
We thank the writers for their comments, which largely underscore our own perspective. We highlight and clarify a few points in response.

First, even when individual studies are themselves underpowered, meta-analysis can provide a way to make inferences from the combined results. This was most elegantly shown by Lau et al., who demonstrated that small underpowered trials provided estimates of the effects of thrombolitics on acute myocardial infarction that wholly anticipated the subsequent mega-trials—mega-trials that arguably were unnecessary or even unethical. In the case of patent foramen ovale and cryptogenic stroke, even the meta-analysis remains underpowered, as evidenced by the wide confidence interval of the summary result.

Second, using transient ischemic attack alone (even if misclassified) should not bias in favor of treatment in carefully performed studies but rather potentially create statistical noise that can obscure a treatment effect. Use of a subjective or unreliable end point (such as transient ischemic attack) can accentuate a bias in favor of therapy, however, if subjects and clinicians are not blinded, as of course they were not in any of the trials. Only CLOSURE I permitted transient ischemic attack as an index event to be eligible for the trial. The transient ischemic attacks in the PC Trial fit the current definition of stroke, that is, a brief ischemic event with confirmatory imaging changes.

Although we agree that observational evidence can often yield useful information, we do not feel that the large body of observational evidence is reliable in the case of patent foramen ovale closure. Furthermore, we are concerned that the Italian position article may be misinterpreted as a guideline and give the impression that patient identification and risk factors for stroke recurrence are established in this population. This may lead to deeper entrenchment into nonevidence-based practice and the further siphoning of patients away from clinical trials. We agree with the authors that patient selection is key, and we are developing risk models (for both attributable fraction and recurrence risk, and their joint probability: attributable recurrence risk) that we hope will help, but the only way to test this rigorously would be to apply them in the context of randomized trials. Our empirical results have yielded some counterintuitive findings that are not always consistent with expert opinion (which itself is conflicted). We agree that more randomized data are needed and, unlike the position article, we urge clinicians and patients to consider participating in ongoing trials. Thankfully, REDUCE and longer follow-up for RESPECT subjects are ongoing.

Sources of Funding
This study was partially funded by grants UL1 RR025752, R01 NS062153, and R21 NS079826 from the National Institutes of Health.

Disclosures
Both Drs Kent and Thaler have consulted for WL Gore Associates. Dr Thaler is a consultant for AGA Medical Corporation. The other author reports no conflicts.

David M. Kent, MD, MS
Institute of Clinical Research and Health Policy Studies
Department of Medicine
Tufts Medical Center
Boston, MA

Georgios D. Kitsios, MD, PhD
Department of Medicine
Lahey Hospital and Medical Center
Burlington, MA

David E. Thaler, MD, PhD
Department of Neurology
Tufts Medical Center
Boston, MA

4. Pristipino C, Anzola GP, Ballerini L, Bartorelli A, Cecconi M, Chessa M, et al. Italian Society of Invasive Cardiology (SICI-GISE); Italian Stroke Association (ISA-AIS); Italian Association of Hospital Neurologists, Neuroradiologists, Neurosurgeons (SNO); Congenital Heart Disease Study Group of Italian Society of Cardiology; Italian Association Of Hospital Cardiologists (ANMCO); Italian Society Of Pediatric Cardiology (SICP); Italian Society of Cardiovascular Echography (SIEC); Italian Society of Hemostasis and Thrombosis (SISET). Management of patients with patent foramen ovale and cryptogenic stroke: a collaborative, multidisciplinary, position paper. Catheter Cardiovasc Interv. 2013;82:E38–E51.
David M. Kent, Georgios D. Kitsios and David E. Thaler

Stroke. 2013;44:e234; originally published online November 5, 2013;
doi: 10.1161/STROKEAHA.113.003654
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
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/e234

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/