
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 thrombolysis 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.2

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.3 Furthermore, we are concerned that the Italian position article may be misinterpreted as a guideline and give the impression that subject 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.5,6 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.

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