Practice advisory update: Patent foramen ovale and secondary stroke prevention

Report of the Guideline Subcommittee of the American Academy of Neurology

Steven R. Messé, MD[1]; Gary S. Gronseth, MD[2]; David M. Kent, MD, MSc[3]; Jorge R. Kizer, MD, MSc[4]; Shunichi Homma, MD[5]; Lee Rosterman, DO[2]; John D. Carroll, MD[6]; Koto Ishida, MD[7]; Navdeep Sangha, MD[8]; Scott E. Kasner, MD, MSCE[1]

[1]Department of Neurology, University of Pennsylvania School of Medicine, Philadelphia

[2]Department of Neurology, University of Kansas Medical Center, Kansas City

[3]Institute for Clinical Research and Health Policy Studies, Tufts University School of Medicine, Boston, MA

[4]Cardiology Section, San Francisco Veterans Affairs Health Care System, and Departments of Medicine, and Epidemiology and Biostatistics, University of California San Francisco, San Francisco, CA.

[5]Division of Cardiology, Columbia University Medical Center, New York, NY

[6]Department of Medicine (Cardiology), University of Colorado School of Medicine, Aurora

[7]Department of Neurology, New York University, New York

[8]Department of Neurology, Kaiser Permanente, Los Angeles, CA

Address correspondence and reprint requests to

American Academy of Neurology:

guidelines@aan.com

Title character count: 78

Abstract word count: 228

Manuscript word count: 3,434

Approved by the American Academy of Neurology (AAN) Guideline Subcommittee on September 18, 2019; by the AAN Quality Committee on February 18, 2020; and by the AAN Institute Board of Directors on March 17, 2020.

This practice advisory update was endorsed by the Society for Cardiovascular Angiography 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.

AUTHOR CONTRIBUTIONS

Dr. 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. Gronseth: Study concept and design, acquisition of data, analysis or interpretation of data, revising the manuscript, critical revision of the manuscript for important intellectual content, study supervision

Dr. Kent: Critical revision of the manuscript for important intellectual content

Dr. Kizer: Critical revision of the manuscript for important intellectual content

Dr. Homma: Critical revision of the manuscript for important intellectual content

Dr. Rosterman: Critical revision of the manuscript for important intellectual content

Dr. Carroll: Critical revision of the manuscript for important intellectual content

Dr. Ishida: Critical revision of the manuscript for important intellectual content

Dr. Sangha: Critical revision of the manuscript for important intellectual content

Dr. Kasner: Critical revision of the manuscript for important intellectual content, study supervision

STUDY FUNDING

This practice advisory was developed with financial support from the American Academy of Neurology (AAN). Authors who serve as AAN subcommittee members or as methodologists (S.R.M., G.S.G., K.I., N.S.) were reimbursed by the AAN for expenses related to travel to subcommittee meetings where drafts of manuscripts were reviewed.

DISCLOSURE

S. Messé has received royalties for articles written for UpToDate, including articles on antiplatelets for secondary stroke prevention, coronary artery bypass graft surgery in patients with cerebrovascular disease, and patent foramen ovale (PFO) and stroke; has received support from WL Gore and Associates for the REDUCE PFO closure study, from GlaxoSmithKline for a study of outcomes from proximal aortic surgeries, from Bayer for a study of rivaroxaban for secondary stroke prevention in patients with embolic stroke of undetermined source, from Mallinkrodt for a study of the impact of inhaled nitric oxide on cerebral perfusion, from Novartis for a study of BAF312 in patients with intracerebral hemorrhage (ICH), from Biogen for a study of glibenclamide for cerebral edema following large hemispheric infarction; and received support from the National Institutes of Health (NIH) for work with the cardiothoracic surgery network, deferoxamine in ICH, neurologic outcomes in a renal insufficiency cohort; and has provided his expert opinion for medical-legal cases involving stroke.

G. Gronseth serves as an associate editor for *Neurology*; has served as chief evidence-based medicine consultant for the American Academy of Neurology (AAN); and serves as an editorial advisory board member of *Brain & Life.*

D. Kent serves on the editorial board for *Diagnostic and Prognostic Research* and has received research and consultant funding from the Patient-Centered Outcomes Research Institute (PCORI), NIH, Veterans Administration Health Services, Biogen, and Janssen.

J. Kizer reports stock ownership in Amgen, Bristol-Myers Squibb, Gilead Sciences, Johnson & Johnson, Medtronic, Merck, and Pfizer; has served as editor of the "Clinical Trials and Their Interpretation" section of *Current Atherosclerosis Reports*; has received research support from NIH (National Heart, Lung, and Blood Institute, National Institute on Aging, National Institute of Allergy and Infectious Diseases) and PCORI; and has given expert witness consultation for a legal case involving hypertension management.

S. Homma served on the data and safety monitoring board for the RESPECT trial; has received funding for travel from the American College of Cardiology; and has received research support from the NIH and the University of South Florida.

L. Rosterman has received honoraria for a lecture on acute stroke management for rural outreach.

J. Carroll serves on the Society of Cardiac Angiography and Intervention's Writing Committee for Operator and Institutional Requirements for PFO Closure; has been on the steering committee for the RESPECT trial, with sponsors including Abbott Vascular, AGA Medical, and St. Jude Medical; has received funding for travel for RESPECT Steering Committee responsibility; holds a patent for 3D coronary reconstruction software–licensed by Phillips

Medical; receives honoraria from grand rounds at various academic institutions; performs PFO closure approximately (3−5 PFO closures per month); has received research support from the Steering Committee of RESPECT trial and Steering Committee of AMULET trial (LAA Occlusion); receives license fee payments related to 3D coronary imaging software; receives royalty payments or has contractual rights for receipt of future royalty payments for 3D coronary imaging software; serves as a member of the editorial board for *Circulation*: *Cardiovascular Interventions* and the journals of the Society for Cardiovascular Angiography and Interventions; receives royalties for publishing from *Structural Heart Disease Interventions* (coedited textbook) and UpToDate (section on mitral valvuloplasty); and has provided consultation for a legal firm defending suits related to alleged inappropriate use of PFO closure by an individual physician.

K. Ishida has received royalties for articles written for UpToDate, including articles on blood biomarkers for stroke and medical complications of stroke, prevention and treatment of venous thromboembolism in patients with acute stroke, and medical complications of stroke, and has received funding for travel from the AAN.

N. Sangha has received travel reimbursement from the AAN.

S. Kasner served as principal investigator for the REDUCE trial (WL Gore); serves as a consultant to Medtronic; served on a trial steering committee for Bayer; served on an endpoint adjudication committee for AbbVie; serves on a trial steering committee for Bristol Meyers Squibb; served on a scientific advisory board for Boehringer Ingelheim; has received funding for travel from WL Gore & Associates and Bayer; has received research support from WL Gore &

Associates, Bayer, Acorda, Medtronic, and the NIH; is a member of the editorial boards of UpToDate, *Stroke, Journal of Stroke and Cerebrovascular Diseases,* and *Practical Neurology*; receives publishing royalties from UpToDate; and has given expert testimony in medical-legal proceedings.

GLOSSARY

AAN: American Academy of Neurology

CE: Conformité Européenne

CI: confidence interval

COI: conflict of interest

CTA: CT angiography

CV: curriculum vitae

DOAC: direct oral anticoagulant

GRADE: Grading of Recommendations Assessment, Development and Evaluation

HR: hazard ratio

MRA: MR angiography

NT-proBNP: N-terminal pro b-type natriuretic peptide

PFO: patent foramen ovale

RD: risk difference

RR: risk ratio

SGS: symmetric Gauss–Seidel

TCD: transcranial Doppler ultrasonography

TEE: transesophageal echocardiography

TTE: transthoracic echocardiography

ABSTRACT

Objective: To update the 2016 American Academy of Neurology (AAN) practice advisory for patients with stroke and patent foramen ovale (PFO).

Methods: The guideline panel followed the AAN 2017 guideline development process to systematically review studies published through December 2017 and formulate recommendations.

Major recommendations: 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 (Level B). In patients with a higher risk alternative mechanism of stroke identified, clinicians should not routinely recommend PFO closure (Level B). 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 (Level B). In patients younger than 60 years with a PFO and embolic-appearing infarct and no other mechanism of stroke identified, clinicians may recommend closure following a discussion of potential benefits (absolute recurrent stroke risk reduction of 3.4% at 5 years) and risks (periprocedural complication rate of 3.9% and increased absolute rate of nonperiprocedural atrial fibrillation of 0.33% per year)) (Level C). In patients who opt to receive medical therapy alone without PFO closure, clinicians may recommend an antiplatelet medication such as aspirin or anticoagulation (Level C).

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.

DESCRIPTION OF THE ANALYTIC PROCESS

This update follows the 2017 AAN's guideline development process manual.[2] In April 2018, the AAN Guideline Subcommittee (appendices e-1 and e-2) convened an author panel of neurologists, internists, and cardiologists with expertise in stroke and PFO. All authors submitted relationship disclosure forms and copies of their curriculum vitae, which were reviewed by the panel lead author (S.R.M.) and AAN methodologist (G.S.G.) as well as AAN staff and Guideline Subcommittee leadership for financial and intellectual conflicts of interest (COI). A majority of the author panel (S.R.M., G.S.G., S.H., K.I., D.M.K., L.R., N.S.) are free of COI relevant to the subject matter of this practice advisory. The systematic literature review was performed by the

lead author (S.R.M.), AAN methodologist (G.S.G.), and members of the Guideline Subcommittee, who had no COI. The author panel performed a literature search of Medline and the Cochrane Library to identify randomized studies published between March 2015 and January 2018 (see appendix e-3 for complete search strategy) pertinent to the clinical questions. Studies were independently rated for their risk of bias by the AAN methodologist (G.S.G.) and lead author (S.R.M.) (appendix e-4). The search was updated in August 2019 to identify studies published since January 2018.

Consistent with prior AAN guidelines on this topic, the primary outcome of interest was recurrent stroke. The panel used study-reported, procedure-related serious adverse events and non-periprocedural atrial fibrillation, whose definition varied across studies, as the primary safety outcomes. Transient periprocedural atrial fibrillation is of uncertain clinical consequence following catheter-based cardiac procedures and generally does not lead to long-term anticoagulation or high risk of stroke.

To minimize bias, the panel relied on intention-to-treat analyses to inform conclusions. For the primary summary analysis, the panel used studies with the lowest risk of bias and excluded studies of devices that are not being manufactured and are not available.

Ratio measures were pooled by meta-analyses to obtain summary estimates of effect. Because of the low event rates, hazard ratios (HRs), risk ratios (RRs), and odds ratios were considered comparable. For pooling effect sizes, a random-effects meta-analytic model was desired because of the substantive heterogeneity between studies in closure devices, inclusion and exclusion criteria, and medical treatments. However, standard inverse variance methods can have poor statistical coverage when event rates are low,[3] such as with the PFO closure trials. In addition,

non−inverse-variance random-effects methods appropriate for studies of rare events have poor precision when the number of studies is low.[4] Thus, for the primary efficacy analysis of recurrent stroke, the panel selected a hybrid approach for meta-analysis[5]: a fixed-effect model for hypothesis testing of a treatment effect using inverse variance methods to pool HRs and a random-effects model of RRs designed for low event rates (the weighted symmetric Gauss–Seidel [SGS] algorithmic method[6]) to explore heterogeneity of effect sizes. Sensitivity analyses were performed to determine the effect of including trials with a higher risk of bias and trials that employed devices that are not available. Additional sensitivity analyses were performed to compare the effect of different meta-analytic techniques. To improve clinical interpretability, the panel calculated risk differences (RDs) or rate differences from pooled RRs and baseline recurrent stroke risk from the nonclosure arms of the included studies. Prespecified subgroups of interest included age, shunt size (as defined by each study), presence of atrial septal aneurysm (as defined by each study), antithrombotic management (antiplatelet vs anticoagulation) in patients who are medically treated, and whether the index stroke appeared embolic (e.g., not a single, small, and subcortical infarct in the distribution of a perforator artery).

The overall confidence in the evidence was determined using a modified Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[2,7,8] The confidence in the evidence (high, moderate, low, or, very low) was anchored to the domain (intrinsic validity, extrinsic validity, and precision) with the highest risk of error. This confidence was upgraded or downgraded by a maximum of one level based on several other factors including heterogeneity, magnitude of effect, presence of a dose-response, and the direction of bias. The panel then derived recommendations using an iterative modified Delphi process after

considering the evidence strength, risks and benefits, cost, availability, and patient preference variations.

ANALYSIS OF EVIDENCE

The initial literature search identified 628 unique articles, of which 8 met inclusion criteria, including one article that provided extended follow-up from a trial that had been included in the prior practice advisory.[1] Each article underwent evidence classification and data extraction (appendices e-4 and e-5). Only those studies that drove conclusions and recommendations are discussed.

In patients with a PFO who have had a cryptogenic ischemic stroke, does percutaneous PFO closure reduce the risk of stroke recurrence compared with medical therapy alone?

Evidence

The 2016 practice advisory included 3 studies.[9-11] The most recent classification of evidence scheme for therapeutic studies[2] downgraded each study to Class II because participants and their caregivers were unblinded to treatment assignment and actual treatment received and, for most studies, initial endpoint ascertainment was unblinded (appendix e-4). These studies were described in detail previously, and the study design and outcomes of all studies included in this guideline are summarized in appendices e-6 and e-7, including stroke risk reduction and adverse events.[1]

The CLOSURE I study (Class II, endpoint ascertainment was unblinded and participants and their caregivers were unblinded to treatment assignment and actual treatment received) was a multicenter, randomized, open-label trial of 909 participants aged 18 to 60 years with PFO and a cryptogenic stroke or TIA (all other studies discussed only included patients with stroke) that compared the STARFlex percutaneous closure device (NMT Medical, Inc.) with medical therapy alone and observed the participants for a median of 2 years.[9] Recurrent stroke occurred in 2.9% of participants who underwent closure and in 3.1% of those receiving medical therapy alone (RD -0.2%, 95% confidence interval [CI] -2.5% to 2.1%). The rate of serious non-periprocedural atrial fibrillation was not different between groups, with a rate difference of 0.7% per year (95% CI -0.07% to 1.6% per year), and major procedural complications were reported in 3.2% (95% CI 1.9% to 5.5%).

The PC Trial (Class II, endpoint ascertainment was unblinded, and participants and their caregivers were unblinded to treatment assignment and actual treatment received) randomized 414 participants younger than 60 years to medical therapy or closure with the AMPLATZER PFO Occluder (Abbot, Inc.) and observed them for an average of 4 years.[10] There was no significant difference in stroke recurrence, with a rate difference of -0.48% per year (95% CI -1.2% to 0.12%) for participants who underwent closure compared with participants assigned to medical therapy. New onset non-periprocedural atrial fibrillation was not different between trial arms, with a rate difference of 0.1% per year (95% CI -0.58% to 0.58%), and major procedural complications were reported in 1.5% (95% CI 0.5% to 4.2%).

In the RESPECT trial (Class II, participants and their caregivers were unblinded to treatment assignment and actual treatment received), 980 participants aged 18 to 60 years were randomized to the AMPLATZER PFO Occluder (St. Jude Medical, Inc.) or medical therapy consisting of antiplatelet medication or anticoagulation.[11] The median duration of follow-up was 2.1 years. In the intention-to-treat analysis, recurrent stroke was reported in 9 of 499 (1.8%) participants assigned to device closure compared with 16 of 481 (3.3%) in the medical arm (rate difference -0.70% per year, 95% CI -1.56% to 0.08% per year).

Four new articles met inclusion criteria, of which 3 are Class II and one Class III for risk of bias. The RESPECT trial (Class II, participants and their caregivers were unblinded to treatment assignment and actual treatment received) continued to follow participants beyond the first prespecified analysis, for a median of 5.9 years.[12] This was the third analysis from this trial, and only these updated data were included in the summary of effects discussion of this guideline. Recurrent strokes occurred in 28 participants randomized to medical therapy and 18 participants assigned to closure (rate difference -0.47% per year, 95% CI -0.97% to -0.01% per year). The rates of new onset non-periprocedural atrial fibrillation were not different, comparing participants receiving closure with those receiving medical treatment, with a rate difference of 0.14% (95% CI -0.2% to 0.49%). Procedural complications occurred in 5% (95% CI 3.4% to 7.3%). Of note, pulmonary embolism was reported to be more common after closure (0.41% per year in the PFO closure arm and 0.11% per year in the medical arm, HR 3.48; 95% CI 0.98 – 12.34; p=0.04) and deep vein thrombosis was numerically more common as well (0.16% per year in the closure arm and 0.04% per year in the medical arm, HR, 4.44; 95% CI, 0.52 to 38.05; p=0.14). This increased risk of venous thromboembolic events in the closure arm was possibly

caused by the difference in use of anticoagulation in the medical arm compared with the closure arm (21.6% vs 3.3%, respectively).

The CLOSE trial (Class II, endpoint ascertainment was unblinded, and participants and their caregivers were unblinded to treatment assignment and actual treatment received) randomized 663 participants aged 18 to 59 years with PFO and cryptogenic non−small-vessel stroke and an atrial septal aneurysm and/or large shunt in a 1:1:1 ratio to aspirin, anticoagulation, or PFO closure with any device marked Conformité Européenne (CE).[13] In total, 11 different devices were used, with the Abbott AMPLATZER PFO Occluder device being the most common (51%), followed by the Cardia Intrasept PFO Occluder (13%). In the anticoagulation arm, 93% of participants received a vitamin K antagonist. The investigators reported no strokes in the closure group and 14 strokes in the antiplatelet group, for a rate difference of -0.78% per year (95% CI -1.22% to -0.43% per year). The study authors did not provide a statistical comparison between anticoagulation and PFO closure but reported 3 strokes in the anticoagulation group, one of which was a subarachnoid hemorrhage, rate difference -0.31% per year (95% CI -0.84% to 0.01%) favoring closure. Procedural complications were reported in 5.9% (95% CI 3.5% to 9.6%), and non-periprocedural atrial fibrillation occurred more commonly in participants who received closure (rate difference 0.76% per year, 95% CI 0.309% to 1.40% per year).

The REDUCE trial (Class II, endpoint ascertainment was unblinded, and participants and their caregivers were unblinded to treatment assignment and actual treatment received) randomized 664 participants with PFO and embolic-appearing cryptogenic stroke in a 2:1 ratio to closure with a GORE HELEX Septal Occluder/CARDIOFORM Septal Occluder or antiplatelet

therapy.[14] After a median 3.2 years of follow-up, recurrent strokes occurred in 1.4% of the closure arm and in 5.4% of participants treated with antiplatelet therapy, for a rate difference of -1.32% per year (95% CI -2.53% to -0.43% per year). Follow-up with MRI at 2 years showed no difference in the rate of new subclinical infarct in a comparison of participants in the closure arm with those in the medical arm, 4.4% vs 4.5%, respectively (HR 0.98, 95% CI 0.43 to 2.23, *p*=0.97). Procedural complications occurred in 3.9% (95% CI 2.4% to 6.1%), and non-periprocedural atrial fibrillation was not different when participants receiving PFO closure were compared with those receiving medical treatment, with a rate difference 0.51% per year (95% CI -0.12% to 1.04%).

The DEFENSE-PFO trial (Class III, endpoint ascertainment was unblinded, participants and their caregivers were unblinded to treatment assignment and actual treatment received, and there was no blinded adjudication of outcomes), performed at 2 sites in South Korea, randomized 120 participants aged 18 to 80 years (mean 52 years) with embolic-appearing cryptogenic stroke and large PFO or with atrial septal aneurysm to closure with the AMPLATZER PFO Occluder (Abbott Medical) or medical therapy consisting of antiplatelet therapy or anticoagulation.[15] Participants were observed for a median of 2.8 years (interquartile range, 0.9–4.1 years). There were no recurrent strokes in those participants who underwent closure and 5 recurrent strokes in participants treated medically, for a rate difference of -3.57% per year (95% CI -7.42% to -0.87%). Periprocedural complications occurred in 3.3% (95% CI 0.9% to 11.3%), and there was no reported non-periprocedural atrial fibrillation.

Evidence synthesis and summary of effects

Incorporating all 4 Class II studies into a fixed-effects meta-analysis (appendix e-8, section A) shows that PFO closure was associated with a summary HR for recurrent stroke of 0.41 (95% CI 0.25 to 0.67, I^2=12%). A random-effects SGS-weighted meta-analysis of these studies yielded a similar summary RR of 0.36 (95% CI 0.05 to 2.58), but the much wider CIs suggest considerable uncertainty regarding the magnitude of the risk reduction. The panel performed sensitivity analyses adding data from CLOSURE I and DEFENSE-PFO, which yielded a similar summary HR for recurrent stroke of 0.48 (95% CI 0.32 to 0.73, I^2=42%) using a fixed-effects model and a similar summary RR of 0.42 (95% CI 0.16 to 1.12) using the SGS-weighted random-effects model. A comparison of varying meta-analytic techniques to pool results also did not substantially affect the effect size estimates (appendix e-8, section B).

When the AAN's modified GRADE process was applied, the overall confidence in the evidence for PFO closure efficacy was judged moderate given the consistent Class II evidence.

Subgroup analyses (appendix e-9) demonstrated no interactions for benefit of closure based on patient age (dichotomized as <45 years vs 45−60 years), presence or absence of atrial septal aneurysm, and medication comparator (antiplatelet vs anticoagulation). There were, however, significant interactions for shunt size and radiographic appearance of the stroke, with no clear benefit of closure in those participants without large shunts ([HR 0.9, 95% CI 0.5 to 1.6) or those with small deep strokes (HR 2.3, 95% CI 0.4 to 13.3). The definition of large shunt varied across studies but ranged from identifying >20-30 microbubbles in the left atrium within three cardiac cycles of seeing opacification of the right atrium (see appendix e-6).

In the medical arms of the included studies, the pooled (random effects, inverse variance) absolute baseline rate of recurrent stroke was 0.9 recurrent strokes per 100 patient-years (95% CI 0.6 to 1.2). The pooled absolute rate reduction of recurrent stroke from closure was -0.67 strokes per 100 patient-years (95% CI -0.9 to -0.4).

Focusing on adverse events, a random-effects meta-analysis of the included studies in the primary analysis finds that PFO closure was associated with a risk of major procedural complications of 3.9% (95% CI 2.3% to 5.7%). The panel's confidence in the evidence for periprocedural complications associated with closure is moderate because of consistent Class II evidence.

Fixed-effect meta-analyses appendix e-8, section C demonstrated an increased risk of developing any atrial fibrillation, RR 3.12 (95% CI 1.71 to 5.68, $I^2 = 45\%$), and study-defined serious non-periprocedural atrial fibrillation, RR 2.72 (95% CI 1.30 to 5.68, $I^2 = 0\%$) (appendix e-8, section C) associated with a pooled absolute rate increase of 0.33 cases per 100 patient-years (95% CI -0.9 to -0.4) in participants who received closure compared with those receiving medical treatment. As with the recurrent stroke risk, a random-effects meta-analysis appropriate for low event rates (SGS weighted) highlighted the uncertainty in the estimate of the magnitude of increased risk of serious non-periprocedural atrial fibrillation, RR 2.87 (95% CI 0.834 to 9.872). The rate of non-periprocedural atrial fibrillation was not meaningfully different when the meta-analysis included the CLOSURE I trial. The panel's confidence in the evidence for the increased risk of atrial fibrillation associated with closure is moderate because of consistent Class II evidence.

Conclusions

For patients with cryptogenic stroke and PFO, percutaneous PFO closure probably reduces the risk of stroke recurrence with an HR of 0.41 (95% CI 0.25 to 0.67, I^2=12%) and an absolute risk reduction of 3.4% (95% CI 2.0% to 4.5%) at 5 years; probably is associated with a periprocedural complication rate of 3.9% (95% CI 2.3% to 5.7%); and probably is associated with the development of serious non-periprocedural atrial fibrillation, with a relative risk of 2.72 (95% CI 1.30 to 5.68, I^2=0%).

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 updated literature search identified 5 trials that met the author panel's inclusion criteria (appendices e-3 and e-5), of which 2 were included in the prior practice advisory[1]. On the basis of the current scheme for risk of bias for therapeutic studies (appendix e-4), each study was rated Class II. The first study was the PFO in Cryptogenic Stroke Study (Class II, owing to being a subgroup analysis of a larger trial), a substudy of a larger randomized trial of warfarin vs aspirin in patients with stroke or TIA without atrial fibrillation or extracranial carotid stenosis, in which 630 participants with stroke referred by their clinicians to undergo transesophageal echocardiography (TEE) were randomized to warfarin (n=312) or aspirin (n=318).[16] Of this cohort, 98 participants were deemed to have had a cryptogenic stroke and had a PFO. In this

subgroup, there was no significant difference in recurrent stroke at 2 years between participants given warfarin and those given aspirin, 2/42 (4.8%) vs 8/56 (14.3%), respectively (HR 0.52, 95% CI 0.16 to 1.67). Another small study randomized 47 participants with cryptogenic stroke and PFO to aspirin 240 mg/d (n = 24) or dose-adjusted warfarin with target international normalized ratio 2 to 3 (n = 23) and observed them for 18 months (Class II, owing to unblinded endpoint ascertainment; participants and their caregivers were unblinded to treatment assignment and actual treatment received).[17] The results did not provide recurrent stroke rates separate from TIA events. However, they reported no difference in ischemic stroke (5) or TIA (2) events between treatment groups (HR combined stroke and TIA favoring aspirin 3.03, 95% CI 0.59 to 16.7). The CLOSE study[13] described previously (Class II, owing to unblinded endpoint ascertainment; participants and their caregivers were unblinded to treatment assignment and actual treatment received) included a 3-way randomization between PFO closure, antiplatelet medication, and anticoagulation. There was no significant difference in stroke recurrence rate among participants given anticoagulation compared with those given antiplatelet therapy, HR 0.44 (95% CI 0.11 to 1.48). Two additional studies compared direct oral anticoagulants (DOACs) to antiplatelet medication in patients with embolic stroke of undetermined source and reported the outcomes separately for patients with PFO. The first is the NAVIGATE-ESUS trial (Class II due to being a subgroup analysis of a larger trial) which randomized patients to aspirin 100 mg daily or rivaroxaban 15 mg once daily (standard dosing for most stroke prevention in patients with atrial fibrillation is 20 mg once daily).[18] A PFO was detected via either transthoracic echocardiography (TTE) or TEE in 534/7,209 (7.4%) overall, and there was no significant difference in recurrent stroke risk comparing patients taking rivaroxaban to those taking aspirin, HR 0.54 (95% CI 0.22 to 1.36). Major bleeding risk was likewise not significantly different, HR 2.05 (95%CI 0.51 –

8.18). The RESPECT-ESUS trial (Class II due to being a subgroup analysis of a larger trial) randomized patients to aspirin 100 mg daily or dabigatran, 150 mg or 110 mg twice daily (150 mg twice daily is the standard dosing for stroke prevention for most patients with atrial fibrillation).[19] Overall 680/5,390 (12.6%) were found to have a PFO via TTE or TEE, and there was no difference in recurrent stroke risk, HR 0.88 (95% CI 0.45 to 1.71). Major bleeding risks were not presented for the subgroup with PFO, although overall there was no difference between those given dabigatran and those given aspirin, RD 0.5% (95% CI -0.4% to 1.3%). Of note, neither use of TEE nor use of bubble contrast studies were mandated for these studies, likely explaining the relatively low rates of PFO prevalence.

Evidence synthesis and summary of effects

A random-effects meta-analysis comparing anticoagulation (with warfarin or a DOAC) to aspirin yields a summary HR of 0.73 (95% CI 0.45 to 1.17). Assuming a linear rate of stroke in aspirin treated patients of 2% per year and a 5-year time horizon, this HR corresponds to a number needed to treat of 21 (95% CI 19 to -60). With use of the AAN's modified GRADE process (appendixe-8, section D), the evidence was anchored at moderate confidence for this question but was then downgraded to low confidence, owing to imprecision.

Conclusion

For patients with cryptogenic stroke and PFO, anticoagulation medication and antiplatelet medication are possibly equally effective at reducing recurrent stroke (HR 0.73, 95% CI 0.45 to 1.17). Of note, the high end of the CI does rule out a clinically important benefit for aspirin.

PRACTICE RECOMMENDATIONS

For a description of the rationale of factors that influence the formulation of recommendations, see appendix e-10.

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 [EVID, PRIN, RELA].[20-22] An appropriately thorough workup depends on the individual patient and whether a compelling stroke etiology has already been identified [PRIN]. The randomized 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 TEE to characterize the PFO and ensure that it was the most likely etiology for the initial event [EVID]. There is accumulating evidence that occult atrial fibrillation accounts for a meaningful portion of cryptogenic stroke [RELA].[23] 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 [RELA].[24,25]

PFO is highly prevalent, found in approximately 25% of the general adult population on agitated-saline TEE and cadaveric studies [RELA].[26,27] 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.[28] 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 [RELA].[29-31]

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 [EVID]. This stroke risk is generally lower than the stroke risk caused by other possible common stroke mechanisms [RELA].[32] Thus, if an alternative plausible higher risk mechanism of stroke is identified, it is likely that the PFO was an "innocent bystander" [INFER].

Statement 1a

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).

Statement 1b

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).

Statement 1c

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 B).

Statement 1d

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

Statement 1e

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 (Level B). 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.[33]

Statement 1f

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 (Level B).

Statement 1g

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)[34] (Level B).

Statement 1h

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 C).

Statement 1i

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).

Statement 1j

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

Statement 1k

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 (Level B).

Statement 1l

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 (Level B).

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 [EVID]. Subgroup analysis suggests that the overall benefit seen across trials may not extend to those patients with small shunts and small, deep infarcts [EVID]. 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 [EVID, RELA].[35,36] 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 [EVID, RELA].[15,30,37]

Statement 2a

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).

Statement 2b

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).

Statement 2c

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).

Statement 2d

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 C).

Statement 2e

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 (Level B).

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 [EVID]. Existing randomized studies comparing anticoagulation therapy with antiplatelet 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 [EVID, RELA].[38, 39] The benefit of performing closure in patients being treated with anticoagulation is unclear [EVID].

Statement 3a

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 C).

Statement 3b

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 (Level B).

SUGGESTIONS FOR FUTURE RESEARCH

Additional PFO closure devices may be acceptable if they are approved for use following demonstration of similar safety profile and successful closure of right-to-left shunting. Direct oral anticoagulants (DOACs) have superior venous thromboembolism treatment and efficacy for stroke prevention in patients with atrial fibrillation.[40, 41] Studies comparing DOACs with PFO closure in younger patients and studies comparing DOACs with antiplatelets in older patients and younger patients not interested in closure are warranted. Studies of PFO and PFO closure in the pediatric stroke population and in select patients older than 60 years are also needed. Additional studies are needed to better understand anatomic characteristics that may influence risk of stroke in patients with PFO, including presence of atrial septal aneurysm, Chiari network, Eustachian valve, and systemic venous abnormalities such as varicose veins. The randomized trials excluded patients with stroke that occurred greater than 6 months previously, and it remains unclear whether closure provides a similar benefit in these patients who otherwise still fit the studies' inclusion criteria. Long-term and large-scale safety registries for patients who have received PFO closure are needed to assess (1) the risk of device erosion, fracture, embolization, and thrombotic and endocarditis risks and (2) the impact of residual shunts and incidence of atrial fibrillation.

DISCLAIMER

Clinical practice guidelines, practice advisories, systematic reviews, and other guidance published by the American Academy of Neurology (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 question(s) 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. 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 American Academy of Neurology (AAN) is committed to producing independent, critical, and trustworthy clinical practice guidelines (CPGs) and evidence-based documents. Significant efforts are made to minimize the potential for conflicts of interest to influence the recommendations of this evidence-based document. Management and disclosure of document

developer relationships is conducted in compliance with the 2017 AAN process manual section titled, “Implementing the AAN Conflict of Interest Policy for Guidelines and Case Definitions,” which can be viewed at aan.com.[2]

REFERENCES

1. Messé SR, Gronseth G, Kent DM, et al. 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. Neurology 2016;87:815–821.

2. Gronseth GS, Cox J, Gloss D, et al. *Clinical Practice Guideline Process Manual*: The American Academy of Neurology;2017.

3. Efthimiou O. Practical guide to the meta-analysis of rare events. Evid Based Ment Health 2018;21:72–76.

4. Guolo A, Varin C. Random-effects meta-analysis: the number of studies matters. Stat Methods Med Res 2017;26:1500–1518.

5. Higgins JP, Thompson SG, Spiegelhalter DJ. A re-evaluation of random-effects meta-analysis. J R Stat Soc Ser A Stat Soc 2009;172:137–159.

6. Shuster JJ Guo JD, Skyler JS. Meta-analysis of safety for low event-rate binomial trials. Res Synth Methods 2012;3:30–50.

7. Guyatt GH, Oxman AD, Schünemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. J Clin Epidemiol 2011;64:380–382.

8. Guyatt GH, Oxman AD, Sultan S, et al. GRADE guidelines: 9. Rating up the quality of evidence. J Clin Epidemiol 2011;64:1311–1316.

9. Furlan AJ, Reisman M, Massaro J, et al. Closure or medical therapy for cryptogenic stroke with patent foramen ovale. N Engl J Med 2012;366:991–999.

10. Meier B, Kalesan B, Mattle HP, et al. Percutaneous closure of patent foramen ovale in cryptogenic embolism. N Engl J Med 2013;368:1083–1091.

11. Carroll JD, Saver JL, Thaler DE, et al. Closure of patent foramen ovale versus medical therapy after cryptogenic stroke. N Engl J Med 2013;368:1092–1100.

12. Saver JL, Carroll JD, Thaler DE, et al. Long-term outcomes of patent foramen ovale closure or medical therapy after stroke. N Engl J Med 2017;377:1022–1032.

13. Mas JL, Derumeaux G, Guillon B, et al. Patent foramen ovale closure or anticoagulation vs. antiplatelets after stroke. N Engl J Med 2017;377:1011–1021.

14. Sondergaard L, Kasner SE, Rhodes JF, et al. Patent foramen ovale closure or antiplatelet therapy for cryptogenic stroke. N Engl J Med 2017;377:1033–1042.

15. Lee PH, Song JK, Kim JS, et al. Cryptogenic stroke and high-risk patent foramen ovale: The DEFENSE-PFO trial. J Am Coll Cardiol 2018; 71:2335–2342.

16. Homma S, Sacco RL, Di Tullio MR, Sciacca RR, Mohr JP. Effect of medical treatment in stroke patients with patent foramen ovale: patent foramen ovale in Cryptogenic Stroke Study. Circulation 2002;105:2625–2631.

17. Shariat A, Yaghoubi E, Farazdaghi 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.

18. Kasner SE, Swaminathan B, Lavados P, et al. Rivaroxaban or aspirin for patent foramen ovale and embolic stroke of undetermined source: a prespecified subgroup analysis from the NAVIGATE ESUS trial. Lancet Neurol 2018;17:1053–1060.

19. Diener HC, Sacco RL, Easton JD, et al. Dabigatran for prevention of stroke after embolic stroke of undetermined source. N Engl J Med 2019;380:1906–1917.

20. Kernan WN, Ovbiagele B, Black HR, et al. 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.

21. Culebras A, Messé SR. Summary of evidence-based guideline update: Prevention of stroke in nonvalvular atrial fibrillation: Report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology 2014;83:1220.

22. Chaturvedi S, Bruno A, Feasby T, et al. Carotid endarterectomy--an evidence-based review: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 2005;65:794–801.

23. Sanna T, Diener HC, Passman RS, et al. Cryptogenic stroke and underlying atrial fibrillation. N Engl J Med 2014;370:2478–2486.

24. Thijs V. Atrial fibrillation detection: fishing for an irregular heartbeat before and after stroke. Stroke 2017;48:2671–2677.

25. January CT, Wann LS, Calkins H, et al. 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 practice guidelines and the Heart Rhythm Society. Circulation 2014;130:e199–e267.

26. Meissner I, Whisnant JP, Khandheria BK, et al. Prevalence of potential risk factors for stroke assessed by transesophageal echocardiography and carotid ultrasonography: the SPARC study. Stroke Prevention: Assessment of Risk in a Community. Mayo Clin Proc 1999;74:862–869.

27. 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.

28. Katsanos AH, Psaltopoulou T, Sergentanis TN, et al. Transcranial Doppler versus transthoracic echocardiography for the detection of patent foramen ovale in patients with cryptogenic cerebral ischemia: a systematic review and diagnostic test accuracy meta-analysis. Ann Neurol 2016;79:625–635.

29. Overell JR, Bone I, Lees KR. Interatrial septal abnormalities and stroke: a meta-analysis of case-control studies. Neurology 2000;55:1172–1179.

30. Handke M, Harloff A, Olschewski M, Hetzel A, Geibel A. Patent foramen ovale and cryptogenic stroke in older patients. N Engl J Med 2007;357:2262–2268.

31. 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.

32. Amarenco P, Lavallée PC, Labreuche J, et al. One-year risk of stroke after transient ischemic attack or minor stroke. N Engl J Med 2016;374:1533–1542.

33. 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 strial 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.

34. 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.

35. Snijder RJ, Luermans JG, de Heij AH, et al. Patent foramen ovale with atrial septal aneurysm is strongly associated with migraine with aura: a large observational study. J Am Heart Assoc 2016;5:pii:e003771.

36. Mas JL, Arquizan C, Lamy C, et al. Recurrent cerebrovascular events associated with patent foramen ovale, atrial septal aneurysm, or both. N Engl J Med 2001;345:1740–1746.

37. Mazzucco S, Li L, Binney L, Rothwell PM; for the Oxford Vascular Study Phenotyped Cohort. Prevalence of patent foramen ovale in cryptogenic transient ischaemic attack and non-disabling stroke at older ages: a population-based study, systematic review, and meta-analysis. Lancet Neurol 2018;17:609–617.

38. Castellucci LA, Cameron C, Le Gal G, et al. Efficacy and safety outcomes of oral anticoagulants and antiplatelet drugs in the secondary prevention of venous thromboembolism: systematic review and network meta-analysis. BMJ 2013;347:f5133.

39. Weitz JI, Lensing AWA, Prins MH, et al. Rivaroxaban or aspirin for extended treatment of venous thromboembolism. N Engl J Med 2017;376:1211–1222.

40. Cohen AT, Harrington RA, Goldhaber SZ, et al. Extended thromboprophylaxis with betrixaban in acutely ill medical patients. N Engl J Med 2016;375:534–544.

41. López-López JA, Sterne JAC, Thom HHZ, et al. Oral anticoagulants for prevention of stroke in atrial fibrillation: systematic review, network meta-analysis, and cost effectiveness analysis. BMJ 2017;359:j5058.

Appendix e-1. AAN Guideline Subcommittee mission

The mission of the Guideline Subcommittee is to develop, disseminate, and implement evidence-based systematic reviews and clinical practice guidelines related to the causation, diagnosis, treatment, and prognosis of neurologic disorders.

The Guideline Subcommittee is committed to using the most rigorous methods available within its budget, in collaboration with other available AAN resources, to most efficiently accomplish this mission.

Appendix e-2. AAN Guideline Subcommittee members 2019–2021

The AAN has structured its subcommittee overseeing guideline development in several ways in recent years. The Guideline Subcommittee was first formed in 2019; it existed under a previous name and structure when this guideline project was inaugurated. At the time this guideline was approved to advance beyond subcommittee development, the subcommittee was constituted as below.

Alexander D. Rae-Grant, MD (Chair); John J. Halperin, MD (Vice-Chair); Lori L. Billinghurst, MD; Brian Callaghan, MD; Anne Constantino, MD; Jeremy K. Cutsforth-Gregory, MD; Gregory S. Day, MD, MSc; James Dorman, MD; Wendy S. Edlund, MD; Jeffrey Fletcher, MD; Gary S. Gronseth, MD; Scott A. Heller, MD; Koto Ishida, MD; Mark Douglas Johnson, MD; Mark Robert Keezer, MD; Benzi Kluger, MD; Shaheen E. Lakhan, MD, PhD, MEd; Nicole J. Licking, DO; Mia T. Minen, MD; Asma Moheet, MD; Pushpa Narayanaswami, MD, MBBS; Maryam Oskoui, MD; Alison M. Pack, MD; Sonja Potrebic, MD, PhD; Vishwanath Sagi, MD; Navdeep Sangha, MD; Sarah T. Sanveer; Nikolaos Scarmeas, MD; Kelly Sullivan, PhD; Courtney Takahashi, MD; Benjamin D. Tolchin, MD; Shawniqua T. Williams, MD

Appendix e-3. Complete search strategy

MEDLINE via PubMed

Closure question

Search Terms:

(((patent foramen ovale or atrial septal defect))

AND

(vascular closure device or amplatzer or starflex or helex or cardioform))

AND

"Therapy/Broad"[Filter]

Translated search:

((("foramen ovale, patent"[MeSH Terms] OR ("foramen"[All Fields] AND "ovale"[All Fields] AND "patent"[All Fields]) OR "patent foramen ovale"[All Fields] OR ("patent"[All Fields] AND "foramen"[All Fields] AND "ovale"[All Fields])) OR ("heart septal defects, atrial"[MeSH Terms] OR ("heart"[All Fields] AND "septal"[All Fields] AND "defects"[All Fields] AND "atrial"[All Fields]) OR "atrial heart septal defects"[All Fields] OR ("atrial"[All Fields] AND "septal"[All Fields] AND "defect"[All Fields]) OR "atrial septal defect"[All Fields])) AND (("vascular closure devices"[MeSH Terms] OR ("vascular"[All Fields] AND "closure"[All Fields] AND "devices"[All Fields]) OR "vascular closure devices"[All Fields] OR ("vascular"[All Fields] AND "closure"[All Fields] AND "device"[All Fields]) OR "vascular closure device"[All Fields]) OR amplatzer[All Fields] OR starflex[All Fields] OR helex[All Fields] OR cardioform[All Fields])) AND "Therapy/Broad"[Filter]

Anticoagulation question

(((patent foramen ovale or atrial septal defect))

AND

(anticoagulant or anticoagulation or warfarin or dabigatran or apixaban or rivaroxaban))

AND

"Therapy/Broad"[Filter]

Translated Search

((("foramen ovale, patent"[MeSH Terms] OR ("foramen"[All Fields] AND "ovale"[All Fields] AND "patent"[All Fields]) OR "patent foramen ovale"[All Fields] OR ("patent"[All Fields] AND "foramen"[All Fields] AND "ovale"[All Fields])) OR ("heart septal defects, atrial"[MeSH Terms] OR ("heart"[All Fields] AND "septal"[All Fields] AND "defects"[All Fields] AND "atrial"[All Fields]) OR "atrial heart septal defects"[All Fields] OR ("atrial"[All Fields] AND "septal"[All Fields] AND "defect"[All Fields]) OR "atrial septal defect"[All Fields])) AND (("anticoagulants"[Pharmacological Action] OR "anticoagulants"[MeSH Terms] OR "anticoagulants"[All Fields] OR "anticoagulant"[All Fields]) OR anticoagulation[All Fields] OR ("warfarin"[MeSH Terms] OR "warfarin"[All Fields]) OR ("dabigatran"[MeSH Terms] OR "dabigatran"[All Fields]) OR ("apixaban"[Supplementary Concept] OR "apixaban"[All Fields]) OR ("rivaroxaban"[MeSH Terms] OR "rivaroxaban"[All Fields]))) AND "Therapy/Broad"[Filter]

Cochrane library

Closure and anticoagulation questions

Search Term: Patent Foramen Ovale

Appendix e- 4. AAN rules for classification of evidence for risk of bias

Class I Criteria

- Randomized controlled clinical trial (RCT) in a representative population

- Triple-masked studies (i.e. the patient, treating provider, and outcome assessors are unaware of treatment assignment)

- Relevant baseline characteristics of treatment groups (or treatment order groups for crossover trials) are presented and substantially equivalent between treatment groups, or there is appropriate statistical adjustment for differences

- Additional Class I criteria:

a. Concealed allocation

b. No more than two primary outcomes specified

c. Exclusion and inclusion criteria clearly defined

d. Adequate accounting of dropouts (with at least 80 percent of participants completing the study) and crossovers

e. For noninferiority or equivalence trials claiming to prove efficacy for one or both drugs, the following are also required*:

i. The authors explicitly state the clinically meaningful difference to be excluded by defining the threshold for equivalence or noninferiority

ii. The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment (e.g., for a drug, the mode of administration, dose, and dosage adjustments are similar to those previously shown to be effective)

iii. The inclusion and exclusion criteria for participant selection and the outcomes of participants on the standard treatment are comparable with those of previous studies establishing efficacy of the standard treatment

iv. The interpretation of the study results is based on a per-protocol analysis that accounts for dropouts or crossovers

f. For crossover trials, both period and carryover effects are examined and statistical adjustments performed, if appropriate

Class II Criteria

- RCT that lacks one or two Class I criteria a–e (see above)

- Cohort studies employing methods that successfully match treatment groups on relevant baseline characteristics (e.g., propensity score matching) meeting Class I criteria b–e (see above)

- Randomized crossover trial missing one of the following two criteria:

a. Period and carryover effects described

b. Baseline characteristics of treatment order groups presented

- All relevant baseline characteristics are presented and substantially equivalent across treatment groups (or treatment order groups for crossover trials), or there is appropriate statistical adjustment for differences

- Masked or objective** outcome assessment

Class III Criteria

- Controlled studies (including studies with external controls such as well-defined natural history controls)

- Crossover trial missing both of the following two criteria:

a. Period and carryover effects

b. Presentation of baseline characteristics

- A description of major confounding differences between treatment groups that could affect outcome**

- Outcome assessment performed by someone who is not a member of the treatment team

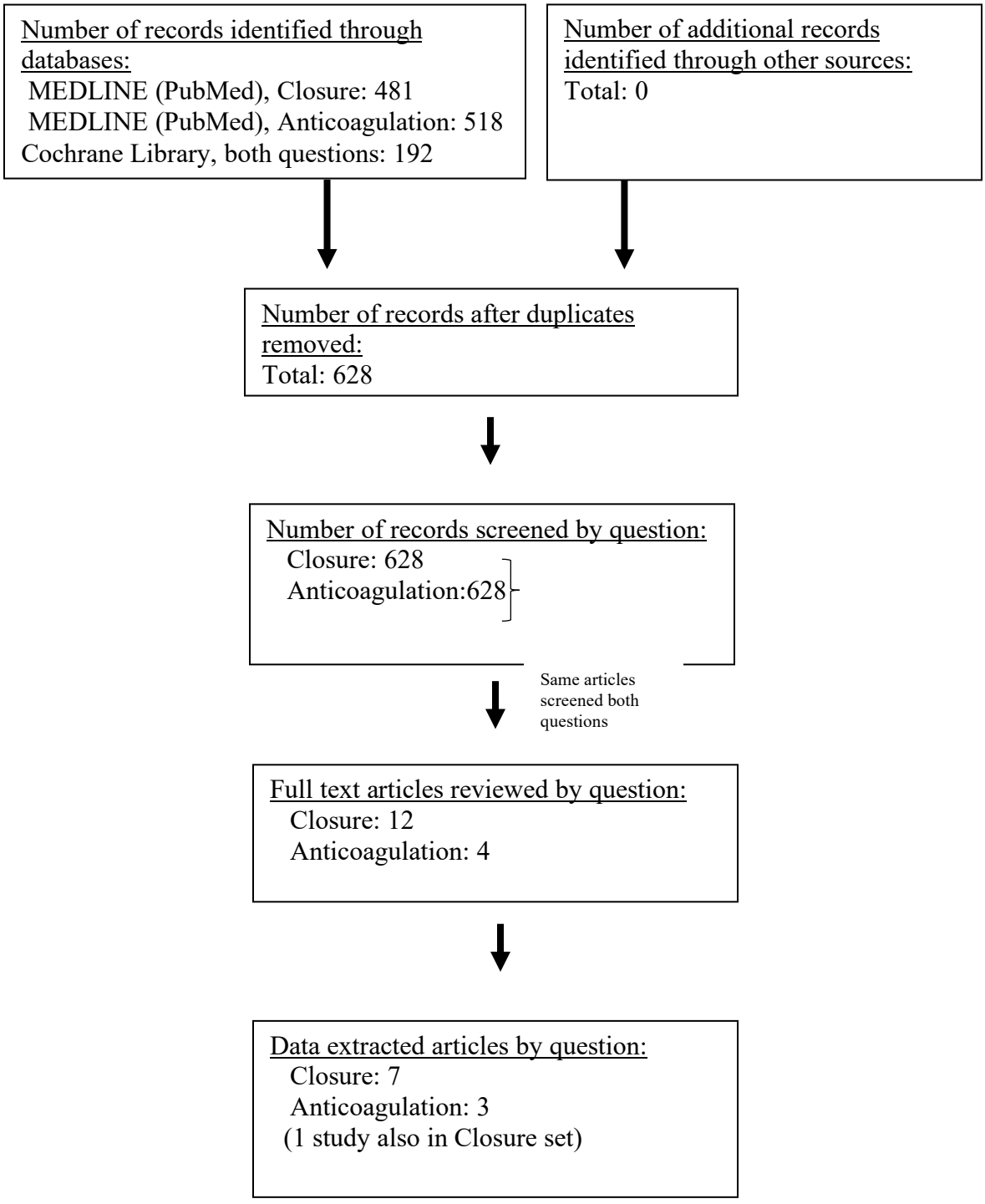
Class IV Criteria

- Studies not meeting Class I, II, or III criteria

*Numbers i–iii in Class Ie are required for Class II in equivalence trials. If any one of the three is missing, the class is automatically downgraded to Class III

**Objective outcome measurement: an outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data)

Appendix e-5. Flow of article selection process (modified PRISMA diagram)



Appendix e-6. Evidence summary notes – PFO closure vs medical therapy

Study	Intervention Closure device	Co-intervention Medical therapy	Definition of large PFO and atrial septal aneurysm	Duration of follow-up	Crossover and dropout rates	Stroke rate reduction	Periprocedural Complications and Adverse event notes
Closure I – Furlan, 2012	Starflex PFO Occluder, plus clopidogrel, 75 mg/day for 6 months, and aspirin, 81 or 325 mg/day	Warfarin (INR goal 2-3), aspirin (325mg/day), or both		Median 2 years	Of 447 randomized to PFO closure, 8 (1.8%) were lost to follow up and 39 (8.7%) were excluded from the modified intention to	-0.07 per 100 patient-years, 95% confidence interval [CI] -1.18 to 1.06	Atrial fibrillation (AF) more common in the closure arm compared to medication only, 5.7% vs 0.7%, (RD 5%, 95% CI 2%–8%, $p < 0.001$),

					treat due to protocol violation or not receiving closure. Of 462 randomized to medical therapy alone, 3 (0.6%) were lost to follow up and 8 were excluded from the modified intention to treat analysis due to protocol violation or		and major vascular procedural complications occurred in 3.2% of the patients who underwent closure.

					refusal of treatment.		
PC Trial – Meier, 2013	Amplatzer PFO Occluder Plus aspirin 100 to 325 mg/d for >5 months, and ticlopidine 250 to 500 mg/d or clopidogrel 75 to 150 mg/d for 1 to 6 months	antiplatelet or anticoagulant medication	Large PFO: >20 microbubbles in the left atrium within 3 cardiac cycles following opacification of the right atrium ASA: protrusion of the septum	Mean 4 years	Twenty-eight patients assigned to medical therapy crossed over to the closure group at a median of 8.8 months after randomization	-0.48 per 100 person-years, 95% confidence interval -1.21 to 0.12	New-onset AF was reported in 2.9% in the closure arm vs 1.0% in the medical 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

			≥15 mm beyond the center plane				the medically treated group (HR 0.66, 95% CI 0.27–1.62, p = 0.40).
RESPECT Trial – Carroll 2013, Saver 2017	Amplatzer PFO Occluder plus aspirin 81 to 325 mg plus clopidogrel 75 mg for 1 month, followed by aspirin monotherapy for >5 months	Antiplatelet or anticoagulation with Coumadin	Large PFO: >20 microbubbles in the left atrium within 3 cardiac cycles following opacification of the right atrium	Mean 2.3 years for 1st publication, 5.9 years for 2nd publication	33% of the medical therapy arm and 21% of the closure arm lost to follow-up.	-0.47 per 100 person-years, 95% confidence interval -0.97 to -0.01	Overall SAE rate 40.3% in closure arm and 36% in the medical arm, p=0.17. There were 22 device or procedure-related SAEs including 2 patients with pericardial

			ASA: ≥10 mm excursion of the septum primum				tamponade. Pulmonary embolism occurred at a rate of 0.41 vs 0.11 per 100 patient-years comparing closure arm to the medical arm, HR 3.48, 95%CI 0.98-12.34, p=0.04), DVT was 0.16 vs 0.04 per 100 patient-years (HR 4.44,

							05%CI 0.52-38.05, p=0.14).
REDUCE – Sondergard, 2017	Gore Helex Septal Occluder or Gore CARDIOFORM Septal Occluder plus aspirin	Antiplatelet	Large PFO: ≥25 microbubbles in the left atrium within 3 cardiac cycles following opacification of the right atrium	Median 3.2 years	32 patients (7.3%) randomized to closure did not undergo the procedure and 37 patients (8.4%) were lost to follow up. 14 patients (6.3%) in the medical arm crossed over to closure and 33	-1.32 per 100 person-years, 95% confidence interval -2.53 to -0.43	Atrial fibrillation was more common after closure, 4.6% vs 0.9% (p=0.02). There were procedure-related SAEs in 2.5% including tamponade in 1 (0.2%) and aortic dissection in 1 (0.2%). Device-related

					were lost to follow up (14.8%).		SAEs occurred in 1.4% including device dislocation in 3 (0.7%), device-related thrombus in 2 (0.5%)
CLOSE – Mas, 2017	Any CE-marked device (11 devices used, 51% received Amplatzer PFO Occluder)	Randomized to aspirin or anticoagulation	Large PFO: ≥30 microbubbles in the left atrium within 3 cardiac cycles following opacification	Mean 5.3	Among patients randomized to closure 3 patients (1.2%) did not receive the device and none were lost to follow up. Among patients	-0.78 per 100 person-years, 95% confidence interval -1.23 to -0.40	Any SAE occurred in 35.7% of subjects assigned to PFO closure, 33.2% of patients assigned to antiplatelet

			of the right atrium ASA: ≥10 mm excursion of the septum primum		randomized to antiplatelet medication, none crossed over to closure and 2 (0.8%) were lost to follow up.		therapy, and 33.2% of patients assigned to anticoagulation. Patients who underwent closure had a higher rate of atrial fibrillation, 6.6% compared to 0.4% of patients treated with medical therapy ($p<0.001$).

							Device- or procedure-related SAEs occurred in 5.9% including
DEFENSE-PFO – Lee, 2018	Amplatzer PFO Occluder plus aspirin 100mg daily plus clopidogrel 75 mg for >6 months though up to 15% of patients were given Warfarin	Warfarin (target INR 2.0 to 3.0) or antiplatelet regimen such as aspirin, aspirin plus clopidogrel, or aspirin plus cilostazol at a dose of 200 mg/day.	Large PFO: ≥30 microbubbles in the left atrium within 3 cardiac cycles following opacification of the right atrium	Median 2.8 years	12% of patients randomized to closure did not undergo procedure and 7% of patients who were randomized to medication underwent closure.	-3.57 per 100 person-years, 95% confidence interval -7.42 to -0.87	Major PFO closure procedural complications occurred in 2, pericardial effusion (n=1) and pseudoaneurysm at the puncture site (n=1). Atrial fibrillation

			ASA: Protrusion of the atrial septum ≥15mm beyond the plane of the septal wall				occurred in 2 patients who underwent closure. Major procedural complications occurred in 2 patients overall (3.3%) including 1 patient with pericardial effusion and 1 with a pseudoaneurysm at the puncture site.

Appendix e-7. Evidence summary notes – antiplatelet versus anticoagulant therapy

Study	Intervention Antiplatelet	Co-intervention Anticoagulant	Duration of follow-up	Crossover and dropout rates	Stroke risk difference	Adverse event notes
PICSS – Homma, 2002	Aspirin	Warfarin	2 years	10 (1.6%) withdrew consent or were lost to follow-up at a mean of 13.2±10.5 months after randomization. Cross-over rate was not reported	-0.095 comparing anticoagulation to antiplatelet therapy, 95% CI -0.22 to 0.04	Major bleeding rates were similar: 1.78 versus 1.91 events per 100 patient-years comparing warfarin to aspirin treated patients, though minor bleeding was more common

						with warfarin 22.9 versus 8.7 events per 100-patient years
Shariat, 2013	Aspirin	Warfarin	18 months		0.15 comparing anticoagulation to antiplatelet therapy, 95% CI -0.07 to 0.37	
CLOSE – Mas, 2017	Aspirin	Warfarin	5.4 years	Out of 187 patients randomly assigned to anticoagulation, 5 were lost to follow up	-0.02 comparing anticoagulation to antiplatelet therapy, 95% CI -0.07 to 0.01	Major or fatal bleeding occurred in 5.3% assigned to anticoagulation versus 2.3% in

				(2.7%) and 39 stopped anticoagulation (21%). Among 174 assigned to antiplatelet medication, 1 was lost to follow up (0.6%) and 9 stopped antiplatelet medication (5%)		those on antiplatelet medications, p=0.18

NAVIGATE-ESUS – Kasner 2018	Aspirin 100mg	rivaroxaban 15mg once daily	Mean 11 months	From the complete cohort: Among 3609 assigned to rivaroxaban 0.7% were lost to follow up and 0.9% withdrew consent. Among 3609 assigned to aspirin, 0.5% were lost to follow up and 0.9% withdrew consent.	-0.02 comparing anticoagulation to antiplatelet therapy, 95% CI -0.07 to 0.02	In the primary NAVIGATE analysis, major bleeding was increased in those assigned to rivaroxaban. There was no interaction for bleeding risk by presence of PFO

RESPECT-ESUS – Deiner, 2019	Aspirin 100mg	Dabigatran 150mg or 110mg (if age > 75 or creatinine clearance of 30 to 50 mL per minute)	Median 19 months (overall cohort)	From the complete cohort: Among 2695 assigned to dabigatran, 19 (0.07%) were lost to follow up and 790 (29%) discontinued study medication. Amonth 2695 assigned to aspirin 14 (0.05%) were		

				lost to follow up and 27% discontinued study medication.		

Appendix e-8. Modified GRADE synthesis tables

A. Pooled hazard ratios of recurrent stroke in patients receiving closure compared to those receiving medical therapy alone

	Therapeutic	Fixed effect		Narrative conclusion: Yes			
	Population	People with cryptogenic stroke or TIA					
	Intervention	who undergo PFO closure					
	Comparator	those who receive medical therapy alone					
	Outcome	have a recurrent stroke					
	Bias resistant effect size	0.500	Effect values less than 1 indicate:				
	Bias prone effect size	0.800	Outcome more likely with comparator -1				
Include	Study (Author Year)	Class	Indirectness	Hazard Ratio	LCL	UCL	
1	Meier 2013	II	Minor	0.200	0.020	1.720	
1	Saver 2017	II	Minor	0.550	0.310	0.999	
1	Søndergaard 2017	II	Minor	0.230	0.090	0.620	
1	Mas 2017	II	Minor	0.030	0.000	0.260	
	Summary (FE)	4; II	Minor	0.412	0.254	0.671	Isq: 12
	Conclusion (moderate confidence)	People with cryptogenic stroke or TIA who undergo PFO closure are probably less likely than those who receive medical therapy alone to have a recurrent stroke					

B. Sensitivity analyses comparing results of various meta-analytic techniques

Model	Effect measure, Method	All Studies			Excluding Lee and Furlan		
		PE	LCL	UCL	PE	LCL	UCL
Fixed Effect	HR*, Inverse Variance	0.48	0.32	0.73	<u>0.41</u>	<u>0.25</u>	<u>0.67</u>
	OR Inverse Variance, Wilson	0.51	0.34	0.76	0.43	0.26	0.70
	OR Inverse Variance, Traditional	0.50	0.33	0.76	0.42	0.25	0.68
	OR, Peto method	0.42	0.29	0.61	0.36	0.23	0.55
	OR, Mantel Haenszel	0.41	0.28	0.61	0.34	0.21	0.56
Random Effects	RR, SGS Weighted method	0.42	0.16	1.12	<u>0.36</u>	<u>0.05</u>	<u>2.60</u>
	HR*, Inverse Variance (DL)	0.41	0.21	0.78	0.38	0.21	0.69
	HR*, Inverse Variance (HK)	0.41	0.17	0.98	0.38	0.15	0.96
	OR, Inverse Variance, Wilson	0.36	0.16	0.82	0.30	0.10	0.87
	OR, Inverse Variance, Traditional	0.37	0.17	0.79	0.29	0.12	0.75

PE-point estimate; LCL-95% lower confidence limit; UCL-95% upper confidence limit
Underlined results represent primary analyses
HR-hazard ratio; OR-odds ratio; RR-risk ratio
Wilson-Wilson Mover-R method for calculating confidence intervals, Traditional-Normal approximation method to calculate confidence intervals
SGS-Shuster-Guo-Skyler method; DL-DerSimonian Laird method; HK-Hartung-Knapp-Sidik-Jonkman method
*For Lee, HR estimated from OR

C. Rate of serious study-defined non-periprocedural atrial fibrillation in patients receiving closure compared to those receiving medical therapy alone

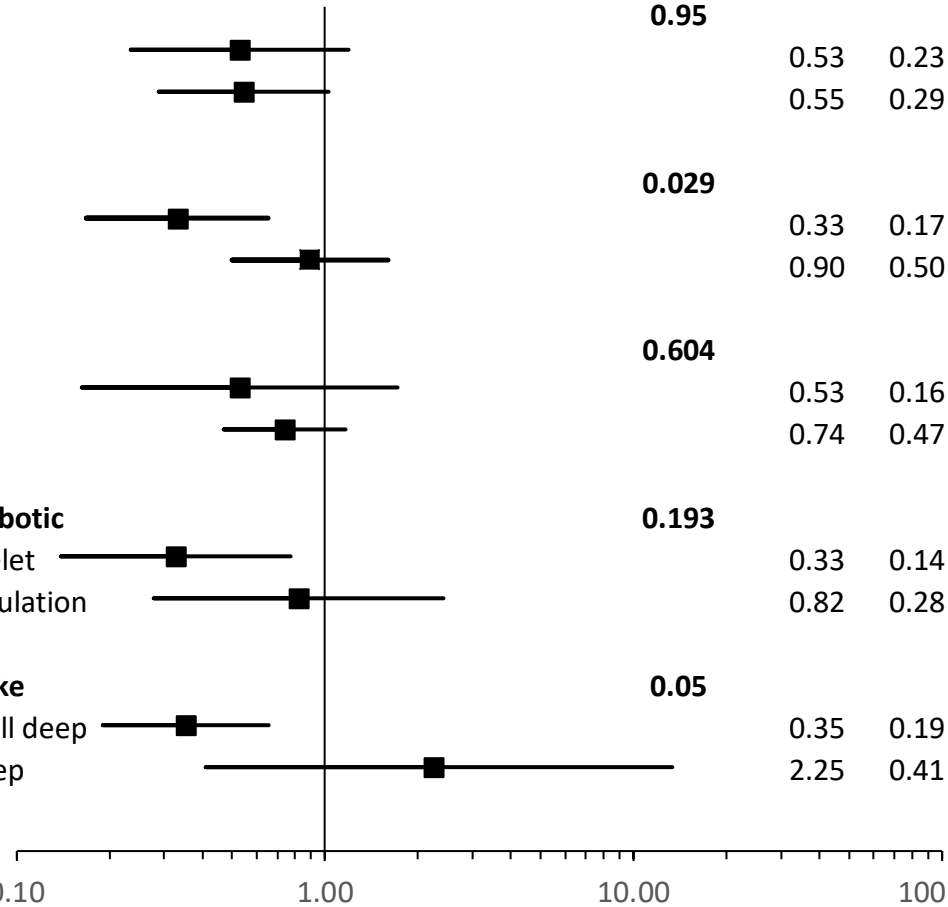
	Therapeutic	Fixed effect		Narrative conclusion: Yes			
	Population	People with cryptogenic stroke or TIA					
	Intervention	who undergo PFO closure					
	Comparator	those who receive medical therapy alone					
	Outcome	develop atrial fibrillation					
	Bias resistant effect size	0.500	Effect values less than 1 indicate:				
	Bias prone effect size	0.800	Outcome more likely with comparator -1				
Include	Study (Author Year)	Class	Indirectness	Hazard Ratio	LCL	UCL	
1	Meier 2013	II	Minor	2.080	0.406	10.216	
1	Saver 2017	II	Minor	1.697	0.507	5.559	
1	Søndergaard 2017	II	Minor	5.151	0.783	31.381	
1	Mas 2017	II	Minor	4.579	1.040	19.087	
	Summary (FE)	4; II	Minor	2.722	1.304	5.680	Isq: 0
	Conclusion (moderate confidence)	People with cryptogenic stroke or TIA who undergo PFO closure are probably more likely than those who receive medical therapy alone to develop atrial fibrillation					

D. Hazard ratios of recurrent stroke in patients receiving anticoagulation compared to those receiving antiplatelet therapy

	Therapeutic	Random effects		Narrative conclusion: Yes			
	Population Intervention Comparator Outcome	People with cryptogenic stroke or TIA and PFO who receive anticoagulation those who receive antiplatelet therapy have recurrent stroke (or TIA)					
	Bias Resistant Effect Size Bias Prone Effect Size	0.500 0.800	Effect values less than 1 indicate: Outcome more likely with intervention				
Include	Study (Author Year)	Class	Indirectness	Hazard Ratio	LCL	UCL	
1	Homma 2002	II	Moderate	0.520	0.160	1.670	
1	Shariat 2013	II	Moderate	3.030	0.588	16.670	
1	Mas 2017	II	Moderate	0.440	0.110	1.480	
1	Kasner 2018	II	Moderate	0.540	0.220	1.360	
1	Diener 2019	II	Moderate	0.880	0.450	1.710	
	Summary (RE)	5; II	Moderate	0.729	0.453	1.173	Isq: 9
	Conclusion (Very low confidence)	For patients with cryptogenic stroke and PFO, there is insufficient evidence to determine the relative efficacy of anticoagulation medication compared with antiplatelet medication (HR 0.73, 95% CI 0.45 to 1.17)					

Appendix e-9. Subgroup analyses

Subgroup	P for interaction	Hazard Ratio	LCL	UCL
Age	**0.95**			
<45		0.53	0.23	1.19
>45		0.55	0.29	1.03
Shunt Size	**0.029**			
Large		0.33	0.17	0.66
Small		0.90	0.50	1.60
ASA	**0.604**			
Present		0.53	0.16	1.72
Absent		0.74	0.47	1.17
Antithrombotic	**0.193**			
Antiplatelet		0.33	0.14	0.77
Anticoagulation		0.82	0.28	2.42
Index stroke	**0.05**			
Non-small deep		0.35	0.19	0.66
Small deep		2.25	0.41	13.32



Appendix e-10. Rationale of factors considered in developing the practice recommendations

In this appendix, *EVID* refers to evidence systematically reviewed; *RELA* to strong evidence derived from related conditions; *PRIN* to axiomatic principles of care; and *INFER* to inferences made from one or more statements in the recommendation rationale.

In the tables that follow, consensus is considered to have been reached if 80% or more of the guideline panel agree on the strength of a given domain. For nonpremise domains, intensity of shading corresponds to the number of panel members who were in agreement (shading of greater intensity indicates a larger number of panel members who reached agreement). The strength of the recommendation is anchored to the strength of the inference. The recommendation strength can be downgraded for any modifier; it can be upgraded only by one level for a moderate to large benefit relative to harm. In addition, domains include the premises and factors on which the recommendations are based.

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 [EVID, PRIN, RELA].[20-22] An appropriately thorough workup depends on the individual patient and whether a compelling stroke etiology has already been identified [PRIN]. The randomized 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 TEE to characterize the PFO and ensure that it was the most likely etiology for the initial event [EVID]. There is accumulating evidence that occult atrial fibrillation accounts for a meaningful portion of cryptogenic stroke [RELA].[23] 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 [RELA].[24,25]

PFO is highly prevalent, found in approximately 25% of the general adult population on agitated-saline TEE and cadaveric studies [RELA].[26,27] 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.[28] 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 [RELA].[29-31]

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 [EVID]. This stroke risk is generally lower than the stroke risk caused by other possible common stroke mechanisms [RELA].[32] Thus, if an alternative plausible higher risk mechanism of stroke is identified, it is likely that the PFO was an "innocent bystander" [INFER].

Statement 1a

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).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 1	Benefit >>> harm 9	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 2	Critically important 8	Yes
Variation in preferences	Large 0	Moderate 1	Modest 6	Minimal 3	Yes
Feasible	Rarely 0	Occasionally 0	Usually 8	Always 2	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 9	Small 1	Yes
Strength of recommendation	R/U	C	B	A	

Statement 1b

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).

1

2

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 3	Benefit >>> harm 7	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 4	Critically important 6	Yes
Variation in preferences	Large 0	Moderate 0	Modest 5	Minimal 5	Yes
Feasible	Rarely 0	Occasionally 0	Usually 6	Always 4	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 8	Small 2	Yes
Strength of recommendation	R/U	C	B	A	

Statement 1c

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 B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 1	Benefit >> harm 2	Benefit >>> harm 7	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 3	Critically important 7	Yes
Variation in preferences	Large 0	Moderate 1	Modest 2	Minimal 7	Yes
Feasible	Rarely 0	Occasionally 0	Usually 7	Always 3	Yes
Cost relative to net benefit	Very large 0	Large 1	Moderate 5	Small 4	Yes
Strength of recommendation	R/U	C	B	A	

Statement 1d

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

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 1	Benefit >>> harm 9	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 2	Critically important 8	Yes
Variation in preferences	Large 0	Moderate 0	Modest 1	Minimal 9	Yes
Feasible	Rarely 0	Occasionally 0	Usually 0	Always 10	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 1	Small 9	Yes
Strength of recommendation	R/U	C	B	A	

Statement 1e

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 (Level B). 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.[33]

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 1	Benefit >> harm 3	Benefit >>> harm 6	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 5	Critically important 5	Yes
Variation in preferences	Large 0	Moderate 1	Modest 6	Minimal 3	Yes
Feasible	Rarely 0	Occasionally 0	Usually 6	Always 4	Yes
Cost relative to net benefit	Very large 0	Large 1	Moderate 7	Small 2	Yes
Strength of recommendation	R/U	C	B	A	

Statement 1f

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 (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 1	Benefit >> harm 4	Benefit >>> harm 5	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 5	Critically important 5	Yes
Variation in preferences	Large 0	Moderate 2	Modest 5	Minimal 3	Yes
Feasible	Rarely 0	Occasionally 0	Usually 9	Always 1	Yes
Cost relative to net benefit	Very large 0	Large 1	Moderate 7	Small 2	Yes
Strength of recommendation	R/U	C	B	A	

Statement 1g

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)[34] (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 2	Benefit >> harm 2	Benefit >>> harm 6	Yes
Importance of outcomes	Not important or unknown 0	Mildly important 0	Very important 7	Critically important 3	Yes
Variation in preferences	Large 0	Moderate 1	Modest 3	Minimal 6	Yes
Feasible	Rarely 0	Occasionally 0	Usually 7	Always 3	Yes
Cost relative to net benefit	Very large 0	Large 2	Moderate 6	Small 2	Yes
Strength of recommendation	R/U	C	B	A	

Statement 1h

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 C).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 1	Benefit > harm 1	Benefit >> harm 5	Benefit >>> harm 3	Yes
Importance of outcomes	Not important or unknown 0	Mildly important 4	Very important 4	Critically important 2	Yes
Variation in preferences	Large 0	Moderate 4	Modest 4	Minimal 2	Yes
Feasible	Rarely 0	Occasionally 7	Usually 3	Always 0	Yes
Cost relative to net benefit	Very large 0	Large 3	Moderate 6	Small 1	Yes
Strength of recommendation	R/U	C	B	A	

Statement 1i

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)

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 1	Benefit >>> harm 9	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 2	Critically important 8	Yes
Variation in preferences	Large 0	Moderate 1	Modest 2	Minimal 7	Yes
Feasible	Rarely 0	Occasionally 1	Usually 6	Always 3	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 2	Small 8	Yes
Strength of recommendation	R/U	C	B	A	

Statement 1j

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

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 2	Benefit >>> harm 8	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 3	Critically important 7	Yes
Variation in preferences	Large 0	Moderate 3	Modest 5	Minimal 2	Yes
Feasible	Rarely 0	Occasionally 0	Usually 3	Always 7	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 2	Small 8	Yes
Strength of recommendation	R/U	C	B	A	

Statement 1k

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).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 1	Benefit >>> harm 9	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 2	Critically important 8	Yes
Variation in preferences	Large 0	Moderate 1	Modest 2	Minimal 7	Yes
Feasible	Rarely 0	Occasionally 1	Usually 6	Always 3	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 2	Small 8	Yes
Strength of recommendation	R/U	C	B	A	

Statement 11

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 (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm > benefit 0	Benefit > harm 0	Benefit >> harm 2	Benefit >>> harm 8	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 1	Critically important 9	Yes
Variation in preferences	Large 0	Moderate 2	Modest 1	Minimal 7	Yes
Feasible	Rarely 0	Occasionally 0	Usually 1	Always 9	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 2	Small 8	Yes
Strength of recommendation	R/U	C	B	A	

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 [EVID]. Subgroup analysis suggests that the overall benefit seen across trials may not extend to those patients with small shunts and small, deep infarcts [EVID]. 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 [EVID, RELA].[35,36] 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 [EVID, RELA].[15,30,37]

Statement 2a

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).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 2	Benefit >> harm 6	Benefit >>> harm 2	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 4	Critically important 6	Yes
Variation in preferences	Large 1	Moderate 4	Modest 4	Minimal 1	Yes
Feasible	Rarely 0	Occasionally 0	Usually 8	Always 2	Yes
Cost relative to net benefit	Very large 0	Large 1	Moderate 8	Small 1	Yes
Strength of recommendation	R/U	C	B	A	

Statement 2b

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).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 2	Benefit >> harm 2	Benefit >>> harm 6	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 6	Critically important 4	Yes
Variation in preferences	Large 0	Moderate 4	Modest 4	Minimal 2	Yes
Feasible	Rarely 0	Occasionally 0	Usually 3	Always 7	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 4	Small 6	Yes
Strength of recommendation	R/U	C	B	A	

Statement 2c

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).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 1	Benefit > harm 4	Benefit >> harm 5	Benefit >>> harm 0	Yes
Importance of outcomes	Not important or unknown 2	Mildly Important 0	Very important 5	Critically important 3	Yes
Variation in preferences	Large 1	Moderate 7	Modest 2	Minimal 0	Yes
Feasible	Rarely 0	Occasionally 0	Usually 9	Always 1	Yes
Cost relative to net benefit	Very large 1	Large 6	Moderate 2	Small 1	Yes
Strength of recommendation	R/U	C	B	A	

Statement 2d

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 C).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 1	Benefit > harm 3	Benefit >> harm 6	Benefit >>> harm 0	Yes
Importance of outcomes	Not important or unknown 0	Mildly important 0	Very important 8	Critically important 2	Yes
Variation in preferences	Large 3	Moderate 4	Modest 3	Minimal 0	No
Feasible	Rarely 0	Occasionally 0	Usually 10	Always 0	Yes
Cost relative to net benefit	Very large 2	Large 2	Moderate 6	Small 0	Yes
Strength of recommendation	R/U	C	B	A	

Statement 2e

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 (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	NA
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	NA
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm > benefit 0	Benefit > harm 0	Benefit >> harm 1	Benefit >>> harm 9	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 3	Critically important 7	Yes
Variation in preferences	Large 0	Moderate 1	Modest 5	Minimal 4	Yes
Feasible	Rarely 0	Occasionally 1	Usually 3	Always 6	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 3	Small 7	Yes
Strength of recommendation	R/U	C	B	A	

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.[38]

However, specific antithrombotic management for patients with stroke thought to be caused by PFO remains uncertain [EVID]. 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 [EVID, RELA].[39, 40] The benefit of performing closure in patients being treated with anticoagulation is unclear [EVID].

Statement 3a

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 C).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm > benefit 0	Benefit > harm 0	Benefit >> harm 5	Benefit >>> harm 5	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 1	Very important 4	Critically important 5	Yes
Variation in preferences	Large 1	Moderate 4	Modest 4	Minimal 1	Yes
Feasible	Rarely 0	Occasionally 0	Usually 4	Always 6	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 6	Small 4	Yes
Strength of recommendation	R/U	C	B	A	

Statement 3b

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 (Level B).

1

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 6	Benefit >>> harm 4	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 6	Critically important 4	Yes
Variation in preferences	Large 0	Moderate 3	Modest 5	Minimal 2	Yes
Feasible	Rarely 0	Occasionally 0	Usually 3	Always 7	Yes
Cost relative to net benefit	Very large 0	Large 1	Moderate 4	Small 5	Yes
Strength of recommendation	R/U	C	B	A	