

Patent foramen ovale closure, antiplatelet therapy or anticoagulation therapy alone for management of cryptogenic stroke? A clinical practice guideline

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Options for the secondary prevention of stroke in patients younger than 60 years who have had a cryptogenic ischaemic stroke thought to be secondary to patent foramen ovale (PFO) include PFO closure (with antiplatelet therapy), antiplatelet therapy alone, or anticoagulants. International guidance and practice differ on which option is preferable.

The *BMJ* Rapid Recommendations panel used a linked systematic review¹ triggered by three large randomised trials published in September 2017 that suggested PFO closure might reduce the risk of ischaemic stroke more than alternatives.²⁻⁴ The panel felt that the studies, when considered in the context of the full body of evidence, might change current clinical practice.⁵ The linked systematic review finds that PFO closure prevents recurrent stroke relative to antiplatelet therapy, but possibly not relative to anticoagulants, and is associated with procedural complications and persistent atrial fibrillation.¹ The review also presents evidence regarding the role of anticoagulants or antiplatelet therapy when PFO closure is not acceptable or is contraindicated.

This expert panel make a

- Strong recommendation in favour of PFO closure plus antiplatelet therapy compared with antiplatelet therapy alone
- Weak recommendation in favour of PFO closure plus antiplatelet therapy compared with anticoagulants
- Weak recommendation in favour of anticoagulants compared with antiplatelet therapy.

The largest challenge in making our recommendation was the low quality evidence for the comparisons that included anticoagulants. We summarised all the highest quality available evidence separately for antiplatelet therapy and anticoagulants because the evidence suggests it is likely their effectiveness and adverse effects differ, and clinicians and patients should be aware of these likely differences. Our panel believes that the mechanism of benefit with PFO closure is prevention of venous clots crossing the PFO. Anticoagulants are likely to be substantially more effective in preventing such clots from initially arising than antiplatelet agents.

WHAT YOU NEED TO KNOW

- The recommendations apply to patients under 60 years old with patent foramen ovale (PFO) who have had a cryptogenic ischaemic stroke, when extensive workup for other aetiologies of stroke is negative
- For patients who are open to all options, we make a weak recommendation for PFO closure plus antiplatelet therapy rather than anticoagulant therapy
- For patients in whom anticoagulation is contraindicated or declined, we make a strong recommendation for PFO closure plus antiplatelet therapy versus antiplatelet therapy alone
- For patients in whom closure is contraindicated or declined, we make a weak recommendation for anticoagulant therapy rather than antiplatelet therapy.
- Further research may alter the recommendations that involve anticoagulant therapy

Box 1 shows the articles and linked evidence in this Rapid Recommendation package. The main infographic presents the recommendations as three paired comparisons, together with an overview of the absolute benefits and harms informing each recommendation, according to the GRADE methodology.

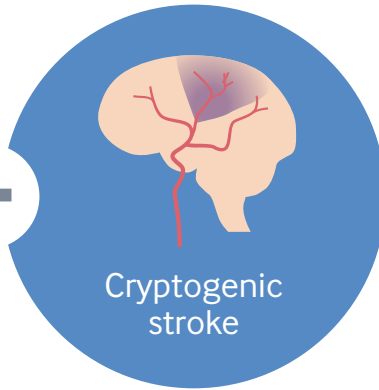
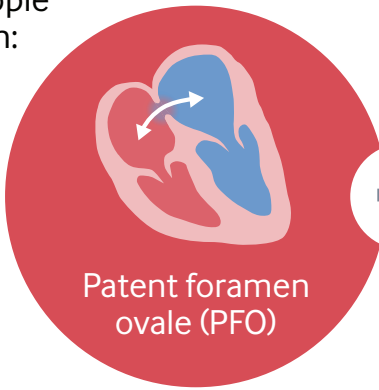
Current practice

Management options for those with patent foramen ovale (PFO) and cryptogenic stroke
Typically, patients with cryptogenic stroke and PFO have three treatment options to reduce the risk of future stroke:

- (a) Closure of the PFO with subsequent antiplatelet therapy that may be continued indefinitely or discontinued some months after PFO closure
- (b) Antiplatelet therapy alone
- (c) Anticoagulant therapy alone.

Population

People with:



- No atrial fibrillation
- No aortic disease
- No left sided heart disease
- No cerebrovascular disease

Treatment options:

PFO closure

Anticoagulants

Antiplatelets

Are all options acceptable?

X Anticoagulants

Anticoagulants contraindicated, unacceptable, or unavailable

✓ Yes

X PFO closure

PFO closure contraindicated, unacceptable, or unavailable

Comparison 1

PFO closure

or

Antiplatelets

Comparison 2

PFO closure

or

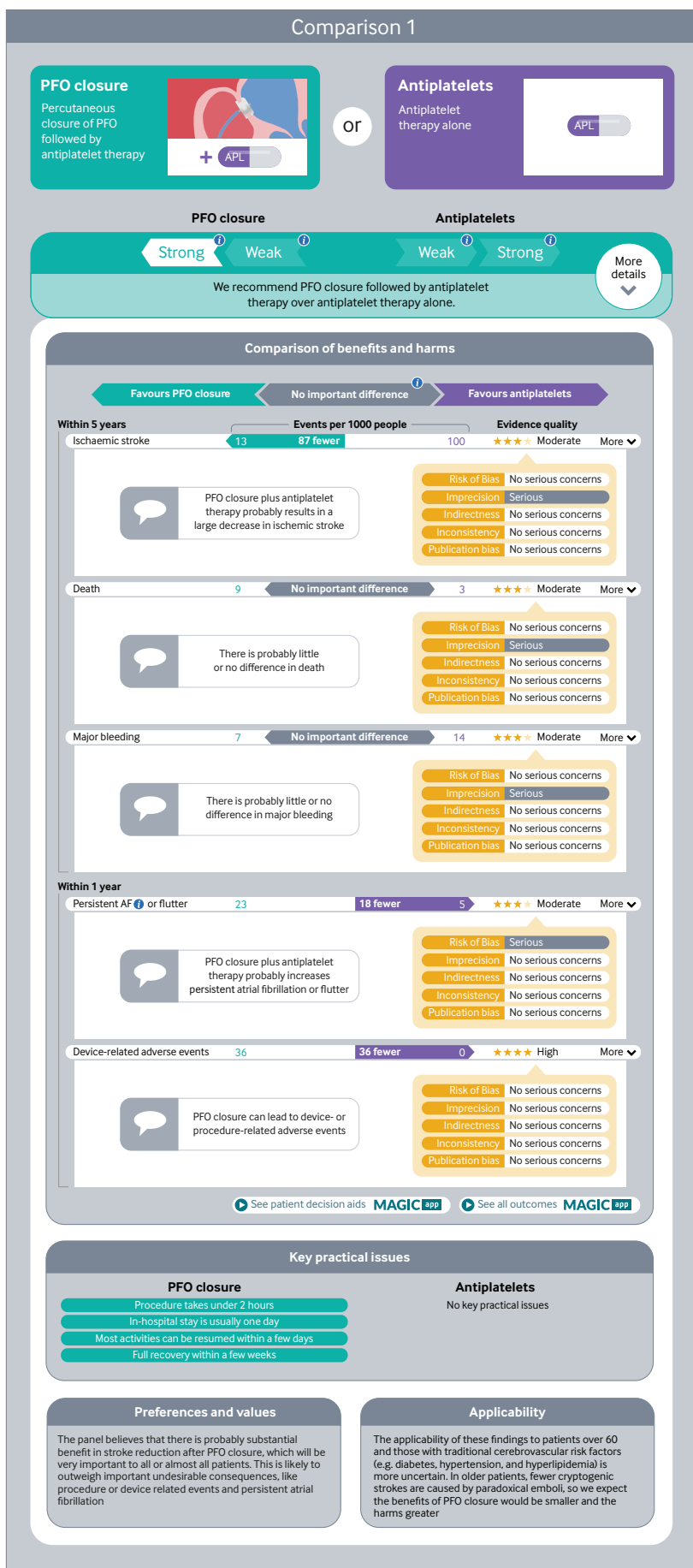
Anticoagulants

Comparison 3

Anticoagulants

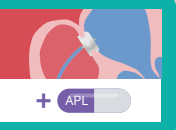
or

Antiplatelets




Comparison 2

PFO closure
Percutaneous closure of PFO followed by antiplatelet therapy



OR

Anticoagulants
Anticoagulation therapy



PFO closure **Anticoagulants**

Strong Weak Weak Strong

We suggest PFO closure followed by antiplatelet therapy over anticoagulation therapy. Discuss both options with each patient.

[More details](#)

Comparison of benefits and harms

Favours PFO closure No important difference Favours anticoagulants

Event	Events per 1000 people	Evidence quality
Within 5 years		
Ischaemic stroke	13 vs 29 (No important difference)	★★★★ Low
<p>There may be little or no difference in ischaemic stroke</p> <ul style="list-style-type: none"> Risk of Bias: No serious concerns Imprecision: Very serious Indirectness: No serious concerns Inconsistency: No serious concerns Publication bias: No serious concerns 		
Death	9 vs 13 (No important difference)	★★★★ Moderate
<p>There is probably little or no difference in death</p> <ul style="list-style-type: none"> Risk of Bias: No serious concerns Imprecision: Serious Indirectness: No serious concerns Inconsistency: No serious concerns Publication bias: No serious concerns 		
Major bleeding	7 vs 27 (20 fewer)	★★★★ Moderate
<p>PFO closure plus antiplatelet therapy probably decreases major bleeding</p> <ul style="list-style-type: none"> Risk of Bias: No serious concerns Imprecision: Serious Indirectness: No serious concerns Inconsistency: No serious concerns Publication bias: No serious concerns 		
Within 1 year		
Persistent AF or flutter	23 vs 5 (18 fewer)	★★★★ Moderate
<p>PFO closure plus antiplatelet therapy probably increases persistent atrial fibrillation</p> <ul style="list-style-type: none"> Risk of Bias: Serious Imprecision: No serious concerns Indirectness: No serious concerns Inconsistency: No serious concerns Publication bias: No serious concerns 		
Device-related adverse events	36 vs 0 (36 fewer)	★★★★ High
<p>PFO closure can lead to device- or procedure-related adverse events</p> <ul style="list-style-type: none"> Risk of Bias: No serious concerns Imprecision: No serious concerns Indirectness: No serious concerns Inconsistency: No serious concerns Publication bias: No serious concerns 		

[See patient decision aids](#) **MAGIC app** [See all outcomes](#) **MAGIC app**

Key practical issues

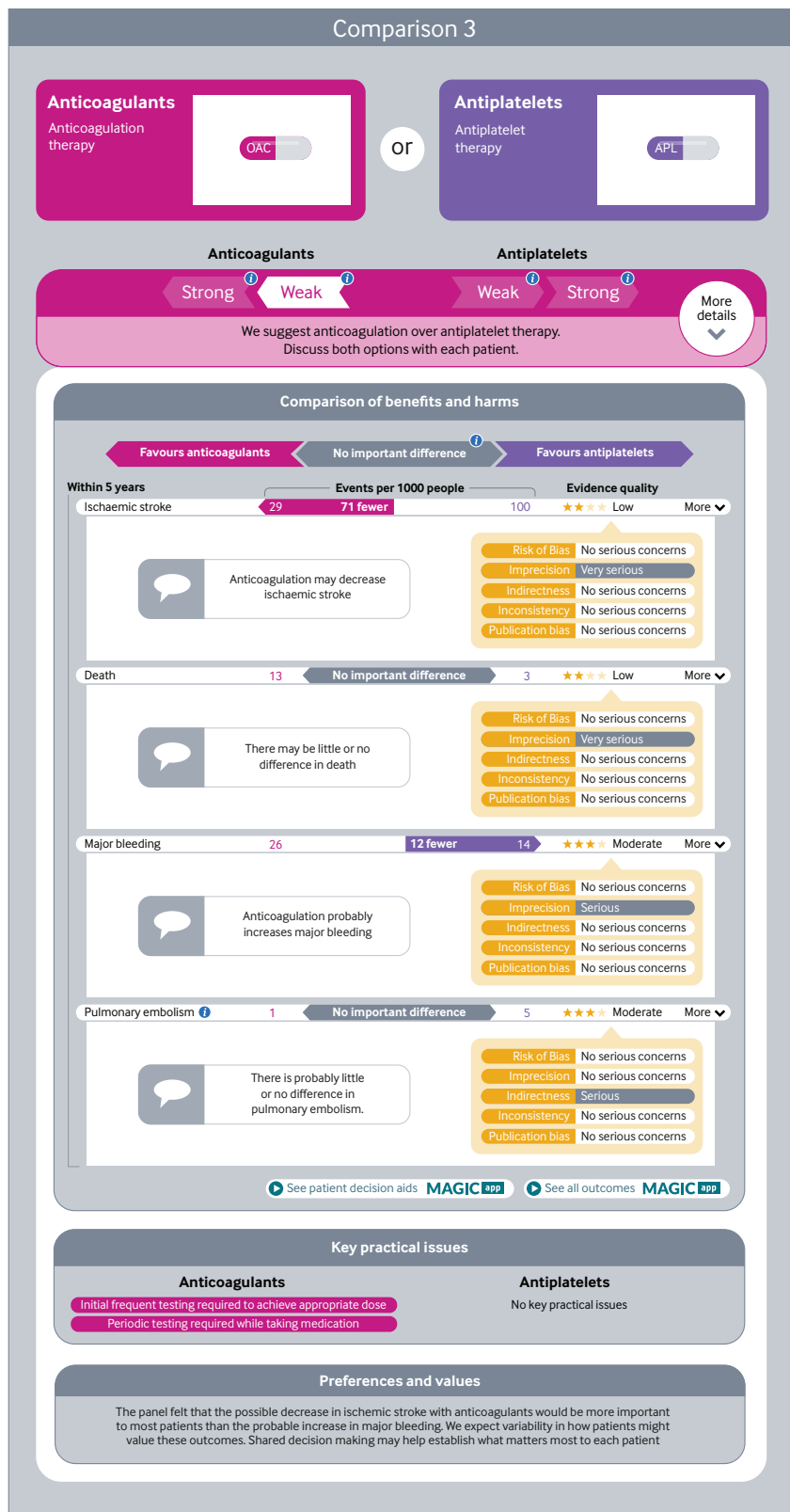
PFO closure	Anticoagulants
Procedure takes under 2 hours	Initial frequent testing required to achieve appropriate dose
In-hospital stay is usually one day	Periodic testing required while taking medication
Most activities can be resumed within a few days	
Full recovery within a few weeks	

Preferences and values

The panel felt that many patients would not want the long-term bleeding risk from anticoagulation therapy, which will usually outweigh the probable risk of procedure or device related events and persistent atrial fibrillation with PFO closure

Applicability

The applicability of these findings to patients over 60 and those with traditional cerebrovascular risk factors (e.g. diabetes, hypertension, and hyperlipidemia) is more uncertain. In older patients, fewer cryptogenic strokes are caused by paradoxical emboli, so we expect the benefits of PFO closure would be smaller and the harms greater



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Box 1 | Linked resources for this *BMJ* Rapid Recommendations cluster

- Kuijpers T, Spencer FA, Siemieniuk RAC, et al. Patent foramen ovale closure, antiplatelet therapy or anticoagulation therapy alone for management of cryptogenic stroke? A clinical practice guideline. *BMJ* 2018;362:k2515
– Summary of the results from the Rapid Recommendation process
- Mir H, Siemieniuk R, Ge L, et al. Percutaneous closure plus antiplatelet therapy versus antiplatelet or anticoagulation therapy alone in patients with patent foramen ovale and cryptogenic stroke: a systematic review and network meta-analysis incorporating complementary external evidence. *BMJ Open* 2018;0:e023761. doi:10.1136/bmjopen-2018-023761
– Review and network meta-analysis of all available randomised trials that assessed PFO closure as adjunct treatment to antiplatelet versus antiplatelet therapy or anticoagulation, and comparing anticoagulants to antiplatelet therapy
- MAGICapp (<https://app.magicapp.org/app#/guideline/2191>)
– Expanded version of the results with multilayered recommendations, evidence summaries, and decision aids for use on all devices

Most current guidelines recommend against routine closure of the PFO in patients with cryptogenic stroke and instead recommend antiplatelets or anticoagulation (the latter if indicated for another reason) (box 2).⁶⁻⁹

Identification of cryptogenic stroke

In about a third of patients in the general population who are diagnosed with an acute ischaemic stroke, investigation finds no clear cause; it is cryptogenic.¹⁰ Clinicians reach the diagnosis by ruling out alternative reasons for stroke through prolonged rhythm monitoring to exclude atrial fibrillation; transoesophageal echocardiography or alternative imaging of the aorta and left atrial appendage to rule out aortic atherothrombosis or left atrial clot; and carotid ultrasonography, computed tomography, or magnetic resonance imaging to rule out cerebrovascular disease.

Patients diagnosed with cryptogenic stroke are less likely to have classic risk factors for atheroembolic stroke such as older age, hypertension, hyperlipidaemia, and diabetes.¹¹ They are more likely to have a PFO than patients in the general population.¹²

Implications of a patent foramen ovale (PFO)

The presence of a PFO does not result in an identifiable increased risk of stroke in the general population.¹³⁻¹⁵ Many meta-analyses have addressed whether closure of a PFO reduces the long term risk of subsequent stroke,^{12 16-18} but most have concluded that there is insufficient evidence.⁶

PFO is a communication between the right and left atrium, typically diagnosed by transthoracic echocardiography with observed flow between the left to right atrium by colour Doppler ultrasonography.¹⁹ If the shunt direction reverses, this communication may allow a venous thrombus or right atrial thrombus to travel

Box 2 | Current guidance for closure of patent foramen ovale (PFO) in patients with PFO and cryptogenic stroke

American Academy of Neurology 2017⁶

- *PFO v medical therapy alone*—Clinicians must counsel patients considering percutaneous PFO closure that having a PFO is common in the general population; it is impossible to determine with certainty whether their PFO caused their stroke or transient ischaemic attack; the effectiveness of the procedure for reducing stroke risk remains uncertain; and the procedure is associated with relatively uncommon, yet potentially serious, complications
- *Anticoagulation v antiplatelet*—In the absence of another indication for anticoagulation, clinicians may routinely offer antiplatelet drugs instead of anticoagulation to patients with cryptogenic stroke and PFO

American Heart Association/American Stroke Association⁷

- For patients with an ischaemic stroke or transient ischaemic attack and a PFO who are not undergoing anticoagulation therapy, antiplatelet therapy is recommended
- For patients with an ischaemic stroke or transient ischaemic attack and both a PFO and a venous source of embolism, anticoagulation is indicated depending on stroke characteristics. When anticoagulation is contraindicated, an inferior vena cava filter is reasonable
- For patients with a cryptogenic ischaemic stroke or transient ischaemic attack and a PFO without evidence for deep vein thrombosis, available data do not support a benefit for PFO closure
- In the setting of PFO and deep vein thrombosis, PFO closure by a transcatheter device might be considered depending on the risk of recurrent deep vein thrombosis

NICE 2013⁸

- Evidence on the safety of percutaneous closure of PFO to prevent recurrent cerebral embolic events shows serious but infrequent complications. Evidence on its efficacy is adequate. Therefore, this procedure may be used with normal arrangements for clinical governance, consent, and audit

Netherlands Society of Cardiology 2016⁹

- Closure of a PFO is not beneficial in unselected patients with transient ischaemic attack or cryptogenic stroke
- Closure of a PFO should be considered in patients with transient ischaemic attack or cryptogenic stroke and a Risk of Paradoxical Embolism (RoPE) score >8 and at least one clinical risk factor

directly into the arterial circulation and cause a stroke—a phenomenon known as a paradoxical embolism.^{20 21} This can be characterised with echocardiography (box 3).

The evidence

The linked systematic review reports the relative and the absolute effects of PFO closure followed by antiplatelet therapy versus antiplatelet therapy alone or versus anticoagulation and the effect of anticoagulation versus antiplatelet therapy in patients with cryptogenic stroke and PFO.¹ Figure 2 provides an overview of the number and types of patients included, the study funding, and patient involvement.

We conducted a network meta-analysis combining direct evidence (from studies of management in people with cryptogenic stroke comparing at least two of the three options) with indirect evidence (inferring benefits

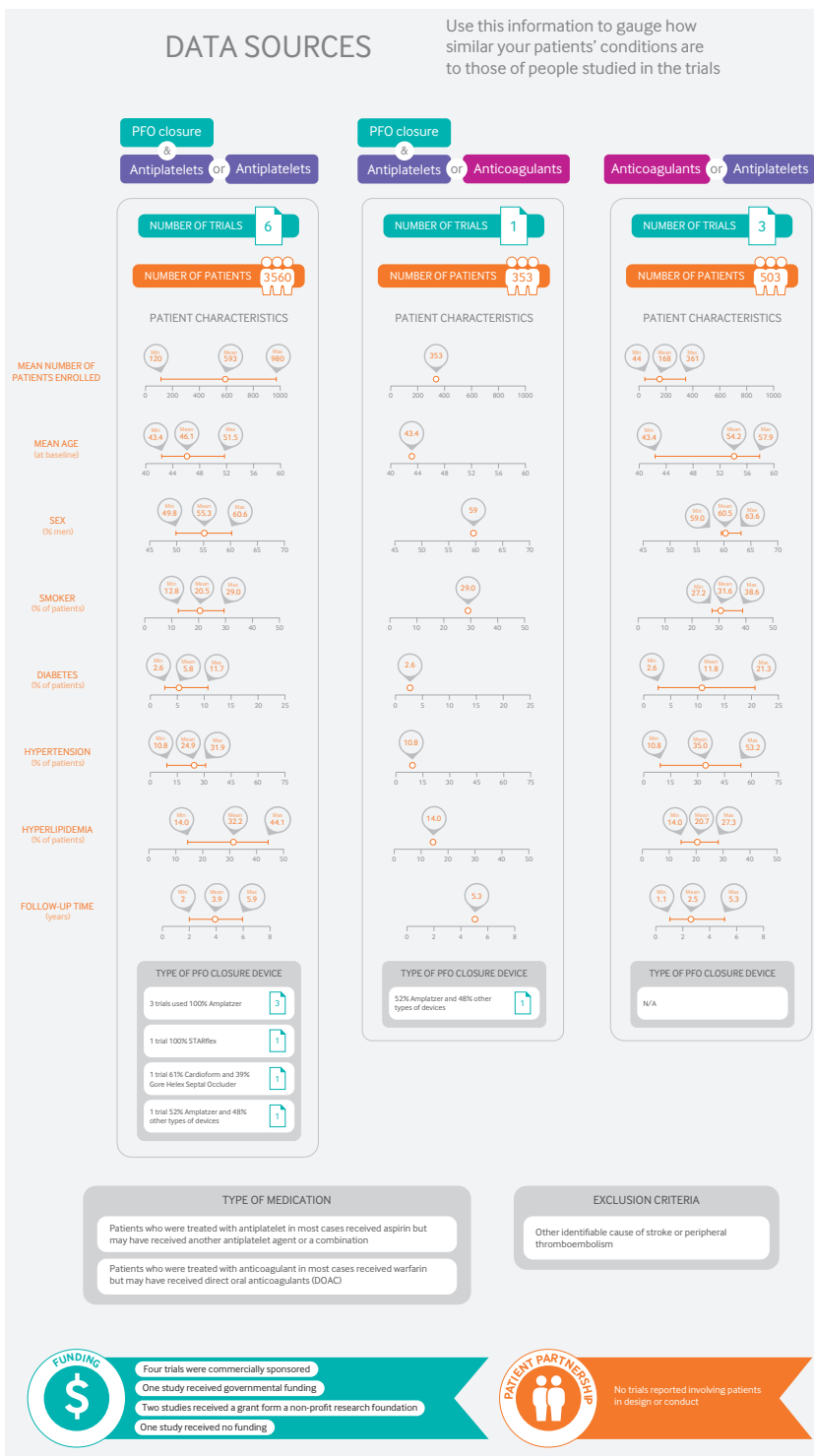


Fig 2 | Characteristics of patients and trials included in systematic review of the effects of percutaneous closure followed by antiplatelet therapy versus antiplatelet or anticoagulation therapy alone in patients with patent foramen ovale (PFO) and cryptogenic stroke. Evidence used from 6 randomised clinical trials^{2-4 31-33} (plus 2 further trials for comparison of antiplatelets and anticoagulants^{34 35})

and harms of two alternatives through relative effects on a third option) to obtain more informative estimates of effect. The paucity of data regarding anticoagulation for this intervention resulted in a sparsely populated network with low certainty evidence. The estimates of relative effect of PFO closure versus anticoagulation were

Box 3 | Details of echocardiographic diagnosis, risk profile, and patent foramen ovale (PFO) procedure planning

- **Which route**—Transesophageal echocardiography has a higher sensitivity for detection of a PFO compared with transthoracic imaging and is recommended in younger adults with unexplained cerebrovascular events
- **Work-up of cryptogenic stroke**—In addition to detection of PFO, rarer causes of embolic events include an atrial septal defect, cardiac tumours (such as myxoma or papillary fibroelastoma), bacterial or non-bacterial valve vegetations, and atrial thrombi
- **Detection of PFO**—Microbubbles enter the right atrium, and, if a PFO is present, they pass into the left atrium within a few beats of appearance in the right atrium. Although shunting usually is predominantly left to right, there is some right to left shunting as the relative pressures in the two chambers change during the cardiac cycle and with respiration
 - Sensitivity of saline contrast for detection of a PFO is increased by asking the patient to perform a Valsalva manoeuvre, which transiently increases right atrial pressure
 - Estimating the size of a PFO based on the amount of contrast seen in the left atrium may be unreliable²²
- **Those with PFO at greater risk**—An atrial septal aneurysm, defined as excessive bulging of atrial septal fossa ovalis, is often associated with septal fenestrations and may be a marker of increased embolic risk
- **Ahead of planned PFO closure**—Transesophageal echocardiography is recommended for more detailed visualisation of the atrial septal anatomy when PFO closure is planned²²

extremely imprecise. Only 353 patients were randomised to PFO closure versus anticoagulation, and 405 patients to anticoagulation versus antiplatelet agents, and events were infrequent. Therefore, to obtain more precise estimates, we performed additional analyses based on indirect evidence.

The systematic review also reports indirect evidence, from participants who did not have PFO and cryptogenic stroke, but venous thromboembolism.²³ This evidence was used to inform the effects of anticoagulation versus on stroke. Similarly, for the outcome of major bleeding, we performed additional analyses based on indirect evidence comparing anticoagulation with antiplatelet therapy for several non-PFO associated indications.¹

Specific groups of PFO patients with cryptogenic stroke

We hypothesised that studies including more patients with larger shunt sizes, and those that included more patients treated with anticoagulants, would demonstrate larger effects. A separate systematic review²⁴ reported that PFO closure, compared with any medical therapy, was more effective in patients with moderate or large size shunts. However, the same clinical trials that included more patients with larger shunts also included fewer patients who were prescribed anticoagulants in the medical therapy arm; this confounding makes it impossible to sort out which association (if either) was responsible for the larger effect. Therefore, the shunt size subgroup effect has low credibility (for more details see the linked systematic review).¹

HOW THE RECOMMENDATION WAS CREATED

Our international panel included general internists, interventional and non-interventional cardiologists, stroke physicians, epidemiologists, methodologists, statisticians, and people with personal experience of cryptogenic stroke and patent foramen ovale (PFO). They decided on the scope of the recommendation and the outcomes that are most important to patients. The panel identified eight patient-important outcomes needed to inform the recommendation: non-fatal ischaemic stroke, death, major bleeding, pulmonary embolism, serious procedure related or device related adverse events, atrial fibrillation, transient ischaemic attack, and systemic embolism.

A parallel team conducted a systematic review addressing the benefits and harms of three patient-relevant clinical questions framed by the panel: (a) PFO closure with subsequent antiplatelet therapy versus antiplatelet therapy alone, (b) PFO closure with subsequent antiplatelet therapy versus anticoagulation, and (c) anticoagulation versus antiplatelet therapy.¹

Because of a lack of evidence in those with PFO, particularly for the anticoagulation option, the panel asked for a summary of the indirect evidence regarding prevention of thrombosis from trials of venous thromboembolism and atrial fibrillation.

We also performed a systematic search for evidence regarding patients' values and preferences (see appendix 1 on bmj.com).

No panel member had financial conflicts of interest; intellectual and professional conflicts were minimised and managed (for full summary see appendix 2 on bmj.com).

The panel followed the *BMJ* Rapid Recommendations procedures for creating a trustworthy recommendation,^{5,28} including using the GRADE approach to critically appraise the evidence and create recommendations (see appendix 3 on bmj.com).²⁹ The panel considered the balance of benefits, harms, and burdens of the procedure, the quality of the evidence for each outcome, typical and expected variations in patient values and preferences, and acceptability.³⁰ Recommendations can be strong or weak, for or against a course of action.

We were unable to stratify our analyses and recommendations by type or generation of PFO closure device because of the limitations in published data and small subset sample sizes.

Procedure or device related adverse events

Procedure or device related adverse events included vascular complications (1%), conduction abnormalities (1%), device dislocation (0.7%), and device thrombosis (0.5%). Less serious adverse events such as minor bleeding and supraventricular tachycardia were inconsistently reported; the panel judged them as important, however, and took them into account in making recommendations.

Values and preferences

No studies had relevant information on values and preferences. We screened 455 titles and abstracts, and six full text articles. Appendix 1 on bmj.com presents our systematic review of the limited evidence. Three people with experience of living with cryptogenic stroke and PFO provided input regarding the choice of outcomes.

Understanding the recommendations

Absolute benefits and harms

The panel considered PFO closure plus antiplatelets better than antiplatelet agents alone. This is a strong recommendation because the absolute differences and patient preferences were aligned to place a high value on stroke prevention. Patients are likely to find an absolute reduction of stroke with PFO closure of 8.7% at five years very important. Although 3.6% will experience an adverse event, such events, including 1.8% increase in atrial fibrillation, do not usually result in long term disability and so were considered less important.

The possible small reduction in stroke and decreased bleeding risk with PFO closure versus anticoagulants alone mandated a weak recommendation for PFO closure.

For those patients who need or want to avoid PFO, the panel judged anticoagulation the best alternative, although the evidence regarding stroke reduction was of low certainty. The risk of major bleeding probably increased with anticoagulation. Although direct anticoagulants have not been evaluated in PFO, their advantages in terms of convenience may render them, rather than warfarin, the best option for those who choose anticoagulants.

The main infographic explains the recommendations and provides an overview (GRADE summary of findings) of the absolute benefits (reduction in recurrent ischaemic stroke) and harms of:

- PFO closure followed by antiplatelet therapy versus antiplatelet therapy alone
 - PFO closure followed by antiplatelet therapy versus anticoagulants alone
 - Anticoagulants versus antiplatelet therapy.
- Estimates of baseline risk for effects come from the control arm of the trials, using the median estimate of risk where available.¹

The panel agreed that, compared with antiplatelet therapy alone, PFO closure followed by antiplatelet therapy:

- Probably has a large decrease in ischaemic stroke (8.7% absolute risk reduction, moderate quality evidence) over five years
- Has a risk of device or procedure related adverse events (3.6% absolute risk, high quality evidence) at one year
- Probably has an increase in persistent atrial fibrillation or flutter (1.8% absolute risk increase, moderate quality evidence) and transient atrial fibrillation or flutter (1.2% absolute risk increase, moderate quality evidence) at one year
- Probably has little or no difference in death, major bleeding, pulmonary embolism, transient ischaemic attack, or systemic embolism (moderate to high quality evidence) at five years.

The panel agreed that, compared with anticoagulation, PFO closure followed by antiplatelet therapy:

- May result in little or no difference in ischaemic stroke (1.6% absolute risk reduction, low quality evidence) at five years
- Probably decreases major bleeding (2.0% absolute risk reduction, moderate quality evidence) at five years
- Has a risk of device or procedure related adverse events (3.6% absolute risk, high quality evidence) at one year
- Probably has an increase in persistent atrial fibrillation or flutter (1.8% absolute risk increase, moderate quality evidence) and transient atrial fibrillation or flutter (1.2% absolute risk increase, moderate quality evidence) at one year
- Probably has little or no difference in death, pulmonary embolism, transient ischaemic attack, or systemic embolism (moderate quality evidence) at five years.

	PRACTICAL ISSUES		
	Antiplatelet	Anticoagulant (warafin or direct oral anticoagulants (DOAC))	PFO closure
MEDICATION ROUTINE	One dose per day	Warafin one dose per day DOAC once or twice a dose per day	One dose per day antiplatelet therapy
TESTS & VISITS		Warafin: Initial frequent testing required to achieve appropriate dose. Periodic testing required while taking medication Patient self-monitoring with a small blood testing device as an alternative to visits to the blood testing laboratory DOAC: Dose adjustment may be required with changes in renal function	A cardiologist appointment every 1-2 years is suggested
PROCEDURE & DEVICE			Device will be implanted using a catheter, inserted through a small cut at the groin, with local anaesthesia and moderate sedation or under general anaesthesia The procedure takes under 2 hours. In-hospital stay is usually one day or less
RECOVERY & ADAPTATION			Most activities can be resumed within a few days, with full recovery within a few weeks. Patients should be given a card to carry, showing the type of device and information to be given in case of a future MRI scan.
ADVERSE EFFECTS & INTERACTIONS, ANTIDOTE	May increase bruising May increase risk of peptic ulcer	May increase risk of bleeding (serious bleeding or nuisance minor bleeding) Some medicines may increase the risk of stroke by reducing the effect of the anticoagulants	May increase risk of peptic ulcer (due to antiplatelet therapy) Uncertainty about the longevity of the device
PREGNANCY & NURSING		Women who are pregnant or considering pregnancy may need to change their medication	Involves low dose radiation exposure to patient and fetus
COSTS & ACCESS	Most can take aspirin (a low-cost medication available without a prescription)	DOACs cost more, but require less monitoring	Insurance plans may or may not cover some or all aspects of the procedure.
FOOD & DRINK		Some foods may increase the risk of stroke by reducing the effect of warfarin. Rivaroxaban should be taken with food	
EXERCISE & ACTIVITIES		May need to limit activities with high injury risk or contact	Need to avoid strenuous activity during recovery
WORK & EDUCATION			Time to return to work depends on speed of recovery
TRAVEL & DRIVING			Driving may be limited during the first days to a week of recovery

Fig 3 | Practical issues about use of percutaneous closure followed by antiplatelet therapy versus antiplatelet or anticoagulation therapy alone in patients with patent foramen ovale (PFO) and cryptogenic stroke

The panel agreed that anticoagulation versus antiplatelet therapy at five years' duration:

- May decrease ischaemic stroke (7.1% absolute risk reduction over 5 years, low quality evidence)
- Probably increases major bleeding (1.2% absolute risk increase over 5 years, moderate quality evidence)
- Probably has little or no difference in death, pulmonary embolism, transient ischaemic attack, or systemic embolism (moderate quality evidence).

Values and preferences

PFO closure followed by antiplatelet therapy versus antiplatelet therapy alone

Patients for whom anticoagulation is unacceptable or contraindicated should consider PFO closure. Our strong recommendation for PFO closure for such patients reflects the high value they place on avoiding recurrent ischaemic stroke. Patients are likely to find absolute reduction of stroke with PFO closure of 8.7% in five years important. Although 3.6% experience serious device or procedure related adverse events, these do not usually result in long term disability, and so we considered them less important. Persistent atrial fibrillation after PFO closure procedure might be a concern; however, the main adverse consequence of atrial fibrillation is increased risk of stroke, which was already shown to be substantially lower in patients randomised to PFO closure.

PFO closure followed by antiplatelet therapy versus anticoagulation

The major downsides of PFO closure are the 3.6% incidence of complications from the procedure and the probable 1.8% absolute increase in persistent atrial fibrillation. The major downside of anticoagulation is the probable 2.0% absolute increase in bleeding risk over five years. Other issues to consider are the burden and costs of long term anticoagulation. Our weak recommendation for PFO closure reflects (in addition to the low certainty in the estimates of effect) that most serious complications of PFO closure are usually short term, whereas anticoagulation imposes a long term burden and increased risk of major bleeding. Most fully informed patients would probably accept the transient risk of major adverse events rather than the long term bleeding risk, but a substantial minority would probably choose anticoagulation.

Anticoagulation versus antiplatelet therapy

Patients to whom PFO closure is unacceptable or contraindicated have to choose between anticoagulant or antiplatelet therapy. A typical patient places a high value in a possible absolute reduction of stroke with anticoagulation of 7.1% over five years and would therefore place higher value on the possible benefit of stroke reduction than the probable increased risk of major bleeding. A systematic review²⁵ and a primary study²⁶ of values and preferences on thromboprophylaxis treatment of patients with atrial fibrillation showed that, though preferences were highly variable, most patients value preventing strokes considerably more than they are concerned about increased risk of bleeding. However, there is substantial uncertainty in our estimates for stroke reduction—how this uncertainty would influence decisions is likely to vary substantially. Therefore, we issue a weak recommendation for anticoagulation. Both options need to be discussed with the patient, ideally in a process of shared decision making.

Practical issues and other considerations

Figure 3 outlines the key practical issues for patients and clinicians discussing PFO closure and is based on the content expertise of the panel members; practical issues are also accessible, along with the evidence, as decision aids

EDUCATION INTO PRACTICE

- Does this article offer you new ways to approach advising patients with cryptogenic ischaemic stroke presumed to be related to a patent foramen ovale (PFO)?
- How might you better respect differences in patients' preferences, particularly their perspective regarding the bleeding risk associated with long term anticoagulation or their feelings about undergoing an invasive procedure?
- What information could you share with your patients to help them reach a decision?
- How might you share this information with colleagues to learn together?

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

The panel included three people with personal experience of cryptogenic stroke and patent foramen ovale (PFO). These panel members identified important outcomes, and led the discussion on values and preferences. The patients agreed that, in general, small reductions in risk of ischaemic stroke are more important to them than small increases in risk of atrial fibrillation or of device or procedure related adverse events. We expect these values to be shared by most patients for ischaemic stroke. The patients participated as full panel members in the teleconferences and email discussions and met all authorship criteria. They had equal input as any other author on the recommendation.

to support shared decision making in MAGICapp. Antiplatelet therapy or anticoagulation are typically given as an oral medication once or twice a day.

Costs and resources

The panel focused on the patient's perspective rather than that of society when formulating the recommendation. Because PFO closure is associated with higher costs related to the procedure, implementation of this recommendation is likely to have an important impact on the costs for health funders in the short term. Over the long term, however, PFO closure may reduce costs as a result of reduced stroke rates and reduction in associated costs.²⁷ Addressing this issue formally would require a cost effectiveness analysis.

Uncertainties to be addressed in future research

The key remaining research question is the relative merit of PFO closure versus anticoagulation alone. It may also be appropriate to conduct further trials of PFO closure versus antiplatelet agents alone in those with small PFOs. Longer trials are also needed to address the longevity of the PFO closure device and ongoing need for monitoring of device performance.

Key research questions to inform decision makers and future guidelines include:

- What are the benefits and harms of PFO closure versus anticoagulants (including direct oral anticoagulants) in patients with PFO and cryptogenic stroke?
- What patient groups are more likely to benefit from PFO closure versus medical therapy? (That is, explore whether the effect of PFO closure versus medical therapy varies with shunt size, presence of atrial septal aneurysm, and age.)

New evidence which has emerged after initial publication

Date	New evidence	Citation	Findings	Implications for recommendation(s)
There are currently no updates to the article.				

- Which device for PFO closure is best?
- What is the longevity of the PFO closure device and ongoing need for monitoring of device performance?

Updates to this article

The table shows evidence which has emerged since the publication of this article. As new evidence is published, a group will assess the new evidence and make a judgment on to what extent it is expected to alter the recommendation.

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- 1 Mir H, Siemieniuk R, Ge L, et al Percutaneous closure plus antiplatelet therapy versus antiplatelet or anticoagulation therapy alone in patients with patent foramen ovale and cryptogenic stroke: a systematic review and network meta-analysis incorporating complementary external evidence. *BMJ Open* 2018;0:e023761. 10.1136/bmjopen-2018-023761.
- 2 Mas JL, Derumeaux G, Guillon B, et al. CLOSE Investigators. Patent foramen ovale closure or anticoagulation vs antiplatelets after stroke. *N Engl J Med* 2017;377:1011-21. 10.1056/NEJMoa1705915 pmid:28902593.
- 3 Saver JL, Carroll JD, Thaler DE, et al. RESPECT Investigators. Long-term outcomes of patent foramen ovale closure or medical therapy after stroke. *N Engl J Med* 2017;377:1022-32. 10.1056/NEJMoa1610057 pmid:28902590.
- 4 Søndergaard L, Kasner SE, Rhodes JF, et al. Gore REDUCE Clinical Study Investigators. Patent foramen ovale closure or antiplatelet therapy for cryptogenic stroke. *N Engl J Med* 2017;377:1033-42. 10.1056/NEJMoa1707404 pmid:28902580.
- 5 Siemieniuk RA, Agoritsas T, Macdonald H, Guyatt GH, Brandt L, Vandvik PO. Introduction to *BMJ* Rapid Recommendations. *BMJ* 2016;354:i5191. 10.1136/bmj.i5191 pmid:27680768.
- 6 Messé SR, Gronseth G, Kent DM, et al. Practice advisory: Recurrent stroke with patent foramen ovale (update of practice parameter): Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology* 2016;87:815-21. 10.1212/WNL.0000000000002961 pmid:27466464.
- 7 Kernan WN, Ovbiagele B, Black HR, et al. American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Peripheral Vascular Disease. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2014;45:2160-236. 10.1161/STR.0000000000000024 pmid:24788967.
- 8 Percutaneous closure of patent foramen ovale to prevent recurrent cerebral embolic events (Interventional procedures guidance IPG472). NICE, 2013: www.nice.org.uk/guidance/ipg472/chapter/1-Recommendations.
- 9 Netherlands Society of Cardiology (NVVC). Guideline for the Closure of Patent Foramen Ovale, 2016: www.nvvc.nl/media/richtlijn/208/2017_Leidraad_PFO-sluiting.pdf
- 10 Li L, Yiin GS, Geraghty OC, et al. Oxford Vascular Study. Incidence, outcome, risk factors, and long-term prognosis of cryptogenic transient ischaemic attack and ischaemic stroke: a population-based study. *Lancet Neurol* 2015;14:903-13. 10.1016/S1474-4422(15)00132-5 pmid:26227434.

- 11 Steiner MM, Di Tullio MR, Rundek T, et al. Patent foramen ovale size and embolic brain imaging findings among patients with ischemic stroke. *Stroke* 1998;29:944-8. 10.1161/01.STR.29.5.944 pmid:9596240.
- 12 Kent DM, Dahabreh IJ, Ruthazer R, et al. Device closure of patent foramen ovale after stroke: pooled analysis of completed randomized trials. *J Am Coll Cardiol* 2016;67:907-17. 10.1016/j.jacc.2015.12.023 pmid:26916479.
- 13 Di Tullio M, Sacco RL, Gopal A, Mohr JP, Homma S. Patent foramen ovale as a risk factor for cryptogenic stroke. *Ann Intern Med* 1992;117:461-5. 10.7326/0003-4819-117-6-461 pmid:1503349.
- 14 Meissner I, Khandheria BK, Heit JA, et al. Patent foramen ovale: innocent or guilty? Evidence from a prospective population-based study. *J Am Coll Cardiol* 2006;47:440-5. 10.1016/j.jacc.2005.10.044 pmid:16412874.
- 15 Petty GW, Khandheria BK, Meissner I, et al. Population-based study of the relationship between patent foramen ovale and cerebrovascular ischemic events. *Mayo Clin Proc* 2006;81:602-8. 10.4065/81.5.602 pmid:16706256.
- 16 Khan AR, Bin Abdulhak AA, Sheikh MA, et al. Device closure of patent foramen ovale versus medical therapy in cryptogenic stroke: a systematic review and meta-analysis. *JACC Cardiovasc Interv* 2013;6:1316-23. 10.1016/j.jcin.2013.08.001 pmid:24139929.
- 17 Li J, Liu J, Liu M, et al. Closure versus medical therapy for preventing recurrent stroke in patients with patent foramen ovale and a history of cryptogenic stroke or transient ischemic attack. *Cochrane Database Syst Rev* 2015;(9):CD009938.pmid:26346232.
- 18 Spencer FA, Lopes LC, Kennedy SA, Guyatt G. Systematic review of percutaneous closure versus medical therapy in patients with cryptogenic stroke and patent foramen ovale. *BMJ Open* 2014;4:e004282. 10.1136/bmjopen-2013-004282 pmid:24607561.
- 19 Fisher DC, Fisher EA, Budd JH, Rosen SE, Goldman ME. The incidence of patent foramen ovale in 1,000 consecutive patients. A contrast transesophageal echocardiography study. *Chest* 1995;107:1504-9. 10.1378/chest.107.6.1504 pmid:7781337.
- 20 Overell JR, Bone I, Lees KR. Interatrial septal abnormalities and stroke: a meta-analysis of case-control studies. *Neurology* 2000;55:1172-9. 10.1212/WNL.55.8.1172 pmid:11071496.
- 21 Alsheikh-Ali AA, Thaler DE, Kent DM. Patent foramen ovale in cryptogenic stroke: incidental or pathogenic? *Stroke* 2009;40:2349-55. 10.1161/STROKEAHA.109.547828 pmid:19443800.
- 22 Silvestry FE, Cohen MS, Armsby LB, et al. American Society of Echocardiography Society for Cardiac Angiography and Interventions. Guidelines for the Echocardiographic Assessment of Atrial Septal Defect and Patent Foramen Ovale: From the American Society of Echocardiography and Society for Cardiac Angiography and Interventions. *J Am Soc Echocardiogr* 2015;28:910-58. 10.1016/j.echo.2015.05.015 pmid:26239900.
- 23 Castellucci LA, Cameron C, Le Gal G, et al. Efficacy and safety outcomes of oral anticoagulants and antiplatelet drugs in the secondary prevention of venous thromboembolism: systematic review and network meta-analysis. *BMJ* 2013;347:f5133. 10.1136/bmj.f5133 pmid:23996149.
- 24 De Rosa S, Sievert H, Sabatino J, Polimeni A, Sorrentino S, Indolfi C. Percutaneous Closure Versus Medical Treatment in Stroke Patients With Patent Foramen Ovale: A Systematic Review and Meta-analysis. *Ann Intern Med* 2018;168:343-50. 10.7326/M17-3033 pmid:29310133.
- 25 MacLean S, Mulla S, Akl EA, et al. Patient values and preferences in decision making for antithrombotic therapy: a systematic review: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;141(Suppl):e1S-23S. 10.1378/chest.11-2290 pmid:22315262.
- 26 Alonso-Coello P, Montori VM, Díaz MG, et al. Values and preferences for oral antithrombotic therapy in patients with atrial fibrillation: physician and patient perspectives. *Health Expect* 2015;18:2318-27. 10.1111/hex.12201 pmid:24813058.
- 27 Pickett CA, Villines TC, Ferguson MA, Hulten EA. Cost effectiveness of percutaneous closure versus medical therapy for cryptogenic stroke in patients with a patent foramen ovale. *Am J Cardiol* 2014;114:1584-9. 10.1016/j.amjcard.2014.08.027 pmid:25248812.
- 28 Vandvik PO, Otto CM, Siemieniuk RA, et al. Transcatheter or surgical aortic valve replacement for patients with severe, symptomatic, aortic stenosis at low to intermediate surgical risk: a clinical practice guideline. *BMJ* 2016;354:i5085. 10.1136/bmj.i5085 pmid:27680583.
- 29 Guyatt GH, Oxman AD, Vist GE, et al. GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924-6. 10.1136/bmj.39489.470347.AD pmid:18436948.
- 30 Andrews JC, Schünemann HJ, Oxman AD, et al. GRADE guidelines: 15. Going from evidence to recommendation—determinants of a recommendation's direction and strength. *J Clin Epidemiol* 2013;66:726-35. 10.1016/j.jclinepi.2013.02.003 pmid:23570745.
- 31 Meier B, Kalesan B, Mattle HP, et al. PC Trial Investigators. Percutaneous closure of patent foramen ovale in cryptogenic embolism. *N Engl J Med* 2013;368:1083-91. 10.1056/NEJMoa1211716 pmid:23514285.
- 32 Furlan AJ, Reisman M, Massaro J, et al. CLOSURE I Investigators. Closure or medical therapy for cryptogenic stroke with patent foramen ovale. *N Engl J Med* 2012;366:991-9. 10.1056/NEJMoa1009639 pmid:22417252.
- 33 Lee PH, Song JK, Kim JS, et al. Cryptogenic stroke and high-risk patent foramen ovale: the DEFENSE-PFO trial. *J Am Coll Cardiol* 2018;71:2335-42. 10.1016/j.jacc.2018.02.046 pmid:29544871.
- 34 Shariat A, Yaghoubi E, Farazdaghi M, Aghasadeghi K, Borhani Haghighi A. Comparison of medical treatments in cryptogenic stroke patients with patent foramen ovale: A randomized clinical trial. *J Res Med Sci* 2013;18:94-8.pmid:23914208.
- 35 Homma S, Sacco RL, Di Tullio MR, Sciacca RR, Mohr JP. PFO in Cryptogenic Stroke Study (PICSS) Investigators. Effect of medical treatment in stroke patients with patent foramen ovale: Patent Foramen Ovale in Cryptogenic Stroke Study. *Circulation* 2002;105:2625-31. 10.1161/01.CIR.0000017498.88393.44 pmid:12045168.

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