

# 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



Steven R. Messé, MD  
Gary Gronseth, MD  
David M. Kent, MD,  
MSc  
Jorge R. Kizer, MD, MSc  
Shunichi Homma, MD  
Lee Rosterman, DO  
Scott E. Kasner, MD,  
MSCE

Correspondence to  
American Academy of Neurology:  
guidelines@aan.com

## 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.<sup>1</sup> 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](http://Neurology.org)

From the Department of Neurology (S.R.M., S.E.K.), University of Pennsylvania School of Medicine, Philadelphia; Department of Neurology (G.G., L.R.), University of Kansas Medical Center, Kansas City; Institute for Clinical Research and Health Policy Studies (D.M.K.), Tufts University School of Medicine, Boston, MA; Departments of Medicine (Cardiology) and Epidemiology and Population Health (J.R.K.), Albert Einstein College of Medicine, Bronx; and Division of Cardiology (S.H.), Columbia University Medical Center, New York, NY.

Approved by the Guideline Development, Dissemination, and Implementation Subcommittee on April 22, 2015; by the Practice Committee on August 25, 2015; and by the AAN Institute Board of Directors on June 2, 2016.

Go to [Neurology.org](http://Neurology.org) for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

process manual, as amended.<sup>2</sup> We summarize the process here and provide more detail in appendix e-1 on the *Neurology*<sup>®</sup> Web site at [Neurology.org](http://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.<sup>3</sup> Because of a lower risk of bias, when available, we used the intention-to-treat analysis<sup>4</sup> 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.<sup>5</sup> 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).<sup>6</sup>

**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.<sup>7-9</sup>

The CLOSURE I study<sup>7</sup> (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<sup>8</sup> (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<sup>9</sup> (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  $\sim 2.5$  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<sup>10</sup> 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,  $p = 0.09$ ).<sup>11</sup> 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)<sup>12</sup> 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.<sup>13</sup> 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.<sup>14</sup> In this study, patients with cryptogenic stroke and PFO were randomly allocated to aspirin  $240\text{ mg/d}$  ( $n = 24$ ) 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.<sup>15</sup> 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.<sup>16</sup> Of note, a cost-effectiveness analysis concluded that PFO closure may be cost-effective in the long term.<sup>17</sup>

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.<sup>18</sup> 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<sup>19</sup> and the difficulty in determining whether their PFOs caused their symptoms will assist patients in selecting an appropriate decision reference frame.<sup>20</sup> Matters other than loss-or-gain framing can also influence patients’ benefit–risk preferences and contribute to variations in patient preferences.<sup>21</sup>

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.<sup>15</sup> 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.<sup>22</sup> 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.

**DISCLAIMER** Clinical practice guidelines, practice advisories, systematic reviews, and other guidance published by the AAN and its affiliates are assessments of current scientific and clinical information provided as an educational service. The information (1) should not be considered inclusive of all proper treatments, methods of care, or as a statement of the standard of care; (2) is not continually updated and may not reflect the most recent evidence (new evidence may emerge between the time information is developed and when it is published or read); (3) addresses only the questions specifically identified; (4) does not

mandate any particular course of medical care; and (5) is not intended to substitute for the independent professional judgment of the treating provider, as the information does not account for individual variation among patients. In all cases, the selected course of action should be considered by the treating provider in the context of treating the individual patient. Use of the information is voluntary. The AAN provides this information on an “as is” basis and makes no warranty, expressed or implied, regarding the information. The AAN specifically disclaims any warranties of merchantability or fitness for a particular use or purpose. The AAN assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of this information or for any errors or omissions.

**CONFLICT OF INTEREST** The AAN is committed to producing independent, critical, and truthful practice advisories. Significant efforts are made to minimize the potential for conflicts of interest to influence the recommendations of this practice advisory. To the extent possible, the AAN keeps separate those who have a financial stake in the success or failure of the products appraised in the practice advisories and the developers of the practice advisories. Conflict of interest forms were obtained from all authors and reviewed by an oversight committee prior to project initiation. The AAN limits the participation of authors with substantial conflicts of interest. The AAN forbids commercial participation in, or funding of, practice advisory projects. Drafts of the practice advisory have been reviewed by at least 3 AAN committees, a network of neurologists, *Neurology* peer reviewers, and representatives from related fields. The AAN Guideline Author Conflict of Interest Policy can be viewed at [www.aan.com](http://www.aan.com). For complete information on this process, access the 2011 AAN process manual.<sup>2</sup>

#### 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.

#### STUDY FUNDING

This practice advisory was developed with financial support from the American Academy of Neurology. Authors who serve as AAN subcommittee members or methodologists (S.R.M., G.G.) were reimbursed by the

AAN for expenses related to travel to subcommittee meetings where drafts of manuscripts were reviewed.

#### DISCLOSURE

S. Messé has received funding from the NIH (U01-DK060990, UM1 HL088957-06, HHSN268200800003C, 1R01HL084375-01A2), is a consultant for GlaxoSmithKline (protocol development), has received research funding from GlaxoSmithKline and WL Gore & Associates as an investigator for the Gore REDUCE trial, and served as a subinvestigator for the CLOSURE-I trial. G. Gronseth was an investigator for the RESPECT trial, serves as an associate editor for *Neurology* and as an editorial advisory board member of *Neurology Now*, and receives compensation from the AAN for work as the chief evidence-based medicine methodologist. D. Kent has received funding from the NIH (R21 NS079826, R01 NS062153), the Patient-Centered Outcomes Research Institute (ME-1306-03758, 11P2-P1000722), Genentech, Inc., and the National Pharmaceutical Council; has received funding for travel from the commercial and nonprofit entities Oregon Health & Science University (Oregon Institute for Patient-Centered Comparative Effectiveness Annual Research Intensive, July 2013), Mayo Clinic (Center for Translational Science Activities Grand Rounds, September 2013), and Pfizer (Learning Series in Dubai, September 2013); and received honoraria from Pfizer (Learning Series in Dubai, September 2013) and *American Scientist* (2015 publication). J. Kizer has received funding from the NIH (R01 HL094555), has received compensation from Pfizer for expert witness consultation relating to PremPro use and stroke, has received honoraria from ClearView Healthcare Partners for consultation on the application of imaging modalities for evaluation of cardiovascular disease, and reports stock ownership in Pfizer, Inc., and Gilead Sciences, Inc. S. Homma has received financial compensation for serving on scientific advisory boards for Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, and Pfizer; has served on the data safety monitoring board (DSMB) for the RESPECT trial; has served on the editorial board for *Circulation Journal*; and has received honoraria from Lankenau Medical Center and research support from the NIH. L. Rosterman reports no disclosures relevant to the manuscript. S. Kasner was an investigator for the CLOSURE-I trial and is the US principal investigator for the REDUCE trial; is a consultant to Novartis (endpoint adjudication committee), Merck (endpoint adjudication committee), Medtronic (DSMB), Pfizer (endpoint adjudication committee), AstraZeneca (trial steering committee), Abbvie (endpoint adjudication committee), Daiichi Sankyo (trial steering committee), and Boehringer Ingelheim (scientific advisory board); has had funding for travel from WL Gore & Associates, AstraZeneca, Boehringer Ingelheim, and Daiichi Sankyo; is a member of the editorial boards of *UpToDate*, *Stroke*, *Journal of Stroke and Cerebrovascular Diseases*, *Frontiers in Stroke*, *Practical Neurology*, and *Stroke Research and Treatment*; receives publishing royalties from *UpToDate*; has received research grant support from WL Gore & Associates, AstraZeneca, GlaxoSmithKline, Bayer, and the NIH; and has given expert testimony in medical-legal proceedings. Go to [Neurology.org](http://Neurology.org) for full disclosures.

Received September 3, 2015. Accepted in final form May 3, 2016.

#### REFERENCES

1. Messé SR, Silverman IE, Kizer JR, et al; Quality Standards Subcommittee of the American Academy of Neurology. Practice parameter: recurrent stroke with patent foramen ovale and atrial septal aneurysm: report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2004;62:1042–1050.
2. American Academy of Neurology. Clinical Practice Guidelines Process Manual, 2011 ed. [online]. Available at: <https://www.aan.com/Guidelines/Home/Development>. Accessed November 1, 2011.
3. Castle J, Mlynash M, Lee K, et al. Agreement regarding diagnosis of transient ischemic attack fairly low among stroke-trained neurologists. *Stroke* 2010;41:1367–1370.
4. The Cochrane Collaboration. Higgins JPT, Green S. eds. *Cochrane Handbook for Systematic Reviews of*

- Interventions, version 5.1.0 [updated March 2011]. Available at: [handbook.cochrane.org](http://handbook.cochrane.org). Accessed November 1, 2011.
5. 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;336:924–926.
  6. Gronseth G. Bedside evidence-based medicine. Conference course, 66th American Academy of Neurology annual meeting; April 30, 2014; Philadelphia.
  7. 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; 366:991–999.
  8. 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;368:1083–1091.
  9. Carroll JD, Saver JL, Thaler DE, et al; RESPECT Investigators. Closure of patent foramen ovale versus medical therapy after cryptogenic stroke. *N Engl J Med* 2013;368:1092–1100.
  10. 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: 907–917.
  11. Kent D, Thaler D. Device closure in patent foramen ovale and stroke: a meta-analysis of individual patient data from randomized trials. Abstract Presented at International Stroke Conference; February 12, 2015; Nashville, TN.
  12. 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;105:2625–2631.
  13. Mohr J, Thompson JLP, Lazar RM, et al; the Warfarin-Aspirin Recurrent Stroke Study Group. A comparison of warfarin and aspirin for the prevention of recurrent ischemic stroke. *N Engl J Med* 2001;345:1444–1451.
  14. Shariat A, Yaghoubi E, Farzadaghi 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;18:94–98.
  15. Kernan WN, Ovbiagele B, Black HR, et al; American Heart Association Stroke Council, Council on Cardiovascular Stroke Nursing, Council on Clinical Cardiology, 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;45:2160–2236.
  16. Rhodes JF. PFO closure for prevention of recurrent cryptogenic stroke: the evidence base is here. *Cardiac Interventions Today* 2008. Available at: [http://citoday.com/2008/11/CIT1108\\_07.php](http://citoday.com/2008/11/CIT1108_07.php). Accessed May 1, 2014.
  17. 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;114:1584–1589.
  18. Kahneman D, Tversky A. Prospect theory: an analysis of decision under risk. *Econometrica* 1979;47:263–291.
  19. Hagen PT, Scholz DG, Edwards WD. Incidence and size of patent foramen ovale during the first 10 decades of life: an autopsy study of 965 normal hearts. *Mayo Clin Proc* 1984; 59:17–20.
  20. Thomas AK, Millar PR. Reducing the framing effect in older and younger adults by encouraging analytic processing. *J Gerontol B Psychol Sci Soc Sci* 2012;67:139–149.
  21. Brett Hauber A, Fairchild AO, Reed Johnson F. Quantifying benefit-risk preferences for medical interventions: an overview of a growing empirical literature. *Appl Health Econ Health Policy* 2013;11:319–329.
  22. Kent DM, Ruthazer R, Weimar C, et al. An index to identify stroke-related vs incidental patent foramen ovale in cryptogenic stroke. *Neurology* 2013;81:619–625.

# Neurology<sup>®</sup>

## **Practice advisory: Recurrent stroke with patent foramen ovale (update of practice parameter) [RETIRED]: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology**

Steven R. Messé, Gary Gronseth, David M. Kent, et al.

*Neurology* 2016;87;815-821 Published Online before print July 27, 2016

DOI 10.1212/WNL.0000000000002961

**This information is current as of July 27, 2016**

<b>Updated Information &amp; Services</b>	including high resolution figures, can be found at: <a href="http://n.neurology.org/content/87/8/815.full">http://n.neurology.org/content/87/8/815.full</a>
<b>Supplementary Material</b>	Supplementary material can be found at: <a href="http://n.neurology.org/content/suppl/2016/07/27/WNL.000000000002961.DC1">http://n.neurology.org/content/suppl/2016/07/27/WNL.000000000002961.DC1</a>
<b>References</b>	This article cites 17 articles, 7 of which you can access for free at: <a href="http://n.neurology.org/content/87/8/815.full#ref-list-1">http://n.neurology.org/content/87/8/815.full#ref-list-1</a>
<b>Citations</b>	This article has been cited by 3 HighWire-hosted articles: <a href="http://n.neurology.org/content/87/8/815.full##otherarticles">http://n.neurology.org/content/87/8/815.full##otherarticles</a>
<b>Subspecialty Collections</b>	This article, along with others on similar topics, appears in the following collection(s): <b>All Cerebrovascular disease/Stroke</b> <a href="http://n.neurology.org/cgi/collection/all_cerebrovascular_disease_stroke">http://n.neurology.org/cgi/collection/all_cerebrovascular_disease_stroke</a>
<b>Permissions &amp; Licensing</b>	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: <a href="http://www.neurology.org/about/about_the_journal#permissions">http://www.neurology.org/about/about_the_journal#permissions</a>
<b>Reprints</b>	Information about ordering reprints can be found online: <a href="http://n.neurology.org/subscribers/advertise">http://n.neurology.org/subscribers/advertise</a>

*Neurology*® is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright © 2016 American Academy of Neurology. All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.

