RAPID RECOMMENDATIONS

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 review2 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.7 The linked systematic review finds that PFO closure prevents recurrent stroke relative to anticoagulation therapy, but possibly not relative to antiplatelet therapy, 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 made 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 antiplatelet therapy
• 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.
RAPID RECOMMENDATIONS

Population

People with:
- Patent foramen ovale (PFO)
- Cryptogenic stroke
- No atrial fibrillation
- No aortic disease
- No left sided heart disease
- No cerebrovascular disease

Treatment options:
- PFO closure
- Anticoagulants
- Antiplatelets

Are all options acceptable?

- Yes
- PFO closure contraindicated, unacceptable, or unavailable

Comparison 1
- PFO closure or Antiplatelets

Comparison 2
- PFO closure or Antiplatelets

Comparison 3
- Anticoagulants or Antiplatelets
The panel believes that there is probably substantial benefit in stroke reduction after PFO closure, which will be very important to all or almost all patients. This is likely to outweigh important undesirable consequences, like procedure or device-related adverse events and persistent atrial fibrillation or flutter.

Within 1 year of PFO closure vs. antiplatelets

- Ischaemic stroke: PFO closure plus antiplatelet therapy probably results in a large decrease in ischaemic stroke (9 vs. 13 events per 1000 people; Evidence quality: Moderate).
- Death: There is probably little or no difference in death (2 vs. 3 events per 1000 people; Evidence quality: Moderate).
- Major bleeding: There is probably little or no difference in major bleeding (14 vs. 7 events per 1000 people; Evidence quality: Moderate).
- Persistent AF or flutter: PFO closure plus antiplatelet therapy probably increases persistent AF or flutter (23 vs. 18 events per 1000 people; Evidence quality: Moderate).
- Device-related adverse events: PFO closure can lead to device- or procedure-related adverse events (30 vs. 36 events per 1000 people; Evidence quality: High).

Key practical issues

- PFO closure: Procedure takes under 2 hours, is typically key in usual care, most patients can be resumed within a few days, full recovery within a few weeks.
- Antiplatelets: No key practical issues.

Preferences and values

- The panel believes that there is probably substantial benefit in stroke reduction after PFO closure, which will be very important to all or almost all patients. This is likely to outweigh important undesirable consequences, like procedure or device-related adverse events and persistent atrial fibrillation or flutter.

Applicability

- The applicability of these findings to patients over 60 and those with traditional cerebrovascular risk factors (e.g., diabetes, hypertension, and hyperlipidaemia) is more uncertain. In older patients, fewer cryptogenic strokes are caused by paradoxical embolus, so we expect the benefits of PFO closure would be smaller and the harms greater.
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Comparison 2

PFO closure: Percutaneous closure of PFO followed by antiplatelet therapy

Or

Anticoagulants: Anticoagulation therapy

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

Comparison of benefits and harms

Favours PFO closure

<table>
<thead>
<tr>
<th>Event</th>
<th>Evidence quality</th>
<th>Within 5 years</th>
<th>Within 1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischaemic stroke</td>
<td>No important difference</td>
<td>13</td>
<td>19</td>
</tr>
<tr>
<td>Death</td>
<td>No important difference</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>No important difference</td>
<td>20</td>
<td>27</td>
</tr>
<tr>
<td>Persistent AF or flutter</td>
<td>No important difference</td>
<td>23</td>
<td>15</td>
</tr>
<tr>
<td>Device-related adverse events</td>
<td>No important difference</td>
<td>35</td>
<td>36</td>
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</table>

Favours anticoagulants

Key practical issues

PFO closure
- Procedure takes under 2 hours
- Most activities can be resumed within a few days
- Full recovery within a few weeks

Anticoagulants
- Initial frequent testing required to achieve appropriate dose
- Periodic testing required while taking medication

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 hyperlipidaemia) 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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Comparison 3

Comparison of benefits and harms

<table>
<thead>
<tr>
<th>Within 5 years</th>
<th>Events per 1000 people</th>
<th>Evidence quality</th>
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<tr>
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<tr>
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<td>No serious concerns</td>
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<tr>
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<td></td>
</tr>
<tr>
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<td><strong>Death</strong></td>
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<td></td>
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</table>

We suggest anticoagulation over antiplatelet therapy. Discuss both options with each patient.

Key practical issues

Anticoagulants
- Initial frequent testing required to achieve appropriate dose
- Periodic testing required while taking medication

Antiplatelets
- No key practical issues

Preferences and values

The panel felt that the possible decrease in ischemic stroke with anticoagulants would be more important to most patients than the possible increase in major bleeding. We expect variability in how patients might value these outcomes. Shared decision making may help establish what matters most to each patient.
RAPID RECOMMENDATIONS

Box 1 | Linked resources for this BMJ Rapid Recommendations cluster

- 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).

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. 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. They are more likely to have a PFO than patients in the general population.

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. Many meta-analyses have addressed whether closure of a PFO reduces the long term risk of subsequent stroke, but most have concluded that there is insufficient evidence.

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. If the shunt direction reverses, this communication may allow a venous thrombus or right atrial thrombus to travel directly into the arterial circulation and cause a stroke—a phenomenon known as a paradoxical embolism.

American Academy of Neurology 2017

- PFO 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 versus 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 Association

- 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 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 2013

- 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 2016

- 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

The evidence

The linked systematic review reports the relative and the absolute effects of PFO closure followed by antplatelet therapy versus antiplatelet therapy alone or versus anticoagulation and the effect of anticoagulation versus antiplatelet therapy in patients with cryptogenic stroke and PFO. 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
Four trials were commercially sponsored or received no funding. 

Evidence used for this intervention resulted in a sparsely populated network with low certainty evidence. The estimates of relative effect of PFO closure versus anticoagulation were 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. 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.

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 review 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).
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. 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 antiplatelets 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 needed to avoid PFO, the panel judged anticoagulation the most effective, 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 plus antiplatelet therapy versus anticoagulants alone
- PFO closure plus 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.

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) 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, major bleeding, pulmonary embolism, transient ischaemic attack, or systemic embolism (moderate to high quality evidence) at five years.

The panel agreed that, compared with antiplatelet therapy alone, 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.
**Rapid Recommendations**

### Practical Issues

<table>
<thead>
<tr>
<th>Antiplatelet</th>
<th>Anticoagulant (warfarin or direct oral anticoagulants [DOAC])</th>
<th>PFO closure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medication routine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One dose per day</td>
<td>One dose three or four times daily</td>
<td>One dose per day antiplatelet therapy</td>
</tr>
<tr>
<td><strong>Tests &amp; Visits</strong></td>
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<tr>
<td>Warfarin: please frequent testing required to achieve adequate international normalised ratio (INR)</td>
<td>Patient self-monitoring with a small blood test required approximately twice daily.</td>
<td>Warfarin: please frequent testing required every 1-2 weeks</td>
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<td>Women who are pregnant or considering pregnancy should avoid anticoagulants</td>
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<td><strong>Travel &amp; driving</strong></td>
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</table>

**Values and preferences**

**PFO closure followed by antiplatelet therapy versus anticoagulation 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 review and a primary study 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.
Rapid Recommendations

Future guidelines include:

- The PFO closure device and ongoing need for monitoring versus antiplatelet agents alone in those with small PFOs.

It may be appropriate to conduct further trials of PFO closure 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.17 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

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<tr>
<th>Date</th>
<th>New evidence</th>
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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.

Competing interests: All authors have completed the BMJ Rapid Recommendations interests disclosure form, and a detailed description of all disclosures is reported in appendix 2 on bmj.com. No authors had relevant financial interests. They declared the following intellectual interests: Elke Hoendermis is co-author of national recommendations on PFO closure and stroke on behalf of the working group of the Netherlands Society of Cardiology. Fred Spencer has published systematic review and meta-analysis on this topic. No panel member had any other intellectual conflicts of interest. None of the BMJ Rapid Recommendations, the executive team and The BMJ judged that no panel member had any financial conflict of interest. Professional and academic interests are minimised as much as possible, while maintaining necessary expertise on the panel to make fully informed decisions.

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Transparency: T Kuijpers affirms that the manuscript is honest, accurate, and transparent account of the recommendation being reported; that no important aspects of the recommendation have been omitted; and that any discrepancies from the recommendation as planned (and, if relevant, registered) have been explained.

8. Percutaneous closure of patent foramen ovale to prevent recurrent cerebral embolic events (Interventional procedures guideline IPG4-2). NICE. 2013: www.nice.org.uk/guidance/pg42/chapter/1-recommendations.
RAPID RECOMMENDATIONS


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