News and Views From the Literature

Electrophysiology

Intermittent Atrial Fibrillation and Stroke

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The appearance of stroke or other thromboembolic events is of substantial concern in patients with atrial fibrillation (AF). While stroke rates and risk factors have been well established in the presence of sustained AF,[1-3] specific stroke risk in patients with paroxysmal AF and relevant event predictors have not been established. In the past, patients with intermittent AF were assumed to have a lower risk rate than those with the sustained form of the arrhythmia.[4-6] This has not been established, however. A study was therefore undertaken to analyze the stroke rates among patients with intermittent AF who were treated with aspirin in the Stroke Prevention in Atrial Fibrillation Trials[7-12] (SPAF I-III). These stroke rates were compared with those of patients with sustained AF in the same trial.

Stroke With Intermittent Atrial Fibrillation: Incidence and Predictors During Aspirin Therapy

Hart RG, Pearce LA, Rothbart RM, et al, for the Stroke Prevention in Atrial Fibrillation Investigators.
J Am Coll Cardiol. 2000;35:183-187.

Included in this study were 460 patients from SPAF I, II, and III, who were assigned to aspirin (325 mg/d) or to a combination of aspirin plus inefficacious fixed-dose warfarin in the SPAF III trial (no international normalized ratio exceeding 1.4). These patients had no mitral stenosis or prosthetic cardiac valves. Diagnosis of intermittent AF required at least 2 ECG-documented episodes before entry. Patients thought to have intermittent AF but with no subsequent documentation of sinus rhythm during 6 months of follow-up were reclassified as having sustained AF.

Hart and colleagues demonstrated that the 460 patients with intermittent AF tended to be younger; were more often women; and had shorter durations of AF, less frequent history of heart failure, and less moderate to severe left ventricular dysfunction than was seen in the 1552 patients with sustained AF. Of SPAF III participants, 72% had recurrent AF based on symptoms and/or rhythm tracings. The ischemic stroke rate (n = 27) was 3.2% per year (95% confidence interval [CI], 2.2 to 4.6) among those with intermittent AF, compared with 3.3% per year (95% CI, 2.7 to 4.0) among those with sustained AF. By univariate analysis, factors associated with ischemic stroke included age, hypertension, prior stroke or transient ischemic attack (TIA), and peripheral artery disease. By multivariate analysis, age, hypertension, and prior stroke or TIA were the strongest predictors of ischemic stroke in intermittent AF patients. Of these patients, 24% had predictors of high risk, with 7.8 events occurring per year. There was no real difference in observed stroke rates between those with intermittent and sustained AF in this analysis, although those with intermittent AF were more frequently classified as having lower risk than were those with sustained arrhythmia (Figure 1). Predictors of ischemic stroke, even in aspirin-treated patients, were similar for those with intermittent or sustained AF.

This study is at odds with at least 3 previous examinations, suggesting a lower risk rate in patients with intermittent AF.[4,5,13] It is similar, however, to other studies showing no difference in stroke occurrence between patients with intermittent or sustained AF.[3,14,15] The authors point out that this study has significant limitations, including:

- SPAF trial patients were recruited mainly from inpatient/hospital-based populations and may not be representative of the general population.
- Because patients younger than 60 years and those with a single documented AF were excluded, these data may not apply to patients with new-onset AF episodes. Therefore, these findings may not apply to younger, healthier, and less symptomatic patients with intermittent AF.
- The frequency and duration of episodes of AF could not be accurately determined, so this information does not establish the frequency or duration of paroxysmal AF, which may be required for the observed risk.
- Because warfarin was not administered in appropriate

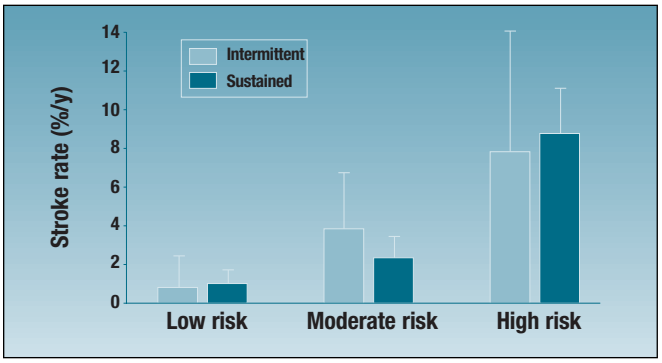

Figure 1. Observed rates of ischemic stroke according to risk category. Adapted with permission from Hart RG et al. *J Am Coll Cardiol*. 2000.

doses, the utility of long-term anticoagulation for reducing stroke risk was not established. Nevertheless, the authors suggest that in the SPAF III trial, those patients given adjusted-dose warfarin had a significantly reduced stroke risk, compared with those treated with aspirin.

Although this study has many limitations, it does provide data from a well-conducted clinical trial involving a large number of patients. Taken together, the data support the presence of significant risk in an elderly population with intermittent AF. Furthermore, the study suggests that the risk factors used in the assessment of patients with chronic AF apply nearly equally in patients with the paroxysmal form of arrhythmia. The event risk in AF patients with underlying ventricular dysfunction may be even higher. Several recent examinations of AF recurrence in patients receiving atrial defibrillators show that up to 75% of recurrent AF episodes are asymptomatic.[15] This presence of underlying disease and the frequent asymptomatic recurrences of AF strongly support the need to reconsider anticoagulation guidelines for these patients. Although data are not available suggesting that treatment alters outcome in these individuals, the strength of a variety of anticoagulation studies suggests that it is highly reasonable to aggressively treat at-risk intermittent AF patients with long-term anticoagulation. Future studies will still be needed to determine the impact of intermittent AF of short duration in younger, healthier individuals and that of asymptomatic AF recurrences that go undetected.

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Thrombosis and Acute Coronary Syndromes

Understanding Plaque Rupture

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Inflammation is increasingly thought to play a significant role in plaque rupture and in its clinical correlate, the acute coronary syndrome. Inflammatory cells, such as macrophages, T-lymphocytes, and neutrophils, are present in the shoulder region of these active plaques.[1] Cytokines, such as interleukin-6 (IL-6), are important messaging systems involved in the stimulation of matrix-degrading enzymes.[2] In parallel, tissue angiotensin-converting enzymes (ACE) with associated higher renin activities are thought to play a role in the acute coronary syndrome as well.[3]

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