SPECIAL ARTICLE

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

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ABSTRACT

Objective: To update the 2004 American Academy of Neurology guideline for patients with stroke and patent foramen ovale (PFO) by addressing whether (1) percutaneous closure of PFO is superior to medical therapy alone and (2) anticoagulation is superior to antiplatelet therapy for the prevention of recurrent stroke.

Methods: Systematic review of the literature and structured formulation of recommendations.

Conclusions: Percutaneous PFO closure with the STARFlex device possibly does not provide a benefit in preventing stroke vs medical therapy alone (risk difference [RD] 0.13%, 95% confidence interval [CI] −2.2% to 2.0%). Percutaneous PFO closure with the AMPLATZER PFO Occluder possibly decreases the risk of recurrent stroke (RD −1.68%, 95% CI −3.18% to −0.19%), possibly increases the risk of new-onset atrial fibrillation (AF) (RD 1.64%, 95% CI 0.07%–3.2%), and is highly likely to be associated with a procedural complication risk of 3.4% (95% CI 2.3%–5%). There is insufficient evidence to determine the efficacy of anticoagulation compared with antiplatelet therapy in preventing recurrent stroke (RD 2%, 95% CI −21% to 25%).

Recommendations: Clinicians should not routinely offer percutaneous PFO closure to patients with cryptogenic ischemic stroke outside of a research setting (Level R). In rare circumstances, such as recurrent strokes despite adequate medical therapy with no other mechanism identified, clinicians may offer the AMPLATZER PFO Occluder if it is available (Level C). In the absence of another indication for anticoagulation, clinicians may routinely offer antiplatelet medications instead of anticoagulation to patients with cryptogenic stroke and PFO (Level C). *Neurology*® 2016;87:815–821

GLOSSARY

AAN = American Academy of Neurology; **AE** = adverse event; **AF** = atrial fibrillation; **CI** = confidence interval; **GRADE** = Grading of Recommendations Assessment, Development and Evaluation; **HR** = hazard ratio; **INR** = international normalized ratio; **NNT** = number needed to treat; **PFO** = patent foramen ovale; **RCT** = randomized controlled trial; **RD** = risk difference; **RESPECT** = Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment.

In 2004, the American Academy of Neurology (AAN) published a practice guideline addressing secondary stroke in patients with patent foramen ovale (PFO). The guideline concluded that the optimal therapy for secondary stroke prevention in this population was unknown.[1] Since that time, additional studies necessitated that we update our prior guideline, addressing the following therapeutic questions:

1. In patients with a PFO who have had a cryptogenic ischemic stroke or TIA, does percutaneous PFO closure reduce the risk of stroke recurrence compared with medical therapy alone?
2. In patients with a PFO who have had a cryptogenic ischemic stroke or TIA, does anticoagulation reduce the risk of stroke recurrence compared with antiplatelet medication?

This practice advisory is not intended to be a comprehensive guideline for the management of other stroke risk factors or causes. The primary audiences are neurologists, cardiologists, and other clinicians caring for patients with cryptogenic ischemic stroke and PFO.

DESCRIPTION OF THE ANALYTIC PROCESS This practice advisory follows the methodologies outlined in the 2011 edition of the AAN's guideline development

Supplemental data at Neurology.org

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process manual, as amended.[2] We summarize the process here and provide more detail in appendix e-1 on the *Neurology*® Web site at Neurology.org.

The AAN's Guideline Development, Dissemination, and Implementation Subcommittee (appendices e-2 and e-3) convened a panel of neurologists and cardiologists with expertise in stroke and PFO who had no financial conflicts. We performed a literature search to identify randomized studies pertinent to the questions (see appendix e-4 for complete search strategy). Studies were rated for their risk of bias (appendix e-5).

We excluded TIAs from the assessed outcomes when feasible because TIA is subjective.[3] Because of a lower risk of bias, when available, we used the intention-to-treat analysis[4] of included studies to inform conclusions.

We determined our overall confidence in evidence using a modified Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[5] We developed recommendations after considering the evidence strength, risks and benefits, cost, availability, and patient preference variations. The recommendations were derived by informal consensus. Each recommendation was endorsed by at least 80% of the authors.

The thoroughness of the literature search, risk of bias ratings, extracted effect sizes, modified GRADE evidence synthesis, and overall strength of recommendations regarding question 1 were also reviewed and confirmed by neurologists participating in a half-day course (see appendix e-6 for participant list and relevant conflicts of interest).[6]

ANALYSIS OF EVIDENCE The initial literature search identified 809 articles, 5 of which were deemed relevant and underwent evidence classification and data extraction (appendix e-7). Only those studies that informed conclusions and recommendations are discussed herein.

In patients with a PFO who have had a cryptogenic ischemic stroke or TIA, does percutaneous PFO closure reduce the risk of stroke recurrence compared with medical therapy alone? ***Evidence.*** The 2004 guideline identified no randomized studies relevant to this question. The updated search identified 3 Class I studies.[7–9]

The CLOSURE I study[7] (Class I) was a multicenter, randomized, open-label trial of percutaneous closure with a STARFlex device (NMT Medical, Boston, MA) compared with medical therapy alone in adult patients with PFO and a cryptogenic stroke/TIA. Percutaneous closure was randomly assigned to 447 participants, and 462 were assigned to medical therapy. Patients were followed for 2 years. Patients assigned to closure were given clopidogrel, 75 mg/d for 6 months, and aspirin, 81 or 325 mg/d for 2 years. Patients in the medical therapy arm were given warfarin (with a target international normalized ratio [INR] of 2.0–3.0) or aspirin (325 mg/d), or both, at the local investigator's discretion. Effective PFO closure was seen in 86% of patients who received the device. Recurrent stroke occurred in 2.9% who underwent closure and in 3.1% of those on medical therapy (risk difference [RD] −0.13%, 95% confidence interval [CI] −2.2% to 2.0%). Recurrent strokes often were due to mechanisms that were unrelated to the PFO, accounting for 87% of the events in the closure group and 76% of events in the medical therapy group. Alternative diagnoses for these recurrent events included new-onset atrial fibrillation (AF), left-atrial thrombus, small-vessel lacunae, aortic atheromatous disease, complex migraine, vasculitis, and conversion disorder. AF accounted for 3 of the 12 strokes in the closure group. In 2 of these cases, transesophageal echocardiography identified device-associated thrombus. One of 13 strokes in the medical therapy group was attributed to AF that developed after implantation of an off-study closure device. Overall, AF was identified more often in patients who underwent closure compared with patients who received medical therapy, 5.7% vs 0.7%, respectively (RD 5%, 95% CI 2%–8%, $p < 0.001$), and major vascular procedural complications occurred in 3.2% of the patients who underwent closure.

The PC Trial[8] (Class I) randomized 414 patients to medical therapy or closure with the AMPLATZER PFO Occluder (St. Jude Medical, Inc., St. Paul, MN) and followed them for an average of 4 years. Patients who underwent closure were given aspirin 100–325 mg/d for at least 5 months, and ticlopidine 250–500 mg/d or clopidogrel 75–150 mg/d for 1–6 months; patients assigned to medical therapy were given antiplatelet or anticoagulant medication, as chosen by the local investigator. Twenty-eight patients assigned to medical therapy crossed over to the closure group at a median of 8.8 months after randomization. Two patients died in the closure group and none in the medical therapy group, although these deaths were not deemed related to the PFO. The studies reported recurrent stroke in 1 (0.5%) patient in the closure arm and in 5 (2.4%) patients in the medically treated arm (hazard ratio [HR] 0.20, 95% CI 0.02–1.72, $p = 0.14$). New-onset AF was reported in 2.9% in the closure arm vs 1.0% in the medical treatment arm (HR 3.15, 95% CI 0.64–15.6, $p = 0.16$). Bleeding adverse events (AEs) occurred in 3.9% in the closure group and in 5.7% in the medically treated group (HR 0.66, 95% CI 0.27–1.62, $p = 0.40$).

In the Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment (RESPECT) trial[9] (Class I), a second randomized controlled trial (RCT) that used the AMPLATZER PFO Occluder (St. Jude Medical, Inc.), 980 patients were randomized and followed for an average of ~2.5 years. Patients who underwent PFO closure received aspirin 81–325 mg plus clopidogrel

75 mg daily for 1 month, followed by aspirin monotherapy daily for 5 months. Subsequently, antiplatelet therapy was administered at the site investigator's discretion. Patients assigned to medical therapy were treated at the investigator's discretion; approximately one-fourth of patients in the medical arm received warfarin, and the remainder took antiplatelet medications. In the intention-to-treat analysis, recurrent stroke was reported in 9 of 499 (1.8%) patients assigned to device closure, compared with 16 of 481 (3.3%) in the medical arm (HR 0.49, 95% CI 0.22–1.11, $p = 0.08$). A prespecified per-protocol analysis showed a statistically significant benefit favoring closure (14 strokes in the medical arm vs 6 in the closure group, HR 0.37, 95% CI 0.14–0.96). The clinical AF incidence did not differ significantly between patients randomized to receive the closure device and those taking medication (3.0% and 1.5%, respectively, $p = 0.13$). Pulmonary embolism occurred in 6 patients (1.2%) in the closure group compared with 1 patient (0.2%) in the medical therapy group ($p = 0.12$). Death occurred in 3 patients in the closure group compared with 6 in the medical therapy group, but these were all late and adjudicated as non-study-related.

From evidence to conclusion. We judged that the differences between the STARFlex and AMPLATZER PFO Occluder were sufficient to warrant separate evidence syntheses and conclusions.

STARFlex. The estimate of the absolute risk reduction over 2 years from CLOSURE I was 0.13%, with 95% CI from −2.2% to 2.0%.

Our confidence in the evidence was anchored at *moderate* (1 Class I study) for the start of the modified GRADE process (appendix e-8). In the CLOSURE I study, the number of patients lost to follow-up or crossing over was 2.9 times more than the number of patients experiencing events—73 (8%) vs 25 (2.8%), respectively. Thus, we judged the risk of bias as large relative to the magnitude of effect, leading to a reasonable likelihood that future studies could change the estimate of effect for the STARFlex PFO closure. As a result, we downgraded our confidence in the efficacy evidence to *low*.

Confidence in the evidence regarding the risk of procedural complications (absolute risk 3.3%, 95% CI 1.9%–5.2%), including cardiac perforation and cardiac tamponade in 2 patients, was judged to be moderate. Because of the low event rate compared with the number of patients lost to follow-up, confidence regarding the increased risk of new-onset AF in patients undergoing closure—RD 5%, 95% CI 2%–8%—was judged as *low*.

Conclusions. For patients with cryptogenic stroke and PFO, percutaneous PFO closure with the STARFlex device:

1. Possibly does not provide a large benefit in preventing stroke in place of medical therapy alone—RD 0.13%, 95% CI -2.2% to 2.0%; possibly increases the risk of new-onset AF—RD 5%, 95% CI 2%–8% (1 Class I study, confidence downgraded to low for risk of bias relative to magnitude of effect);
2. Probably is associated with a serious periprocedural complication risk of 3.2%, 95% CI 1.9%–5.2% (1 Class I study).

AMPLATZER PFO Occluder. Although the intention-to-treat results of both RESPECT and PC Trial demonstrated no significant difference in stroke rates between treatment groups, the precision of the trials was insufficient to exclude moderate effects. We thus pooled the results in a random-effects meta-analysis (appendix e-9). The summary RD of recurrent stroke significantly favored closure (RD −1.68%, 95% CI −3.18% to −0.19%). The number needed to treat (NNT) to prevent 1 stroke for the time horizons of the studies (~3–4 years) is 56. Although this result is significant and we judge that the point estimate of effect is moderately important, the precision of the pooled studies is consistent with a magnitude of benefit that many would deem unimportant (the 95% CI for the NNT ranges from 31 through 526 over the same period). The result did not change substantially when obtained using HRs (see appendix e-10). Finally, a recently published patient-level meta-analysis[10] of data from all 3 randomized PFO closure studies demonstrated a significant benefit of closure for stroke prevention overall (adjusted HR 0.58, 95% CI 0.34–0.99, $p = 0.04$), with a greater effect size when the analysis was limited to the AMPLATZER PFO Occluder studies (adjusted HR 0.41, 95% CI 0.20–0.88, $p = 0.02$). This estimate of stroke risk reduction was judged to be substantively similar to our meta-analysis result.

Our confidence in the evidence was anchored at *moderate* (2 Class I studies demonstrating a significant difference only when combined) for the start of the modified GRADE process (appendix e-8). As was the case in CLOSURE I, in both RESPECT and PC Trial, the number of patients lost to follow-up or crossing over was much larger than the number of patients experiencing events: RESPECT 129 (13.2%) vs 25 (2.6%), respectively; PC Trial 98 (24%) vs 6 (1.4%), respectively. Thus, we judged the risk of bias as large relative to the magnitude of effect, leading to a reasonable likelihood that future studies could change the estimate of effect of closure with the AMPLATZER PFO Occluder. In addition, as mentioned previously, the limited precision of the combined studies fails to exclude a clinically unimportant effect. As a result of these concerns, we downgraded our confidence in the evidence to *low*.

The combined results of both AMPLATZER PFO Occluder studies showed that serious procedural or device-related events occurred in 3.4% (95% CI 2.3%–5.0%) of patients. Confidence in this evidence

was determined to be high. The risk of new-onset AF was not significantly different in either study. However, combining the results in a meta-analysis demonstrated a significant increased risk of AF in patients undergoing closure—RD 1.64% (95% CI 0.07%–3.2%). It is important to note that the previously discussed patient-level meta-analysis did not report a statistically significant increase in AF using a relative measure from the intention-to-treat analysis for the combined AMPLATZER PFO Occluder trials (HR 1.94, 95% CI 0.91–4.12, $p = 0.09$).[11] For reasons similar to those described for the efficacy outcomes, confidence in the evidence pertinent to the AF outcome was judged as *low*.

Conclusions. For patients with cryptogenic stroke and PFO, percutaneous PFO closure with the AMPLATZER PFO Occluder:

1. Possibly decreases the risk of recurrent stroke—RD −1.68%, 95% CI −3.18% to −0.19%;
2. Possibly increases the risk of new-onset AF—RD 1.64%, 95% CI 0.07%–3.2% (2 Class I studies; confidence downgraded to *low* for risk of bias relative to magnitude of effect and imprecision);
3. Is highly likely to be associated with a procedural complication risk of 3.4%, 95% CI 2.3%–5% (2 Class I studies).

In patients with a PFO who have had a cryptogenic ischemic stroke or TIA, does anticoagulation reduce the risk of stroke recurrence compared with antiplatelet medication? ***Evidence.*** The 2004 guideline identified 1 Class II study relevant to this question. The PFO in Cryptogenic Stroke Study (PICSS)[12] was a substudy of a randomized trial of warfarin vs aspirin in patients with stroke or TIA not due to AF or extracranial carotid stenosis.[13] A total of 312 patients with stroke were randomized to warfarin and 318 to aspirin. Only 265 had experienced a cryptogenic stroke. For the cryptogenic stroke group, the study found no significant difference in recurrent stroke or death at 2 years between patients given warfarin and those given aspirin (9.5% vs 17.9% [RD 8.4%, 95% CI −6.8% to 23.6%]). Although the point estimate suggests a potential benefit of warfarin, the results in patients without a PFO were very similar (8.3% vs 16.3%, RD 8%, 95% CI −2.4% to 18.2%), suggesting that any effect was unrelated to the presence of a PFO. Regardless, the range of CIs indicates that the study lacked the statistical precision to exclude clinically important superiority or inferiority of anticoagulation or antiplatelet therapy.

Our updated search identified a second randomized Class II study comparing aspirin with warfarin for secondary prevention in patients with cryptogenic stroke and PFO.[14] In this study, patients with cryptogenic stroke and PFO were randomly allocated to aspirin 240 mg/d (n = 24) or adjusted-dose warfarin with target INR 2 to 3 (n = 23) and followed for 18 months. Using the results reported, we were unable to compare recurrent stroke rates without including TIA events. However, the authors observed no significant difference in ischemic stroke risk (total 5) or TIA risk (total 2) between treatment groups (RD combined stroke and TIA favoring aspirin 15%, 95% CI −7.3% to 37%).

From evidence to conclusion. Because these Class II studies lacked the precision to exclude a potential benefit (or harm) of anticoagulation, we combined them in a random-effects meta-analysis (appendix e-9). There was no significant difference between treatments, and the summary estimate of effect was an RD of 2% favoring antiplatelet treatment (95% CI −21% to 25%). The CI of the pooled effect included potentially substantial benefits or harms of anticoagulation compared with antiplatelets.

For the start of the modified GRADE process, the confidence in evidence was anchored at *moderate* (appendix e-8) and then downgraded to *very low* because of severe imprecision and heterogeneity ($I^2 = 65\%$).

Conclusion. For patients with cryptogenic stroke and PFO, there is insufficient evidence to determine the efficacy of anticoagulation compared with antiplatelet therapy in preventing recurrent stroke (RD 2%, 95% CI −21% to 25% [2 Class II studies, confidence downgraded for severe imprecision and inconsistency]).

RECOMMENDATIONS Patients with stroke or TIA should have a careful evaluation to determine the cause and to optimize secondary stroke prevention.[15] Because of PFO prevalence in the general population and the high rate of alternative etiologies for recurrent strokes in the prospective studies of PFO, other causes must be excluded before attributing the stroke to the PFO. Judgment regarding any net benefit relative to harm for PFO closure requires a comparison of the magnitudes of effect and the confidence in evidence summarized in appendix e-8. Complicating this comparison is the unknown long-term potential for cumulative increased stroke reduction and late-onset closure device complications. Because of the limitations of the efficacy evidence and the potential for serious AEs, we judge the risk–benefit tradeoffs of PFO closure by either the STARFlex or AMPLATZER PFO Occluder to be uncertain.

Additional factors influence our recommendations (appendix e-11, clinical contextual profile). The STARFlex is not available for use. Some countries have the AMPLATZER PFO Occluder available for clinical use. (At the time of this writing, the AMPLATZER PFO Occluder is undergoing review by the US Food and Drug Administration.)

The costs associated with uncomplicated PFO closure are estimated to be $15,000 or higher.[16] Of note, a cost-effectiveness analysis concluded that PFO closure may be cost-effective in the long term.[17]

However, this analysis did not account for the uncertainty in the estimates of closure efficacy. We conclude that the cost-effectiveness and closure efficacy remain equally uncertain.

A final factor influencing the recommendations is anticipated variations in patient preferences because of varying perceptions of risk and ambiguity.[18] For example, patients who view having a PFO as a loss (as a "hole in the heart") may be more likely to seek closure despite the uncertainty of its benefits or known risks, whereas patients who view the potential reduction in stroke risk as a gain are more likely to be averse to the uncertainty of the benefits and associated risks of closure. Informing patients about the commonness of PFO within the general population[19] and the difficulty in determining whether their PFOs caused their symptoms will assist patients in selecting an appropriate decision reference frame.[20] Matters other than loss-or-gain framing can also influence patients' benefit–risk preferences and contribute to variations in patient preferences.[21]

1. Clinicians must counsel patients considering percutaneous PFO closure that having a PFO is common; it occurs in about 1 in 4 people; it is impossible to determine with certainty whether their PFOs caused their strokes or TIAs; the effectiveness of the procedure for reducing stroke risk remains uncertain; and the procedure is associated with relatively uncommon, yet potentially serious, complications (Level A).
2. Clinicians should not routinely offer percutaneous PFO closure to patients with cryptogenic ischemic stroke outside of a research setting (Level R). In rare circumstances, such as recurrent strokes despite adequate medical therapy with no other mechanism identified, clinicians may offer the AMPLATZER PFO Occluder if it is available (Level C).

Guidelines on secondary stroke prevention also recommend lifelong antithrombotic therapy.[15] Appendix e-8 summarizes the risk–benefit tradeoffs associated with the selection of antiplatelet therapy or anticoagulation for preventing recurrent strokes in patients with PFO. This recommendation assumes that there is no other indication (e.g., deep venous thrombosis) for anticoagulation. Because of the uncertainty surrounding the benefit of anticoagulation in the setting of PFO and anticoagulation's well-known harm profile, we judge that the risk–benefit tradeoff favors the use of antiplatelet medication.

3. In the absence of another indication for anticoagulation, clinicians may routinely offer antiplatelet medications instead of anticoagulation to patients with cryptogenic stroke and PFO (Level C).
4. In rare circumstances, such as stroke that recurs while a patient is undergoing antiplatelet therapy, clinicians may offer anticoagulation to patients with cryptogenic stroke and PFO (Level C).

RECOMMENDATIONS FOR FUTURE RESEARCH At least 3 large RCTs comparing PFO closure with medications are ongoing. Because of the low number of events in the trials that have been completed thus far, it is possible that these ongoing trials may fail to provide definitive evidence for efficacy, and the aggregate data may not define a patient population with a clear reduction in stroke risk and acceptable procedural risk profile. If so, additional RCTs may be required, and these future studies should make great efforts to carefully select patients who have limited vascular risk factors and have undergone a thorough evaluation to exclude other stroke etiologies.[22] This will enrich the study population with patients who have an increased chance of their PFOs being causally related to their strokes and, thus, increase the chance of potential benefit from closure. However, this will make recruitment difficult—especially if clinicians continue to close PFOs outside of a trial using off-label devices. In addition, these studies should use blinded endpoint ascertainment and adjudication (as opposed to open ascertainment with blinded endpoint adjudication), assess subsequent stroke risk and safety, and follow patients over a reasonably long period to compare the near- and long-term safety fairly with any subsequent stroke risk reduction. If a PFO closure device is approved in the United States, a postmarketing prospective, observational, long-term registry should be established to further inform our understanding of long-term benefits and risks. Finally, there are ongoing studies comparing novel anticoagulants, factor Xa inhibitors, and direct thrombin inhibitors with antiplatelet medications for the prevention of recurrent embolic stroke of uncertain source. Because the novel anticoagulant medications have less bleeding risk, effective venous thrombosis prevention, and greater convenience than warfarin, these medications may be viable alternatives for patients with stroke and a PFO, and it would be reasonable to consider studies in this patient population.

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AUTHOR CONTRIBUTIONS

Dr. Steven R. Messé: study concept and design, acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content, study supervision. Dr. Gary Gronseth: study concept and design, acquisition of data, analysis or interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content, study supervision. Dr. David M. Kent: acquisition of data, analysis or interpretation of data, critical revision of the manuscript for important intellectual content. Dr. Jorge R. Kizer: acquisition of data, analysis or interpretation of data, critical revision of the manuscript for important intellectual content. Dr. Shunichi Homma: acquisition of data, analysis or interpretation of data, critical revision of the manuscript for important intellectual content. Dr. Lee Rosterman: acquisition of data, analysis or interpretation of data, critical revision of the manuscript for important intellectual content. Dr. Scott E. Kasner: acquisition of data, analysis or interpretation of data, critical revision of the manuscript for important intellectual content.

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