EDITORIAL COMMENT

Closure of Patent Foramen Ovale in Cryptogenic Stroke

Ready or Not, Here Come the Trials*

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In the consecutive series of patients with ischemic stroke and patent foramen ovale (PFO) reported by Windecker et al. (1) in this issue of the Journal, nonrandomized therapies chosen by treating physicians with patient input (referral for PFO closure, n = 158; antiplatelet therapy, n = 79; or anticoagulation, n = 79), suggest the acceptance of paradoxical embolization as the most likely mechanism for stroke. During an average follow-up of 2.3 years, individuals were evaluated systematically for recurrent events by an unblinded study neurologist. Strokes occurred in two patients with device closure, in one patient on antiocoagulation therapy, and in six patients taking aspirin. Transient ischemic attack (TIA) was the most frequent event, occurring in seven device-closure patients, five anticoagulation patients, and six patients taking aspirin. A trend toward benefit associated with device closure versus the two medical therapy groups combined was observed. A significant difference was found for closure versus antiplatelet therapy but not closure versus antiocoagulation. Univariate analysis suggested a benefit from complete PFO occlusion and device occlusion in the setting of multiple previous neurologic events at baseline.

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On the basis of results of studies such as these, advocates of PFO closure in cryptogenic stroke are in the planning or early-execution phase of randomized, controlled, clinical trials (2) (Respect PFO Trial, AGA Medical, Golden Valley, Minnesota; Closure I Trial, NMT Medical, Boston, Massachusetts). Arguments in favor of PFO closure include the association of PFO and larger PFO with cryptogenic stroke, the prevalence of PFO in approximately one-quarter of the population, the high proportion of strokes that are classed as cryptogenic, the fear of recurrent stroke by patients and caregivers, the degree of sophistication reached by device developers and interventionalists, and low event rates after closure in nonrandomized studies (3–9). The inclusion criteria for the proposed trials include first cryptogenic stroke, or stroke or definite TIA, and documentation of PFO. No evidence for past or concurrent venous thromboembolism (VTE) is required, nor is the failure of anticoagulation prophylaxis. There is no requirement for anticoagulation as part of “best medical therapy.” Thus, these trials will venture far beyond the current Food and Drug Administration-approved indication for PFO closure devices, which is defined as recurrent cerebral or peripheral embolization in the setting of PFO despite adequate anticoagulant therapy.

A principal argument against conducting the trials as currently proposed is the inability to verify precisely how often cryptogenic stroke with PFO is actually due to paradoxical embolization. In past studies of patients with suspected paradoxical embolization and no clinical signs or past history of VTE, the diagnostic yield for VTE ranged from 0% to 30% (10–14). In these series, VTE was usually clinically silent calf deep vein thrombosis (DVT) detected by venography, but VTE may be occult in other sites as well. In a recent provocative study of magnetic resonance venography in cryptogenic stroke patients with PFO, pelvic DVT was detected in 6 of 28 patients, although not all of the cases appeared to be acute (15). Does this low prevalence of VTE in cryptogenic stroke with PFO mean that paradoxical embolism is not the dominant mechanism and that stroke remains cryptogenic in most patients? Or, must we assume that VTE could have existed but is undetectable? In acute pulmonary embolism (PE), a search for residual DVT has yielded positive findings in 71% to 82% of patients (16,17).

Results from the sole randomized treatment trial, Patent foramen ovale in Cryptogenic Stroke Study (PICSS), also raise doubts as to the frequency of paradoxical embolism in cryptogenic stroke. Anticoagulation is estimated to reduce the risk of VTE recurrence by approximately 90% (18) and late low-dose warfarin secondary VTE prophylaxis with target international normalized ratio (INR) 1.5 to 2.0, achieved INR median 1.7, resulted in a 64% risk reduction versus placebo (19). In the PICSS, the median achieved INR was 2.04, and cryptogenic stroke patients with PFO on warfarin (n = 42) had a 9.5% rate of stroke or death (three-quarters of the events were strokes) per 24 months, whereas patients on aspirin (n = 56) had 17.9% rate of stroke or death during the course of 24 months (20). As was pointed out by Windecker et al. (1), the hazard ratio, 0.52, for warfarin versus aspirin was virtually identical of that found for patients without PFO, or a hazard ratio of 0.50. This is consistent with a trend toward benefit from warfarin irrespective of PFO status. Adding TIA to stroke or death with PFO weakened the apparent affect, yielding a nonsignificant risk reduction estimate of 28%.

A second potential problem with the clinical trials as currently structured is the failure to mandate anticoagulation as “best medical therapy.” Acceptance of paradoxical embolism as the mechanism of cryptogenic stroke with PFO implies the presence of acute VTE and suggests the imperative of anticoagulation. Anticoagulated patients in...
the series of Windecker et al. (1) fared quite well; most events were TIs, which are difficult to adjudicate, and were assayed in an unblinded manner. In a meta-analysis of nonrandomized treatment of PFO associated stroke, Orgera et al. (21) concluded that warfarin was superior to antplatelet therapy and that surgical closure and anticoagulation were similar. Without treatment, approximately 25% of calf DVT and 50% of proximal DVT or PE patients have recurrent thrombosis within three months. Recurrences after three months of therapy approximate 25% to 50% in five years. One-half of symptomatic proximal DVT patients have evidence of PE, and symptomatic PE is fatal in approximately 15% of patients (22). Current VTE guidelines suggest three to six months of anticoagulation, more than six months if VTE was idiopathic, and consideration of lifelong therapy if VTE was recurrent or associated with hypercoagulable states (23).

Finally, device implantation (and anticoagulation) can be associated with complications. In addition to the 6% procedural complication rate reported by Windecker et al. (1), including four devices of device embolization, there is the issue of device-related thrombus formation. In a recent report, device-related thrombi were reported in 2.5% of 593 implants for PFO (24). If more than one-half of patients with spontaneous VTE have a hypercoagulable state, as is now suspected (18), then the identification of PFO stroke patients with definite coexisting VTE will likely yield a study population prone to device-related thrombi. The Closure I Investigators have chosen to exclude patients with known hypercoagulable states from entry.

Application of recent advances in VTE diagnostic testing to the cryptogenic stroke with PFO population would be expected to improve specificity. A review of four outcome studies in suspected VTE suggested that diagnostic imaging and therapy could be safely withheld in the presence of a negative D-dimer (25,26). Indeed, D-dimer is now featured early in the algorithm of recently published guidelines for evaluation of VTE (27) or PE (28,29) and has been applied to stroke subtyping (30,31). Based on these data, a negative D-dimer early after stroke presentation would exclude the possibility of paradoxical embolism and avoid unnecessary anticoagulation or device placement. Imaging modalities, such as magnetic resonance direct thrombus imaging or computerized tomographic venography, may allow the noninvasive detection of clinically silent calf, axillary-subclavian, or pelvic vein thrombi in PFO stroke patients with elevated D-dimer (15,31,32). Without such supportive evidence regarding VTE and paradoxical embolism and without anticoagulation as the required medical treatment, the planned clinical trials will result in more device placement than is warranted and the prescription of inadequate or excessive medical therapy.

## References