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EDITORIAL COMMENT

PFO

"Please Figure Out," or Now "Potentially Figured Out?"*

Barry A. Love, MD,[a] Hans-Christoph Diener, MD, PhD[b]

In 2001, one of us (B.A.L.) was asked to give medicine grand rounds on the topic of patent foramen ovale (PFO) closure for cryptogenic stroke. The copresenting neurologist creatively titled it "PFO = Please Figure Out." Fifteen years and 3 randomized trials later, the witty title still resonates. The recurrent theme of the 3 trials comparing medical management and transcatheter device closure of PFO to prevent recurrent cryptogenic stroke has favored device closure but fallen short of the "holy grail" of statistical significance ($p < 0.05$) in the intention-to-treat analysis.

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One of the difficulties in studying this disease is that the recurrence rate for cryptogenic stroke is relatively low, so to find a significant difference in treatment strategies, one needs to follow patients for a long period or enroll huge numbers, both of which are difficult and expensive. In this issue of the *Journal*, Kent et al. (1) take us a step closer to "figuring it out." The investigators performed a meta-analysis of the primary data from the 3 randomized controlled trials of PFO closure for cryptogenic stroke. By pooling the trial data and standardizing outcome measures, the investigators demonstrated a statistically significant difference showing superiority of device closure over medical therapy for preventing recurrent stroke.

The foramen ovale persists as a normal variant in 20% to 30% of the adult population (2). PFO is more often found in adults <60 years of age with cryptogenic stroke than in the normal population: upward of 40% (3). The mechanism of stroke in these patients is thought to be right-to-left embolization of small venous thrombi or thrombus formation within the PFO itself. It is not known why the vast majority of people with PFO will never have embolic events, yet there exists a small subset of patients with PFO who have strokes and then are at higher risk for recurrent events. The recurrence risk for cryptogenic stroke in some studies has been as high as 3% to 5% per year (4). However, in the current meta-analysis, the annual recurrence rate in the medically treated group was only about 1%. Even with that low event rate, PFO closure halved the event rate. One explanation for the lower than expected event rate in the medical arm is that many patients thought to be at "high risk" were undoubtedly siphoned away and treated with PFO closure outside the trials. An event rate of 1% per year is a relatively low recurrence rate compared with other stroke mechanisms; nevertheless, given the young age at which these events occur, with a potentially long exposure period for subsequent events, that risk may be more substantial than it first appears. Stroke in young people is potentially devastating. After a first stroke, patients are often terrified of having another. The societal cost of stroke in young adults becomes astronomical when one considers the potential inability to work combined with the cost of rehabilitation and potential lifelong care needs for residual neurological disability.

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From the [a]Mount Sinai Medical Center, New York, New York; and the [b]Department of Neurology and Stroke Center, University Hospital Essen, Essen, Germany. Dr. Love has received honoraria for participating in clinical trials, proctoring, contribution to advisory boards, and oral presentations from St. Jude Medical and W.L. Gore and Associates. Dr. Diener has received honoraria for participation in clinical trials, contribution to advisory boards, and oral presentations from Abbott, Allergan, AstraZeneca, Bayer Vital, Bristol-Myers Squibb, Boehringer Ingelheim, CoAxia, Corimmun, Covidien, Daiichi-Sankyo, D-Pharm, Fresenius, GlaxoSmithKline, Janssen-Cilag, Johnson & Johnson, Knoll, Lilly, Merck Sharpe & Dohme, Medtronic, MindFrame, Neurobiological Technologies, Novartis, Novo Nordisk, Paion, Parke-Davis, Pfizer, Sanofi, Schering-Plough, Servier, Solvay, St. Jude Medical, Syngis, Talecris, Thrombogenics, WebMD Global, Wyeth, and Yamanouchi; and financial support for research projects from AstraZeneca and GlaxoSmithKline.

The current meta-analysis calculated the number needed to treat (NNT) at 67 to prevent 1 stroke over 2.5 years, which really is too short a horizon to consider for this disease. For the average 45-year-old patient in the trials, the appropriate time frame to be considering benefit is 15 or 20 years, which would reduce the NNT to 11 and 8, respectively. This very reasonable number is far lower than the NNT used to justify many other invasive medical procedures, such as implantable defibrillators (NNT 15 to 20 for primary prevention) (5). The results of the continued follow-up from the RESPECT (Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment) trial were recently presented at Transcatheter Cardiovascular Therapeutics 2015 with 5-year follow-up; these data again appeared to show further benefit to PFO closure when patients are followed for a longer duration (6).

From a risk standpoint, PFO closure appears to be a very safe procedure in experienced hands. The current meta-analysis showed the bleeding rates to be comparable with those of medical therapy. Risk for atrial fibrillation was higher in the device cohort, but this difference disappeared when only the Amplatzer (disc occluder) device trials were considered. It is reasonable to base the risk assessment of atrial fibrillation on just the disc occluder trials, as the other device in this analysis was an older generation occluder (STARFlex Septal Closure System [umbrella occluder]) that is no longer available.

Clinical trial purists will insist that there has not been a randomized controlled study that proves a benefit to PFO closure over medical therapy. We await the results of the last remaining randomized trial (Gore REDUCE), which completed enrollment in February 2015 with results expected in 2017. However, because this trial is similar in design and follow-up duration, with 664 patients enrolled, it is unlikely that the results will be markedly different. A larger, longer clinical trial is not feasible given the expense and difficulty in following patients for long periods of time, as evidenced by the substantial dropout rate over time in all 3 previously conducted randomized trials.

The best medical strategy against which device therapy is compared continues to be a matter of debate. In all 3 trials, the medical arm had antiplatelet and anticoagulation regimens that were decided at the treating physician's discretion. Comparison of different medical strategies in these PFO closure trials, although nonrandomized, has not shown a benefit of anticoagulation over antiplatelet therapy. It is important to keep in mind that in all the device trials, device patients were treated with antiplatelet agents for a minimum of 6 months, and many were treated for longer. These studies really compared PFO closure plus medical therapy versus medical therapy alone. Trials of the newer oral anticoagulant agents in patients with cryptogenic stroke are under way and include patients with PFO, which will allow (nonrandomized) comparison of newer oral anticoagulant agents and aspirin (7).

Given the number of patients with recurrent stroke after effective PFO closure (especially in the umbrella occluder trial), we have learned that a complete work-up for alternate sources of stroke is imperative. PFO closure will not reduce the risk for other causes of stroke and potentially misdirect treatment when there is another stroke mechanism. How much should we weigh the presence of an atrial septal aneurysm or PFO size in our risk assessment? The current meta-analysis does not support a difference in efficacy for these patients, while the RESPECT trial and 5-year follow-up data do suggest that patients with atrial septal aneurysms derive more benefit from PFO closure. It makes logical sense that PFO anatomy must have some influence on the PFO's potential to transmit thrombi. In reality, PFO size and classification of atrial septal aneurysm can be highly variable. So the diagnosis of an atrial septal aneurysm and a large PFO may make the argument for treatment more compelling, while the absence may give one pause to even more carefully exclude other factors before proceeding.

Finally, should we restrict PFO closure to younger patients, and if so, how young? The present study did not show a difference in outcomes between younger (<45 years) and older patients. The 5-year RESPECT data confirm this but also indicate increasing numbers of patients with attributable (as opposed to cryptogenic) mechanisms of stroke beyond 60 years. Certainly the benefit of PFO closure in cryptogenic stroke appears largest for younger patients, diminishing with advancing age.

Current stroke guidelines classify PFO closure for treatment of cryptogenic stroke as class III (8). The present meta-analysis and follow-up RESPECT data should cause us to reconsider this recommendation. From a U.S. regulatory standpoint, there are currently no approved devices for PFO closure, although atrial septal defect occluders are being used off label. The U.S. Food and Drug Administration is considering an application for the Amplatzer PFO occluder on the basis of the current data; it is expected to go to panel in the first quarter of 2016.

The science, including the present meta-analysis, enables us to say that PFO is now "potentially figured out" and supports PFO closure plus medical therapy over medical therapy alone to reduce the risk

for recurrent cryptogenic stroke in patients <60 years of age. Modest over the short term, risk reduction increases over decades. Patients, presented with the current (albeit imperfect) state of knowledge, should be given the autonomy to make the choice.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Barry A. Love, Mount Sinai Medical Center, 1 Gustave L. Levy Place, Box 1201, New York, New York 10029. E-mail: barry.love@mssm.edu.

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