Editorial

Epidemiological and Mechanistic Studies of Atrial Fibrillation as a Basis for Treatment Strategies

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In this issue of Circulation, Benjamin et al1 provide evidence from the Framingham cohort that atrial fibrillation (AF) increases the mortality rate and that this association persists when adjusted for age, hypertension, smoking, diabetes, electrocardiographic left ventricular hypertrophy, myocardial infarction, congestive heart failure, valvular heart disease, and stroke or transient ischemic attack. The current analysis showed that of the 5209 residents of Framingham who originally enrolled in this population study, 621 developed AF during follow-up. Participants who developed AF were more likely to have hypertension, a smoking habit, electrocardiographic left ventricular hypertrophy, myocardial infarction, congestive heart failure, valvular heart disease, and stroke or transient ischemic attack at baseline. Echocardiographic left atrial dimension was not available for analysis. The age-adjusted odds ratios for death with AF were 2.4 for men and 3.5 for women. After adjusting for risk factor status at each biennial examination, the odds ratios for death were 1.5 for men and 1.9 for women. Much of the excess mortality burden for AF was attributable to AF occurring soon after diagnosis of AF, but after the first 30-day mortality experience was excluded, there was still a significant association of AF with death during follow-up. There was no interaction between age and AF for death during follow-up; ie, AF increased the likelihood of dying at all ages.

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There was a significant interaction between AF and sex with respect to mortality; the presence of AF substantially decreased the survival advantage women usually have over men. The morbidity of patients with AF is well known. The present study documents an independent mortality burden for AF as well. This finding extends previous studies3,5 and motivates the renaissance of research in AF that is currently underway.

The high incidence of AF (more than 2 million Americans), particularly in elderly men,2 and the morbidity and mortality associated with AF3,4 provide strong motivation to determine the mechanisms of AF and to prevent and treat AF.

However, the article by Benjamin et al1 leaves some epidemiological questions unanswered. The Framingham sample did not permit a meaningful examination of the relationship between race and the incidence of AF or outcome of patients with AF. AF has been classified as paroxysmal, persistent, or permanent and has also been classified by its association with cardiac diseases or metabolic disorders.5 In the Framingham study, AF was not classified, so we cannot know from that study whether different categories of AF have a different prognosis.

The Framingham study presented in this issue of Circulation (Benjamin et al1) compares causes of death in patients with AF with age- and sex-matched control subjects. The causes of death potentially could guide further inquiry and suggest hypotheses about useful interventions. AF-associated deaths probably are caused by heart failure, stroke, and adverse drug effects, eg, ventricular arrhythmias or hemorrhage. Table 4 in the Framingham report (Reference 1) indicates that the distribution of causes of death for the AF patients was similar to that of matched control patients without AF. At face value, this finding suggests that AF increases the probability of death without changing the mode of death. However, if the causes of death were examined more closely, additional meaningful findings might be uncovered.

The effects of treatment on outcomes are hard to delineate in a longitudinal observational study because sicker patients are more likely to be treated. Nevertheless, a study of treatment patterns, especially with anticoagulants, drugs used for control of ventricular rate, and antiarrhythmic drugs could highlight issues that warrant further study. This information may well be available in the Framingham files.

We know that AF is associated with morbidity and mortality, but we do not know enough about the risk-to-benefit ratio of therapies under evaluation for patients with AF. Placebo-controlled trials with warfarin have shown a substantial reduction in stroke rates.6,7 The risk-to-benefit ratio of the many new therapies can only be determined from controlled clinical trials after they have shown promise in mechanistic and pilot studies.

The magnitude of the AF problem ensures funding of discovery and development of diagnostic and therapeutic modalities. Improved knowledge of how AF is initiated and perpetuated will direct and correct the direction of inquiry. A wonderful example is research by Allessie’s group (Wijffels and colleagues8,9) showing that the electrical properties of the atria change rapidly in the first hours and days of AF; ie, the atrial effective refractory period shortens dramatically, and its dependence on atrial cycle length is substantially reduced. These findings have been confirmed, and this important new knowledge has prompted new treatment strategies. Thanks to Allessie’s research there is even hope that sinus rhythm can
be restored in patients with permanent AF. There is some preliminary evidence that this surprising outcome can be obtained with implanted atrial cardioverters. As time goes on after implantation of atrial cardioverters, periods of sinus rhythm last longer, and the intervals between shocks increase.

Current therapeutic developments encompass new antiarrhythmic drugs, several pacemaker strategies, AV node ablation and rate responsive pacing, implantable atrial defibrillators, and surgical or catheter ablation procedures to restore and permanently maintain sinus rhythm. As these treatment modalities are refined, each of them is likely to benefit some patients who suffer from AF. To me, it seems that catheter ablation has the furthest to go but potentially the most to offer.

A simple catheter ablation procedure in the lower right atrium restores sinus rhythm in nearly all cases of atrial flutter. Catheter ablation already has had significant impact on rate control in AF. Catheter ablation of the specific targets in the right atrium can produce complete AV block (a rate-responsive pacemaker is required) or decrease the ventricular rate in AF without producing AV block. These procedures can achieve rate control after drugs fail. The benefits of ablation-induced rate control include marked improvement in symptoms and a substantial increase in left ventricular ejection fraction. AF continues after these procedures, so the need for anticoagulant therapy continues.

Surgery or catheter ablation of AF can restore sinus rhythm. To develop catheter ablation of AF as a mainstream therapy will require that a long list of problems be solved. The targets for ablation must be defined. Rarely, a simple target can be identified. Rare cases of AF have been demonstrated to be focal and easily ablated. Most often, AF is a complex reentrant rhythm with several circulating wave fronts. Surgical ablation using a complex maze operation has a high probability of success. Simpler surgical procedures that focus on the posterior left atrium are successful also. There is already substantial evidence that there are critical targets for catheter ablation in the common forms of AF. The posterior left atrium is one critical zone for AF ablation to restore sinus rhythm. It is likely that some ablation targets for AF will be in inaccessible locations and will benefit from better imaging and catheter guidance systems. CT, intracardiac echocardiography, and magnetic methods are being explored as imaging techniques to support catheter ablation. Better catheter-steering systems or preformed catheters that seek the ablation targets are being evaluated now, and computerized mapping systems continue to improve. Better energy sources or application strategies for ablation will also help to bring catheter ablation of AF into the mainstream.

Only after catheter ablation becomes successful for most cases of AF and becomes relatively quick and efficient can we better evaluate whether conversion of AF to sinus or atrial paced rhythm will substantially reduce stroke, heart failure, hospitalization, and death. Also, controlled trials can determine how much conversion of AF to sinus or atrial paced rhythm will improve symptoms, exercise capacity, and functional status. If we can achieve permanent sinus or atrial paced rhythm, we have reason to hope that outcomes will improve. The benefits of sinus rhythm to reduce the morbidity and mortality should be quantified by controlled clinical trials. If we are not careful about the strategy for research on AF, these trials may never be done, because at some point they will be deemed unethical. Hopefully, the National Heart, Lung, and Blood Institute will take responsibility for conducting and monitoring the critical research pathways for AF so that a coherent picture of the risks, benefits, and costs will be made available.

Beyond finding effective treatments for AF, it should be possible to prevent AF. The Cardiovascular Health Study and the Framingham study have shown that some of the risk factors for AF are subject to control, eg, systolic blood pressure, blood glucose, and valvular heart disease. Importantly, the Cardiovascular Health Study showed, in a prospective study, the very strong relationship between left atrial enlargement and the incidence of AF during follow-up. That study made it clear that the left atrial enlargement preceded the development of AF and strongly suggests that control of the conditions that lead to left atrial enlargement will decrease the development of AF. Successful treatment of risk factors could prevent the development of left ventricular hypertrophy and left atrial enlargement and thereby prevent AF. In this regard, in randomized trials of antihypertensive therapy that sought to prevent or to obtain regression of left ventricular hypertrophy, AF could be considered to have been an outcome of those pathological conditions. Presumably, there should be less AF in groups treated with antihypertensive drugs, especially in those that showed regression of left ventricular hypertrophy and smaller left atrial size. It has been shown that long-term treatment of hypertension with certain drugs causes a reduction in left atrial size.

The relationship between left atrial enlargement and incidence of AF was so strong in the Cardiovascular Health Study that it would be reasonable to plan and conduct prophylaxis trials in patients with substantially enlarged left atria who have yet to develop AF. β-Blockade and anticoagulation would be candidates for prophylaxis trials. Epidemiological studies have already shown that β-blocker use is associated with a large decrease in the incidence of AF. This finding is impressive since the expectation in an epidemiological study is that β-blockers would be associated with an increase in AF because β-blocker use is an indicator of hypertension, angina pectoris, myocardial infarction, and hyperthyroidism. An inverse association between β-blocker use and AF must have overcome the indicator effect for disease.

Although the best strategies for management of AF and the diagnostic and therapeutic critical pathways have yet to be defined, new knowledge is accumulating at an impressive rate, and patients already benefit substantially from the effort.

References


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