Letter by Furlan Regarding “Critique of Closure or Medical Therapy for Cryptogenic Stroke With Patent Foramen Ovale: The Hole Truth?”

To the Editor:

Thaler and Wahl repeatedly characterize the CLOSURE I trial as having gone wrong. Such moralistic (mis)characterizations betray the prevalent bias toward devices in patients with cryptogenic stroke and a patent foramen ovale (PFO). Although disappointing to some, better to say CLOSURE I failed to prove that the StarFlex device was superior to medical therapy for stroke prevention, in this particular cryptogenic population with PFO. This result is neither wrong nor right.

Wrong patient—Contrary to clinical practice, CLOSURE I used an independently adjudicated and rigorous definition of transient ischemic attack (TIA). In clinical practice, failure to use a rigorous definition of TIA can lead to inappropriate device closure of a PFO for spells unrelated to ischemia or paradoxical embolism. If by wrong, Thaler and Wahl also meant patients were randomized who were more or less likely to have paradoxical embolism that is indeed possible, that is, the population could be optimized. It is another matter altogether to demonstrate that device is superior to medical therapy even in a population optimized for paradoxical embolism.

Wrong device—Devices indeed differ. For example, the Amplatz device being used in RESPECT has recently been cited by the Food and Drug Administration for potentially fatal erosions, which may occur several years after implantation. The most worrisome procedural complication seen in CLOSURE I, atrial fibrillation, has been reported with all devices. The rate of residual shunting seen at 6 months in CLOSURE I was based on independent core laboratory readings; and also residual shunting was not dramatically different from other devices reported in less reliable cohort series. Furthermore, residual shunting did not seem to play a role in recurrent neurological events.

Wrong outcome assumptions—We agree stroke is the best end point. Possibly a stroke only event driven outcome will be more informative and have sufficient power to be conclusive. We also agree that a longer follow-up or a larger sample size would be desirable (but possibly not feasible). However, in CLOSURE I, the stroke rates were identical at 2 years making it unclear how long patients would need to be followed to be confident there is no significant difference. Of note, a recent propensity observational study from Bern found no difference in stroke outcome at 9 years; the favorable outcome claimed for device was driven by (unspecified) TIA.

Despite disingenuous protests from some, many CLOSURE I patients possibly would have received off-label devices with no apparent benefit before this trial. CLOSURE I suggests that patient selection criteria for device closure must be restricted and more narrowly defined. Before CLOSURE I, we do not believe interventionalists were restricting device closure only to patients who met the humanitarian device exemption criteria, or who had magnetic resonance imaging demonstrating cortical infarction, or who first saw a board-certified neurologist. Would it be wrong to think reimbursement was a factor? Will Centers for Medicare & Medicaid Services require interventionalists to follow more restricted selection criteria if a device is approved? We hope the ongoing trials will build on the foundation laid by CLOSURE I and identify specific criteria for a subset of cryptogenic stroke patients who may benefit from device closure. Thaler and Wahl are right to say that no single trial provides all the answers (dangerous knowledge). But treating patients based on opinion or without considering all the evidence would be truly wrong.

Disclosures

Anthony J. Furlan is principal investigator of CLOSURE I. CLOSURE I was funded by NMT Medical Boston.

Anthony J. Furlan, MD
University Hospitals Case Medical Center
Cleveland, Ohio

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Anthony J. Furlan

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