Letter to the Editor

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To the Editor:

A meta-analysis of published randomized trials performed by Kitsios et al failed to resolve current uncertainties regarding the optimum secondary prevention strategy against cryptogenic stroke in patients with a patent foramen ovale. The results of their analysis are enticing. All 3 individual randomized studies in their analysis exhibited major limitations that rendered their interpretation problematic. First, despite broad definitions of composite primary end points, all 3 studies were underpowered because the a priori risk estimate was far from the actual outcome incidence observed in each study. Therefore, both positive and negative results could have been because of chance. Second, the enrollment of patients with transient ischemic attacks—a diagnosis that is difficult to confirm—and the inclusion of transient ischemic attack among the primary outcomes in 2 of the 3 studies may have generated significant bias. Third, the external validity of each study is weak, given the disparate characteristics of the devices and heterogeneous pharmacological therapy offered to control groups in the different trials. Such methodological pitfalls cannot be resolved merely by pooling questionable data from multiple studies. For these reasons, further randomized studies are necessary to generate more definitive evidence, a conclusion admitted by the authors who performed meta-analysis. However, keeping in mind that ≈10 years were necessary to perform each of these underpowered trials, often in high-volume expert centers, it is unlikely that any industry will sponsor trials that require even more time and larger numbers to obtain more interpretable results. Also taking into account the overall clinical complexity of the association between patent foramen ovale and cryptogenic stroke, we therefore must acknowledge that the scientific community may never be able to conduct conclusive randomized trials to address this issue.

As acknowledged by other experts, it is important that scientific societies take responsibility and express official scientific positions regarding controversial issues, especially when evidence is likely to be lacking for a prolonged period of time. To address this need, for the first time regarding this subject, a position statement was drafted in 2012 in Italy via the collaboration of 9 national scientific societies across the fields of cardiology, neurology, and hematology to allocate treatments individually on the basis of the available evidence of both randomized and nonrandomized studies while considering the strengths and the limitations of each conclusion. This strategy requires a multidisciplinary approach to estimate the probability of recurrence of stroke and the probability of any association between cerebrovascular accidents and patent foramen ovale while ensuring the adequate empowerment of patients at all decision stages during diagnosis and treatment. Of course, this position statement is open to modification as soon as (and if) conclusive evidence is produced. In the absence of such proof, we still believe that this statement may help clinicians and patients to make rational choices while avoiding the disparate behaviors of the medical community, wherein patent foramen ovale closure is overperformed in some jurisdictions and completely banned in others.

Disclosures

None.

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Stroke. 2013;44:e233; originally published online November 5, 2013;
doi: 10.1161/STROKEAHA.113.003604
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/44/12/e233

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