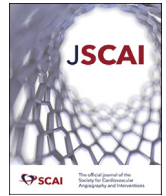




Contents lists available at ScienceDirect

# Journal of the Society for Cardiovascular Angiography & Interventions

journal homepage: [www.jsc.ai.org](http://www.jsc.ai.org)

## Editorial

## New SCAI Guidelines: Trying to Close the Holes in the PFO Literature

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The idea that recurrent ischemic stroke could be prevented by closing a patent foramen ovale (PFO) was a source of intense controversy between the cardiology and stroke neurology communities since publication of the first PFO closure series in 1992.<sup>1</sup> But after 25 years, the publication of 4 large randomized PFO-stroke trials in 2017-2018<sup>2-5</sup> conclusively demonstrated significant stroke risk reduction in patients treated with PFO closure and antithrombotic therapy compared with those treated with antithrombotic therapy alone. Over the last 5 years, in part due to comprehensive practice recommendations from the American Academy of Neurology and from the Society for Cardiovascular Angiography and Interventions,<sup>6,7</sup> a clear consensus has been established on how to manage the PFO-related stroke in patients who meet the randomized trial criteria.

We find ourselves now in all new PFO discussions. Having proven the most basic principle that closing the PFO is a better solution than medication to prevent recurrent paradoxical embolization, there remain a host of related and unrelated questions about PFO management. Unquestionably, the most significant problem we face in this field is the 25% prevalence of PFO in the population. It is easy to attribute unexplained symptoms to the defect, but the presence of the PFO in many cases is likely to be incidental and unrelated. With interventional cardiologists now armed with commercially approved PFO closure devices, the field is in dire need of clear consensus and standards, for clinicians and for policy-makers, in situations other than those settled by the randomized trials.

In this issue of *JSCAI*, a highly experienced/qualified panel of interventional cardiologists along with a stroke neurologist long associated with the PFO field present broad new guidelines for the management of many clinical situations left unresolved by the randomized trials.<sup>8</sup> These include PFO closure for nonstroke indications, for patients with additional ischemic stroke risk factors, and for patients requiring long-term anticoagulation for other reasons.

The panel's methodology is clearly described in the document. As is appropriate, only the PFO-related stroke patients who met randomized trial criteria received a "strong" recommendation from the panel favoring

PFO closure over antiplatelet therapy. All other recommendations, for or against PFO closure, were graded as "conditional" based both on the panelists' experience and on exhaustive review of observational data from the past 3 decades.

Some of the more important recommendations will be highlighted below. But in reading this document, it is critical to recognize that most of these guidelines represent consensus opinion only. As such, the panel's heavy emphasis on proactive patient participation in a shared decision-making process makes these guidelines different from previous societal guidelines and strengthens the weight of the recommendations.

### Guideline recommendations

We agree with most of the panel's recommendations. Perhaps the most impactful is the conditional recommendation for closure in the PFO-related stroke patient who falls outside of the age range studied in the randomized trials. While few would argue with PFO closure in children with embolic stroke, there remains considerable clinical resistance to PFO closure in patients older than 60 years because of the increasing alternative potential stroke sources as the population ages. But these sources are finite, and once a careful cryptogenic stroke workup (by a neurologist) is negative, there is no physiologic reason that the PFO might not have been the source of paradoxical embolization. The single factor which most distinguishes an older stroke population is the incidence of atrial fibrillation (AF), which rises rapidly with advancing age. Prior to consideration of the PFO as a stroke source, extended rhythm monitoring becomes more critical, with implantable loop recorders playing an increasing role in the screening of patients older than 65 years.

We applaud the conditional recommendations in favor of PFO closure for rare clinical issues like platypnea-orthodeoxia and systemic thromboembolism in which there exists a significant volume of accumulated clinical experience, but for which there are insufficient number of patients to ever allow for randomized data collection.

We support the panel's handling of thrombophilia in the setting of a PFO. Despite the increasing sophistication of thrombophilia evaluations,

DOI of original article: <https://doi.org/10.1016/j.jsc.ai.2022.100039>.

Keywords: Guidelines; PFO closure.

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Received 28 March 2022; Accepted 29 March 2022

Available online 19 May 2022

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without a prior stroke history, thrombophilia has not been demonstrated to increase the risk of paradoxical embolization in the PFO population. The panel appropriately gave a conditional recommendation *against* PFO closure. In contrast, the recognition that PFO closure is superior to medical therapy at preventing recurrent paradoxical thromboembolic events led the panel to favor PFO closure *in addition* to antithrombotic therapy over antithrombotic therapy alone (antiplatelet or oral anticoagulants) in the setting of both thrombophilia and stroke.

After a PFO-related stroke, the panel rightly recommends PFO closure in patients with concurrent deep vein thrombosis but interestingly fails to discuss pulmonary embolism. Closure of a PFO, after ischemic stroke or other systemic arterial embolization, with a clear venous source, is a common-sense solution. Without a PFO-related stroke, while the presence of the PFO is worrisome in individuals prone to venous thrombosis, oral anticoagulation remains the standard of care, and the recommendation against closing the PFO is appropriate. Similarly, when a patient is found to have both AF and PFO, the source of the embolus is far more likely to be the arrhythmia than the PFO, and the patient should be treated for AF.

It is critical for readers of this document to keep in mind that every patient requires individualized evaluation with respect to treatment of the PFO (like any other condition). A reasonable indication for intervention in one patient may be wildly inappropriate in another. The inherent danger of promoting broad negative recommendations as policy is their misuse in the American medical system to justify blanket denials of insurance coverage to patients who, in the judgment of their physicians, would benefit from the intervention.

A perfect example is that of transient ischemic attacks (TIAs), which the panelists may have handled too broadly with their conditional recommendation against PFO closure. Without magnetic resonance imaging evidence of ischemic injury, these events cannot often be easily differentiated from complex migraines, focal seizure activity, or other neurologic entities like Meniere's disease. For the majority of these patients, a PFO closure would be inappropriate, as it would be unlikely to treat the underlying issue. But for some, with clear focal neurologic findings or prolonged symptoms ("imaging-negative" stroke), a PFO closure may be indicated since the TIA may have the same underlying paradoxical thromboembolic event as an ischemic stroke. The recent European guidelines<sup>8</sup> do recommend PFO closure after a neurologist-diagnosed TIA, as should ours.

Similarly with decompression illness, while a typical patient could be instructed to stop diving to avoid the risk of recurrent episodes as a satisfactory alternative to PFO closure, professional divers would lose their livelihood if the PFO could not be closed.

In the case of migraine headaches without prior stroke, we agree that PFO closure, in general, is not warranted. Hopefully, the GORE RELIEF clinical study set to enroll patients later this year will provide further insight into patient selection in the near future.

There are a few issues such as PFO-related hypoxemia in settings other than platypnea-orthodeoxia on which the panel did not comment but we feel are deserving of mention. As one example, there are over 5 million Americans with chronic obstructive pulmonary disease, many of whom are utilizing supplemental oxygen to treat hypoxemia. In many cases, patients demonstrate a greater degree of hypoxemia than can be explained by the severity of the lung disease and can have an unrecognized intracardiac right-to-left shunt. The potential clinical impact of a PFO closure in those proven to have a significant shunt, with improved systemic oxygenation, could dwarf that of cryptogenic recurrent stroke prevention.<sup>9,10</sup>

The consideration of PFO closure for primary stroke prophylaxis may be appropriate on a case-by-case basis in a number of clinical

scenarios including planned surgical procedures which are at high risk of venous thrombosis (eg, lower extremity joint replacement, liver transplant), medical conditions that require the use of long-term hormonal therapy, and patients with chronic indwelling transvenous pacemaker leads or central venous catheters who are not anticoagulated.<sup>11,12</sup>

The panel elected not to address ad hoc observations from the randomized trials, which suggested that patients with a PFO-related stroke who have an atrial septal aneurysm and/or a large shunt seem to have greater benefit from PFO closure than those with smaller PFOs. In some cases, these features can help guide patient selection.

In conclusion, we are supportive of the recommendations made by these guidelines which help spotlight and clarify the growing list of potential indications for PFO closure. While the panel plainly discusses the potential risks/harms of PFO closure for each clinical scenario, in experienced hands, PFO closure is one of the safest cardiac interventions we are currently performing. Having proven its benefits for PFO-related stroke, the cardiology and neurology communities need to maintain an active collaboration to continue to refine the role of PFO closure for these and other clinical scenarios. Hopefully the Society for Cardiovascular Angiography and Interventions and this highly qualified group of experts will consider follow-up documents, as understanding of the science advances.

## Declaration of competing interest

Dr Sommer has a relationship with W. L. Gore & Associates. He is the national cardiology PI for the GORE RELIEF clinical study and was the national co-PI for the ASSURED trial. He is currently an investigator in the REDUCE PAS study. W. L. Gore & Associates provide institutional support to the Columbia University for Dr Sommer's work. Dr Aboulhosn reports a consulting relationship with Abbott Medical.

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