Abstract—Atrial fibrillation is a common arrhythmia associated with increased risk for embolic stroke. Restoration of sinus rhythm in patients with atrial fibrillation is a logical strategy to prevent the cardiovascular and thromboembolic complications of this dysrhythmia. The most common strategy for restoration of sinus rhythm is pharmacological antiarrhythmic therapy with or without electrical cardioversion. Five randomized clinical trials compared rhythm to rate-control strategies in patients with atrial fibrillation. These trials examined mortality, thromboembolic complications, exercise tolerance, quality of life, hospital admissions and drug-related adverse reactions. Mortality ranged from 2.9% to 23.8% among the trial subjects randomized to rhythm control versus 1.0% to 21.3% in the rate control subjects. The risk of thromboembolism was greater: 2.9% to 7.9% in the rhythm-control subjects compared with 0% to 5.5% in the rate control subjects. Hospital admissions and drug-related adverse events were increased in the rhythm-control subjects. Stroke and systemic emboli occurred more often in the rhythm-control subjects many of whom had been withdrawn from anticoagulation. Rhythm-control offered no advantage compared with rate control for patients with atrial fibrillation at increased risk for stroke. One explanation for this finding is that those patients thought to have been successfully converted to sinus rhythm in fact had asymptomatic paroxysmal episodes of atrial fibrillation increasing their risk of stroke because they were unprotected by anticoagulation. Pharmacological attempts to restore atrial fibrillation to sinus rhythm do not improve mortality or reduce thromboembolic events. All patients with atrial fibrillation at increased risk for stroke should be continued on long-term anticoagulation even if they appear to have been successfully restored to sinus rhythm. (Stroke. 2007;38[part 2]:615-617.)

Key Words: atrial fibrillation ■ antiarrhythmic drugs ■ cardioversion ■ stroke

Atrial fibrillation (AF) is the most common dysrhythmia in the general population. Currently, there are an estimated 2 260 000 individuals in the United States with AF. The median age of individuals with AF is 75 years.1 As the population ages, AF becomes an increasingly prevalent disorder with estimates of 5 600 000 people with AF by 2050.2 Nine percent of the population over the age of 80 has AF. Congestive heart failure and AF are cardiac disorders increasing in prevalence and in need of better methods of prevention and treatment. Stroke is the most important complication of AF. About 15% of ischemic strokes are attributed to an embolus generated from a left atrial thrombus. These strokes tend to be unheralded by transient ischemic attacks (TIA) and are larger with a higher mortality and morbidity than ischemic strokes related to atherothrombotic or small artery occlusive mechanisms.

Five randomized trials established the value of warfarin anticoagulation for the prevention of stroke in high-risk individuals with AF.3 These trials also outlined criteria whereby an individual’s risk for stroke could be estimated based on the presence of certain coexistent conditions such as prior TIA or stroke, hypertension, age over 65, congestive heart failure or diabetes mellitus. Long-term anticoagulation reduced stroke risk by 67%. Despite this highly effective therapy, many patients cannot or will not take warfarin for a variety of medical, social and personal reasons. AF leads to stasis in the left atrium with thrombus formation concentrated in the left atrial appendage. Because this thrombus is the source of emboli to the brain and systemic circulation, it seems logical that eliminating AF would abolish the perturbed physiology generating atrial thrombi. This hypothesis is one of the basis for attempts to return patients with AF to sinus rhythm and maintain sinus rhythm indefinitely. Other potential benefits to restoration of sinus rhythm include improved cardiac hemodynamics, restoration of atrial systolic function, reduced atrial thrombus formation and its associated stroke risk, reduced heart rate, improved exercise tolerance and quality of life, and reduced mortality. The strategies used to restore and maintain sinus rhythm include electrical cardioversion, antiarrhythmic drugs, ablation techniques and surgical approaches. This review will summarize those clinical trials comparing pharmacological control of AF by...
Mortality and Thromboemboli in the Randomized Clinical Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>No.</th>
<th>F/U, y</th>
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<tr>
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<td>60.8</td>
<td>2.9</td>
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<tr>
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<td>69.7</td>
<td>23.8</td>
<td>21.3</td>
<td>7.1</td>
<td>5.5</td>
</tr>
</tbody>
</table>

NA indicates information not available; F/U, follow-up.

Methods

Randomized clinical treatment trials enrolling at least 200 subjects were selected for analysis. Each trial was examined and compared with the others with respect to the characteristics of the enrolled population, the pharmacological therapies studied, the frequency and nature of follow-up, and the end points evaluated. Primary and secondary end points were extracted as defined by the original authors.

Results

Five randomized trials conformed to the selection criteria and are the basis for this review. These trials along with the total number of subjects enrolled and the mean duration of follow-up are listed in the Table.

The Pharmacological Intervention in Atrial Fibrillation (PIAF) trial enrolled 252 subjects and followed them for a mean of 1 year.4 All patients received anticoagulation therapy. The primary end point was symptom improvement including the elimination of palpitations, dyspnea, and shortness of breath. Other secondary end points included the number of hospital admissions, quality-of-life assessments, exercise tolerance and drug-related adverse effects. Sinus rhythm was maintained in 56% of the rhythm-control and in 10% of the rate-control subjects. Symptomatic improvement, the primary end point, was not significantly different between the 2 groups. Quality-of-life assessments did not differ but the number of hospitalizations and drug-related adverse events was greater in the rhythm-control group. Rhythm-control subjects did significantly better on the 6-minute walk test. This study did not report mortality or stroke occurrence. Thus, the PIAF study failed to show that attempts to control rhythm were accompanied by improved symptoms related to their AF. It also showed that hospitalizations and adverse events were increased in the rhythm-control subjects.

The Strategies of Treatment of Atrial Fibrillation (STAF) study enrolled 200 subjects and followed them for an average of 19.6 months.5 The primary end point was the occurrence of death, cardiopulmonary resuscitation, stroke or TIA, and systemic embolism. Secondary end points included syncope, major bleeding, quality of life, echocardiographic characteristics, resting heart rate and maintenance of sinus rhythm. Anticoagulation was prescribed in both treatment arms in accordance with the American College of Chest Physicians guidelines.6 The combined primary end point occurred in 5.54% of the rhythm and 6.09% of the rate-control subjects failing to demonstrate a benefit to the rhythm-control strategy. Five patients in the rhythm-control and 2 in the rate-control group experienced stroke or systemic embolus. There was no difference in syncope or bleeding events. The rhythm-control group had significantly more hospitalizations. AF-related symptoms (dyspnea, palpitations, and dizziness) did not differ between the groups.

The Rate Control versus Electrical conversion (RACE) study enrolled 522 subjects with 2.3 years of mean follow-up.7 The primary end point was a composite of death from cardiovascular causes, heart failure, thromboembolic complications, bleeding, implantation of a pacemaker and severe adverse effects of drugs. Sinus rhythm was present in 39% of the rhythm and 10% of the rate-control subjects at follow-up. There was a trend favoring the rate control group where 17.2% experienced a composite primary end point compared with 22.6% of the rhythm-control group. There was also a trend for fewer thromboembolic complications (5.5%) in the rate control than in the rhythm-control group (7.9%).

The How to Treat Chronic Atrial Fibrillation (HOT-CAFE) study enrolled 205 subjects with a mean follow-up of 1.7 years.8 The primary end point was the composite of all-cause mortality, thromboembolic events or major bleeding. The primary end point was not significantly different between the treatment groups. The incidence of hospital admissions was much less in the rate control group (12% versus 74%). Exercise tolerance improved significantly in the rhythm-control group. The study concluded that there were no significant differences in the major end points between the rate and rhythm-control groups.

The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study was the largest trial, enrolling 4060 subjects and following them for a mean of 3.5 years.9 The primary end point was all-cause mortality. Mortality showed a trend favoring the rate-control (21.3%) compared with the rhythm-control (23.8%) group. There were more hospitalizations and drug-related adverse events in the rhythm-control group. Some type of stroke occurred in 211 (8.2%) of enrolled subjects10 (Figure). Ischemic stroke occurred in 5.5% and 7.1% of the rate and rhythm-control groups respectively, a statistically insignificant difference. More subjects in the rhythm-control group had their warfarin anticoagulation discontinued because subjects were thought to be in sinus rhythm. An attempt to determine the probable

![Rate Rhythm](AFFIRM stroke events.)
stroke mechanism concluded that 60% of the ischemic strokes were cardioembolic in origin. Eighty-six patients could not be assigned a probable stroke mechanism usually because a complete battery of diagnostic studies was not available. The variables associated with stroke risk were age, female sex, a qualifying AF event of 2 or more days, a history of stroke or TIA, diabetes mellitus and the presence of AF. Continued use of warfarin anticoagulation was associated with a 69% reduction in stroke risk.

Discussion

The restoration of sinus rhythm seems, and probably is, a logical strategy for the management of patients with AF. Unfortunately, the clinical trials comparing rhythm-control using the currently available antiarrhythmic drugs and rate-control failed to show a benefit in death or stroke (Table). In addition, rhythm-control was associated with more hospitalizations, more drug-related adverse events and no improvement in quality-of-life measures. One likely explanation for the failure of cardioversion and antiarrhythmic drug therapy is that many patients did not have their restoration of sinus rhythm sustained. Sixty percent or less of subjects randomized to the rhythm-control strategy were documented to consistently have sinus rhythm at regular follow-up assessments. It is reasonable to assume that some of the subjects recorded to have sinus rhythm may have continued to have asymptomatic episodes of paroxysmal AF. One study found that with intensive monitoring of heart rhythm in patients with paroxysmal AF, 12 asymptomatic AF episodes occurred for every symptomatic episode. A quarter or more of patients with stroke and AF had not been diagnosed with AF before their stroke. In the larger randomized trials, RACE and AFFIRM, warfarin anticoagulation was discontinued more often in the rhythm-control subjects based on the evidence and belief that the patient had been “successfully” converted to sinus rhythm. Those subjects were likely unprotected from the formation of left atrial thrombi and associated emboli during silent bouts of AF. Thus, it seems clear that even an apparently successful pharmacological restoration of sinus rhythm does not unburden the patient or physician of the need for long-term anticoagulation. Never the less it seems possible, and highly likely, that if a patient has sustained sinus rhythm without intervening bouts of AF the ill effects and complications of AF could be eliminated along with the need for long-term anticoagulation. This goal requires more effective and safer antiarrhythmic drugs and careful documentation of heart rhythm during treatment.
Stroke Prevention in Atrial Fibrillation: Pharmacological Rate Versus Rhythm Control

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