

RoPE

A safety line but tangles remain

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In our health care system, we strive to provide the right patients with the right care at the right time. The charter of the Institute of Medicine Roundtable on Value & Science-Driven Health Care states: “By the year 2020, 90% of clinical decisions will be supported by accurate, timely, and up-to-date clinical information, and will reflect the best available evidence.”¹ The optimal management of patients with ischemic stroke and a patent foramen ovale (PFO) remains unclear, although we applaud the novel analytic approach from the Tufts-based international consortium.²

PFO is a remnant of normal fetal circulation found in approximately 25% of the adult population. PFO does not confer risk for stroke in the general population,³ but the higher than expected prevalence of PFO in patients with cryptogenic stroke (CS) has raised concern for paradoxical embolism as a pathophysiologic mechanism. This association might lead to targeted therapy, including consideration of PFO closure with the insertion of a medical device.⁴

Prior publications by the Tufts collaborative group have created an approach to stratifying patients with CS and PFO into a spectrum of groups that are more likely to have an incidental than a pathogenic PFO.^{5,6} The Risk of Paradoxical Embolism (RoPE) score is derived from patient factors such as age, presence or absence of traditional vascular risk factors, and neuroimaging findings of the index stroke. While not definitive, the stratification provides a reasonable model to guide patient selection for future clinical trials. Such a tool might also guide individual patient decision-making for selection of the most appropriate treatment strategy.

The current publication focuses on applying the RoPE score to assess the frequency and determine predictors of recurrent stroke. The analytic approach has numerous strengths:

- The analysis provides a meaningful and rational disaggregation of the CS–PFO population into subgroups, yielding different predictors of recurrence that might correspond to different treatment strategies.

- It pools data from multiple trials, which enhances the power of the analysis.
- It is a novel approach for a troubled field that has seen off-label PFO closure become widespread with inadequate evidence to support broad use in the CS-PFO population, and no approach to understand the underlying heterogeneity of possible treatment effect.

The data and application of RoPE as a tool for decision-making by patients and providers has clear limitations as well:

- The analysis included only 1,342 patients with follow-up limited to 3 years, limiting power to provide subgroup analyses on what likely should be an even longer list of variables than currently included in both the RoPE score and predictors of recurrent stroke.
- Prior to use as an individual patient decision support, RoPE must be validated with the completed randomized trials in PFO closure.
- While logical, given the focus on predictors of stroke recurrence on medical therapy, the exclusion of patients having PFO closure likely introduced bias, given that treatment was not randomly assigned in several of the studies.
- The approach only applies to a narrowly defined CS-PFO population. The RoPE score does not include factors related to venous thromboembolic disease that clinically trump other factors included in the RoPE score. These include deep venous thrombosis, right-sided thrombus on pacemaker leads, indwelling catheters, anatomic considerations such as Chiari network and atrial septal aneurysm (ASA), and pulmonary embolism as well as venous hypercoagulability factors.
- The authors point out the lack of standardization of echocardiographic techniques in detecting and characterizing PFO in their data.

We do not know with certainty the mechanism of stroke in the majority of patients. Concrete evidence of a paradoxical embolism causing a stroke remains elusive, and thus validation of disaggregation of the

See page 221

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CS-PFO population by the statistical likelihood of an incidental vs pathogenic stroke, while helpful, cannot serve as the sole basis for major treatment strategy choices. The finding that a small shunt predicts recurrence in the high RoPE score is inconsistent with presumed pathophysiology, contrary to observations in the RESPECT trial, and to the established association of ASA with large PFOs.^{7–10}

We hope the authors will have unfettered access to datasets from randomized trials of PFO closure. The goals would be to refine and validate methods, enhance analytical power, and provide insight into trial results through RoPE scores.

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REFERENCES

1. The Learning Health System and its Innovation Collaboratives. Available at: <http://www.iom.edu/Activities/Quality/~media/Files/Activity%20Files/Quality/VSRT/Core%20Documents/ForEDistrib.pdf>. Accessed April 18, 2014.
2. Thaler DE, Ruthazer R, Weimar C, et al. Recurrent stroke predictors differ in medically treated patients with pathogenic vs other PFOs. *Neurology* 2014;83:221–226.
3. Di Tullio M, Jin Z, Russo C, et al. Patent foramen ovale, subclinical cerebrovascular disease, and ischemic stroke in a population-based cohort. *J Am Coll Cardiol* 2013;62:35–41.
4. Overell JR, Bone I, Lees KR. Interatrial septal abnormalities and stroke: a meta-analysis of case controlled studies. *Neurology* 2000;55:1172–1179.
5. Kent DM, Ruthazer R, Weimar C, et al. An index to identify stroke-related vs incidental patent foramen ovale in cryptogenic stroke. *Neurology* 2013;81:619–625.
6. Thaler DE, Di Angelantonio E, Di Tullio MR, et al. The Risk of Paradoxical Embolism (RoPE) Study: initial description of the completed database. *Int J Stroke* 2013;8:612–619.
7. Windecker S, Meier B. Is closure recommended for patent foramen ovale and cryptogenic stroke? *Circulation* 2008;118:1989–1998.
8. Carroll JD, Saver JL, Thaler DE, et al. Closure of patent foramen ovale versus medical therapy after cryptogenic stroke. *N Engl J Med* 2013;368:1092–1100.
9. Schuchlenz HW, Sauerer G, Weihs W. Patent foramen ovale, atrial septal aneurysm, and recurrent stroke. *N Engl J Med* 2002;346:1331–1332.
10. Homma S, Sacco RL. Patent foramen ovale and stroke. *Circulation* 2005;112:1063–1072.