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Standards and Guidelines

SCAI Technical Review on Management of Patent Foramen Ovale

Andrew M. Goldsweig, MD, MS, FSCAI [a,*], Sarosh P. Batlivala, MD, MSCI, FSCAI [b], Karim Al-Azizi, MD, FSCAI [c], Vikas Aggarwal, MD, MPH, FSCAI [d,e], Ifeoluwa Babatunde, PharmD, MS [f], Yngve Falck-Ytter, MD [f,g,h], Rebecca L. Morgan, PhD, MPH [f,h,i]

[a] Division of Cardiovascular Medicine, University of Nebraska Medical Center, Omaha, Nebraska
[b] Heart Institute, Cincinnati Children's Hospital Medical Center & Division of Pediatric Cardiology, University of Cincinnati College of Medicine, Cincinnati, Ohio
[c] Baylor Scott & White Health, The Heart Hospital, Plano, Texas
[d] Division of Cardiovascular Medicine, Department of Internal Medicine, University of Michigan (Frankel Cardiovascular Center), Ann Arbor, Michigan
[e] Section of Cardiology, VA Ann Arbor Healthcare System, Ann Arbor, Michigan
[f] Evidence Foundation, Cleveland Heights, Ohio
[g] VA Northeast Ohio Healthcare System, Cleveland, Ohio
[h] Case Western University, Cleveland, Ohio
[i] Department of Health Research Methods, McMaster University, Hamilton, Ontario, Canada

A B S T R A C T

Background: Patent foramen ovale (PFO) is a common anatomic variant associated with intermittent right-to-left shunting. Transcatheter PFO closure has been proposed to address multiple clinical conditions including stroke, transient ischemic attack, migraine, and decompression illness.

Methods: A systematic review was conducted using the GRADE approach to address 5 questions formulated by the Society for Cardiovascular Angiography and Interventions (SCAI) Guideline Panel in patient, intervention, comparator, outcome (PICO) format. Medical literature from January 2015 through May 2021 was searched. Extracted data underwent review and risk-of-bias assessment by 2 independent researchers. Pooled effect estimates were calculated. Certainty of evidence was determined for each query.

Results: Our search identified 2701 titles and abstracts, of which 30 met eligibility criteria and informed the technical review. Data were abstracted to address outcomes of PFO closure for patients with and without prior stroke, in comparison to antiplatelet therapy, in comparison to anticoagulation, and with various post-procedure antithrombotic regimens.

Conclusion: In appropriately selected patients with prior stroke, transcatheter PFO closure reduces the risk of recurrent stroke more than antiplatelet therapy alone. Evidence to support PFO closure is weaker regarding older patients, anticoagulation, thrombophilia, transient ischemic attack, migraine, and decompression illness. Data from this technical review will inform the SCAI Guideline for Transcatheter Patent Foramen Ovale Closure.

Introduction

Patent foramen ovale (PFO) is an anatomic variant in which a fetal communication between the right and left atria persists postnatally. Present in up to 25% of humans, PFO can allow a thrombus from the venous system to pass into the arterial system and embolize to the cerebral vasculature leading to an embolic stroke.[1] Four randomized controlled trials (RCTs) have thus far demonstrated that transcatheter PFO closure reduces the risk of recurrent stroke more than medical therapy alone in selected patients.[2-5] However, given the high prevalence of PFO, best practices would target closure procedures to individuals most likely to benefit, as inappropriate use results in unnecessary procedures with their incumbent risks and expenses. Furthermore, the potential benefits of PFO closure for patients with advanced age, thrombophilia, migraine, deep venous thrombosis, pulmonary embolism, platypnea-orthodeoxia, or decompression illness also remain unclear.

Patients with PFO may be anxious and eager to prevent future adverse events. Physicians lack synthesized information to recommend PFO closure appropriately across the spectrum of clinical scenarios. There are published position papers on PFO closure from European societies[6,7] and the American Academy of Neurology.[8] While these articles have addressed PFO closure, new data have emerged in recent years, and no American cardiovascular society has published guidelines for transcatheter of PFO closure. Thus, at present, there is limited guidance for appropriate use of PFO closure in the United States.

In this technical review, the Society for Cardiovascular Angiography and Intervention (SCAI) conducted a systematic review on indications for transcatheter PFO closure and post-procedure antithrombotic therapy to

* Corresponding author.
E-mail address: andrew.goldsweig@unmc.edu (A.M. Goldsweig).

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answer a series of research questions. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach[9,10] was used to assess the strength of evidence and guide decision-making. In areas where insufficient evidence exists, directions for further research are suggested. The findings from this review inform the SCAI clinical guideline panel's recommendations on the management of PFO to guide cardiologists, neurologists, and patients to maximize the benefits of PFO closure. This review focuses on indications for PFO closure among persons with and without prior stroke, as well as management options following closure; however, specific techniques and devices for PFO closure are beyond the scope of this review.

Objectives of the review

This technical review assessed the evidence about PFO closure to address 5 clinical questions formulated in the PICO (patient, intervention, comparator, outcomes) format.

1. In adults *without prior PFO-associated stroke*, should PFO closure rather than medical therapy be used to prevent stroke, migraine, platypnea-orthodeoxia syndrome, or decompression illness?
2. In adults with prior PFO-associated stroke who have other stroke risk factors, should PFO closure rather than *antiplatelet* therapy be used to prevent recurrent stroke?
3. In adults with prior PFO-associated stroke who have other stroke risk factors, should PFO closure rather than *anticoagulation* be used to prevent recurrent stroke?
4. In adults with prior PFO-associated stroke with a *separate indication for lifelong anticoagulation*, should PFO closure be combined with anticoagulation to prevent recurrent stroke rather than medical therapy alone?
5. In adults undergoing transcatheter PFO closure, should a regimen of 1 month of dual antiplatelet therapy followed by at least 6 months of aspirin be used rather than other regimens to prevent stroke and bleeding events?

Methods

Overview of the systematic review process

This technical review was conducted to inform the development of SCAI guidelines regarding the use of transcatheter PFO closure in the management of patients with or without prior stroke. The Technical Review Panel was composed of both clinical interventional cardiologists and methodological experts. The development of this systematic review, following the GRADE approach, included the following steps:

1. Research question identification and development; classification of outcomes critical and important for clinical decision making.
2. Systematic review of the literature to identify primary studies and relevant high-quality systematic reviews.
3. Risk of bias assessment of individual studies.
4. Synthesis of the evidence using meta-analysis or narrative synthesis.
5. Assessment of the certainty of evidence using GRADE.

The GRADE approach provided the basis and methodology for deriving focused clinical questions, systematically reviewing and rating the certainty of evidence for each outcome, and rating the overall certainty of evidence.

Formulation of clinical questions and determining outcomes of interest

The panel formulated and prioritized the questions to be addressed by this guideline using the PICO format.[11] The final set of questions and statements was approved by the SCAI Guideline Panel. Members of the Guideline Panel selected patient-important outcomes for each question *a priori*. Outcomes were rated numerically for their relative importance to clinical decision-making on a scale of 1-9. Outcomes receiving a score of 7-9 were considered critical, 4-6 were considered important, while 1-3 were considered less important for clinical decision-making.[11] Only critical outcomes (7-9) were included in the final list of PICO questions (Supplement, Table 2).

Literature search strategy and study selection

A literature search was conducted to identify primary studies (ie, comparative randomized and non-randomized studies) and systematic reviews published on the PICO questions derived by the Panel. Studies were eligible if they were published in 2015 and after. This date limit was selected in order to reflect currently-used PFO closure devices, excluding studies which described the use of discontinued devices. The Technical Review and Guideline Panels collectively re-evaluated the evidence identified and independently determined the certainty of the evidence as outlined below.

A search of the medical literature was conducted by an information specialist in the following databases: PubMed, EMBASE (OVID), and the Cochrane Central Register of Controlled Trials from January 2015 to September 2020. This search was updated to include additional studies that were published from September 2020 to May 2021. The search strategy comprised controlled vocabulary, including the National Library of Medicine's Medical Subject Headings (MESH) and keywords (Supplement, Table 1). We excluded studies published in any language other than English, narrative reviews, individual case reports, and studies without human participants.

Abstracts and full-text reports were uploaded to Covidence (Cochrane) for screening and review. RCTs and comparative non-randomized studies (NRSs) were considered the gold standard source of evidence for each PICO question. However, in the absence of RCTs and comparative NRSs, single-arm, non-comparative studies were included to reflect the extent of literature for each PICO question.

For studies containing insufficient published data on populations of interest, corresponding authors were contacted to provide additional information on trials when required. Two attempts were made to contact the author. If there was no response after 2 attempts, the study was excluded based on incomplete information.

Data extraction and risk-of-bias assessment

Data from the included studies were extracted by 1 Technical Review team member and reviewed by a second Technical Review team member for each PICO question. From the available evidence, data extracted included: last name of author(s), year of publication, country of origin, funding source, protocol registration, study abbreviation (eg, CLOSE), study duration, population information, procedure conducted, comparative drug (eg, antiplatelet, anticoagulant), and outcome measures (including adverse events). The risk of bias of eligible studies was assessed independently by 2 Technical Review team members using the Cochrane risk of bias tool for randomized controlled trials.[12] Non-randomized studies were assessed using the ROBINS-I (Risk of Bias In Non-randomized Studies – of Interventions) tool.[13] A consensus of risk of bias judgements was compiled for each study and judgement disagreements were resolved by a methodologist.

Analytic approach

A pooled effect estimate was calculated for each outcome with an intervention and comparison. These quantitative analyses were expressed as either a relative risk (RR) for categorical variables or mean difference (MD) for the continuous variables. The Der Simonian and Laird method for random effect or fixed-effects models was used to determine the overall effect size with 95% confidence intervals (CIs).

Fixed-effects models were used when only 2 trials were pooled for the overall effect size.[14]

For instances where insufficient quantitative data made pooling impossible, a narrative summary of the results was developed. Heterogeneity between studies was assessed using the I^2 statistic. All analyses and resultant figures such as forest plots were developed in Review Manager (RevMan) version 5.3 (The Cochrane Collaboration).

Certainty of evidence

The GRADE approach was used to assess the certainty of evidence (CoE).[10] The CoE was rated as "High," "Moderate," "Low," or "Very Low." Evidence from RCTs, which initially provide high certainty, could be rated down due to concerns in domains such as risk of bias (ie, study limitations), inconsistency (ie, unexplained heterogeneity), indirectness (ie, applicability to population of interest), imprecision (ie, confidence in effect estimate), and/or publication bias within GRADE. Conversely, evidence from observational studies, which typically provide low certainty due to potentially unknown confounders, could also be rated down due to concerns in the previously mentioned domains. CoE in the evidence could be strengthened on the basis of a large magnitude of effect, a dose-response gradient, or opposing residual confounding.[9]

CoE was first ascertained for each outcome and then assessed across all outcomes for each PICO question. For each PICO question, an evidence profile was prepared using the GRADEpro Guideline Development Tool (www.gradepro.org).

Results

The initial literature search identified 2701 titles and abstracts, of which 30 met eligibility criteria and informed the technical review on management of PFO closure (Supplement, Figure 1. PRISMA Flow Diagram).

Question 1 In adults without prior PFO-associated stroke, should PFO closure rather than medical therapy be used to prevent stroke, migraine, or decompression illness?

The Technical Review Panel identified 14 eligible studies[15-28] that reported on persons with a PFO without the history of a PFO-associated stroke but who had another indication for transcatheter PFO closure (eg, migraine, decompression illness, platypnea-orthodeoxia) (Supplement, Table 3). Three of the eligible studies were RCTs.[17,21,26] All 3 studies were assessed to be of low risk of bias (Supplement, Table 4). The remaining 11 NRSs[15,16,18-20,22-25,27,28] had concerns with risk of bias, including controlling for critical confounders, selection bias, and measurement of the outcomes (Supplement, Table 5). Our search was unable to identify studies which reported on PFO closure in patients with a history of atrial septal aneurysm (ASA), transient ischemic attack (TIA), or deep vein thrombosis (DVT) who had no prior PFO-associated stroke. The evidence for this question is summarized in the supplementary material.

In adults with prior PFO-associated stroke, PFO closure has been the standard of care in the absence of any contraindications.[29] PFO closure has also been proposed for primary prevention of PFO-associated stroke in patients with thrombophilia, ASA, systemic embolism, TIA, DVT, and pulmonary embolism (PE) who would receiving prophylactic antiplatelet/anticoagulant therapy. In addition, PFO closure has been proposed as an appropriate therapy in patients without a prior PFO-associated stroke for the secondary prevention of migraines, diving decompression illness (DCI), and platypnea-orthodeoxia syndrome (POS).

PFO closure for the treatment of migraine headaches was studied in 3 RCTs.[17,21,26] The aggregate of the 3 RCTs failed to demonstrate that PFO closure resulted in migraine cessation (risk ratio [RR]: 3.46, 95% confidence interval [CI]: 0.65-18.40, moderate certainty of evidence). However, results did reveal small decreases in the number of migraine attacks per month (mean difference [MD]: −0.59 attacks, 95% CI: −1.03 to −0.15, moderate certainty of evidence) and in the number of migraine days per month (MD: −1.33 days; 95% CI: −2.32 to −0.33, moderate certainty of evidence) (Supplement, PICO Question 1.1). We rated down for imprecision across all outcomes because it was unclear that the estimate and 95% CI indicated a clinically meaningful reduction. There were also few events reported suggesting fragility of the effect estimate.

SCUBA divers returning to the surface are at risk for DCI as the rapid decrease in pressure allows dissolved nitrogen to emerge from solution in the blood, more likely in the lower-pressure venous system than the higher-pressure arterial system. PFO has been hypothesized to permit travel of nitrogen bubbles from the venous to the arterial circulation. Three comparative observational studies[15,20,30] reported on the outcome of DCI. Persons receiving PFO closure may trend towards a reduction in DCI; however, the evidence is very uncertain (RR: 0.31, 95% CI: 0.08-1.13, very low certainty of evidence) (Supplement, PICO Question 1.2). We rated down for risk of bias, indirectness to the population of interest, and imprecision.

POS is a condition in which recumbent positioning is thought to potentiate intracardiac right-to-left shunting, causing systemic hypoxemia.[31] The efficacy of PFO closure for treating POS has been assessed in 3 single-arm prospective studies.[22,24,25] While no comparative data are available, PFO closure was reported in these single-arm studies to result in increased systemic oxygen saturations (MD: 14.21, 95% CI: 12.18-16.25, very low certainty of evidence) and improved quality of life, tempered by some procedure-associated adverse events and atrial fibrillation (AF) (Supplement, PICO Question 1.3). The certainty of evidence was rated down due to concerns with imprecision and indirectness.

PFO closure for primary prevention of stroke has been considered in several patient populations. In a retrospective observational study of 136 patients with genetic and acquired thrombophilias, Buber et al. reported that PFO closure may reduce stroke (RR: 0.21, 95% CI: 0.07-0.65, very low certainty of evidence).[16] The certainty of the evidence was rated down due to imprecision. Furthermore, another retrospective observational study, Wintzer-Wehekind et al. found that patients with a prior TIA had a composite stroke/TIA rate of 6.2% during the follow-up period (median 12 years).[27] Although the majority of the TIA patients had not had a prior stroke, it is important to note the presence of some overlap between the population patients who had experienced prior stroke (153 [76.1%]) and those who had prior TIA at baseline (65 [32.3%]) reported in the study. Furthermore, 1.5% of patients were enrolled with systemic embolism as the indication for PFO closure. This indication appears to be rare, and we are unable rule out the presence of a prior stroke event in this sub-population of patients.[27] For these populations we rated down the certainty of evidence due to concerns with risk of bias due to confounding, indirectness, and imprecision.

Discussion

The evidence to support PFO closure in patients without prior PFO-associated stroke is limited and relatively weak. With respect to migraine, meta-analysis of the RCTs suggests that monthly attacks and migraine days may decrease numerically with PFO closure, but the clinical meaning of the effect is limited by the small magnitude of this decrease.

There was a lack of data from randomized studies for DCI. Given that DCI is uncommon and may be prevented with more conservative diving practices, future RCTs are unlikely to be conducted.

POS is extremely rare, but in cases with documented PFO-mediated right-to left shunting, case series suggest that PFO closure may be useful on select patients.

For patients with a thrombophilia, data from the single retrospective study are insufficient to define a role for PFO closure for primary prevention of stroke. Similarly, for patients with TIA but no stroke, data are limited and cannot define a role for PFO closure. In the case of TIA, the uncertainty of the diagnosis makes ascribing an ischemic etiology particularly challenging: for patients with a short-lived neurologic

symptom and normal neuroimaging, complex migraine and neuropathy may be easily confused with TIA.

Question 2 In adults with prior PFO-associated stroke who have other stroke risk factors, should PFO closure rather than antiplatelet therapy be used to prevent recurrent stroke?

The Technical Review Panel identified 7 cohort studies[16,23,27,32-36] and 4 RCTs[2-5] comparing PFO closure to antiplatelet therapy alone (Supplement, Table 3). The 4 RCTs provided data to address the broad primary question of whether PFO closure or antiplatelet therapy is superior for secondary stroke prevention after PFO-associated stroke.[2-5] Sub-group analyses were performed utilizing randomized data from the CLOSE trial as well as 7 NRSs (cohorts). The 4 RCTs were assessed to have a low risk of bias. All studies had concerns with blinding (ie, interventional cardiologists performing the closure were not blinded and blinded outcome adjudication was also not reported) (Supplement, Table 4). This concern was judged not to substantially affect the risk of bias in these studies. The risk of bias in the NRSs was generally judged to be low; however, there was moderate to severe risk of bias in the domains of selection bias and bias due to confounding (Supplement, Table 5). The evidence is summarized in the supplementary material.

The primary outcome of interest for PICO question 2 was recurrent stroke, with additional outcomes being TIA, major bleeding events, pulmonary embolism, DVT, AF, procedure-related serious adverse events (SAEs), and device-related adverse effects. The data for these comparisons, outlined in the Supplement, Table 3, demonstrate a reduction in recurrent stroke after PFO closure as compared to antiplatelet therapy alone (RR: 0.16, 95% CI: 0.05-0.52, moderate certainty of evidence). Patients receiving PFO closure compared to those treated with antiplatelet therapy exhibited a trend toward reduced incidence of recurrent TIA (RR: 0.63, 95% CI: 0.26-1.54, low certainty of evidence) and major bleeding (RR: 0.55, 95% CI: 0.24-1.30, low certainty of evidence). Patients treated with PFO closure may not experience greater SAEs than those treated with antiplatelet therapy (RR: 0.95, 95% CI: 0.74-1.22, moderate certainty of evidence). Very few events were reported for pulmonary embolism and DVT. In patients who received PFO closure, 2 pulmonary embolism events were reported while 1 event was reported in the group of patients who received antiplatelet therapy (RR: 1.01, 95% CI: 0.09-10.66, low certainty of evidence). Furthermore, a single event of DVT was reported which occurred in the group of patients who received antiplatelet therapy (RR: 0.17, 95% CI: 0.01-4.13, low certainty of evidence). Patients who received PFO closure had a higher risk of AF compared with patients who received antiplatelet therapy alone (RR: 7.33, 95% CI: 2.41-22.25, moderate certainty of evidence). Device-related complications were only present in patients undergoing PFO closure (RR: 4.23, 95% CI: 0.22-80.30, low certainty of evidence), (Supplement, PICO Question 2.1). We rated down across outcomes here for imprecision due to the few events recorded in the different studies and the wide confidence intervals around the effect estimates which suggested appreciable benefit and harm.

Although we were unable to identify studies that compared PFO closure to antiplatelet therapy in patients older than 60 years of age, there were 4 cohort studies which provided outcomes stratified by age ($<$60 vs. $\geq$60 years).[28,33,34,36] These studies were all observational and included a small number of participants experiencing outcomes of stroke, AF, TIA, DVT/PE, device complications, and death. Meta-analysis of these studies suggests a reduction of recurrent stroke from PFO closure among patients $<$60 years rather than patients $\geq$60 years in the (RR: 0.23, 95% CI: 0.09-0.57, very low certainty of evidence). To estimate the potential benefit of PFO closure in comparison to antiplatelet therapy in stroke prevention among this population, we pooled and analyzed data from the antiplatelet arm from the NAVIGATE-ESUS trial[37] together with the cohort of patients $\geq$60 years who received PFO closure. Patients who received PFO closure may trend towards a reduction in recurrent stroke compared to patients treated with antiplatelet therapy, however this evidence is very uncertain (RR: 0.85, 95% CI: 0.38-1.91, very low certainty of evidence). Across outcomes, the evidence was rated down due to risk of bias and imprecision. Given the lack of comparative studies, we were unable to provide data on the relative risk reduction for the other outcomes (eg, AF, bleeding, death) (Supplement, PICO Question 2.2).

Two studies investigated recurrent neurological events among patients with a known hypercoagulable disorder(s).[16,32] Both studies suggest a reduction in recurrent stroke among patients receiving PFO closure rather than antiplatelet therapy (RR: 0.18, 95% CI: 0.07-0.47, very low certainty of evidence) and TIA (RR: 0.31, 95% CI: 0.13-0.70, very low certainty of evidence). The evidence was rated down due to risk of bias and imprecision.

Comparisons among patients with ASA were informed primarily from the CLOSE RCT, with additional information from an observational study by Musto et al. comparing PFO closure devices.[3,23] Patients with ASA who underwent PFO closure had fewer strokes than those who received antiplatelet therapy alone in the CLOSE subgroup (RR: 0.05, 95% CI: 0-0.87, very low certainty of evidence). Patients with ASA studied by Musto et al. were observed to have a procedural complication rate of 3.33%.[23]

We attempted to evaluate the benefit of PFO closure over antiplatelet therapy alone in patients who were assessed to have higher RoPE (Risk of Paradoxical Embolism) score (ie, RoPE score $\geq$7) and those assessed to have lower RoPE scores (ie, RoPE score $<$7). RoPE score here is used in an attempt to define the likelihood that a cryptogenic stroke was related to a PFO, with a higher score being associated with a "pathogenic" PFO. Data from the CLOSE trial demonstrated a benefit in the reduction of recurrent stroke incidence PFO closure group among those with a RoPE score $\geq$7 when compared to those with a RoPE score or $<$7 (RR: 0.04, 95% CI: 0.01-0.71, very low certainty of evidence).[3] The certainty of evidence here was rated down due to very serious concerns with imprecision from fragility and very few events.

Discussion

Among patients with prior PFO-associated stroke, the evidence strongly favors PFO closure compared to antiplatelet therapy alone in terms of reducing the likelihood of recurrent stroke among the majority of patients. However, the risk of AF is increased with PFO closure. Furthermore, evidence to support PFO closure among sub-cohorts of interest is highly limited given the relative paucity of studies, small sample sizes, and the inherent risks of bias associated with such NRSs. Nevertheless, there were trends to suggest that PFO closure may be superior to antiplatelet therapy alone in many sub-cohorts. For example, a lower recurrent stroke rate in younger PFO patients is consistent with an age-related increase in non–PFO-mediated stroke. On the other end of the spectrum, older patients develop additional co-morbidities that are independently associated with stroke, potentially decreasing the benefit of PFO closure among patients $>$60 years of age. Older patients' rates of SAEs were similar to younger patients' though, so PFO closure may remain a consideration in older patients.

Similarly, the 2 relatively recent studies by Buber[16] and Liu[32] among patients with known thrombophilia suggest the superiority of PFO closure over medical therapy alone. Interestingly, these studies suggested a benefit both in terms of recurrent stroke as well as TIA, which likely further corroborates the higher risk of neurologic events from a paradoxical embolus in these patients. Similar results were noted regardless of ASA, large shunt size, and higher RoPE scores.

The relationship between PFO, stroke, and AF is complicated. Atrial fibrillation is both an independent risk factor for stroke as well as a potential procedure-related complication. There is a paucity of data addressing this issue. Scacciatella et al. measured the incidence of silent AF in patients with PFO and stroke. They performed loop-recorder monitoring on all patients with a PFO-associated stroke who qualified for PFO closure per their institutional protocol. They found that ~11% of patients had silent AF.[34] The authors posited that such AF may have confounded prior studies since the PFO may have been an "innocent

bystander" in those patients, and post-PFO closure treatment with antiplatelet therapy as opposed to anticoagulation may have led to inadequate treatment in the setting of AF. Future, well-designed studies are needed to understand better the interaction, and optimal treatment, of PFO in patients with pre-existing AF who have suffered a stroke.

Question 3 In adults with a PFO-associated stroke who have other stroke risk factors, should PFO closure rather than anticoagulant therapy alone to prevent stroke?

We identified 3 RCTs comparing PFO closure to anticoagulant therapy.[2-4] The CLOSE trial included anticoagulation alone as 1 of the 3 study arms; the RESPECT and DEFENSE-PFO trials permitted operators to select anticoagulation as an antithrombotic strategy in the medical therapy arm. CLOSE and DEFENSE-PFO specifically studied patients with PFO-associated stroke and high-risk anatomic features. We also identified 5 single-arm NRS[23,28,33,34,36] of patients undergoing PFO closure that reported data on our subpopulations of interest: patients >60 years of age, with known thrombophilia, with high-risk PFO anatomy (ie, ASA and large shunt size), and with ROPE score <7 vs. ≥7 (Supplement, Table 3).

The evidence for this question is summarized in the supplementary material. Overall, the 3 RCTs[2-4] were judged to have a generally low risk of bias (Supplement, Table 4). Neither study participants nor providers were blinded to the intervention. The 5 NRSs[23,28,33,34,36] had concerns with bias due to confounding and participant selection (Supplement, Table 5).

Three RCTs with a mean follow up duration of 5 years provided the best available evidence for outcomes in this PICO question. PFO closure failed to demonstrate a benefit in ischemic stroke compared to anticoagulation (RR: 0.94, 95% CI: 0.37-2.42, low certainty of evidence). Patients receiving PFO closure rather than anticoagulation may have a reduction in the risk of major bleeding (RR: 0.24, 95% CI: 0.06-0.91, low certainty of evidence). However, there was no significant difference in recurrent TIA in patients who received PFO closure compared to anticoagulation alone (RR: 1.45, 95% CI: 0.48-4.21, low certainty of evidence). The only event of pulmonary embolism was reported in the PFO closure arm during follow-up. Other outcomes of interest such as AF and quality of life were not reported (Supplement, PICO Question 3.1). The certainty of evidence was rated down due to concerns with imprecision from fragility and wide confidence intervals.

Regarding patient age, our pooled analysis of 5 observational studies of patients undergoing PFO closure suggested a recurrent stroke rate of 3.4% (12/357) in patients ≥60 years and 0.7% (7/978) in patients <60 years, over the follow-up period (range, 2-16 years) (Supplement, PICO Question 3.2).[27,33,35,36] To estimate the potential benefit of PFO closure in comparison to anticoagulant therapy when preventing stroke among this population, we pooled the anticoagulant therapy arm from the NAVIGATE-ESUS trial[37] and analyzed this data indirectly in comparison with the cohort of patients ≥60 years who received PFO closure. There may be a trend toward increased risk of recurrent stroke among patients receiving PFO closure rather than anticoagulation; however, this evidence is very uncertain (RR: 1.49, 95% CI: 0.58-3.86, Very Low certainty of evidence). Furthermore, in the ≥60-year-old patient cohort undergoing PFO closure, AF occurred in 5.9% (15 of 255) during the follow up period (range, 4-16 years), whereas TIA and DVT/PE incidences were 2.7% (7 of 255) and 0.8% (2 of 241) respectively. Mortality rate in this cohort of ≥60-year-olds was 7.8% (7 of 90) over the follow-up period (range, 2-16 years). There were no device-related complications (0 of 165) documented for patients ≥ 60 years of age over the follow-up period (range, 4-16 years).[27,33,34,36] The certainty of evidence was rated down due to concerns with risk of bias, as a result of a lack of adjustment for some confounders. It was also rated down due to imprecision from fragility and wide confidence intervals.

We did not identify any studies comparing PFO closure to anticoagulation alone in patients with ASA. However, 1 single-arm study[23] reported outcomes in ASA patients who underwent PFO closure. Among the 90 patients who had PFO closure, supraventricular tachycardia was reported in 2.2% (2 of 90) and device related adverse effects in 1.1% (1 of 90) patients with PFO associated paradoxical embolism and ASA.

RoPE score assessment was reported in CLOSE and the observational study by Mariucci et al. In the CLOSE trial's anticoagulation alone arm 4.2% (2 of 48) participants with a ROPE score <7 and 0.7% (1 of 139) with a ROPE score ≥7 suffered an ischemic stroke during follow up.[3] No strokes were noted in the PFO closure arm of that trial. Similarly, recurrent stroke and TIA were more frequent in the RoPE <7 arm of the Mariucci et al. study compared to those with a RoPE score ≥7.[33]

Discussion

Overall, there was a paucity of direct evidence comparing anticoagulation alone to PFO closure in patients with prior PFO-associated stroke. Nonetheless, PFO closure demonstrated a reduced RR of major bleeding compared to anticoagulation alone.

The evidence for PFO closure among our sub-populations of interest is limited to a few observational studies with relatively small sample sizes and concerns with risk of bias due to uncontrolled confounders and patient selection. PFO closure was appears to be safe and not associated with significant major severe adverse events. Similar to PICO 2, the age-related increase in non–PFO-mediated stroke likely explains the lower recurrent stroke rate in younger PFO patients while potentially decreasing the benefit of PFO closure among patients >60 years of age. And as with PICO 2, older patients did not suffer significantly more SAEs, so PFO closure may remain a consideration in this age group.

Most importantly, there are several competing issues that complicate comparisons between PFO closure and anticoagulation. While conclusive evidence supporting PFO closure over anticoagulation alone may not be present, anticoagulation therapy is associated with a continued risk of bleeding that increases over time as patients age.[38] This risk needs to be balanced with the benefits of anticoagulation (eg, decreasing the risk of major adverse events from both venous thromboembolic disease and AF).

Question 4 In adults with prior PFO-associated stroke with a separate indication for lifelong anticoagulation, should PFO closure be combined with anticoagulation to prevent recurrent stroke rather than medical therapy alone?

The role of PFO closure for patients with conditions requiring long-term anticoagulation such as thrombophilia, DVT, or PE is not clear. We did not identify any RCTs that directly addressed this question. We identified 3 NRSs (observational cohort) that provided data on PFO closure in patients with other indications for anticoagulation therapy.[16,27,32] These 3 studies' overall risk of bias was judged to be low, however there was moderate to critical risk of bias due to confounding.

Buber et al. studied 136 patients with PFO and a hypercoagulable state without prior stroke undergoing either PFO closure or antithrombotic therapy alone.[16] Stroke occurred in 4.7% (4 of 85) patients with thrombophilia in the PFO closure group vs. 20.7% (11 of 53) events in the medical management only group during a mean follow-up of 41 months. A study by Liu et al. followed 591 patients with PFO, hypercoagulable state, and prior stroke.[32] Recurrent stroke occurred in 1.1% (1 of 89) in the PFO closure group vs. 1.5% (6 of 45) in the antithrombotic therapy only group. Patients receiving PFO closure rather than antithrombotic therapy may experience a reduction in the risk of stroke (RR: 0.15, 95% CI: 0.04-0.50, very low certainty of evidence) and TIA (RR: 0.32, 95% CI: 0.13-0.77, very low certainty of evidence). Few catheter and device-related events were reported in the PFO closure group (3.5% [3 of 85]). We rated down for imprecision here due to the few events reported in the different studies. The wide confidence intervals around the estimates were also points of concern.

Wintzer-Wehekind et al. reported on 201 patients with the history of DVT and/or PE and prior PFO-associated stroke who underwent PFO

closure. Due to small sample size, only 2 strokes and 6 TIA events were recorded, so no findings were statistically significant.[27]

Discussion

Data supporting PFO closure in patients with PFO associated strokes and prior history of thrombophilia, DVT and/or PE are limited to 3 observational studies. The low certainty of evidence suggests a potentially large magnitude of benefit with PFO closure as compared to anticoagulation alone for both primary and secondary prevention of stroke.

Question 5 In adults undergoing transcatheter PFO closure, should a regimen of 1 month of dual antiplatelet therapy followed by 6 months of aspirin be used rather than other regimens to prevent stroke and bleeding events?

Intracardiac device implantation generally requires subsequent antithrombotic therapy until the device is endothelialized to prevent platelet-mediated thrombus formation. The optimal course of antiplatelet therapy following PFO closure is unknown. RESPECT was the largest and longest of the RCTs studying PFO closure to prevent recurrent stroke.[4] In RESPECT, patients received 1 month of dual antiplatelet therapy (DAPT) with aspirin plus a thienopyridine followed by aspirin monotherapy until at least 6 months post-closure. The investigators reported 6 stroke events per 1000 patient-years. The rate of bleeding events was not reported.

Four other NRSs (3 observational[33,35,39]) and 1 RCT[3] reported a regimen of 3 months of DAPT followed by aspirin monotherapy. Respectively, these 4 studies reported associated stroke rates of 0, 4.3, 1, and 0 per 1000 patient-years. Only 1 study captured bleeding events, reporting a rate of 20 bleeding events per 1000 patient-years over 6 months of follow-up.[39]

Aside from these 2 regimens (1 month or 3 months of DAPT), data regarding other antithrombotic regimens are limited. One observational study utilized 6 months of DAPT.[40] This study did not disaggregate stroke from TIA but reported an event rate of 28 per 1000 patient-years. Another observational study utilized monotherapy with either aspirin, clopidogrel, cilostazol, ticlopidine, or warfarin, reporting 0 strokes among 67 patients at 27.8 months follow-up.[41] One RCT did not specify the duration of antithrombotic therapy but reported no strokes regardless of antithrombotic regimen and bleeding rates of 125 per 1000 patient-years with warfarin and 17 per 1000 patient-years with DAPT.[2]

Five other studies included multiple antithrombotic regimens, but stroke rates were not disaggregated per antithrombotic regimen.[5,27,36,42,43]

Discussion

The evidence to support a specific antithrombotic regimen following PFO closure is limited. Antithrombotic therapy is standard to prevent thrombosis following implantation of any intracardiac device. Antithrombotic agents may include aspirin, thieonpyridines, and anticoagulants. Following transcatheter PFO closure, a greater duration and intensity of antithrombotic therapy would be expected to reduce recurrent stroke at the expense of increasing bleeding events. Comparison between different studies suggests that 3 months of DAPT could be associated with lower rates of recurrent stroke than 1 month of DAPT. However, data regarding the associated bleeding rates are inadequate for comparison. Anticoagulation may also be associated with a low stroke rate but data are again inadequate for comparison between regimens.

Conclusion

Using the GRADE approach, this systematic review identified and evaluated the literature regarding the utilization of transcatheter PFO closure. In appropriately selected patients with prior stroke, transcatheter PFO closure reduces the risk of recurrent stroke more than antiplatelet therapy alone. There is a paucity of evidence regarding older patients, anticoagulation, thrombophilia, transient ischemic attack, migraine, and decompression illness. Data from this technical review inform the SCAI Guideline for Transcatheter Patent Foramen Ovale Closure.

Strengths and limitations

This technical review provides a rigorous and transparent assessment of the evidence regarding the benefits of PFO closure versus medical therapy including among less studied subpopulations, such as older age, pre-existing comorbidities and structural defects (eg, ASA, shunts). We used the GRADE approach to rigorously assess the certainty of the body of evidence for each outcome, considering the evidence from both randomized and non-randomized studies.

While there are several strengths to this review, we would also like to highlight a few limitations. First, we limited our search strategy to English-only peer reviewed publications. While this strategy may have missed relevant studies published in other languages, we checked systematic reviews and guidelines, as well as their reference lists for eligible studies that may not have been identified in our search. In addition, we reached out to authors for additional information or publications to supplement the search results. Second, while there were a number of RCTs which investigated PFO closure compared to medical therapy or antiplatelet therapy, there were a paucity of trials comparing PFO closure to anticoagulation therapy. Therefore, when studies clearly disaggregated the anticoagulation arm results of studies comparing PFO closure to medical therapy we used that information in our analysis; however, that information was not always available and may limit generalizability of the results. To address this, for studies without clearly disaggregated arms, we reached out to authors to confirm the correct number of patients receiving anticoagulation.

Areas for future research

This technical review highlighted the challenges in determining the benefits of PFO closure in a few sub-populations missing from or poorly represented in previous randomized and non-randomized trials. While it is understood that the number of patients with some of these comorbidities might be numerically few in the general population, it is still important to properly document experiences of some of these clinical scenarios for a better understanding of characteristics and outcomes. Cohorts of which we were unable to identify sufficient data on included: patients with a history of atrial fibrillation, DVT, PE, and systemic embolism, thrombophilia(s), and structural abnormalities such as ASA and shunt size. Clinicians are encouraged to document experiences with PFO closure in such patient groups.

Due to the exclusion of patients over the age of 60 from the majority of RCTs investigating the benefit of PFO closure, observational studies were used to form the evidence for this cohort of patients. These studies had several concerns in their certainty which highlighted a need for better quality studies to be conducted in this patient group. Observational studies which were identified to investigate the benefit of PFO closure in SCUBA divers, and patients with hypercoagulable disorders also had similar concerns. Furthermore, the lack of comparative studies conducted in patients with platypnea-orthodeoxia also highlighted a limitation in determining the benefits of PFO closure in reducing the risk of decompression illness.

There was insufficient data to determine the benefit of PFO closure in patients with structural features such as shunt size and the presence of ASA. Similarly, we were unable to determine if the RoPE score of a patient influences the level of benefit derived from PFO closure also due to a lack of data. Future studies are encouraged to determine if RoPE score influences the outcome of patients who undergo PFO closure. Furthermore, researchers are encouraged to investigate the outcomes of patients who undergo PFO closure stratified by their time since prior stroke.

Several studies have employed different post-procedure management antithrombotic therapies for patients after PFO closure. Although one study[4] proposed that 1 month of DAPT followed by 6 months of aspirin monotherapy might produce optimal benefits regarding the incidence of

recurrent stroke, it is important that more research is done to investigate this antithrombotic approach before it is established as standard of care.

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.2022.100040.

Peer review statement

Given his role as Associate Editor, Andrew M. Goldsweig had no involvement in the peer review of this article and has no access to information regarding its peer review.

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