

## Editorial Comment

# Should Patients With Lone Atrial Fibrillation Be Treated With Anticoagulant Therapy?\*

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Although it is clinically well recognized that patients with atrial fibrillation and organic heart disease have a markedly increased embolic risk, it is far less certain whether a lower risk is involved in patients with lone atrial fibrillation. Kumagai et al. (1) recently reported a comparable increase in D-dimer level in patients with lone atrial fibrillation and those with structural heart disease, indicating a similar increase in intracardiovascular clotting state in the two groups. This interesting finding leads one to suspect that patients with lone atrial fibrillation may have an increased risk of thromboembolism equal to that of patients with structural heart disease. If this is the case, both groups of patients should be treated with anticoagulant therapy.

Previous reports on the incidence of thromboembolic stroke in lone atrial fibrillation contradict one another. The 1985 population-based Framingham study demonstrated a more than 5-fold increase in embolic stroke in lone atrial fibrillation (2.6%/year), as opposed to an 18-fold increase in those with rheumatic heart disease (2,3). A later report from the Mayo Clinic, another population-based study (4), showed a much lower risk of stroke (0.55%/year). The reason for the conflicting results is not apparent, although the Mayo data were derived retrospectively and patients from the Framingham study were much older and 32% of them had preexisting hypertension. A more recent report by Shimomura et al. (5) indicated an embolic rate of 1.5%/year. However, it is not a population-based study and 29% of the patients had either hypertension, hypertensive heart disease or thyroid disease. Two latest multicenter trials (6,7) again showed somewhat contrasting data: the Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators (6) reported a 1.3%/year incidence of stroke, and the preliminary report of the Stroke Prevention in Atrial Fibrillation Study Group Investigators (7) showed a zero incidence at a mean follow-up of a little over a year. Unfortunately, in the former study 95% of the lone atrial fibrillation group had

either left atrial enlargement, mitral annular calcification or mitral regurgitation. In the latter study half of the patients received 325 mg of aspirin daily.

Taking into account these study limitations, the weighed evidence suggests a much lower incidence of stroke in patients with lone atrial fibrillation. How then can one reconcile the lower incidence of stroke in this group with the finding of an increased intracardiovascular clotting state similar to that of patients with organic heart disease?

First, the method of D-dimer determination employed by Kumagai et al. (1) is an extremely sensitive and specific assay. Thus, the increased D-dimer level truly reflects an increased clotting state in both groups. Obviously, this cannot be interpreted to mean an equally increased embolic rate in either group because many hemostatic factors (8) are involved in the coagulation system and other clinical variables also play a role in systemic embolization. Apart from this, the study of Kumagai et al. (1) is small, not population based and therefore subject to selection biases: 4 of the 24 patients with lone atrial fibrillation had a history of an embolic event and the D-dimer level is higher in patients with than in those without a positive history of embolization, although the difference does not reach statistical significance.

Second, several abstracts and articles published within the past 2 years provide insightful findings that help explain the present dilemma. Left atrial size gradually increases in lone atrial fibrillation and this suggests that the arrhythmia itself is a direct cause of left atrial enlargement (9,10). Because a larger left atrium in patients with both atrial fibrillation and mitral valve disease carries an increased thromboembolic risk (11), can such a cause and effect relation also exist between an enlarging left atrium and an increased risk of thromboembolism in lone atrial fibrillation? Such a relation would be in agreement with the Framingham and Mayo data showing, respectively, that stroke events occurred at a mean of 8.5 years of follow-up and 12.3 years after the onset of atrial fibrillation. Because left atrial dimension is not reported by Kumagai et al. (1), it is not known whether left atrial enlargement is associated with an elevated level of D-dimer in these patients with atrial fibrillation.

Left atrial spontaneous contrast echo was shown to be associated with an increased risk of stroke in both valvular and nonvalvular atrial fibrillation (11,12). Although it is logical to assume that left atrial spontaneous contrast echoes may lead to an increased D-dimer level as a result of increased turbulence within the left atrium, it remains to be confirmed if such a mechanism operates in the lone atrial fibrillation group. Alternatively, atrial fibrillation alone may account for the elevated D-dimer level.

Finally, with recent advances in cardiac imaging, it has become evident that patients with lone atrial fibrillation in previous studies were not well defined. All were identified clinically with or without transthoracic echocardiography. Transesophageal echocardiography has now been shown to

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identify many atrial structural abnormalities that are missed by transthoracic echocardiography (13,14). Cine computed tomography has also demonstrated in lone atrial fibrillation a high incidence of structural abnormalities undetected by transthoracic echocardiography (15). Therefore, some of the patients with lone atrial fibrillation from previous studies may actually have underlying cardiac abnormalities, a finding that may account for the observed increase in D-dimer levels (1) and the different embolic rates reported (2-7).

**Conclusions.** There is growing evidence to suggest that patients with true lone atrial fibrillation may have a much lower embolic risk than previously presumed. Hence, it becomes less clear than before regarding the need for anticoagulant therapy in these patients, especially since two multicenter stroke prevention trials (6,16) have demonstrated that low dose, long-term warfarin is safe and efficacious in preventing stroke in patients with nonrheumatic atrial fibrillation. The preliminary report of the Stroke Prevention Atrial Fibrillation Study (7) also shows a 49% reduction of stroke with aspirin (325 mg/day) alone in such patients  $\leq 75$  years of age. Because this study is still ongoing, the relative merits of warfarin and aspirin in stroke prevention in lone atrial fibrillation remain unknown. Whatever the outcome might be, additional studies are needed to identify subsets of patients with lone atrial fibrillation who may benefit from prophylactic anticoagulant therapy either because of its paroxysm, an advanced age, left atrial abnormalities, an increased clotting state or other unrecognized factors that predispose them to an increased risk of embolism.

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