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Rate versus rhythm control in atrial fibrillation: no one-size-fits-all

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“...atrial fibrillation can affect a patient’s overall quality of life, with symptoms of fatigue, palpitations and shortness of breath, among others.”

Atrial fibrillation (AF) is an arrhythmia that affects over 2 million individuals in the USA alone. There are many potential health consequences for a patient who develops AF. For example, AF can affect a patient’s overall quality of life, with symptoms of fatigue, palpitations and shortness of breath, among others. It can lead to hospitalization for management of the tachyarrhythmia, to initiate drug therapy or to treat comorbidities such as thromboembolic complications or heart failure. AF is associated with multiple other conditions such as hypertension, and it is associated with an increased risk of cardiovascular mortality. Hospitalizations, medications and procedure-related costs associated with treating AF all contribute to healthcare costs. Thus, decisions about the management of AF are important in order to improve patients’ quality of life and to minimize morbidity and mortality.

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If a group of physicians was asked whether they prefer to use a primary strategy of rate control or rhythm control to treat AF, the results would likely be split somewhere down the middle. A pivotal study in this area was the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial published in 2002 [1]. The investigators

studied a primary strategy of rate control versus rhythm control in patients with AF who were at a high risk of stroke and death. There was no significant difference in all-cause mortality between the two groups. In addition, there was no difference in quality of life. The Rate Control Versus Electrical Cardioversion (RACE) trial likewise showed that rate control was not inferior to rhythm control in patients followed for 2 years with recurrent, persistent AF [2]. The Atrial Fibrillation and Congestive Heart Failure (AF-CHF) trial enrolled patients with systolic heart failure and compared rhythm versus rate control strategies. There was no difference in mortality or progression of congestive heart failure between the two groups [3]. Another pilot study, Strategies of Treatment of Atrial Fibrillation (STAF), had similar findings [4]. Some physicians have interpreted the results of these studies in such a way that they began to use the rate control strategy in every patient and abandoned attempts to restore sinus rhythm in patients with persistent AF.

In the trials that compared the two treatment strategies, the limited value of a rhythm-control strategy was likely due to several factors. In the AFFIRM trial, enrolled patients had to be eligible for both the rate and the rhythm-control arms, which would likely have excluded highly symptomatic patients from participation. Second, not all patients randomized to the rate control arm were in persistent AF and, conversely, not all patients randomized to rhythm control maintained sinus rhythm throughout follow-up. Thus, the absolute

difference in actual rhythm between the two treatment arms was much less than the total number of patients in the study. The AFFIRM trial gives us information on the outcomes with different treatment strategies, not the differences between sinus rhythm and AF *per se*. Further insight may be gained from a substudy analysis of AFFIRM, in which sinus rhythm was associated with better survival, whereas the use of antiarrhythmic drugs was associated with worse survival [5]. It is likely that the adverse effects of antiarrhythmic drugs offset the benefits of maintaining sinus rhythm, indicating that a safer yet effective antiarrhythmic drug, or a nonpharmacologic approach to attaining sinus rhythm, might be associated with better outcomes in patients with AF.

“It is potentially misleading to extrapolate the data from these trials and apply it to younger, healthier patients.”

In general, the patients in these studies were older, with significant comorbidities such as congestive heart failure. It is potentially misleading to extrapolate the data from these trials and apply it to younger, healthier patients. There are many patients who are symptomatic while in AF, and even if adequately rate controlled, still do not feel well. At the other end of the spectrum are patients with cardiomyopathies who are at a high risk for developing AF, approximately 6–8% per year. The Candesartan in Heart Failure – Assessment of Reduction in Mortality and Morbidity (CHARM) study demonstrated that the combination of AF and cardiomyopathy leads to worse outcomes, including increased hospitalizations and death [6]. The 2006 American College of Cardiology/American Heart Association guidelines recommend that when a patient first develops AF, the physician should carefully consider whether to try to restore sinus rhythm, as it is easier to accomplish this earlier in the disease process [7].

At the time of these earlier trials, the options for achieving and maintaining sinus rhythm were somewhat more limited than they are now. With the widespread adoption of ablation techniques for the cure of AF and new antiarrhythmic medications, there are alternatives for the rhythm-control strategy that may prove to be safer and/or more effective, potentially shifting the balance in favor of a rhythm-control strategy. Dronedarone is a new antiarrhythmic drug with multiple effects on cardiac ion channels that is similar to amiodarone, but without the iodine moiety and thus without its adverse effects on thyroid and pulmonary function. In the Placebo-Controlled, Double-Blind, Parallel-Arm Trial to Assess the Efficacy of Dronedarone 400 mg BID for the Prevention of Cardiovascular Hospitalization or Death From Any Cause in Patients With Atrial Fibrillation/Atrial Flutter (ATHENA), there was a significant reduction in the primary end point of cardiovascular hospitalization or death with dronedarone compared with placebo [8]. In addition, a *post hoc* analysis of ATHENA showed a reduction in stroke with the use of dronedarone [9]. ATHENA was thus the first trial to show a beneficial effect on important cardiovascular outcomes in AF with an antiarrhythmic drug.

Ablation therapy has become an important option for patients with recurrent or persistent symptomatic AF [10]. Many patients are free of symptomatic AF after undergoing pulmonary vein isolation and/or linear ablation, most without the use of antiarrhythmic drugs. In addition, there is evidence that successful ablation for AF can lead to improvement in left ventricular ejection fraction in patients with heart failure [11,12]. The recently published ThermoCool AF trial showed that patients with symptomatic AF who failed a single antiarrhythmic drug and underwent catheter ablation had better intermediate outcomes versus antiarrhythmic drug use alone [13]. The Catheter Ablation Versus Anti-Arrhythmic Drug Therapy for Atrial Fibrillation (CABANA) trial is a prospective trial that is currently enrolling high-risk patients with AF to be randomized to catheter ablation or medical management with either a rate- or rhythm-control strategy [14]. The primary end point of the trial is all-cause mortality.

Until these new trials are completed, it is important to tailor the treatment of AF to each individual patient. The young, healthy patient will likely benefit from a strategy to achieve and maintain sinus rhythm with a combination of cardioversion, antiarrhythmic drugs and possibly catheter ablation. On the other hand, it is not uncommon for older patients to have minimal to no symptoms with AF, particularly if they have some element of underlying conduction system disease and their ventricular rates in AF are moderate. In such cases, it is difficult to argue that restoration of sinus rhythm is necessary in these patients, given the clinical trial data we have to date. Thus, rate control and anticoagulation with warfarin would be a perfectly acceptable strategy. Patients with heart failure may be a particularly challenging group to manage. Options for rhythm control are somewhat limited, with amiodarone and dofetilide as the best options, and dronedarone reserved for selected patients who do not have a history of recently decompensated heart failure. Rate control may be difficult if patients do not tolerate adequate doses of β -blockers or calcium channel blockers. Finally, ablation procedures are less successful in patients with persistent AF or enlarged left atria, which are more likely in patients with chronic systolic heart failure.

“Patients with heart failure may be a particularly challenging group to manage.”

Thus, each physician should take the time to talk to their patients about symptoms and treatment goals and options for the management of AF in order to achieve the best outcomes and quality of life for their patients.

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