Patent Foramen Ovale and Cryptogenic Stroke: The Controversy Continues

To the Editor:

We read with interest the recently reported results of the Patent Foramen Ovale in Cryptogenic Stroke Study (PICSS) evaluating the effect of randomized medical treatment with aspirin (325 mg) or warfarin (International Normalized Ratio: 1.4 to 2.8) on recurrent ischemic stroke or death rate.1 Once again, the suggestive finding of an association between patent foramen ovale (PFO) and cryptogenic stroke has been demonstrated (39.2% for cryptogenic stroke versus 29.9% for known stroke subtypes, P<0.02). Even more impressive is the demonstrated association with large PFO (20.0% versus 9.7%, P<0.001). These previously demonstrated findings continue to allude to an as-yet unproven causative role of PFO in cryptogenic stroke.

Intuitively, it is somewhat surprising that despite the association with the primary event, the presence of a PFO was not found to increase the incidence of a recurrent event. Others have found that only the combination of a PFO and atrial septal aneurysm (ASA) imparts an increased risk of recurrent event.2 These potential predictors of recurrent ischemic stroke risk have necessarily come under more scrutiny with the advent of percutaneous means to close PFO and ASA.4

Unfortunately, only 42.1% (265) of the 603 patients included in this study met criteria for cryptogenic stroke. After exclusion of those with inadequate transesophageal imaging for the diagnosis of PFO, this population was further reduced to 250 patients. In a prospective study of this kind, the measure of interest should be the incidence, not the time to event (such as was reported in the incidence of hemorrhage rate).5 Given the available published data, we estimate the recurrent event incidence in PFO patients with cryptogenic stroke as 7.69/100 patient-years (estimated assuming 84 patients event-free at 2 years and 14 patients with an average of 1 year to event).

We would consider a PFO group to have a clinically significantly higher recurrent event incidence in cryptogenic stroke if it was 20% greater than a non-PFO group. On the basis of the data from the PICSS (7.69/100 patient-years) with a power of 80% and α=0.05, this would require 674 patient-years per group (at a power of 90%, 902 patient-years per group are required). It is our contention that with patient follow-up of approximately 182 and 285 patient-years, this study was inadequately powered to address the question of the association of PFO and recurrent events in patients with cryptogenic stroke on medical therapy. The controversy surrounding PFO and cryptogenic stroke continues unabated.

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Response

Contrary to the opinion of Drs McGaw and Ugoni, our review of the literature indicates that a survival (time to event) approach is favored over analysis of incidence for this type of study.1,2 Furthermore, the log-rank statistic is known to be the most locally powerful test for proportional hazards models.1 It also yields essentially equivalent estimates of relative risk compared with those obtained by incidence analysis when the required assumptions are met.3 There are also circumstances where proportional hazards models are appropriate, but incidence analysis yields biased results because of non-Poisson distribution of events.

It is true that only 250 of the 601 cases analyzed in PFO In Cryptogenic Stroke Study (PICSS)4 experienced a cryptogenic stroke. However, the calculation by McGaw and Ugoni that only 674 patient-years of follow-up per group would be required to detect a 20% increase in incidence with 80% power is incorrect. The correct number is more than 6500 patient-years per group.5 Given that a successful execution of such a study is quite difficult, we believe that the PICSS result of a hazard ratio of 1.17 for the presence of patent foramen ovale (PFO) in a cryptogenic stroke population stands as the best estimate available at this time.

Paradoxical embolization through a PFO undoubtedly is a cause of ischemic stroke. However, given the large number of patients with PFO, it becomes important to identify those at high risk for recurrent events. Through further analysis of PICSS data, we hope to identify this group of patients to be targeted in future therapeutic studies.

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