medication-only group (6 of 60 patients; 2-year event rate: 12.9% [log-rank p ¼ 0.013]; 2-year rate of ischemic stroke: 10.5% [p ¼ 0.023]). The events in the medication-only group included ischemic stroke (n ¼ 5), cerebral hemorrhage (n ¼ 1), Thrombolysis In Myocardial Infarction–defined major bleeding (n ¼ 2), and transient ischemic attack (n ¼ 1). procedural complications included development of atrial fibrillation (n ¼ 2), pericardial effusion (n ¼ 1), and pseudoaneurysm (n ¼ 1). Kaplan-Meier 2-year cumulative estimate of the probability of stroke was 10.5% in the medication-only group (95% confidence interval: 1.68 to 19.32; standard error 4.5; p ¼ 0.023 when compared with the PFO closure group), a finding suggesting that the number of patients needed to treat to avoid 1 stroke at 2 years would be 10.	Bias – open label No blinded events adjudication Well balanced risk characteristics despite no stratification Medication especially warfarin was unbalanced between groups

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672	P.H. Lee et al (2018). Cryptogenic Stroke and High-Risk Patent Foramen Ovale: The DEFENSE-PFO Trial. J Am Coll Cardiol. 71: 20. 2335–2342.	RCT, multicentre (2 S Korean sites) OPen label, superiority trial. in patients with cryptogenic stroke and high-risk PFO Ischaemic stroke, <6 months, no other cause: work up defined in methods, standardised. Didn't use criteria, but looks complete. (>50% stenosis for large artery)	combined transcatheter PFO closure (Amplatzer) and medical therapy alone. TEE to assess PFO and shunting. High risk = ASA (15mm), hyopermobility (10mm), large (>2mm separation). Medical therapy at investigator discretion	The primary endpoint was a composite of stroke, vascular death, or Thrombolysis In Myocardial Infarction (TIMI)–defined major bleeding during 2 years of follow-up	Early termination due to CLOSE results. Would have been under-powered event rate. Differences in medical therapy between groups (warfarin in 20% medical, DAPT in). No primary endpoint in Closure v 6/60 in medical.; 2 year event rate 12.9%. 5/6 IS, 1/6 haemorrhage, bleeding 2, TIA 1. Silent infarcts on MRI 8.8% v 18.4% (not sig, but presume not powered).	**+** ?low quality, risk of bias. No blinded outcome analysis described. Difference in medical therapy between arms. Randomised, intention to treat