# Letter to the Editor

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## Letter by Zaman et al Regarding Article, "Safety Outcomes After Percutaneous Transcatheter Closure of Patent Foramen Ovale"

*To the Editor:*

We read with interest the recent article by Merkler et al.[1] In a retrospective cohort study, the authors investigated the safety of transcatheter patent foramen ovale (PFO) closure in patients with ischemic stroke/transient ischemic attack who underwent PFO closure within 1 year. The study concluded that closure was associated with adverse events in 7% of patients; the rate of events was higher in patients >60 years old compared with those aged ≤60 years (10.9% versus 4.9%; $P<0.001$). We commend the authors for their work and describe lessons learned from 5 randomized trials, which add to our interpretation of these results.

Contrary to prior observational studies, the CLOSURE I trial (Evaluation of the STARFlex Septal Closure System in Patients With a Stroke and/or Transient Ischemic Attack due to Presumed Paradoxical Embolism Through a PFO) failed to demonstrate superiority of PFO closure for secondary stroke prevention in patients with cryptogenic stroke. Failure of CLOSURE I has been attributed to ineffective PFO closure in the device group, with significant residual right-to-left shunting present in 14% on 6-month follow-up imaging. Additionally, the STARFlex device (NMT Medical, Boston, MA) has been associated with more atrial fibrillation and thrombogenesis compared with other devices.[2] Although the PC trial (Percutaneous Closure of PFO Using the Amplatzer PFO Occluder With Medical Treatment in Patients With Cryptogenic Embolism) demonstrated a trend favoring closure, the study was statistically underpowered. Additionally, inclusion of individuals with transient ischemic attack and other peripheral embolism was not representative of the population included in previous observational studies.[2]

More recently, the long-term follow-up data from the RESPECT trial (Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment; median 5.9 years) demonstrated superiority of PFO closure over medical therapy (62% relative risk reduction in recurrent cryptogenic stroke) in the intention-to-treat analysis. There was even greater reduction in recurrent stroke in those with an atrial septal aneurysm (1.7% versus 7.6%; HR, 0.20; $P=0.005$) or large shunt (2.0% versus 6.9%; HR, 0.26; $P=0.005$).[3] The the REDUCE trial[4] (Gore Helex Septal Occluder/Gore Cardioform Septal Occluder and Antiplatelet Medical Management for Reduction of Recurrent Stroke or Imaging-Confirmed Transient Ischemic Attack in Patients With PFO) and the CLOSE trial[5] (PFO or Anticoagulants Versus Antiplatelet Therapy to Prevent Stroke Recurrence) were also published recently. REDUCE showed lower risk of recurrent stroke in patients with a device (1.4% versus 5.4%; HR, 0.23; $P=0.002$) at 3.2 years median follow-up; CLOSE showed similar promise with closure (0% versus 6.0%; HR, 0.03; $P<0.001$) at mean follow-up of 5.3±2.0 years. The greater efficacy seen in CLOSE and REDUCE is reflective of stricter patient selection. REDUCE used stringent exclusion criteria to omit other causes of stroke including large artery atherosclerosis, atrial fibrillation, and small-vessel disease (lacunar infarcts). CLOSE only enrolled patients with a large shunt or atrial septal aneurysm. The extended follow-up from RESPECT, and the CLOSE and REDUCE data confirm that PFO-occluding devices decrease risk of recurrent stroke compared with medical therapy, in patients with cryptogenic stroke. Transcatheter PFO closure should be recommended as first line therapy for stroke of unknown pathogenesis in future guidelines, at least for the subset at highest risk of recurrent paradoxical embolism (large shunt or atrial septal aneurysm).

Merkler et al[1] demonstrated a 4.9% incidence of adverse events with closure, in patients with stroke aged ≤60 years. However, all the cryptogenic stroke trials (patients aged ≤60 years) showed no increase in serious adverse events or major bleeding with percutaneous PFO closure compared with medical therapy ($P>0.05$ in all trials). Although risk of atrial fibrillation is higher with closure, most incidents in the trials occurred early (<6 months) postclosure, consisting of a single paroxysm that resolved spontaneously or with cardioversion.[2–5] Future trials should focus on the long-term prognostic outcomes of postdevice atrial fibrillation, which remain unknown.

## Disclosures

None.

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