How Much Atrial Fibrillation Is Too Much Atrial Fibrillation?

Gervasio Lamas, M.D.

Modern cardiac pacemakers and defibrillators function as permanently implanted cardiac monitors, detecting atrial and ventricular arrhythmias. Although the principal purpose of collecting this information is to manage the patient’s cardiac rhythm, these data can also be used to detect and study clinically inapparent arrhythmias and their consequences. In this issue of the Journal, Healey and coworkers report the results of a prospective study involving patients in whom a pacemaker or defibrillator had recently been implanted (Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial [ASSERT]).

Study Design

A total of 2580 patients 65 years of age or older with hypertension, in whom a pacemaker or defibrillator had recently been implanted, were enrolled in 23 subsets of breast cancer. Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

From the Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Chicago.

This article (10.1056/NEJMe1113641) was published on December 7, 2011, at NEJM.org.

countries and were followed for an average of 2.5 years. Episodes of subclinical atrial fibrillation had a standard definition: an atrial rate of at least 190 beats per minute for at least 6 minutes had to be recorded by the implanted device. These episodes of high atrial rate were recorded for the initial 3 months of the study, and strokes or peripheral emboli were adjudicated for the entirety of the study. The results resemble those of similar, less well-powered studies.4,5 The presence of any event of subclinical atrial fibrillation in the first 3 months of the study more than doubled the annualized risk of stroke or peripheral emboli (hazard ratio, 2.49) and also markedly increased the risk of clinically evident atrial fibrillation or flutter (hazard ratio, 5.56). This robust, prospective, observational study leads the clinician to accept the association as true. Questions remain, however, about cause and effect, as well as about clinical significance.

The hypothesis of causation is easy to understand. It strains logic that a 6-minute episode of atrial fibrillation would cause a cardioembolic stroke. However, patients with brief episodes of atrial fibrillation are likely to have longer ones, and it is these longer episodes that lead to cardioembolic events. To support the hypothesis of a direct link, atrial fibrillation should precede stroke. There should also be a time-threshold effect, whereby a greater burden of atrial fibrillation or longer episodes of atrial fibrillation should confer a greater risk of stroke.

An alternative hypothesis, of course, is that short events of atrial fibrillation are simply a marker of stroke risk — possibly indicating myocardial fibrosis or hypertrophy, mitral valve disease, or other structural heart disease — rather than being the proximate cause of a thrombus in the left atrial appendage. Alternatively, a proinflammatory state, such as that associated with diabetes or the metabolic syndrome, could be associated with both brief episodes of atrial fibrillation and stroke. In fact, in ASSERT, patients with a CHADS2 score6 (an index of the risk of stroke in patients with atrial fibrillation) of higher than 2 (on a scale from 0 to 6, with higher scores indicating a greater risk of stroke) had a stroke event rate of almost 4% per year.

The present study has to be viewed in conjunction with previous data in order to form a more complete picture of the whole. In a 1.4-year observational study involving patients with implantable devices, Glotzer et al.5 studied the association between device-detected atrial fibrillation and stroke in the 30 days after an event of high atrial rate (which was defined in a way similar, although not identical, to the way it was defined in ASSERT). Although the study by Glotzer et al. was underpowered, there was a strong trend to a doubling of the risk of stroke in the 30 days after any day in which there were at least 5.5 hours of atrial fibrillation, providing a hint of a logical temporal sequence (atrial fibrillation precedes stroke) and of a threshold effect (more atrial fibrillation is a better predictor of stroke than less atrial fibrillation). The design of the study by Healey et al. does not allow us to define sequence in such a satisfying way. ASSERT, however, did have sufficient power to address the time-threshold question. Among subjects in whom the longest episode of atrial fibrillation lasted longer than 17.7 hours, there was an increase by a factor of nearly 5 in the risk of stroke or systemic embolism. Thus, a more complete, albeit still hazy, picture emerges: short episodes of atrial fibrillation serendipitously captured by an implanted device increase the risk of stroke, and, perhaps, longer episodes increase the risk of stroke more than do shorter episodes.

The real question, of course, is to define a take-home message for the nonelectrophysiologist, like myself, who has a patient with an implanted pacemaker or defibrillator. But now we reach the limits of the present data. Specifically, until clinical trials targeting the population with short, asymptomatic episodes of high atrial rate are carried out, the current evidence simply does not address the question of whether treatment with warfarin or other anticoagulants is justifiable for the asymptomatic patient who has had a 6-minute episode of atrial fibrillation.

For now, therefore, I will continue to turn to the now-venerable CHADS2 score, consider applying it to patients with asymptomatic episodes of atrial fibrillation lasting for hours, and make a clinical judgment about the need for anticoagulation. I will also wait for definitive studies to be performed in this interesting, at-risk population.
From the Columbia University Division of Cardiology at Mount Sinai, Miami Beach, FL.