Percutaneous Closure of Patent Foramen Ovale
A Near-Perfect Treatment Ruined by Careful Study?

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For patients with cryptogenic stroke found to have a patent foramen ovale (PFO), the rationale for mechanical closure can seem deeply compelling. PFO appears to be a common cause of cryptogenic stroke,1 most likely through a "paradoxical" (venous to arterial) embolism. Since this conduit can be eliminated with a minimally invasive percutaneous procedure, why wait around for a second, possibly disabling, event?

Indeed, the logic of closure also has strong support from a wealth of observational studies. Our recent review uncovered 57 studies, describing mostly single-arm case series, but also 7 comparative studies of closure versus medical treatment.2 All together, this observational evidence included 8916 patients: 1903 medically treated, 7013 undergoing closure. The summary incidence rate (IR) of recurrent neurological events (stroke or transient ischemic attack) in closure studies was extremely low (0.8 [0.6–1.2] per 100 person-years). Notably, of 49 studies investigating closure-treated patients, more than half had absolutely no stroke recurrences on follow-up. In contrast, the IR of recurrent events among medically treated patients was considerably higher (4.7 [3.4–6.6] per 100 person-years). Meta-analysis of the 7 comparative studies showed that closure was associated with a 78% reduction in the IR of recurrent events compared with medical treatment (IR ratio, 0.22 [0.07–0.64]). This would seem to validate the decision to have the procedure done by choice rather than trusting random assignment in a clinical trial.

The results of the recently reported CLOSURE I trial3 remind us that randomized clinical trial (RCT) results are bounded neither by compelling clinical logic or consistent observational findings. This study found no benefit for device closure compared with medical therapy among 909 randomly assigned subjects. Most tellingly, among closure-treated patients, the estimated IR for recurrent events was more than 3-fold higher in the CLOSURE I trial than the observational summary estimate (3.0 [1.9–4.4] versus 0.8 [0.6–1.2] per 100 person-years). Such discrepant outcome rates were not observed between the medical therapy arms of the CLOSURE I trial and the observational studies. Juxtaposing the outcome rates in the RCT arms with those of the synthesized observational studies (Figure), the divergent outcomes between mechanical and medical therapy seen in the latter seem (literally) incredible.

Discrepancies between observational and randomized data may be due to noncomparability of treatment groups in nonrandomized studies (ie, confounding by indication). However, there are other important differences between experimental and observational data unlikely to be corrected even by strong methods of statistical adjustment. For example, RCTs typically have protocol-driven outcome ascertainment and careful adjudication to minimize bias—rarely the case for observational studies. Neurological outcomes for procedurally treated patients in registries may be ascertained by the performing proceduralists, whereas medically treated patients might more likely be followed by stroke specialists, a difference that can lead to differential outcome ascertainment.2 Even subtle biases, with small absolute effects, can have a relatively large influence when outcomes are rare. Here, the opportunity for bias is particularly pertinent because transient ischemic attacks and minor strokes can be "soft" calls and because near-perfect results in single-center studies can serve as persuasive advertisements not only for the procedure generally but, more specifically, for the expertise of the practitioners (usually the study authors) and the excellence of their center. Indeed, after a number of studies showing near-perfect procedure-related results, who would dare to publish single-center results appearing substantially worse?

To be sure, CLOSURE I represents only a single RCT; the confidence interval of the treatment effect includes clinically significant effect sizes (even while excluding the effects seen in observational studies). For the many patients who have already undergone mechanical closure, we can be thankful the trial confirms that closure appears relatively safe; future studies may yet help us better select patients who benefit from closure.4

What is most striking, though, is how a mountain of remarkably consistent observational data—together including 10-fold more patients than CLOSURE I—could be rendered suspect by a single modestly sized RCT. We are left wondering why such a trial was not completed sooner and whether the favorable noneperimental results played any role in encouraging off-protocol closure and slowing recruitment into randomized studies.5

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In the era of comparative effectiveness, some have advocated a more prominent role for observational evidence. Observational studies can be substantially quicker, more feasible, and less expensive; they permit participants to select among therapies, which may not be a matter of indifference even when clinical equipoise is undisturbed by reliable data. They also usually provide reliable estimates of therapeutic effects—except when they don’t. For the time being, there is but one consensually accepted method to reliably discriminate between these two diametric possibilities: perform a carefully designed RCT.

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**References**

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