



Editorial

Patent Foramen Ovale Closure for Remote Stroke: Better Late Than Never?

Razi Khan, MD, MSc,^a Farshad Hosseini, MD,^b and Natasha Kohli, RN^a

^aRoyal Columbian Hospital, University of British Columbia, New Westminster, British Columbia, Canada

^bSchool of Medicine, University of British Columbia, New Westminster, British Columbia, Canada

See article by Guedeney et al., pages 1228–1234 of this issue.

Cryptogenic stroke accounts for one-sixth of all patients with ischemic stroke, and an estimated 200,000 to 300,000 cases occur annually in North America.^{1,2} A patent foramen ovale (PFO) is thought to play a pathophysiological role in cryptogenic stroke by acting as a tunnel for passage of paradoxical emboli from the venous to the cerebrovascular system. In the absence of other identifiable causes of cryptogenic stroke, PFO closure has been advocated as a therapy to reduce risk of recurrent neurologic events.

The discussion of PFO closure benefit for treatment of cryptogenic stroke has evolved considerably over the last decade. In 2012 and 2013, 3 randomized controlled trials (RCTs) demonstrated no clear benefit of PFO closure over medical therapy for cryptogenic stroke.^{3–5} Limitations with regard to patient selection, device efficacy, and early cessation of antiplatelet therapy in these earlier trials led to a re-evaluation of mechanical closure in the form of RCTs involving selected patients with cryptogenic stroke and “high-risk” PFOs deemed anatomically favourable for causing stroke.^{6–9} In these newer studies, PFO closure compared with medical therapy was associated with a relative and absolute risk reduction for recurrent neurologic events of between 45% and 97% and 0.37% and 1.25% per year, respectively. The evidence for PFO closure benefit from these RCTs has led to changes in guidelines advocating for closure in young (≤ 60 years) patients with cryptogenic stroke and PFO.^{10–12}

Despite the current consensus regarding PFO closure benefit in selected patients with cryptogenic stroke, a preferred treatment strategy for patients with remote stroke remains unclear. Timing from cryptogenic stroke to PFO closure is not addressed in North American or European guidelines. The Asian-Pacific expert statement on embolic stroke of undetermined source remains the only consensus document addressing timing of PFO closure, suggesting that late PFO

closure (> 1 year after stroke) can be considered in the absence of stroke-risk factors.¹³ This ambiguity stems from the fact that thus far few studies, and no RCTs, have attempted to examine the benefits of PFO closure in patients with remote stroke. All RCTs comparing PFO closure with medical therapy for cryptogenic stroke noted a median or maximum time from index event to randomization of ≤ 6 months.^{3–8}

In this issue of the *Canadian Journal of Cardiology*, Guedeney et al. provide valuable insights into the benefits of PFO closure both early and late after index paradoxical embolic events.¹⁴ In summary, the Guedeney study was an ambispective analysis that included a cohort of 1179 consecutive patients who underwent PFO closure at 2 sites in Canada and France. Patients were divided into those who underwent closure early or late after index event (median time to PFO closure: early: 102 days per 3.4 months vs late: 337 days per 11.2 months), with a primary endpoint that was a composite of recurrent stroke or transient ischemic attack (TIA). After a median follow-up of 2.61 years, patients had similar rates of the primary endpoint following the index procedure regardless of closure timing (early: 0.51 events per 100 patient-years vs late: 0.29 events per 100 patient-years; $P = 0.24$). In univariate analysis, late compared with early closure was not a predictor of recurrent neurologic events. Independent predictors of undergoing late closure included closure being performed at the French Centre, closure occurring during or after 2018, female sex, and lower Risk of Paradoxical Embolism (RoPE) scores. The Guedeney study also highlights the recent increase in frequency of PFO closure by noting a 5-fold increase in closure rates between 2014 and 2018, with the French centre included.

Guedeney and colleagues should be commended for identifying and examining a subgroup of patients with cryptogenic stroke and PFO that have not been well studied. Based on timing from last embolic event to PFO closure, more than one-half of the patients in the Guedeney study would not have qualified for inclusion in the RCTs cited. Therefore, the current findings offer new evidence for PFO closure benefit in patients with remote cryptogenic stroke as well as suggesting that delays in PFO closure do not adversely

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Corresponding author: Dr Razi Khan, 3203-1028 Barclay Street, Vancouver, British Columbia V6E 0B1, Canada. Tel.: +1-604-515-9830; fax: +1-604-515-8924.

E-mail: razi.khan@gmail.com

See page 1133 for disclosure information.

affect future outcomes. This is particularly relevant, as clinicians—both neurologists and cardiologists—will increasingly be involved in the decision-making process for patients with remote stroke, particularly among those individuals who until recently had been advised against PFO closure.

There are a number of other important features that make this an important study in the overall landscape of PFO closure literature. The Guedeney study is considerably larger than most RCTs, providing observations from a registry that included > 1100 all-comer, secondary-prevention patients. In addition, despite having a patient population that dates back over 20 years, Guedeney et al. have used contemporary standardized primary and secondary outcomes, increasing the general applicability of the results to current-day practice. Finally, the Guedeney study highlights that female gender is an independent predictor of late compared with early closure for treatment of cryptogenic stroke. The authors note that the persistence of potential gender bias relating to delay in PFO closure therapy is similar to that observed for women undergoing diagnostic testing and therapies associated with other cardiovascular diseases and should be explored further in future studies.

Several weaknesses in the current analysis must be highlighted. Guedeney et al. imply PFO closure benefit for patients with remote cryptogenic stroke by demonstrating that rates of recurrent neurologic events after closure are similar regardless of whether the procedure is performed soon or late after an index event. Furthermore, there were no differences in the primary outcomes when directly comparing early and late closure in univariate analysis. However, Guedeney et al. did not directly compare late closure with medical therapy, which has been the de facto standard of care for patients with remote stroke. Therefore, the true benefit of PFO closure in this patient population remains uncertain.

A demonstration of PFO closure benefit would have been enhanced if Guedeney and colleagues had examined event rates before and after PFO closure in the late-closure group. Instead, PFO-closure benefit was assessed by comparing event rates after closure with those estimated by the RoPE standardized score, with the latter serving to predict hypothetical event rates with ongoing medical therapy. The RoPE score does estimate 2-year recurrent stroke and TIA risk after an index stroke and was derived from a cohort of patients with ischemic stroke in which a large majority (> 96%) were treated medically.¹⁵ However, in their discussion, Guedeney et al. note that the RoPE score was not predictive of recurrent stroke or TIA before PFO closure in the late-closure cohort, and therefore its use as a predictor of future outcomes with medical therapy in this study appears contradictory. As an alternative point of comparison, historical-event rates for patients with cryptogenic stroke treated with medical therapy may have been used. For example, in the 5 large RCTs, the annualized rate of stroke or TIA in the medically treated arms ranged from 0.9% to 3.4%, which is comparatively less than the 6.67% to 7.06% 2-year RoPE-score estimates cited by the Guedeney study.³⁻⁸

Guedeney and colleagues attempt to highlight that delay in PFO closure does not affect postclosure clinical outcomes. However, median time from index event to mechanical closure was 11.2 months in the late-PFO closure group compared with 3.4 months in the early-closure group. An

~8-month difference in time from embolic event to closure may be statistically significant, but its clinical impact remains questionable. Overall, the Guedeney study results imply that short delays from embolic event to PFO closure do not adversely affect postclosure outcomes but offer little evidence on the importance of extended closure delays. More specifically, Guedeney et al. fail to provide insight into the question of whether closure benefit exists for patients several years removed from index neurologic events, which likely represents a much larger patient population.

In conclusion, patients with remote stroke have often been neglected in both research and clinical practice. The Guedeney study forces a re-evaluation of these patients by demonstrating the potential benefit of PFO closure in patients with remote cryptogenic stroke. In their analysis, Guedeney and colleagues highlight that use of arbitrary cutoffs for timing of closure after last embolic events, such as those used in RCTs, may result in suboptimal treatment and exposure to an increased risk of recurrent events for patients with cryptogenic stroke. Further evidence—ideally, in the form of RCTs or similarly large observational studies offering a direct comparison of delayed PFO closure with medical therapy—will be required for a more conclusive determination of therapeutic benefit for PFO closure in this patient population.

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