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SCAI Guidelines for the Management of Patent Foramen Ovale

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Standards and Guidelines

SCAI Guidelines for the Management of Patent Foramen Ovale

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ABSTRACT

Background: Patent foramen ovale (PFO) is a vestigial congenital cardiovascular structure present in around 25% of adults. In most cases, PFO is entirely benign and requires no treatment. However, it may cause serious complications under certain circumstances.

Objective: These evidence-based guidelines from the Society for Cardiovascular Angiography and Interventions (SCAI) aim to support patients, clinicians, and other stakeholders in decisions about management of PFO.

Methods: SCAI convened a multidisciplinary guideline panel balanced to minimize potential bias from conflicts of interest. The Evidence Foundation, a registered 501(c)(3) nonprofit organization, provided methodological support for the guideline-development process. Following the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, the guideline panel formulated and prioritized clinical questions in population, intervention, comparison, outcome (PICO) format. A separate technical review team of clinical and methodological experts conducted systematic reviews of the evidence, synthesized data, and graded the certainty of the evidence across outcomes. The guideline panel then reconvened to formulate recommendations and supporting remarks informed by the results of the technical review and additional contextual factors described in the GRADE evidence-to-decision framework.

Results: The panel agreed on 13 recommendations to address variations on 5 clinical scenarios.

Conclusions: Key recommendations address patient selection for PFO closure in the prevention of recurrent PFO-associated stroke, including populations not commonly included in randomized studies, and scenarios where the PFO closure might serve a role in the prevention of other outcomes such as migraine headaches and decompression illness. The panel has also identified future research priorities to advance the field.

Abbreviations: AF, atrial fibrillation; ASA, atrial septal aneurysm; DAPT, dual antiplatelet therapy; DCI, decompression illness; DVT, deep vein thrombosis; GIN, Guidelines International Network; GRADE, Grading of Recommendations Assessment, Development and Evaluation; PE, pulmonary embolism; PFO, patent foramen ovale; PICO, population, intervention, comparison, and outcome; POS, platypnea-orthodeoxia syndrome; RCT, randomized controlled trial; RoPE, Risk of Paradoxical Embolism Score; SCUBA, self-contained underwater breathing apparatus; TIA, transient ischemic attack; VTE, venous thromboembolism.

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Summary of Recommendations

Background

Patent foramen ovale (PFO) is common, present in around 25% of adults. It occurs when a small opening between the right and left atria, known as the foramen ovale, remains open despite pulmonary resistance and blood pressure decrease in the right side of the heart after birth. PFO may become symptomatic by allowing clots from the venous system to pass into the arterial system and embolize to the cerebral vasculature, or more rarely into the coronary, visceral, or peripheral arteries. The most well-established complication of PFO is stroke, defined as an ischemic stroke with cortical, large white matter, or retinal infarct in the presence of a PFO and no other identified likely cause, but it has also been associated with other adverse neurological and embolic events. PFO may be treated with blood thinning medication alone, or with a percutaneous procedure to close the PFO and medication. Clinicians and patients may be uncertain about the best management option because of limited evidence and guidance available for certain clinical scenarios.

Methods

These SCAI guidelines are based on original systematic reviews of evidence conducted with support from the Evidence Foundation. The panel followed best practices for guideline development described by the Institute of Medicine and the Guidelines International Network (GIN).[1-3] The panel used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to assess the certainty in the evidence and formulate recommendations.[4,5]

Interpretation of strong and conditional recommendations

The strength of a recommendation is expressed as either strong ("the guideline panel recommends…"), or conditional ("the guideline panel suggests…") and has the following interpretation:

Strong recommendation

- For patients: most individuals in this situation would want the recommended course of action, and only a small proportion would not.
- For clinicians: most individuals should receive the intervention or test. Formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences.
- For policy makers: the recommendation can be adopted as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.

Conditional recommendation

- For patients: the majority of individuals in this situation would want the suggested course of action, but many would not.
- For clinicians: recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their values and preferences.
- For policy makers: policymaking will require substantial debate and involvement of various stakeholders. Performance measures about the suggested course of action should focus on documentation of an appropriate decision-making process.

Summary of Recommendations

1. **Percutaneous PFO closure versus medical therapy (antiplatelet or anticoagulation or composite)/no therapy in adults without a prior PFO-associated stroke**
   - 1.1. In persons experiencing migraines without a prior PFO-associated stroke, the SCAI guideline panel suggests against the routine use of PFO closure for the treatment of migraine (conditional recommendation, moderate certainty of evidence).
     Remarks: Patients, particularly those with debilitating migraines who have failed to benefit from conventional medical therapy, who place a high value on the uncertain benefits of having their PFO closed and a lower value on the uncertain harms, may reasonably choose PFO closure.
   - 1.2. In self-contained underwater breathing apparatus (SCUBA) divers with prior decompression illness (DCI) and without a prior PFO-associated stroke, the SCAI guideline panel suggests against the routine use of PFO closure to prevent DCI (conditional recommendation, very low certainty of evidence).
     Remarks: Patients who place a high value on the potential, but uncertain, benefits of having their PFO closed and a lower value on risks may reasonably choose PFO closure.
   - 1.3. In persons with platypnea-orthodeoxia syndrome (POS) and without a prior PFO-associated stroke, in whom other causes of hypoxia have been excluded, the SCAI guideline panel suggests PFO closure rather than no PFO closure (conditional recommendation, very low certainty of evidence).
     Remarks: Patients who place a higher value on the risks of closure and a lower value on the uncertain benefits may reasonably decline PFO closure.
   - 1.4. In persons with thrombophilia and without a prior PFO-associated stroke, the SCAI guideline panel suggests against the use of PFO closure in addition to antithrombotic therapy (conditional recommendation, very low certainty of evidence).
   - 1.5. In persons with atrial septal aneurysm (ASA) and without a prior PFO-associated stroke, the SCAI guideline panel suggests against the use of PFO closure (conditional recommendation, very low certainty of evidence).
   - 1.6. In persons with systemic embolism and without a prior PFO-associated stroke, in whom other embolic etiologies have been excluded, the SCAI guideline panel suggests PFO closure rather than medical therapy alone (conditional recommendation, very low certainty of evidence).
     Remarks: Patients who place a high value on the risks and a lower value on the uncertain benefits may reasonably decline PFO closure.
   - 1.7. In persons with a history of transient ischemic attack (TIA) and without a prior PFO-associated stroke, the SCAI guideline panel suggests against PFO closure (conditional recommendation, very low certainty of evidence).
     Remark: Patients, particularly those with recurrent, high-probability TIAs, who place a high value on the uncertain benefits and a low value on procedural risks may reasonably choose PFO closure.
   - 1.8. In persons with a history of deep vein thrombosis (DVT) and without a prior PFO-associated stroke, the SCAI guideline panel suggests against PFO closure (conditional recommendation, very low certainty of evidence).

2. **Percutaneous PFO closure versus antiplatelet therapy in adults with a prior PFO-associated stroke**
   - 2.1. In patients between the ages of 18 and 60 with a prior PFO-associated stroke, the SCAI guideline panel recommends PFO closure rather than antiplatelet therapy alone (strong recommendation, moderate certainty of evidence).

Remark: This recommendation is independent of patient anatomy (ie, presence of ASA, size of shunt) due to limited clinical data on these sub-populations. A RoPE (risk of paradoxical embolism) score ≥7 may identify patients who are likely to receive greater benefit from PFO closure.

2.2. In patients 60 years or older with a prior PFO-associated stroke, the SCAI guideline panel suggests PFO closure rather than long-term antiplatelet therapy alone (conditional recommendation, very low certainty of evidence).

Remark: Patients in this age group who place a lower value on the uncertain benefits of PFO closure and a higher value on the possible procedure related risks may reasonably decline PFO closure.

2.3. In patients with a history of atrial fibrillation (AF) who have had an ischemic stroke, the SCAI guideline panel suggests against the routine use of PFO closure (conditional recommendation, very low certainty of evidence).

2.4. In patients with thrombophilia on antiplatelet therapy and not anticoagulation therapy and who have had a prior PFO-associated stroke, the SCAI guideline panel suggests PFO closure rather than antiplatelet therapy alone (conditional recommendation, very low certainty of evidence).

Remark: Patients who place lower value on the uncertain benefits of PFO closure and a higher value on the possible procedure related risks may reasonably decline PFO closure.

2.5. Patients with high-risk anatomy (ie, ASA) - refer to Recommendation 2.1

2.6. Patients evaluated with a RoPE score - refer to Recommendation 2.1

2.7. The SCAI guideline panel makes no recommendation regarding PFO closure based on prolonged time since stroke (no recommendation, knowledge gap).

3. **Percutaneous PFO closure versus anticoagulation therapy in adults with a prior PFO-associated stroke**

3.1. In patients between the ages of 18 and 60 with a prior PFO-associated stroke and no other indication for treatment with anticoagulation, the SCAI guideline panel suggests PFO closure plus antiplatelet therapy rather than anticoagulation therapy alone (conditional recommendation, low certainty of evidence).

Remark: This recommendation is independent of patient anatomy (ie, presence of ASA, size of shunt) due to limited clinical data on these sub-populations. A RoPE score ≥7 may identify patients who are likely to receive greater benefit from PFO closure.

3.2. In patients 60 years or older with a prior PFO-associated stroke and no other indications for treatment with anticoagulation, the SCAI guideline panel suggests PFO closure plus antiplatelet therapy rather than long-term anticoagulation therapy alone (conditional recommendation, very low certainty of evidence).

Remark: Patients in this age group who place a lower value on the uncertain benefits of PFO closure and a higher value on the possible procedure related risks may reasonably decline PFO closure.

3.3. Patients with high-risk anatomy (ie, ASA) - refer to Recommendation 3.1

3.4. Patients evaluated with a RoPE score - refer to Recommendation 3.1

3.5. The SCAI guideline panel makes no recommendation regarding PFO closure based on prolonged time since stroke (no recommendation, knowledge gap).

4. **Percutaneous PFO closure plus lifelong anticoagulation versus anticoagulation alone in adults with a prior PFO-associated stroke**

4.1. In patients with thrombophilia and a prior PFO-associated stroke, the SCAI guideline panel suggests PFO closure in addition to lifelong anticoagulation therapy rather than anticoagulation therapy alone (conditional recommendation, very low certainty of evidence).

Remark: Patients who need long term anticoagulation and who place a lower value on the uncertain benefits of PFO closure and a higher value on the possible procedure related risks may reasonably decline PFO closure.

4.2. In patients with a history of DVT requiring lifelong anticoagulation and a concomitant PFO-associated stroke, the SCAI guideline panel suggests PFO closure plus lifelong anticoagulation rather than lifelong anticoagulation alone (cconditional recommendation, very low certainty of evidence).

Remark: Patients who need lifelong anticoagulation and who place a lower value on the uncertain benefits of PFO closure and a higher value on the possible procedure related risks may reasonably decline PFO closure.

4.3. In patients with a history of pulmonary embolism (PE) requiring lifelong anticoagulation and a concomitant PFO-associated stroke, the SCAI guideline panel suggests PFO closure plus lifelong anticoagulation rather than lifelong anticoagulation alone (conditional recommendation, very low certainty of evidence).

Remark: Patients who need lifelong anticoagulation may place a lower value on the uncertain benefits of PFO closure and a higher value on the possible procedure related risks and may reasonably decline PFO closure.

5. **Post-procedure management of patients undergoing percutaneous PFO closure with a regimen of 1 month of aspirin plus clopidogrel followed by 5 months of aspirin versus another antiplatelet regimen or anticoagulation**

5.1. The SCAI guideline panel makes no recommendation regarding duration beyond 1 month of dual antiplatelet therapy after PFO closure (no recommendation, knowledge gap).

Introduction

Since Cohnheim first described a PFO-associated stroke in a young woman in 1877, the treatment of patients with PFO-associated stroke, defined as an ischemic stroke with cortical, large white matter, or retinal infarct in the presence of a PFO and no other identified likely cause, has been steeped in controversy and hampered by a paucity of clinical data.[6] In 1992, Bridges et al described successful percutaneous closure of PFO in 36 patients with paradoxical embolic events using a double umbrella device.[7] Subsequent clinical data on the treatment of similar patients throughout the 1990s and 2000s was largely observational and retrospective. During this period, many cardiologists were optimistic about the application of percutaneous techniques to closing PFO for the prevention of recurrent, PFO-associated stroke. At the same time, others urged caution about subjecting patients, many of whom are young, to an invasive procedure and its associated risks in the absence of strong supporting evidence. The early randomized clinical trials (RCTs) were hampered by slow enrollment, often taking years to complete because of the large number of patients and long duration of follow up required to demonstrate a treatment effect. Some of the early devices for PFO closure had design flaws and were subject to thrombosis and failure. In addition, the number of patients meeting the primary efficacy endpoint was small leading to losses to follow up and imprecision in the effect estimate. There was also a lack of clinical data and consensus regarding the best medical therapy for this patient population to prevent recurrent ischemic stroke. Finally, many patients were undergoing PFO closure outside of a randomized trial setting. In retrospect, it is no surprise that the early RCTs (Evaluation of the Safety and Efficacy of the STARFlex Septal Closure System Versus Best Medical Therapy in Patients With a Stroke and/or Transient Ischemic Attack Due to Presumed Paradoxical Embolism Through a Patent Foramen Ovale [CLOSURE I], Percutaneous Closure of Patent Foramen Ovale Using the Amplatzer PFO Occluder with Medical Treatment in Patients with Cryptogenic Embolism [PC Trial],

Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment [RESPECT]) of PFO closure did not meet the primary efficacy endpoints.[8-10] The later RCTs (long term analyses of RESPECT, Septal Occluder and Antiplatelet Medical Management for Reduction of Recurrent Stroke or Imaging-Confirmed TIA in Patients With Patent Foramen Ovale [REDUCE], Closure of Patent Foramen Ovale or Anticoagulants Versus Antiplatelet Therapy to Prevent Stroke Recurrence [CLOSE], Device Closure Versus Medical Therapy for Secondary Prevention in Cryptogenic Stroke Patients With High-Risk Patent Foramen Ovale [DEFENSE PFO]) of PFO device closure versus best medical therapy to prevent recurrent ischemic stroke in young patients ($\leq$60) published 2017-2018 clearly demonstrated a beneficial treatment effect of PFO device closure plus medical therapy compared to medical therapy alone.[11-14] Based on robust data from the later clinical trials the FDA has approved, thus far, 2 devices for PFO closure procedures. The FDA labeling has mandated alignment of cardiology and neurology multi-disciplinary team members in patient selection for PFO closure as well as the task of excluding all other potential causes of stroke. The manner or extent to which patients are evaluated for other causes of stroke is beyond the purview of this document.

With commercialization of PFO closure procedures post-FDA approval it becomes the responsibility of stakeholder societies to ensure safe dissemination of this technology to the public. First, it must be assured that proceduralists have the necessary cognitive and technical skillsets to perform PFO device closure in a safe and effective manner. This issue was addressed in the first SCAI-sponsored document addressing operator and institutional requirements for PFO closure published in 2019 with affirmation from the American Academy of Neurology (AAN).[15,16] The FDA also mandated industry-sponsored post approval studies to track outcomes out to 5 years, which are currently ongoing. These studies will provide an accurate assessment of procedural and device related complications (thrombosis, embolization, residual leaks) in a real-world setting. Secondly, since PFO is common; found in approximately 25% of all adults, proper patient selection for PFO closure is critical to fulfill stakeholder society's responsibility to patients and mitigate unnecessary procedures. For this purpose, SCAI prioritized the development of clinical practice guidelines adhering to rigorous requirements for the collection, appraisal, and synthesis of available data. Questions prioritized by the guideline panel centered around 5 general areas: 1) PFO closure after PFO-associated ischemic stroke, 2) PFO closure in patients without prior stroke for other indications, 3) PFO closure in patients with other stroke risk factors, 4) PFO closure in patients requiring long term anti-coagulation for other reasons, and 5) post-PFO closure medical management. There has been interest in the benefits of PFO device closure in subsets of patients who were not included in the large RCTs. These include patients who are advanced in age or have certain comorbid conditions such as platypnea-orthodeoxia syndrome, diving decompression illness, thrombophilia, systemic embolism, venous thromboembolism (VTE) and patients with PFO and refractory migraine headaches. Although lacking in RCT data, there are data from observational studies to inform guideline recommendations with respect to these patient subsets.[17-21] The implementation of validated techniques for clinical question formulation and evidence rating permitted the guideline panel to craft consistent, transparent, and rigorous guidelines with respect to the clinical areas of interest described above.

Prior guidance documents from European societies[16,22] and from the AAN[23] have reviewed PFO closure for stroke, focusing on the RCT data. A recent European position paper described preliminary recommendations for some heterogenous patient populations including those with PFO and decompression sickness, desaturation syndromes, and migraine.[16] These guidelines, developed by SCAI with representation by the AAN, aim to expand and augment these prior efforts. Historically, the field of interventional cardiology has been guided by recommendations developed using variable methodologies that are not consistently aligned with the National Academies (formerly Institute of Medicine) standards for trustworthy clinical practice guidelines. For these guidelines, SCAI has adopted a standardized, rigorous, and internationally recognized method for evidence collection and appraisal.

The SCAI Guidelines on the Management of Patent Foramen Ovale, along with the previously published guidance document on operator and institutional requirements, will serve as a resource for clinical practice, and future research in the area of PFO closure. The guidelines have been composed to aide interventional cardiologists and neurologists in confronting a broad spectrum of questions encountered in contemporary practice. Most importantly, these guidelines should help patients and clinicians to achieve the best evidence-based care, consistent with patients' values and preferences. Finally, these guidelines focus on adults >18 years old. Extending these guidelines to the pediatric population is discouraged. PFO closure in the pediatric population represents an area for future study.

Methods

The guideline panel developed and graded the recommendations and assessed the certainty in the supporting evidence following the GRADE approach.[4,24,25] The evidence profile and certainty of the evidence for each question are discussed in detail in the accompanying technical review manuscript.[26] Readers should refer to the technical review for additional detail about the evidence supporting the recommendations discussed here.

The overall guideline development process, including funding of the work, panel formation, management of conflicts of interest, internal and external review, and organizational approval, was guided by SCAI policies and procedures derived from the GIN-McMaster Guideline Development Checklist (http://cebgrade.mcmaster.ca/guidecheck.html) and intended to meet standards for trustworthy guidelines from the Institute of Medicine.[27]

Organization, panel composition, planning, and coordination

The work of this panel was coordinated and sponsored by SCAI. Project oversight was provided by the Publications Committee, which reports to the Executive Committee. SCAI vetted and appointed individuals to the guideline panel and researchers to conduct systematic reviews of evidence and contribute to the guideline-development process, including application of GRADE methodology. The membership of the guideline panel and the technical review team is described in Supplement 1.

The guideline panel includes interventional cardiologists and a neurologist representing the American Academy of Neurology (AAN) who have clinical and research expertise on the management of persons with PFO, methodologists with expertise in evidence appraisal and guideline development, and 3 patient representatives. The panel's work was conducted via a series of virtual meetings.

Guideline funding and management of conflicts of interest

Development of these guidelines was wholly funded by SCAI, a nonprofit medical specialty society that represents interventional cardiologists. Most members of the guideline panel are members of the society. SCAI staff provided logistical support for the technical review, guideline development process, and manuscript preparation but had no role in choosing the guideline questions or determining the recommendations.

Physician members of the guideline panel received no financial compensation for their participation in this effort; patient representatives received an honorarium of 100 USD per hour of participation in virtual meetings. Methodological support for the guideline was provided by Evidence Foundation, a registered 501(c)(3) nonprofit organization.

Conflicts of interest of all participants were managed according to SCAI policies based on recommendations of the Institute of Medicine (now National Academy of Medicine) and the Guidelines International

Network.[28] At the time of appointment, a majority of the guideline panel, including the chair and the vice-chair, had no conflicts of interest as defined and judged by the Publications Committee. Some panelists disclosed new interests or relationships during the development process, but the balance of the majority was maintained. None of the Evidence Foundation-affiliated researchers who contributed to the technical review or who supported the guideline development process had any current material interest in a commercial entity with any product that could be affected by the guidelines.

Before appointment to the panel, individuals disclosed financial and nonfinancial interests. Members of the Publications Committee reviewed the disclosures and judged which interests were conflicts and should be managed. Supplement 1 provides the complete "Disclosure of Interest" forms of all panel members. In Part A of the forms, individuals disclosed material interests from the 12 months prior to appointment. In Part B, they disclosed interests that were not mainly financial. Part C summarizes SCAI decisions about which interests were judged to be conflicts. Part D describes new disclosure updates after appointment.

Recusal was also used to manage conflicts of interest. During all deliberations, panel members with a current, direct financial interest in a commercial entity with any product that could be affected by the guidelines were recused from making judgments about relevant recommendations. Panel members who participated in making judgments about each recommendation were duly noted.

Formulating specific clinical questions and determining outcomes of interest

The SCAI guideline panel and methodologists formulated each clinical question and prioritized outcomes a priori using the GRADE approach.[24] Selected outcomes were rated as critical or important according to their relevance for clinical decision making. Each question identifies a specific population, intervention, comparator, and patient-important outcomes. PICO questions were further reviewed by the technical review panel. The guideline panel elected to focus on areas of persistent uncertainty, specifically PFO closure in patients without prior stroke, patients with other stroke risk factors, patients requiring long term anti-coagulation for other reasons, and other subpopulations who have not been studied in RCTs (Supplement 2).

Evidence review and development of recommendations

Rigorous, high-quality systematic reviews were conducted to address each PICO question and findings were summarized in GRADE evidence profiles (EP).[4,29] These results are reported in detail in the companion technical review manuscript.[26] The certainty of the evidence (also known as the level or quality of the evidence) relevant to each outcome was assessed using the GRADE approach based on the risk of bias, consistency, directness, precision, likelihood of publication bias, magnitude of effect, and dose-response relationship. The certainty of the evidence for each outcome was rated from very low to high (Table 1).[5] Guideline panel members received the evidence profiles prior to deliberating on recommendations and reviewed the included data for completeness.

The panel developed recommendations during 3, 2-hour virtual consensus meetings. Recommendations are informed by data presented in the evidence profiles, certainty of evidence ratings, the balance of benefits and harms of the intervention and comparator, and patient values and preferences. The panel agreed on each recommendation statement including the strength of recommendation, remarks, and narrative text by consensus. The final manuscript has been reviewed and approved by all members of the panel.

Table 1. Interpretation of certainty of evidence[5,30-32]

Certainty	Interpretation
High	The panel is very confident that the true effect is similar to the estimate of the effect.
Moderate	The panel is moderately confident that the true effect is similar to the estimate of the effect, but there is a possibility that it is substantially different.
Low	The panel's confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very Low	The panel has very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of the effect.

Interpretation of strong and conditional recommendations

Recommendations are classified as either "strong" or "conditional." The phrase "the guideline panel recommends" indicates a strong recommendation; the phrase "the guideline panel suggests" indicates a conditional recommendation. The interpretation and implication of strong and conditional recommendations for patients, clinicians, researchers, and policy makers is presented below (Table 2).[30-32]

Document review

The draft manuscript was reviewed by all members of the panel then made available online March 7-21, 2022, for external review by stakeholders, including medical professionals, patients, and the public. The document was revised to address pertinent comments, but no changes were made to the recommendations. In April 2022, the SCAI Publications Committee approved that the society guideline-development process was followed; in May 2022, the officers of the SCAI Executive Committee

Table 2. Interpretation of strong and conditional recommendations[30-32]

Implication for:	Strong	Conditional
Patients	Most of the individuals in this situation would want the recommended course of action and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not. Decision aids may be useful in helping patients to make decisions consistent with their individual risks, values, and preferences.
Clinicians	Most individuals should follow the recommended course of action. Formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences.	Different choices will be appropriate for individual patients, and clinicians must help each patient arrive at a management decision consistent with the patient's values and preferences. Decision aids may be useful in heling individual risks, values, and preferences.
Researchers	The recommendation is supported by credible research or other convincing judgments that make additional research unlikely to alter the recommendation. On occasion, a strong recommendation is based on low or very low certainty in the evidence. In such instances, further research may provide important information that alters the recommendation.	This recommendation is likely to be strengthened (for future updates or adaptation) by additional research. An evaluation of the conditions and criteria (and the related judgments, research evidence, and additional considerations) that determined the conditional (rather than strong) recommendation will help identify possible research gaps.
Policy makers	The recommendation can be adopted as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Policy making will require substantial debate and involvement of various stakeholders. Performance measures about the suggested course of action should focus on whether an appropriate decision-making process is duly documented.

approved submission of the guidelines for publication under the imprimatur of SCAI.

How to use these guidelines

These guidelines are intended to help clinicians and patients make decisions about the management of patients with PFO, including transcatheter closure and its alternatives. Other purposes are to inform policy, education, and advocacy, and to describe knowledge gaps to be filled by future research. These guidelines are not intended to serve or be construed as a standard of care. Clinicians must make decisions based on the unique circumstances of each individual patient, ideally through a collaborative process that considers the patient's values and preferences. Decisions may be constrained by the context of the clinical setting and local resources, including institutional policies and availability of treatments, technologies, or providers. These guidelines may not include all appropriate methods of care for the clinical scenarios described. As science advances and new evidence becomes available, recommendations may become outdated. Following these guidelines cannot guarantee successful outcomes. SCAI does not warrant or guarantee any products described in these guidelines.

Statements about the underlying values and preferences, as well as qualifying remarks accompanying each recommendation, are integral to implementation. They should never be omitted when recommendations from these guidelines are quoted or translated.

Recommendations

1. Percutaneous PFO closure versus medical therapy (antiplatelet or anticoagulation or composite)/no therapy in adults without a prior PFO-associated stroke

Recommendation 1.1

In persons experiencing migraines without a prior PFO-associated stroke, the SCAI guideline panel suggests against the routine use of PFO closure for the treatment of migraine (conditional recommendation, moderate certainty of evidence).

Remarks: Patients, particularly those with debilitating migraines who have failed to benefit from conventional medical therapy, who place a high value on the uncertain benefits of having their PFO closed and a lower value on the uncertain harms, may reasonably choose PFO closure.

Summary of the evidence

Three randomized controlled trials (RCTs) assessed the effect of PFO closure on patients who experience migraines.[33-35] The MIST (Migraine Intervention with STARFlex Technology) trial, the PRIMA (Percutaneous Closure of PFO in Migraine with Aura) trial, and the PREMIUM (Prospective, Randomized Investigation to Evaluate Incidence of Headache Reduction in Subjects With Migraine and PFO Using the Amplatzer PFO Occluder to Medical Management) trial were included in the meta-analysis conducted to support these recommendations (Supplement 3).[26] Although the MIST trial failed to demonstrate a clinically significant effect for its primary endpoint, it met the criteria for inclusion. Results of a sensitivity analysis showed that exclusion of the MIST trial would not have a significant impact on the overall estimate of the effect of PFO closure.

Benefits, harms, and burden

The thee RCTs did not achieve their primary efficacy endpoints in terms of eliminating or reducing migraine attacks per month (mean difference [MD], 0.59; 95% confidence interval [CI], 0.15-1.03) and migraine days per month (MD, 1.33; 95% CI, 0.33-2.32). However, these studies also showed that PFO closure likely increases the number patients who experience cessation of their migraines (relative risk [RR], 3.46; 95% CI, 0.65-18.40).

Other considerations

Several studies have reported an association between migraines with aura and PFO. Anzola et al found that 48% of patients who experience migraines with aura have also been diagnosed with PFO.[36] The PRIMA trial included patients who had migraines with aura,[34] while the PREMIUM trial included patients who had migraines with and without aura.[35] Results of these studies suggest that patients who experience migraines with aura may have better outcomes from PFO closure compared to those without aura.[37] In addition, A pooled analysis of the PRIMA and PREMIUM which utilized the AMPLATZER PFO occluder suggested PFO closure resulted in statistically significant reductions in monthly migraine days (-3.1 days vs -1.9 days; P=0.02), monthly migraine attacks (-2.0 vs -1.4; P=0.01) and increased number of patients with complete cessation of migraine (14 [9%] vs 1 [.7%]; P=0.001).[38]

Conclusions and research needs for this recommendation

The guideline panel determined that there is moderate certainty evidence that PFO closure is not preferable to other therapies for the treatment of migraine. Because of this, the panel agreed on a conditional

Table 3. Summary of recommendations for PICO question 1

Recommendation	Strength of recommendation	Certainty of evidence
1.1. In persons experiencing migraines without a prior PFO-associated stroke, the SCAI guideline panel suggests against the routine use of PFO closure for the treatment of migraine. **Remarks:** Patients, particularly those with debilitating migraines who have failed to benefit from conventional medical therapy, and who place a high value on the uncertain benefits of having their PFO closed and a lower value on the uncertain harms, may reasonably choose PFO closure.	Conditional	Moderate
1.2. In SCUBA divers with prior DCI and without a prior PFO-associated stroke, the SCAI guideline panel suggests against the routine use of PFO closure to prevent DCI. **Remarks:** Patients who place a high value on the potential, but uncertain, benefits of having their PFO closed and a lower value on risks may reasonably choose PFO closure.	Conditional	Very Low
1.3. In persons with platypnea-orthodeoxia syndrome (POS) and without a prior PFO-associated stroke, in whom other causes of hypoxia have been excluded, the SCAI guideline panel suggests PFO closure rather than no PFO closure. **Remark:** Patients who place a higher value on the risks of closure and a lower value on the uncertain benefits may reasonably decline PFO closure.	Conditional	Very Low
1.4. In persons with thrombophilia and without a prior PFO-associated stroke, the SCAI guideline panel suggests against the use of PFO closure in addition to antithrombotic therapy.	Conditional	Very Low
1.5. In persons with ASA and without a prior PFO-associated stroke, the SCAI guideline panel suggests against the use of PFO closure.	Conditional	Very Low
1.6. In persons with systemic embolism and without a prior PFO-associated stroke, in whom other embolic etiologies have been excluded, the SCAI guideline panel suggests PFO closure rather than medical therapy alone. **Remark:** Patients who place a high value on the risks and a lower value on the uncertain benefits may reasonably decline PFO closure.	Conditional	Very Low
1.7. In persons with a history of TIA and without a prior PFO-associated stroke, the SCAI guideline panel suggests against PFO closure. **Remark:** Patients, particularly those with recurrent high-probability TIAs, who place a high value on the uncertain benefits and a low value on procedural risks would reasonably choose PFO closure.	Conditional	Very Low
1.8. In persons with a history of DVT and without a prior PFO-associated stroke, the SCAI guideline panel suggests against PFO closure.	Conditional	Very Low

recommendation against the routine use of closure. The panel acknowledges a persistent signal between PFO and migraines and supports more research on benefits and harms of PFO closure in these patients. The panel encourages clinicians who close PFOs in these patients to contribute their experiences to the limited body of literature and to preferentially encourage patients to participate in a randomized trial, if available (Table 3).

Recommendation 1.2

In SCUBA divers with prior DCI and without a prior PFO-associated stroke, the SCAI guideline panel suggests against the routine use of PFO closure to prevent DCI (conditional recommendation, very low certainty of evidence).

Remarks: Patients who place a high value on the potential, but uncertain, benefits of having their PFO closed and a lower value on risks may reasonably choose PFO closure.

Summary of the evidence

The panel found 3 observational studies that assessed the effect of PFO closure on patients with a history of DCI.[19-21] These studies investigated outcomes in patients who underwent PFO closure after experiencing DCI compared to patients who practiced conservative diving measures after experiencing DCI.

Benefits, harms, and burden

These data showed that PFO closure may reduce the incidence of recurrent DCI. However, the data is observational, non-randomized and inconclusive (RR, 0.31; 95% CI, 0.08-1.13); for these reasons, the conditional recommendation suggests against routine closure in this setting. Patients who underwent PFO closure also had an increased risk of AF and other procedural complications such as bleeding.[21]

Other considerations

PFO may contribute to DCI by permitting nitrogen bubbles to travel from the venous to the arterial circulation. There are multiple options to prevent recurrent DCI in SCUBA divers with a PFO, including conservative diving, complete cessation of diving, and PFO closure with post-closure management. SCUBA divers who present with acute DCI should immediately be referred to a specialist for hyperbaric oxygen therapy.

Conclusions and research needs for this recommendation

The guideline panel agreed on a conditional recommendation against routine PFO closure in this patient population due to the absence of comparative RCT data and uncertainty of the available observational data, and the reasonable conservative option for most patients to limit high risk diving. Ongoing registries and trials will lend clarity to this issue and hopefully allow for revision of this guideline in the future.

Recommendation 1.3

In persons with platypnea-orthodeoxia syndrome (POS) and without a prior PFO-associated stroke, in whom other causes of hypoxia have been excluded, the SCAI guideline panel suggests PFO closure rather than no PFO closure (conditional recommendation, very low certainty of evidence).

Remark: Patients who place a higher value on the risks of closure and a lower value on the uncertain benefits may reasonably decline PFO closure.

Summary of the evidence

The panel found 3 observational studies that estimate the effect of PFO closure on POS.[17,18,39] These studies reported on oxygen saturation, quality of life, incidence of AF, bleeding, mortality, and other procedural adverse events.

Benefits, harms, and burden

Patients with POS may experience an increase in oxygen saturation after PFO closure (MD, 14.21; 95% CI, 12.18-16.25). A majority of patients who underwent closure also reported an improvement in quality of life and a decrease in their POS symptoms (76%). However, there were reports of adverse events such as AF (9.6%), mortality (8.7%), and other procedural complications (8.7%) in the cohort of patients who underwent closure.

Conclusions and research needs for this recommendation

There is very low certainty of evidence for the benefits of PFO closure in patients with POS, yet the evidence is compelling for the objective outcome of improvement in oxygenation after PFO closure. Consequently, the panel agreed on a conditional recommendation for the use of PFO closure in these patients. Further research is encouraged to confirm these findings.

Recommendation 1.4

In persons with thrombophilia and without a prior PFO-associated stroke, the SCAI guideline panel suggests against the use PFO closure in addition to antithrombotic therapy (conditional recommendation, very low certainty of evidence).

Summary of the evidence

The panel identified 1 cohort study that described the effect of PFO closure in patients with thrombophilia and without a prior PFO-associated stroke.[40] This study reported on the incidence of stroke, TIA, AF, and other serious adverse events in patients who underwent PFO closure compared to patients who received medical therapy.

Benefits, harms, and burden

PFO closure may reduce the incidence of stroke and TIA in patients with thrombophilia as reported in the identified study.[40] It may also lead to an increased risk of AF and other serious adverse events when compared to medical therapy. However, the panel judged the evidence demonstrating this effect to be of very low certainty due to fragility of the reported estimate and concerns of confounding in the study.

Conclusions and research needs for this recommendation

The panel determined that there is very low certainty in the evidence on the effects of PFO closure in this patient population and consequently suggests against closure in patients with thrombophilia who have not had a prior PFO-associated stroke. Although closure is not routinely carried out in these patients, further research is necessary to confirm the benefits of PFO closure reported by Buber et al.[40]

Recommendation 1.5

In persons with atrial septal aneurysm (ASA) and without a prior PFO-associated stroke, the SCAI guideline panel suggests against the use of PFO closure (conditional recommendation, very low certainty of evidence).

Summary of the evidence

The panel did not identify any studies that investigated the long-term effect of PFO closure in patients with ASA.

Benefits, harms, and burden

One observational study[41] reported procedural adverse events in this population. Three patients who underwent PFO closure experienced device-related adverse events and supraventricular tachycardia (SVT). Benefits from PFO closure were not reported in this study.

Conclusions and research needs for this recommendation

The guideline panel determined that there is very uncertain benefit from PFO closure in this population and conditionally recommends against the use of PFO closure in patients with ASA and without a prior PFO-associated stroke. Further research is necessary to determine whether this population may benefit from closure.

Recommendation 1.6

In persons with systemic embolism and without a prior PFO-associated stroke, in whom other embolic etiologies have been excluded, the SCAI guideline panel suggests PFO closure rather than medical therapy alone (conditional recommendation, very low certainty of evidence).

Remark: Patients who place a high value on the risks and a lower value on the uncertain benefits may reasonably decline PFO closure.

Summary of the evidence

The panel did not identify any studies directly investigating the effect of PFO closure in patients with systemic embolism.

Benefits, harms, and burden

A subgroup analysis[42] provided data on the composite outcome of recurrent stroke and TIA in patients with systemic embolism. Three patients with a history of systemic embolism underwent PFO closure with no observed recurrent stroke nor TIA.

Other considerations

Systemic embolic events attributed to PFO occur less frequently than cerebral embolic events due to the anatomical pathway traveled by clots, which must pass the cerebral vessels before reaching the renal, splenic, or peripheral arteries.[43-45] Additionally, the brain is much more sensitive even to brief periods of ischemia than other organs. Randomized studies to demonstrate the prevention of paradoxical systemic embolism with PFO closure are not feasible because of the rarity of these events. However, the benefit of PFO closure is well established for recurrent embolic stroke prevention. Thus, similar benefit may be extrapolated to patients with non-cerebral or systemic embolic events.[10,46,47]

Conclusions and research needs for this recommendation

The evidence of benefit from PFO closure is very uncertain for patients with systemic embolic events who have not had a prior PFO-associated stroke. The guideline panel conditionally recommends the use of PFO closure rather than medical therapy alone in these patients, only when other embolic etiologies have been excluded. Further research is necessary to estimate the precise benefits and harms of closure under these circumstances.

Recommendation 1.7

In persons with a history of TIA and without a prior PFO-associated stroke, the SCAI guideline panel suggests against PFO closure (conditional recommendation, very low certainty of evidence).

Remark: Patients, particularly those with recurrent, high-probability TIAs, who place a high value on the uncertain benefits and a low value on procedural risks may reasonably choose PFO closure.

Summary of the evidence

The panel did not identify any studies directly investigating the effect of PFO closure in patients with TIA.

Benefits, harms, and burden

A subgroup analysis[42] provided data on the composite outcome of recurrent stroke and TIA in patients with a history of TIA and without a prior PFO-associated stroke. Out of 65 patients who underwent PFO closure, 4 (6.2%) were observed to have recurrent stroke or TIA.

Other considerations

By definition, TIA patients have normal neuroimaging and no persistent clinical neurologic deficits, so an ischemic etiology for any given neurologic clinical presentation cannot be proven with confidence. Therefore a suspected TIA cannot be differentiated from complex migraine nor from any other cause of transient neurological symptoms.

Conclusions and research needs for this recommendation

The guideline panel determined that there is very uncertain benefit from PFO closure in this population. Consequently, the panel agreed on a conditional recommendation against the use of PFO closure in patients with a history of TIA and without a prior PFO-associated stroke. Further research is necessary to ascertain the benefits and harms of closure in this population

Recommendation 1.8

In persons with a history of DVT and without a prior PFO-associated stroke, the SCAI guideline panel suggests against PFO closure (conditional recommendation, very low certainty of evidence).

Summary of the evidence

The panel did not identify any studies directly investigating the effect of PFO closure in patients with DVT.

Benefits, harms, and burden

A subgroup analysis[42] provided data on the composite outcome of recurrent stroke and TIA in patients with a history of DVT. Out of 10 patients who underwent PFO closure, none were observed to have recurrent stroke or TIA.

Conclusions and research needs for this recommendation

The guideline panel determined that there is very uncertain benefit from PFO closure in this population and agreed on a conditional recommendation against the use of PFO closure in patients with DVT and without a prior PFO-associated stroke. Further research is necessary to ascertain the benefits and harms of closure in this population

2. Percutaneous PFO closure versus antiplatelet therapy in adults with prior PFO-associated stroke

Recommendation 2.1

In patients between the ages of 18 and 60 with a prior PFO-associated stroke, the SCAI guideline panel recommends PFO closure rather than antiplatelet therapy alone (strong recommendation, moderate certainty of evidence).

Remark: This recommendation is independent of patient anatomy (ie, presence of ASA, size of shunt) due to limited clinical data on these sub-populations. A RoPE score $\geq$7 may identify patients who are likely to receive greater benefit from PFO closure.

Summary of the evidence

The panel identified 4 RCTs that reported outcomes of patients with a prior PFO-associated stroke who underwent PFO closure compared to patients treated with antiplatelet therapy. These studies described recurrent stroke, major bleeding events, PE, DVT, AF, and serious adverse events, including device or procedure related events (Supplement 3). The panel did not identify any studies that evaluated the more beneficial treatment strategy between PFO closure and antiplatelet therapy when a patient's RoPE score is taken into consideration. However, a pooled analysis of data from the CLOSURE-I trial, RESPECT trial, and PC trial demonstrated that RoPE score is correlated to the magnitude of risk reduction derived from PFO closure compared to medical therapy.[44] In patients with higher RoPE scores ($\geq$7, n=1221), the rate of recurrent strokes per 100 person-years was 0.30 in the PFO closure group versus 1.03 in the medical therapy group (hazard ratio [HR], 0.31; 95% CI, 0.11-0.85; P=0.02). Furthermore, in patients with lower RoPE scores (<7, n=912), the rate of recurrent strokes per 100 person-years was 1.37 in the PFO closure group versus 1.68 in the medical therapy group (HR, 0.82; 95% CI, 0.42-1.59; P=0.56).

Benefits, harms, and burden

Data from the included RCTs indicates a reduced risk of recurrent stroke in patients who underwent PFO closure compared to patients treated with antiplatelet therapy (relative risk [RR], 0.26; 95% CI, 0.12-0.58). Patients who underwent PFO closure also had a lower rate of DVT.

Three of the included studies described a higher risk of AF events (RR, 7.33; 95% CI, 2.41-22.25) in patients who underwent PFO closure, and that 86% of AF events occurred within 45 days post-procedure. Serious adverse events occurred more frequently in patients who underwent PFO closure (RR, 0.95; 95% CI, 0.79-1.14); a total of 4.5% of patients experienced device- or procedure-related adverse events.

Other considerations

The panel considered evidence for disparate effects of closure in patients with high-risk anatomy and various RoPE scores. However, the data are limited and the panel found no evidence that these patients would benefit from a different management strategy than the broader population.

Conclusions and research needs for this recommendation

The guideline panel determined that there is moderate certainty evidence for a net health benefit for patients with a prior PFO-associated stroke who undergo PFO closure compared to patients who are treated with antiplatelet therapy. The increased risk of transient AF is offset by a greater reduction in risk of recurrent stroke. Therefore, the panel strongly recommends PFO closure and antiplatelet therapy rather than antiplatelet therapy alone for these patients regardless of anatomical features. Additional research is necessary to determine if the benefits and harms of PFO closure vary based on patient anatomy (ie, ASA, shunt size) or RoPE score (Table 4).

Recommendation 2.2

In patients 60 years or older with a prior PFO-associated stroke, the SCAI guideline panel suggests PFO closure rather than long-term antiplatelet therapy alone (conditional recommendation, very low certainty of evidence).

Table 4. Summary of recommendations for PICO question 2

Recommendation	Strength of recommendation	Certainty of evidence
2.1 In patients between ages of 18 and 60 with a prior PFO-associated stroke, the SCAI guideline panel recommends PFO closure rather than antiplatelet therapy alone. **Remark:** This recommendation is independent of patient anatomy (ie, presence of ASA, size of shunt) due to limited clinical data on these sub-populations. A RoPE score ≥ 7 may identify patients who are likely to receive greater benefit from PFO closure.	Strong	Moderate
2.2 In patients 60 years or older with a prior PFO-associated stroke, the SCAI guideline panel suggests PFO closure rather than long-term antiplatelet therapy alone. **Remark:** Patients in this age group who place a lower value on the uncertain benefits of PFO closure and a higher value on the possible procedure related risks may reasonably decline PFO closure.	Conditional	Very Low
2.3 In patients with a history of AF who have had an ischemic stroke, the SCAI guideline panel suggests against the routine use of PFO closure.	Conditional	Very Low
2.4 In patients with thrombophilia on antiplatelet therapy and not anticoagulation therapy and who have had a prior PFO-associated stroke, the SCAI guideline panel suggests PFO closure rather than antiplatelet therapy alone. **Remark:** Patients who place a lower value on the uncertain benefits of PFO closure and a higher value on the possible procedure related may reasonably decline PFO closure.	Conditional	Very Low
2.5 Patients with high-risk anatomy (ie, ASA) - refer to Recommendation 2.1	-	-
2.6 Patients evaluated with a RoPE score - refer to Recommendation 2.1	-	-
2.7 The SCAI guideline panel makes no recommendation regarding PFO closure based on prolonged time since stroke.	No recommendation	Knowledge gap

Remark: Patients in this age group who place a lower value on the uncertain benefits of PFO closure and a higher value on the possible procedure related risks may reasonably decline PFO closure.

Summary of the evidence

The panel did not identify any studies that evaluated the outcomes of treatment with PFO closure versus antiplatelet therapy in patients 60 years of age or older who have had a prior PFO-associated stroke. However, 4 observational studies compared outcomes in patients <60 years of age versus patients ≥60 years of age after closure. The panel also included data from the NAVIGATE ESUS sub-analysis of patients with PFO. This study compared the incidence of recurrent stroke in patients treated with aspirin (antiplatelet therapy) versus patients treated with Rivaroxaban (anticoagulation therapy). The aspirin arm of this study was used as an indirect comparator group in our analysis.

Benefits, harms, and burden

PFO closure in patients ≥60 years of age showed unclear benefit when compared to the historical comparison group from the NAVIGATE ESUS trial[48] (RR, 0.85; 95% CI, 0.38-1.91). The number of events reported in both the PFO closure group and the aspirin therapy group was relatively small. The rate of AF was 7.6% (10/132) in patients ≥60 years who underwent PFO closure. This is slightly higher than the rate of AF in patients <60 years age (5.7%) who underwent PFO closure in the RCTs. Finally, the mortality rate in patients ≥60 years was 7.8% (7/90) (Supplement 3). Deaths after PFO closure during follow up were predominantly due to non-cardiac causes and peri-procedural complications were no different between older and younger patients undergoing PFO closure.[49]

Other considerations

Non-PFO-associated stroke is more common with advancing age. Hence, patients who are 60 years or older should be evaluated to rule out AF and cerebrovascular disease before considering PFO closure for the prevention of recurrent stroke. Patients with additional characteristics that place them at higher risk, such as ASA, large shunt size, or history of systemic embolism, may derive greater benefit from closure versus medical therapy based on evidence extrapolated from other age groups with similar characteristics.[11] Whether or not PFO closure is performed, clinicians should also consider lifelong aspirin therapy for these patients to reduce the risk of recurrent stroke of non-PFO-associated etiology.

Conclusions and research needs for this recommendation

The guideline panel determined that indirect, very uncertain evidence for the benefits of PFO closure in patients 60 years and older who have had a prior PFO-associated stroke supports a conditional recommendation for the use of closure in this population. Researchers may consider including patients ≥60 years of age in future comparative, randomized studies of PFO closure.

Recommendation 2.3

In patients with a history of AF who have had an ischemic stroke, the SCAI guideline panel suggests against the routine use of PFO closure (conditional recommendation, very low certainty of evidence).

Summary of the evidence

The panel did not identify any studies investigating the benefits or harms of PFO closure in patients with a history of AF.

Other considerations

Patients without any underlying history of AF who undergo PFO closure are at greater risk of developing AF compared to patients who are treated with medical therapy. A meta-analysis of observational studies and clinical trials demonstrated an incidence of atrial fibrillation after PFO closure of 3.7 patients per 100 patient years, most of which were concentrated in the first 45 days post-procedure (95% CI, 2.6-4.9). Additionally, this risk of post-procedure AF increases with advancing age.[43]

Conclusions and research needs for this recommendation

The guideline panel suggests against the use of PFO closure versus antiplatelet therapy in patients with a history of AF and a prior PFO-associated stroke. Clinicians are encouraged to document any experience with this patient population.

Recommendation 2.4

In patients with thrombophilia on antiplatelet therapy and not anticoagulation therapy and who have had a prior PFO-associated stroke, the SCAI guideline panel suggests PFO closure rather than antiplatelet therapy alone (conditional recommendation, very low certainty of evidence).

Remark: Patients who place a lower value on the uncertain benefits of PFO closure and a higher value on the possible procedure related risks may reasonably decline PFO closure.

Summary of the evidence

The panel identified 2 observational studies that evaluated outcomes of patients with thrombophilia who underwent PFO closure compared to patients treated with antiplatelet therapy after prior PFO-associated stroke. These studies reported on the risk of recurrent stroke, AF, and other serious adverse events.

Benefits, harms, and burden

Both observational studies found a lower risk of recurrent stroke among patients with thrombophilia who underwent PFO closure compared to patients treated with antiplatelet therapy (RR, 0.17; 95% CI, 0.07-0.44). One study reported 3 serious adverse events in the group of 85

patients who underwent PFO closure which was compared to no adverse events in the group of 51 patients who received antiplatelet therapy.

Other considerations

Patients with thrombophilia have a higher baseline risk for recurrent stroke.[45] Consequently, these patients may experience greater risk reduction after PFO closure. However, evidence of this effect is inconclusive.

Conclusions and research needs for this recommendation

The panel determined that these limited and indirect data comprise very uncertain evidence for the benefits of PFO closure among patients with thrombophilia and a prior PFO-associated stroke. The panel agreed on a conditional recommendation in favor of closure versus antiplatelet therapy alone for the prevention of recurrent stroke. Additional, comparative studies are necessary to more precisely estimate the benefits and harms of PFO closure in this population.

Recommendation 2.5 (refer to Recommendation 2.1)

Patients with high-risk anatomy (ie, ASA)

Summary of the evidence

There is limited evidence describing the outcomes of PFO closure versus antiplatelet therapy in patients with high-risk anatomy. One study provided disaggregated data on the rate of recurrent stroke and TIA in patients with concomitant ASA.[12] There were no events of stroke/TIA recurrence among the 81 patients with ASA who underwent PFO closure compared to 9 stroke/TIA events among the 74 patients with ASA who received antiplatelet therapy (RR, 0.05; 95% CI, 0.00-0.87).

Conclusions and research needs for this recommendation

Refer to recommendation 2.1. Further research is encouraged.

Recommendation 2.6 (refer to Recommendation 2.1)

Patients evaluated with a RoPE score

Summary of the evidence

The panel did not identify any randomized studies that investigated the outcomes of PFO closure versus antiplatelet therapy based on RoPE score. However, Mas et al provided disaggregated data from their study for additional analysis.[12] The panel found that the risk ratio for recurrent stroke among patients with a RoPE score <7 who underwent PFO closure versus antiplatelet therapy was 0.15 (95% CI, 0.01-2.66) and the risk ratio for patients with a RoPE score ≥7 was 0.04 (95% CI, 0.01-0.71).

Conclusions and research needs for this recommendation

Refer to recommendation 2.1. Further research is encouraged.

Recommendation 2.7

The SCAI guideline panel makes no recommendation regarding PFO closure based on prolonged time since stroke (no recommendation, knowledge gap).

Summary of the evidence

The panel did not identify any studies that compared outcomes after various time periods between a PFO-associated stroke and a PFO-closure procedure.

Conclusions and research needs for this recommendation

The panel recognizes this as a knowledge gap. Further research is necessary to determine whether the amount of time between a stroke and a closure procedure affects the outcomes of closing a PFO.

3. Percutaneous PFO closure versus anticoagulation therapy in adults with prior PFO-associated stroke

Recommendation 3.1

In patients between the ages of 18 and 60 with a prior PFO-associated stroke and no other indications for treatment with anticoagulation, the SCAI guideline panel suggests PFO closure plus antiplatelet therapy rather than anticoagulation therapy alone (conditional recommendation, low certainty of evidence).

Remark: This recommendation is independent of patient anatomy (ie, presence of ASA, size of shunt) due to limited clinical data on these sub-populations. A RoPE score ≥7 may identify patients who are likely to receive greater benefit from PFO closure.

Summary of the evidence

The panel identified 3 RCTs that compared outcomes in patients with a prior PFO-associated stroke who underwent PFO closure versus patients treated with anticoagulation therapy.[11-13] These studies reported on recurrent stroke, major bleeding events, PE, DVT, AF, and serious adverse events including device or procedure related events (PICO 3.1 – Evidence Profile). The panel did not identify studies that evaluated the more beneficial treatment strategy between PFO closure and anticoagulant therapy when patients are stratified by their RoPE score. However, a pooled analysis that collated data from the CLOSURE-I trial, RESPECT trial, and PC trial determined that the RoPE score was correlated to the degree of risk of reduction received from PFO closure versus medical therapy.[44] In patients with higher RoPE scores (≥7, n=1221), the rate of recurrent strokes per 100 person-years was 0.30 in the PFO closure group versus 1.03 in the medical therapy group (HR, 0.31; 95% CI, 0.11-0.85; P=0.02). Furthermore, in patients with lower RoPE scores (<7, n=912), the rate of recurrent strokes per 100 person-years was 1.37 in the PFO closure group versus 1.68 in the medical therapy group (HR, 0.82; 95% CI, 0.42-1.59; P=0.56).

Benefits, harms, and burden

Results from these RCTs did not show a reduction in the incidence of recurrent stroke in patients who underwent PFO closure compared to patients treated with anticoagulant therapy (RR, 0.94; 95% CI, 0.37-2.42). Patients who underwent PFO closure had a lower rate of major bleeding events compared to anticoagulant therapy (RR, 0.24; 95% CI, 0.06-0.91). However, patients who underwent PFO closure were at higher risk of AF (RR, 18.1; 95% CI, 1.07-305.04) and 86% of AF events occurred within 45 days post-procedure.

Other considerations

The panel considered evidence for disparate effects of closure in patients with high-risk anatomy and various RoPE scores. However, the data are limited and the panel found no evidence that these patients

Table 5. Summary of recommendations for PICO question 3

Recommendation	Strength of recommendation	Certainty of evidence
3.1 In patients between ages of 18 and 60 with a prior PFO-associated stroke and no other indications for treatment with anticoagulation, the SCAI guideline panel suggests PFO closure plus antiplatelet therapy rather than anticoagulation therapy alone. **Remark:** This recommendation is independent of patient anatomy (ie, presence of ASA, size of shunt) due to limited clinical data on these sub-populations. A RoPE score ≥7 may identify patients who are likely to receive greater benefit from PFO closure.	Conditional	Low
3.2 In patients 60 years or older with a prior PFO-associated stroke and no other indications for treatment with anticoagulation, the SCAI guideline panel suggests PFO closure plus antiplatelet therapy rather than long-term anticoagulation therapy alone. **Remark:** Patients in this age group who place a lower value on the uncertain benefits of PFO closure and a higher value on the possible procedure related risks may reasonably decline PFO closure.	Conditional	Very Low
3.3 Patients with high-risk anatomy (ie, ASA) - refer to Recommendation 3.1	-	-
3.4 Patients evaluated with a RoPE score - refer to Recommendation 3.1	-	-
3.5 The SCAI guideline panel makes no recommendation regarding PFO closure based on prolonged time since stroke.	No recommendation	Knowledge gap

would benefit from a different management strategy than the broader population.

Conclusions and research needs for this recommendation

The panel determined that there is low certainty evidence for a net health benefit for patients with a prior PFO-associated stroke who undergo PFO closure plus antiplatelet therapy compared to patients who receive anticoagulant therapy. Together, the decreased risk of major bleeding, increased risk of AF and similar rate of recurrent stroke comprise a mixed benefit profile of PFO closure over anticoagulant therapy. Therefore, the panel conditionally recommends PFO closure plus antiplatelet therapy rather than anticoagulation for these patients regardless of anatomical features. Additional research is necessary to determine if the benefits and harms of PFO closure vary based on patient anatomy (ie, ASA, shunt size) or RoPE score (Table 5).

Recommendation 3.2

In patients 60 years or older with a prior PFO-associated stroke and no other indications for treatment with anticoagulation, the SCAI guideline panel suggests PFO closure plus antiplatelet therapy rather than long-term anticoagulation therapy alone (conditional recommendation, very low certainty of evidence).

Remark: Patients in this age group who place a lower value on the uncertain benefits of PFO closure and a higher value on the possible procedure related risks may reasonably decline PFO closure.

Summary of the evidence

The panel did not identify any studies that evaluated the outcomes of treatment with PFO closure versus anticoagulation therapy in patients 60 years of age or older who have had a prior PFO-associated stroke. However, 4 observational studies compared outcomes in patients $<$ 60 years of age versus patients $\geq$ 60 years of age after closure. The panel also included data from the NAVIGATE ESUS sub-analysis of patients with PFO. This study compared the incidence of recurrent stroke in patients treated with aspirin (antiplatelet therapy) versus patients treated with Rivaroxaban (anticoagulation therapy). The anticoagulation arm of this study was used as an indirect comparator group in our analysis.

Benefits, harms, and burden

PFO closure in patients $\geq$60 years of age showed unclear benefit when compared to the historical comparison group from the NAVIGATE ESUS trial (RR, 1.49; 95% CI, 0.58-3.86). The number of events reported in both the PFO closure group and the anticoagulation therapy group was relatively small. The rate of AF was 7.6% (10/132) in patients $\geq$60 years who underwent PFO closure. This is slightly higher than the rate observed in patients $<$60 years age (6.4%) who underwent PFO closure in the RCTs. Finally, the mortality rate in patients $\geq$60 years was 7.8% (7/90).

Other considerations

Non–PFO-associated stroke is more common with advancing age. Hence, patients who are 60 years or older should be evaluated to rule out AF and cerebrovascular disease before considering PFO closure for the prevention of recurrent stroke. Patients with additional characteristics that place them at higher risk, such as ASA, large shunt size, or history of systemic embolism, may derive greater benefit from closure versus medical therapy based on evidence extrapolated from other age groups with similar characteristics.[11] Whether or not PFO closure is performed, clinicians should also consider lifelong aspirin therapy for these patients to reduce the risk of recurrent stroke of non–PFO-associated etiology.

Conclusions and research needs for this recommendation

The guideline panel determined that indirect, very uncertain evidence for the benefits of PFO closure in patients 60 years and older who have had a recent PFO-associated stroke supports a conditional recommendation for the use of closure in this population. Researchers may consider including patients $\geq$60 years of age in future comparative, randomized studies of PFO closure.

Recommendation 3.3 (refer to Recommendation 3.1)

Patients with high-risk anatomy (ie, ASA)

Summary of the evidence

There are limited data evaluating the effect of PFO closure versus anticoagulant therapy in patients with high-risk anatomical features.

Conclusions and research needs for this recommendation

Refer to recommendation 3.1. Further research is encouraged.

Recommendation 3.4 (refer to Recommendation 3.1)

Patients evaluated with a RoPE score

Summary of the evidence

The panel did not identify any randomized studies that investigated the outcomes of PFO closure versus anticoagulation based on RoPE score. However, Mas et al provided disaggregated data from their study for additional analysis.[12] The panel found that the risk ratio for recurrent stroke among patients with a RoPE score $<$7 who underwent PFO closure versus anticoagulation was 0.17 (95% CI, 0.009-3.50) and the risk ratio for patients with a RoPE score $\geq$7 was 0.26 (95% CI, 0.01-6.21).

Conclusions and research needs for this recommendation

Refer to recommendation 3.1. Further research is encouraged.

Recommendation 3.5

The SCAI guideline panel makes no recommendation regarding PFO closure based on prolonged time since stroke (no recommendation, knowledge gap).

Conclusions and research needs for this recommendation

The panel recognizes this as a knowledge gap. Further research is necessary to determine whether the amount of time between a stroke and a closure procedure affects the outcomes of closing a PFO.

4. Percutaneous PFO closure plus lifelong anticoagulation versus anticoagulation alone in adults with prior PFO-associated stroke

Recommendation 4.1

In patients with thrombophilia and a prior PFO-associated stroke, the SCAI guideline panel suggests PFO closure in addition to lifelong anticoagulation therapy rather than anticoagulation therapy alone (conditional recommendation, very low certainty of evidence).

Remark: Patients who need long term anticoagulation and who place a lower value on the uncertain benefits of PFO closure and a higher value on the possible procedure related risks may reasonably decline PFO closure.

Summary of the evidence

The panel identified 2 observational studies that evaluated outcomes of patients with thrombophilia who underwent PFO closure versus patients treated with antiplatelet therapy after prior PFO-associated stroke.[40,45] These studies reported on the risk of recurrent stroke, AF, and other serious adverse effects.

Benefits, harms, and burden

Both observational studies found a decreased risk of recurrent stroke in patients with thrombophilia who underwent PFO closure (RR, 0.17; 95% CI, 0.07-0.44). One study reported 3 procedure-related adverse events in the closure group and no adverse events in the antiplatelet group during the study period.[40]

Other considerations

Patients with thrombophilia have a greater baseline risk for recurrent stroke.[45] This risk is mitigated by oral anticoagulants. However, issues of non-compliance or intentional interruption of therapy for bleeding or surgical procedures suggest that these patients may experience greater risk reduction after PFO closure. However, evidence of this effect is inconclusive.

Conclusions and research needs for this recommendation

The panel determined that these limited and indirect data comprise very uncertain evidence for the benefits of PFO closure in addition to lifelong antithrombotic therapy among patients with thrombophilia and a prior PFO-associated stroke. The panel agreed on a conditional recommendation in favor of closure plus lifelong antithrombotic therapy over antithrombotic therapy alone for the prevention of recurrent stroke.

Table 6. Summary of recommendations for PICO question 4

Recommendation	Strength of recommendation	Certainty of evidence
4.1. In patients with thrombophilia and a prior PFO-associated stroke, the SCAI guideline panel suggests PFO closure in addition to lifelong anticoagulation therapy rather than anticoagulation therapy alone. **Remark:** Patients who need long term anticoagulation and who place a lower value on the uncertain benefits of PFO closure and a higher value on the possible procedure related risks may reasonably decline PFO closure.	Conditional	Very Low
4.2. In patients with a history of DVT requiring lifelong anticoagulation and concomitant PFO-associated stroke, the SCAI guideline panel suggests PFO closure plus lifelong anticoagulation rather than lifelong anticoagulation alone. **Remark:** Patients who need lifelong anticoagulation and who place a lower value on the uncertain benefits of PFO closure and a higher value on the possible procedure related risks may reasonably decline PFO closure.	Conditional	Very Low
4.3. In patients with a history of PE requiring lifelong anticoagulation and concomitant PFO-associated stroke, the SCAI guideline panel suggests PFO closure plus lifelong anticoagulation rather than lifelong anticoagulation alone. **Remark:** Patients who need lifelong anticoagulation may place a lower value on the uncertain benefits of PFO closure and a higher value on the possible procedure related risks may reasonably decline PFO closure.	Conditional	Very Low

Additional, comparative studies are necessary to more precisely estimate the benefits and harms of PFO closure in this population (Table 6).

Recommendation 4.2

In patients with a history of DVT requiring lifelong anticoagulation and a concomitant PFO-associated stroke, the SCAI guideline panel suggests PFO closure plus lifelong anticoagulation rather than lifelong anticoagulation alone (cconditional recommendation, very low certainty of evidence).

Remark: Patients who need lifelong anticoagulation and who place a lower value on the uncertain benefits of PFO closure and a higher value on the possible procedure related risks may reasonably decline PFO closure.

Summary of the evidence

The panel did not identify any randomized studies reporting the outcomes of treatment with PFO closure plus anticoagulation compared to anticoagulation alone in patients with a history of DVT and concomitant PFO-associated stroke. One observational study reported disaggregated outcomes in patients with a history of DVT who underwent PFO closure.[42] None of the 10 patients with a history of DVT who received PFO closure in addition to long term anticoagulation experienced recurrent stroke during the study period.

Other considerations

The CHEST guidelines for antithrombotic therapy recommend that patients who receive long term anticoagulation should be reevaluated on a regular basis (eg, annually) to monitor the risk-benefit balance of continuing therapy over time.[50,51] The typical follow-up duration for studies on the effects of long term anticoagulation is 2-4 years.[50] Although rare, anticoagulation failure is possible. In this situation, the CHEST guidelines recommend further assessment after failure and a temporary switch from oral anticoagulation to systemic options such as low-molecular-weight heparin (LMWH).[50] In addition, common issues such as non-compliance and interruption of anticoagulants for bleeding or invasive procedures must be factored into treatment considerations.

Conclusions and research needs for this recommendation

The panel determined that there is very uncertain evidence for the effects of PFO closure in addition to lifelong anticoagulation therapy in patients with a history of DVT and PFO-associated stroke. The panel agreed on a conditional recommendation in favor of closure plus lifelong anticoagulation over anticoagulation alone for the prevention of recurrent stroke. Additional, comparative studies are necessary to more precisely estimate the benefits and harms of PFO closure in this population.

Recommendation 4.3

In patients who have a history of PE requiring lifelong anticoagulation and a concomitant PFO-associated stroke, the SCAI guideline panel suggests PFO closure plus lifelong anticoagulation rather than lifelong anticoagulation alone (conditional recommendation, very low certainty of evidence).

Remark: Patients who need lifelong anticoagulation may place a lower value on the uncertain benefits of PFO closure and a higher value on the possible procedure related risks and may reasonably decline PFO closure.

Summary of the evidence

The panel did not find any randomized studies that reported on outcomes in patients with a history of PE and concomitant PFO-associated stroke who received PFO closure plus anticoagulation compared to anticoagulation alone. One observational study reported disaggregated outcomes in patients with PE who had received PFO closure.[42] There were no recurrent strokes among the 8 patients with a history of PE who received PFO closure in addition to long-term anticoagulation.

Other considerations

The CHEST guidelines for antithrombotic therapy recommend that patients who receive long term anticoagulation should be reevaluated on a regular basis (eg, annually) to monitor the risk-benefit balance of continuing therapy over time.[50,51] The typical follow-up duration for studies on the effects of long term anticoagulation is 2-4 years.[50] Although rare, anticoagulation failure is possible. In this situation, the CHEST guidelines recommend further assessment after failure and a temporary switch from oral anticoagulation to systemic options such as LMWH.[50] In addition, common issues such as non-compliance and interruption of anticoagulants for bleeding or invasive procedures must be factored into treatment considerations.

Conclusions and research needs for this recommendation

The panel determined that there is very uncertain evidence for the effects of PFO closure in addition to lifelong anticoagulation therapy in patients with a history of PE and PFO-associated stroke. The panel agreed on a conditional recommendation in favor of closure plus lifelong anticoagulation over anticoagulation alone for the prevention of recurrent stroke. Additional, comparative studies are necessary to more precisely estimate the benefits and harms of PFO closure in this population.

5. Post-procedure management of patients undergoing percutaneous PFO closure with a regimen of 1 month of aspirin plus clopidogrel followed by 5 months of aspirin versus another antiplatelet regimen or anticoagulation

Recommendation 5

The SCAI guideline panel makes no recommendation regarding duration beyond 1 month of dual antiplatelet therapy after PFO closure (no recommendation, knowledge gap).

Summary of the evidence

Most studies of PFO closure report on the post-procedure antithrombotic regimen prescribed to patients. However, follow-up data that could illustrate the comparative efficacy of different antithrombotic regimens is absent from the literature.

The panel found 8 studies (2 RCT, 6 observational) that reported on antithrombotic regimens including duration and outcomes (Table 3). Four other studies (3 observational[52-54] and 1 RCT[12]) reported a regimen of 3 months of dual antiplatelet therapy (DAPT) followed by aspirin monotherapy. These studies reported associated stroke rates of 0, 4.3, 1, and 0 per 1000 patient-years, respectively. Only 1 study captured

bleeding events, reporting a rate of 20 bleeding events per 1000 patient-years over 6 months of follow-up.[52]

Apart from these 2 regimens (1 month versus 3 months of DAPT), data regarding other antithrombotic regimens are limited and summarized as follows. One observational study utilized 6 months of DAPT,[55] but did not disaggregate stroke from TIA. This study reported a combined event rate of 28 per 1000 patient-years. Another observational study utilized monotherapy with either aspirin, clopidogrel, cilostazol, ticlopidine, or warfarin, reporting no strokes among 67 patients at 27.8 months follow-up.[56] One RCT did not specify the duration of antithrombotic therapy but reported no strokes regardless of antithrombotic regimen. The reported bleeding rates are 125 per 1000 patient-years with warfarin and 17 per 1000 patient-years with DAPT.[11] Five other studies included multiple antithrombotic regimens, but stroke rates were not disaggregated per antithrombotic regimen.[14,42,57-59] The various regimens used in different studies have negligible reports of complications in patients who undergo PFO closure.

Conclusions and research needs for this recommendation

Given the lack of studies to identify a superior antithrombotic therapy regimen following PFO closure, the SCAI panel makes no recommendation on the optimal duration of post-procedure antiplatelet therapy. Further research comparing antithrombotic regimens, including various durations, is needed.

Discussion

These guidelines add clarity to a field which, for almost thirty years, has been guided by small observational and retrospective studies. With the publication of multiple positive PFO closure trials, the FDA approval of devices to close PFOs, and the high prevalence of PFOs in adults, SCAI members realized the importance of developing recommendations to aid health care providers, interventional cardiologists, neurologists, and payors in the optimal application of this procedure. To assure the highest level of transparency, the SCAI guideline panel, consisting of experienced methodologists and experts in the fields of structural heart disease and neurology, employed the GRADE approach to develop a series of clinical questions and outcomes. Each question was reviewed by a technical review panel and these findings informed judgements by the guideline panel to develop each recommendation. SCAI acknowledges the importance of alignment with stroke neurology for any guidance surrounding PFO closure and carried out this effort with representation from the American Academy of Neurology. Patient representatives with a variety of backgrounds and experiences were also included on the guideline panel to inform discussions about values and preferences. Finally, critics who describe percutaneous PFO procedures as invasive with procedural and device related complications should remember that PFO closure has an excellent safety profile and that oral anti-platelet and anti-coagulant therapies are associated with significant bleeding events. A survey study of 13,736 implants revealed a need for surgery in only 0.2% after a PFO closure procedure.[60,61]

There was sufficient certainty in the data on PFO closure for prevention of recurrent PFO-associated stroke to support a strong recommendation. This recommendation is independent of other features such as shunt size, tunnel length, of presence of ASA. The RCTs enrolled patients within a few months of their index event. Therefore, the evidence for treating patients with longer time periods from their index event is lacking and the guideline panel deferred making recommendations regarding this patient subset. Patients who did not meet the RCT inclusion criteria due to their age (60+) may still experience PFO-associated stroke and could benefit from PFO closure. Although this recommendation is conditional and the strength of supporting evidence very low, the panel agreed that PFO closure in patients with PFO-associated stroke combined with antiplatelet therapy is preferable to oral anticoagulants alone. However, the guideline panel did not make any recommendation regarding duration of antiplatelet therapy due to absence of clinical data. The data regarding treatment of patients with stroke, atrial fibrillation, and PFO are particularly murky. Although these patients may experience PFO-associated stroke, the guideline panel felt compelled to recommend against routine PFO closure in such patients due to the absence of data suggesting a benefit. Further complicating the issue of atrial fibrillation is the increased incidence of post-procedure atrial fibrillation after PFO closure which has been noted in multiple clinical studies and highlighted in a recent meta-analysis (41). These episodes are concentrated in the first 45 days post-procedure and are not thought to be etiologic cause of the index stroke. Rather, localized irritation and inflammation of the atrial septum by the newly placed occluder device can serve as a substrate for atrial fibrillation which will occur shortly after device placement and generally resolve with endothelialization of the occluder. The management of post-procedure atrial fibrillation remains an issue of controversy and beyond the scope of this paper. In patients with thrombophilia, DVT, and PFO (with or without ASA) without an antecedent stroke, the guideline panel advises against routine PFO closure. In patients with PFO who experience a systemic embolism (coronary, visceral, and peripheral, among others) without an alternative identifiable cause, PFO closure would be reasonable despite absence of clinical data due to the mechanistic similarity to PFO-associated stroke. Patients with PFO and without a prior stroke but with symptoms of TIA represent a subset of patients who were excluded from the RCTs and whom the guideline panel agreed should not undergo routine PFO closure due to the difficulty of adjudicating a TIA from a complex migraine or other transient neurologic condition. For patients with a PFO-associated stroke who require lifelong oral anticoagulation for a variety of indications including DVT, PE, or thrombophilia, the panel determined that PFO closure in addition to long term oral anticoagulation is preferable because of issues related to non-compliance or interruption of therapy.

The guideline panel recognized that observational and retrospective studies suggest an association between PFO and certain subsets of patients with migraine headaches, while acknowledging that all RCTs of PFO closure for refractory migraine headaches did not meet their primary efficacy endpoint. Based on the RCTs, the guideline panel recommended against routine PFO closure for such patients. Ongoing RCTs will add clarity to this important question. Given the excellent safety profile of PFO closure procedures, certain patients with debilitating migraines despite medical therapy may seek out this procedure despite uncertainty of the clinical benefits. Likewise, although the risk of decompression sickness in SCUBA divers is 5 times higher in those with PFO, the option for most patients to limit high risk diving, and a lack of clinical data suggesting benefit from PFO closure in these patients precludes a recommendation for closure in this population. For patients with platypnea-orthodeoxia syndrome the panel recognizes the significant clinical benefits in these patients. The panel also recognizes the lack of supportive clinical data due largely to the small numbers of these patients. For these reasons, the recommendation in favor of PFO closure is conditional.

This guideline represents the most comprehensive effort to date to synthesize and interpret the evidence supporting PFO closure in a wide variety of clinical scenarios. For most scenarios, evidence regarding the efficacy of PFO closure has some degree of uncertainty. The panel recognizes that many of these scenarios do not lend themselves to RCT design due to small numbers of patients, small numbers of events, and the extremely large numbers of patients necessary to demonstrate a clinically relevant benefit. The recommendations of the panel are based on available data, which is sometimes indirect or imprecise, by necessity. The decision to perform PFO closure on any patient for any clinical scenario should be highly individualized and nuanced in the context of a mandatory multi-disciplinary team of primary stakeholders which, most importantly, should include the patient and a neurologist. We hope that future clinical trials will support clarification of these guidelines in the future.

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Supplementary material

To access the supplementary material accompanying this article, visit the online version of the Journal of the Society for Cardiovascular Angiography & Interventions at 10.1016/j.jscai.2022.100039.

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