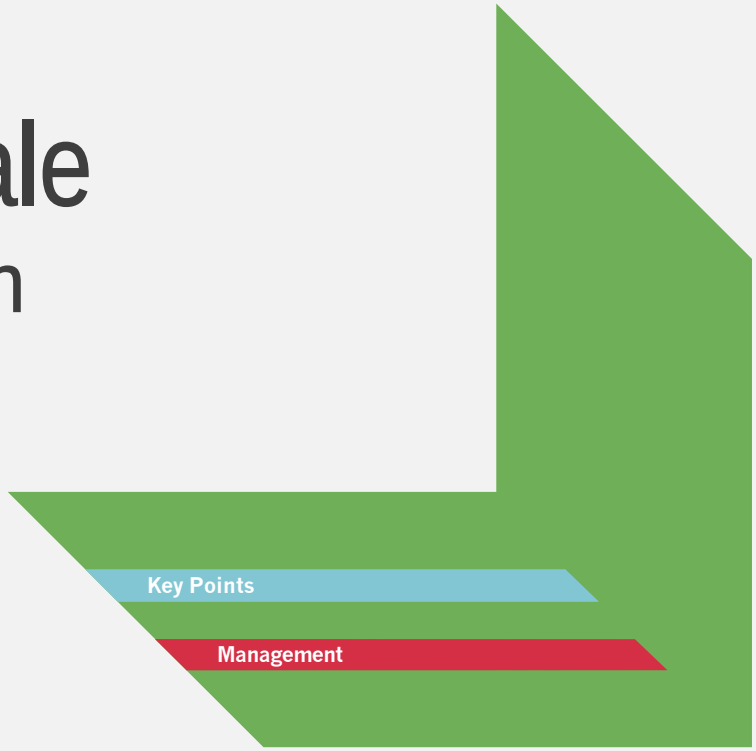
AMERICAN ACADEMY OF NEUROLOGY

Patent Foramen Ovale

Secondary Stroke Prevention



Adapted from:
Messé SR et al. Neurology 2020 May 19 doi: 10.1212/WNL.0000000000009443

Introduction

- The American Academy of Neurology (AAN) published a practice advisory in 2016 regarding secondary stroke in patients with patent foramen ovale (PFO).1 Since then, additional randomized trials have been published, and the Food and Drug Administration approved the AMPLATZER PFO Occluder and GORE CARDIOFORM Septal Occluder for use in the United States, necessitating an update.

- The clinical questions for this advisory remain unchanged:
  1. In patients with a PFO who have had an otherwise cryptogenic ischemic stroke, does percutaneous PFO closure reduce the risk of stroke recurrence compared with medical therapy alone?
  2. In patients with a PFO who have had an otherwise cryptogenic ischemic stroke, does anticoagulation reduce the risk of stroke recurrence compared with antiplatelet medication?

- This update does not address management of stroke risk factors or causes aside from PFO.

Key Points

- For patients with cryptogenic stroke and PFO, percutaneous PFO closure probably reduces the risk of stroke recurrence (HR-0.41, summary rate difference -0.67% per year), probably is associated with a periprocedural complication rate of 3.9%, and probably is associated with the development of serious non-periprocedural atrial fibrillation (RR-2.72, summary rate difference 0.33% per year).

- For patients with cryptogenic stroke and PFO, anticoagulation medication and antiplatelet medication are possibly equally effective at reducing recurrent stroke.

Management – Percutaneous PFO Closure

- In patients being considered for PFO closure, clinicians should ensure that an appropriately thorough evaluation has been performed to rule out alternative mechanisms of stroke, as was performed in all positive PFO closure trials (**B**).

- In patients being considered for PFO closure, clinicians should obtain brain imaging to confirm stroke size and distribution, assessing for an embolic pattern or a lacunar infarct (typically involving a single deep perforator <1.5 cm in diameter) (**B**).

- In patients being considered for PFO closure, clinicians should obtain complete vascular imaging (MRA or CTA) of the cervical and intracranial vessels to look for dissection, vasculopathy, and atherosclerosis (**B**).

Management – Percutaneous PFO Closure

- In patients being considered for PFO closure, clinicians must perform a baseline ECG to look for atrial fibrillation (**A**).

- Select patients being considered for PFO closure thought to be at risk of atrial fibrillation should receive prolonged cardiac monitoring for at least 28 days (**B**).

    - Note: Risk factors for atrial fibrillation include: age ≥50 years, hypertension, obesity, sleep apnea, enlarged left atrium, elevated NT-proBNP, frequent premature atrial contractions, and increased P wave dispersion. Recently published guidelines from the American Heart Association, American College of Cardiology, and Heart Rhythm Society recommend prolonged ECG monitoring following cryptogenic stroke for patients older than 40 years, although more research is needed to define the yield in unselected young patients and in patients with PFO.[1]

1. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/ HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Heart Rhythm 2019;16:e66-e93.

Management – Percutaneous PFO Closure

- In patients being considered for PFO closure, clinicians should assess for cardioembolic sources using TTE, followed by TEE assessment if the first study does not identify a high-risk stroke mechanism. Studies should use bubble contrast, with and without Valsalva maneuver, to assess for right-to-left shunt and determine degree of shunting (**B**).

- In patients being considered for PFO closure, clinicians should perform hypercoagulable studies that would be considered a plausible high-risk stroke mechanism that would lead to a change in management, such as requiring lifelong anticoagulation (e.g., persistent moderate- or high-titer antiphospholipid antibodies in a younger patient with cryptogenic stroke)[2] (**B**).

2. Tektonidou MG, Andreoli L, Limper M, et al. EULAR recommendations for the management of antiphospholipid syndrome in adults. Ann Rheum Dis 2019;78:1296-1304.

Management – Percutaneous PFO Closure

- In patients being considered for PFO closure, clinicians may use TCD agitated saline contrast as a screening evaluation for right-to-left shunt, but this does not obviate the need for TTE and TEE to rule out alternative mechanisms of cardioembolism and confirm that right-to- left shunting is intracardiac and transseptal (**C**).

- Before undergoing PFO closure, patients should be assessed by a clinician with expertise in stroke to ensure that the PFO is the most plausible mechanism of stroke (**B**).

- If a higher risk alternative mechanism of stroke is identified, clinicians should not routinely recommend PFO closure (**B**).

Management – Percutaneous PFO Closure

- Before undergoing PFO closure, patients should be assessed by a clinician with expertise in assessing the degree of shunting and anatomical features of a PFO and performing PFO closure, to assess whether the PFO is anatomically appropriate for closure, to ascertain whether other factors are present that could modify the risk of the procedure, and to address post-procedure management (**B**).

- In patients with a PFO detected after stroke and no other etiology identified after a thorough evaluation, clinicians should counsel patients that having a PFO is common, that it occurs in about 1 in 4 adults in the general population, that it is difficult to determine with certainty whether their PFO caused their stroke, and that PFO closure probably reduces recurrent stroke risk in select patients (**B**).

Management – Percutaneous PFO Closure

- In patients younger than 60 years with a PFO and an embolic-appearing infarct and no other mechanism of stroke identified, clinicians may recommend closure following a discussion of potential benefits (reduction of stroke recurrence) and risks (procedural complication and atrial fibrillation) (**C**).

- Clinicians may inform patients that presence of a large shunt probably is associated with benefit from closure. Conversely, there probably is less likelihood of benefit in patients with a small shunt or a non–embolic-appearing single, small, deep infarct, and it is uncertain whether atrial septal aneurysm in the absence of a large shunt influences the likelihood of benefitting from PFO closure (**C**).

Management – Percutaneous PFO Closure

- PFO closure may be offered in other populations, such as for a patient who is 60–65 years old with a very limited degree of traditional vascular risk factors (i.e., hypertension, diabetes, hyperlipidemia, or smoking) and no other mechanism of stroke detected following a thorough evaluation, including prolonged monitoring for atrial fibrillation (**C**).

- PFO closure may be offered to younger patients (e.g., <30 years) with a single, small, deep stroke (<1.5 cm), a large shunt, and absence of any vascular risk factors that would lead to intrinsic small-vessel disease such as hypertension, diabetes, or hyperlipidemia (**C**).

Management – Percutaneous PFO Closure

- In a patient for whom PFO closure is being considered, a shared decision-making approach between clinicians and the patient should be used, exploring how well the patient's attributes match those included in the positive PFO closure trials and the patient's preferences and concerns regarding risk of stroke recurrence and risk of adverse events (**B**).

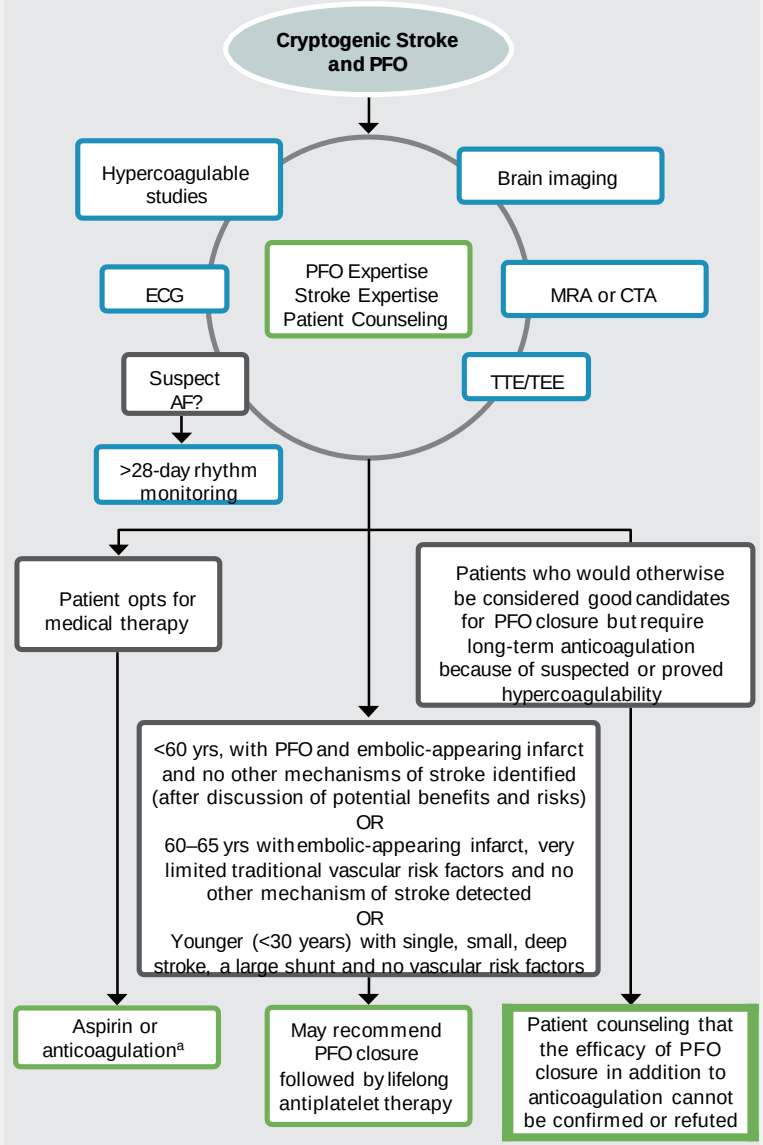
Management – Medical Therapy

- In patients who opt to receive medical therapy alone without PFO closure, clinicians may recommend either an antiplatelet medication such as aspirin or anticoagulation (using a vitamin K antagonist, a direct thrombin inhibitor, or a factor Xa inhibitor) (**C**).

- In patients who would otherwise be considered good candidates for PFO closure but require long-term anticoagulation because of suspected or proven hypercoagulability (defined thrombophilia, unprovoked deep venous thrombosis, or unprovoked pulmonary embolism), clinicians should counsel the patient that the efficacy of PFO closure in addition to anticoagulation cannot be confirmed or refuted (**B**).

Management – Algorithm

Figure 1. Management Algorithm



[a] Vitamin K antagonist, a direct thrombin inhibitor, or a factor Xa inhibitor.

Classification of Management Recommendations

Classification	Definition
Level (A)	Denotes a practice recommendation that must be done. In almost all circumstances, adherence to the recommendation will improve health-related outcomes. Almost all patients in this circumstance would desire that the recommendation be followed.
Level (B)	Corresponds to the helping verb should. Should recommendations tend to be more common, as the requirements are less stringent but still based on the evidence and benefit-risk profile.
Level (C)	Corresponds to the helping verb may. May recommendations represent the lowest allowable recommendation level the AAN considers useful within the scope of clinical practice and can accommodate the highest degree of practice variation.
Level (U)	Indicates that the available evidence is insufficient to support or refute the efficacy of an intervention.
Level (R)	Assigned when the balance of benefits and harms is unknown and the intervention is known to be exorbitantly expensive or have important risks. This level designates that the intervention should not be used outside of a research setting.

Abbreviations and Source

- **AF**, atrial fibrillation; **CTA**; computed tomographic angiography; **HR**; hazard ratio; **MRA**; magnetic resonance angiography; **PFO**; patent foramen ovale; **RR**; risk ratio; **TCD**; transcranial Doppler ultrasonography; **TEE**; transesophageal echocardiography; **TTE**; transthoracic echocardiography

- Steven R. Messé, MD; Gary S. Gronseth, MD; David M. Kent, MD, MSc; Jorge R. Kizer, MD, MSc; Shunichi Homma, MD; Lee Rosterman, DO; John D. Carroll, MD; Koto Ishida, MD; Navdeep Sangha, MD; Scott E. Kasner, MD, MSCE. Practice advisory update: Patent foramen ovale and secondary stroke prevention. Report of the Guideline Subcommittee of the American Academy of Neurology. Neurology 2020;94(20):876-885. This practice advisory was endorsed by the Society for Cardiovascular Angiography and Interventions, the American Heart Association/American Stroke Association, and the European Academy of Neurology.

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