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Still No Closure On the Question of PFO Closure

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In approximately 30% of young stroke survivors, no clear cause is identified despite a thorough evaluation.¹ Patent foramen ovale (PFO) is found on transesophageal echo in about half of these patients, compared to ~25% in the general population. Clinicians, then, often assume the PFO was the cause, although it may be incidental in some patients.^{2–4} Management in this setting is uncertain and some experts recommend PFO closure to prevent future embolic events, although high level data have been lacking.

This issue of the *New England Journal of Medicine* presents the long-awaited results of the Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment (the RESPECT trial)⁵ (ClinicalTrials.gov number NCT00465270) and the Clinical Trial Comparing Percutaneous Closure of the Patent Foramen Ovale Using the Amplatzer PFO Occluder with Medical Treatment in Patients with Cryptogenic Embolism (the PC trial)⁶ (ClinicalTrials.gov number NCT00166257). These two international multicenter trials both randomized patients to medical therapy or closure with the Amplatzer PFO occluder (St. Jude Medical, Inc.) for secondary prevention of stroke. The investigators and subjects of both studies deserve gratitude for completing the trials despite slow enrollment, likely due to widespread off-label use of atrial septal closure devices.^{7,8}

Prior to the RESPECT and PC Trials, the only published randomized study was the Evaluation of the STARFlex Septal Closure System in Patients with a Stroke and/or Transient Ischemic Attack due to Presumed Paradoxical Embolism through a Patent Foramen Ovale (the CLOSURE I trial)⁹ (ClinicalTrials.gov number, NCT00201461). In CLOSURE I, which randomized 909 patients and followed them for two years, the Starflex PFO closure device (NMT Medical, Inc) failed to reduce the primary endpoint of stroke, transient ischemic attack (TIA), or systemic embolism (5.5% in the closure group versus 6.8% in the medical-therapy group, $P=0.37$) or the secondary outcome of stroke alone (2.9% and 3.1%, respectively, $P=0.79$).⁹

Like CLOSURE, neither the RESPECT nor PC Trials demonstrated a significant reduction of the primary endpoints in their intention-to-treat analyses. The PC Trial investigators

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randomized 414 patients and followed them for an average of ~4 years and reported a TIA, stroke, or systemic embolism in 7 (3.4%) patients in the closure group versus 11 (5.2%) patients in the medical group (hazard ratio, [HR] 0.63, 95% confidence interval [CI] 0.24 to 1.62, $p=0.34$). For the stroke endpoint alone, they reported one (0.5%) stroke in the closure arm and five (2.4%) strokes in the medically treated arm (HR 0.20, 95% CI 0.02 to 1.72, $p=0.14$). In RESPECT, 980 patients were randomized and followed for an average of ~2.5 years; 9 patients assigned to device closure experienced recurrent stroke compared to 16 in the medical arm (HR 0.49; 95% CI, 0.22 to 1.11; $P=0.08$).

Unlike the results of CLOSURE, however, the results of PC and RESPECT have encouraged those who believe that PFO closure might be an effective therapeutic option for this common clinical problem. Advocates of closure will surely focus on the substantial relative effect size of the point estimates in both trials, the significance of the “per protocol” and “as treated” analyses of RESPECT, the arbitrariness of the conventional p -value threshold of 0.05, and various other intriguing signals. Yet these trials likely will not convince skeptics, who will focus on the fact that three consecutive trials have failed to reject the null hypothesis in their primary intention-to-treat analyses, on the imprecision in the effect estimates, and on potential sources of bias, which included uneven dropout rates and unblinded (and imbalanced) referral for endpoint adjudication (which can introduce bias even when the adjudication itself is blinded).¹⁰

While the controversy over efficacy may not be settled, it is worth noting that the safety profile for the Amplatzer device appeared to be superior to the Starflex device tested in CLOSURE I. The incidence of clinical atrial fibrillation was 10-fold higher in the closure arm compared to the medically treated cohort in CLOSURE I and only 2-to-3-fold higher in RESPECT and PC. Importantly, however, there was also a trend toward more right atrial thrombus and increased pulmonary embolism in the RESPECT trial. Thus, as with any cardiac intervention, it is likely that potentially disastrous complications do occur, though they may be relatively rare with this device.

Some may point out that failure to show benefit in the primary intention-to-treat analysis of these trials is due to their modest statistical power; yet it is true too that low statistical power can lead to spurious misleading results, and make trials more sensitive to potential bias. Misclassification of even one or two events can have dramatic effects on the p -value of trials with low outcome rates. Some may hold hope that the modest power of the individual trials will be overcome by pooling results in a meta-analysis, but the summary main effect of such an analysis will depend on post-hoc data-driven design choices, such as whether to exclude CLOSURE or which outcome measure to use in the primary analysis.

Thus, we are for the moment left to make decisions under conditions of uncertainty. In such circumstances, evidentiary standards vary for different decision makers—patients, clinicians, writers of practice guidelines, and regulatory authorities—depending not only on the interpretation of the results, but also on the potential consequences of their decisions. Some may look at the data as supporting closure as a viable therapeutic option, even while conceding the failure to prove superiority to medical therapy. Yet given the prevalence of PFO in the general population, the enormous potential for overuse of percutaneous PFO

closure, and the relatively low risk of stroke in patients treated medically, routine use of this therapy seems unwise without a clearer view of who, if anyone, is likely to benefit. To that end, it is excellent news that the RESPECT trial is continuing to accrue data on enrolled patients and other PFO closure studies are ongoing. For now, at least; all eyes will be on the regulatory agencies to see how they will interpret these results in light of their own evidentiary standards.

References

1. Putaala J, Metso AJ, Metso TM, et al. Analysis of 1008 consecutive patients aged 15 to 49 with first-ever ischemic stroke: the Helsinki young stroke registry. *Stroke*. 2009; 40:1195–203. [PubMed: 19246709]
2. Meissner I, Whisnant JP, Khandheria BK, et al. Prevalence of potential risk factors for stroke assessed by transesophageal echocardiography and carotid ultrasonography: the SPARC study. *Stroke Prevention: Assessment of Risk in a Community*. Mayo Clin Proc. 1999; 74:862–9. [PubMed: 10488786]
3. Overell JR, Bone I, Lees KR. Interatrial septal abnormalities and stroke: a meta-analysis of case-control studies. *Neurology*. 2000; 55:1172–9. [PubMed: 11071496]
4. Alsheikh-Ali AA, Thaler DE, Kent DM. Patent foramen ovale in cryptogenic stroke: incidental or pathogenic? *Stroke*. 2009; 40:2349–55. [PubMed: 19443800]
5. Carroll JD, Saver JL, Thaler DE, et al. Transcatheter PFO closure versus medical therapy after cryptogenic stroke. *N Engl J Med*. in press.
6. Meier B, Kalesan B, Mattle HP, et al. Percutaneous closure of patent foramen ovale in cryptogenic embolism. *N Engl J Med*. in press.
7. Opatowsky AR, Landzberg MJ, Kimmel SE, Webb GD. Trends in the use of percutaneous closure of patent foramen ovale and atrial septal defect in adults, 1998–2004. *JAMA*. 2008; 299:521–2. [PubMed: 18252881]
8. Stackhouse KA, Goel SS, Qureshi AM, et al. Off-label closure during CLOSURE study. *J Invasive Cardiol*. 2012; 24:608–11. [PubMed: 23117318]
9. Furlan AJ, Reisman M, Massaro J, et al. Closure or medical therapy for cryptogenic stroke with patent foramen ovale. *N Engl J Med*. 2012; 366:991–9. [PubMed: 22417252]
10. Psaty BM, Prentice RL. Minimizing bias in randomized trials: the importance of blinding. *JAMA*. 2010; 304:793–4. [PubMed: 20716744]