AAN Summary of Practice Advisory Update for **Clinicians**

Practice Advisory Update Summary: Patent Foramen Ovale and Secondary Stroke Prevention

This is a summary of the American Academy of Neurology (AAN) "Practice Advisory Update Summary: Patent Foramen Ovale and Secondary Stroke Prevention" which was published in *Neurology*® online on April 29, 2020, and appears in the May 19, 2020, print issue.

Please refer to the full guideline on the AAN Guidelines web page for more information, including full descriptions of the processes for classifying evidence, deriving conclusions, and making recommendations.

Recommendation 1

Rationale

Ischemic stroke may be caused by a variety of heterogeneous mechanisms, and secondary stroke prevention is optimized by targeting the most likely etiology of the preceding event.[1-3] An appropriately thorough workup depends on the individual patient and whether a compelling stroke etiology has already been identified. The randomized patent foramen ovale (PFO) closure trials all mandated thorough evaluations for participants before enrollment, including CT angiography (CTA) or MR angiography (MRA) of the head and neck vessels in all studies and hypercoagulable screening in many to rule out other stroke mechanisms; moreover, all studies required transesophageal echocardiography (TEE) to characterize the PFO and ensure that it was the most likely etiology for the initial event. There is accumulating evidence that occult atrial fibrillation accounts for a meaningful portion of cryptogenic stroke.[4] Given that they were designed and initiated before atrial fibrillation monitoring became routine, none of the PFO closure trials required prolonged monitoring before enrollment, although it is important to note that the incidence of atrial fibrillation is strongly correlated with increasing age and is unlikely to occur in patients <50 years. Other risk factors and biomarkers have been associated with atrial fibrillation and may increase clinical suspicion, including systemic hypertension, obesity, sleep apnea, enlarged left atrium, hyperthyroidism, diabetes, alcohol abuse, cigarette smoking, elevated serum N-terminal pro b-type natriuretic peptide (NT-proBNP), frequent premature atrial contractions, and increased P wave dispersion on ECG.[5,6]

PFO is highly prevalent, found in approximately 25% of the general adult population on agitated-saline TEE and cadaveric studies.[7,8] Transcranial Doppler ultrasonography (TCD) has been demonstrated to have similar sensitivity and specificity to TEE to detect right-to-left shunting, although TCD does not rule out other cardioembolic sources seen on TEE and cannot confirm that shunting is intracardiac or assess PFO morphology, including anatomic size, location, and length of the tunnel.[9] Multiple studies have identified an association between PFO and otherwise cryptogenic stroke, with increasing PFO prevalence in younger patients with stroke and those lacking traditional vascular risk factors such as hypertension, hypercholesterolemia, and diabetes.[10-12]

The risk of stroke recurrence in patients with PFO and no other etiology identified is low, approximately 1% per year while individuals are treated with medication alone. This stroke risk is generally lower than the stroke risk caused by other possible common stroke mechanisms.[13] Thus, if an alternative plausible higher risk mechanism of stroke is identified, it is likely that the PFO was an "innocent bystander."

Level	Recommendation
Level B	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.
Level 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).
Level 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.
Level A	In patients being considered for PFO closure, clinicians must perform a baseline ECG to look for atrial fibrillation.
Level B	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. (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.[14])
Level B	In patients being considered for PFO closure, clinicians should assess for cardioembolic sources using transthoracic echocardiography (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.

Level	Recommendation
Level 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).[15]
Level C	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 cardio embolism and confirm that right-to-left shunting is intracardiac and transseptal.
Level B	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.
Level B	If a higher risk alternative mechanism of stroke is identified, clinicians should not routinely recommend PFO closure.
Level B	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 postprocedure management.
Level B	In patients with a PFO detected after stroke and no other etiology identified after a thorough evaluation, clinicians should counsel 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.

Recommendation 2

Rationale

Among patients younger than 60 years with no other etiology identified after a thorough diagnostic evaluation, transcatheter PFO closure probably reduces the risk of recurrent stroke (summary rate difference -0.67% per year, 95% CI -0.39 to -0.94%, I^2=0), with a number needed to treat of 29 to reduce one stroke at 5 years. PFO closure was associated with a small risk of procedural complications (summary risk 3.9% [95% CI 2.3% to 5.7%]) and non-periprocedural atrial fibrillation (summary rate difference 0.33% per year [95% CI 0.04% to 0.65%]), although most of these events were reported to be self-limited and are of uncertain long-term clinical consequence given the lower rate of stroke in patients whose PFOs were closed. Subgroup analysis suggests that the overall benefit seen across trials may not extend to those patients with small shunts and small, deep infarcts. Clinical studies of PFO closure have characterized PFO size as the greatest degree of right-to-left shunting under different testing states rather than the anatomical size of a PFO since the size of the opening is dynamic. Importantly, some small deep strokes may be caused by embolism, most likely in younger patients without traditional vascular risk factors. Of note, the subgroup analysis also does not demonstrate any benefit interaction for presence or absence of atrial septal aneurysm, despite some studies reporting a larger shunt and higher risk of stroke recurrence if atrial septal aneurysm is present.[16,17] In addition, the subgroup meta-analysis showed no difference in the benefit of PFO closure in patients aged 45–60 years compared to those <45 years. Further, there is evidence that PFO may play a role in some cryptogenic stroke in patients older than 60 years, and the DEFENSE-PFO trial included patients older than 60 years.[18,11,19]

Level	Recommendation
Level C	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).
Level 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.
Level C	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.
Level 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.
Level B	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.

Recommendation 3

Rationale

All patients with prior stroke should be treated with an antithrombotic medication indefinitely if there is no bleeding contraindication regardless of whether a PFO is present or if it is closed.[20] However, specific antithrombotic management for patients with stroke thought to be caused by PFO remains uncertain. Existing randomized studies comparing anticoagulation with antiplatelet therapy do not demonstrate that either treatment regimen is superior (HR 0.73, 95% CI 0.45 to 1.17). However, the finding that closure of the PFO appears to reduce recurrent stroke risk suggests that paradoxical embolization of a venous thromboembolism is the mechanism for a substantial portion of recurrent strokes. In addition, there is high-level evidence that anticoagulation is superior to antiplatelet medication for venous thromboembolism.[21,22] The benefit of performing closure in patients being treated with anticoagulation is unclear.

Level	Recommendation
Level C	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).
Level B	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.

This practice advisory was endorsed by the Society for Cardiovascular Angiography and Interventions on February 28, 2020; the American Heart Association/American Stroke Association on March 12, 2020; and the European Academy of Neurology on March 30, 2020.

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