EDITORIAL COMMENT

Restoring Sinus Rhythm in Atrial Fibrillation

A Pyrrhic Victory?*

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“The future ain’t what it used to be.”
—Yogi Berra

Atrial fibrillation (AF), at the very least, is a fruitful subject for both the clinician and basic scientist. Since 1965, PubMed has listed 6,329 publications with “atrial fibrillation” in the title, with 1,235 such articles between January 2001 and December 2002. In light of the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) parent study (1), which showed that in patients with AF and a risk of stroke, the strategy of restoring and maintaining sinus rhythm was not superior to the strategy of rate control, one must ask whether the relative efficacy of different drugs used to restore and maintain sinus rhythm is a topic worth discussion.

Despite the parent AFFIRM study, most clinicians would answer “yes,” because the treatment of AF remains important, and many patients are sufficiently symptomatic that a strategy of rate control is inadequate. The clinician treating a patient with highly symptomatic AF is thus faced with the difficult choice between the rhythm control strategy, which is associated with a nontrivial risk of serious, potentially fatal adverse events as well as the burden of drug toxicity and the likelihood of drug inefficacy, and the rate control strategy, which may have limitations for symptom control in the individual patient. It is important to recall that patients were eligible for the AFFIRM parent study only if the investigator and patient were prepared to undertake either rhythm or rate control strategies, thus suggesting, importantly, that patients with severe symptoms during AF may not have been included in the study.

With that background, the AFFIRM First Antiarrhythmic Drug Substudy investigators (2), in this issue of the Journal, have added important information to the available data on the effectiveness of antiarrhythmic drug therapy in patients with AF. In particular, the AFFIRM investigators have chosen a potentially more clinically relevant end point of antiarrhythmic drug efficacy, as compared with the more “conventional” end points, such as the “time to first recurrence of AF.” In the current study, “efficacy” is defined as the presence of sinus rhythm at follow-up visits, without the requirement for intervening electrical or pharmacological cardioversion, and the absence of highly symptomatic AF episodes, which would lead to the discontinuation of the initially assigned antiarrhythmic drug. Although the definition of “drug failure” in this study is not unambiguous (recurrent AF with spontaneous reversion to sinus rhythm did not necessarily constitute a drug failure), this study, appropriately, does not consider asymptomatic or minimally symptomatic recurrences as a “failure” or as necessitating drug discontinuation or change. Such an approach is much more similar to routine clinical care than previous antiarrhythmic drug trials in AF, where the end points almost always included any symptomatic occurrence of AF, as well as some asymptomatic occurrences.

The conclusions with respect to drug efficacy and adverse effects are nevertheless quite consistent with previous studies of various antiarrhythmic therapies in AF. For example, in the Canadian Trial of Atrial Fibrillation (3), the one-year rate of freedom from recurrent AF was 69% in the amiodarone group and 39% in patients treated with either sotalol or propafenone, remarkably similar to the composite end points of drug success in the current study (amiodarone vs. class I: 62% vs. 23%; amiodarone vs. sotalol: 60% vs. 38%; sotalol vs. class I: 34% vs. 23%). The inventive analysis of the First Antiarrhythmic Drug Substudy investigators, comparing drugs or classes of drugs to each other in a pairwise fashion, thereby allowing individual patients to be “counted more than once,” makes it somewhat difficult to interpret the overall probability of effectiveness of any given drug, but the overall results quite convincingly show that amiodarone is superior to either sotalol or class I drugs, even in patients carefully selected to have the lowest possible risk of adverse effects from any of these therapies. Furthermore, the investigators show that by one year, at most two-thirds of patients on amiodarone are in sinus rhythm and receiving effective drug therapy, and by five years, far fewer than one-half of patients on any drug therapy, including amiodarone, are still receiving effective therapy. Given that AF rarely remits spontaneously and, in fact, tends to progress, the current report suggests that rhythm control using antiarrhythmic drugs is frequently not a useful or effective long-term strategy.

Despite a relatively low incidence of adverse effects severe enough to cause drug discontinuation at one year (13% on amiodarone and 16% on sotalol), in the very long run, no drug therapy was both superbly effective at maintaining sinus rhythm and associated with good patient tolerance. Additionally, the substudy results suggest that therapy with class I antiarrhythmic agents is frequently associated with adverse effects requiring drug discontinuation (39% at 1 year) and inefficacy (only 35% of patients meeting the composite end point of success by four months in any of the...
comparisons). Thus, although the comparison of efficacy between sotalol and class I agents is limited because of early termination of this arm of the study due to futility, one may still reasonably conclude that the use of class I agents, even in patients selected to have a low risk of adverse events, is not a rewarding strategy in patients meeting the AFFIRM entry criteria. Furthermore, there is a substantially higher mortality rate in patients initially assigned to class I drug therapy than in those initially assigned to amiodarone or sotalol, even though most of the deaths occurred well after the class I drugs were stopped and the majority of deaths occurred after the first year. Additionally, most of these deaths were not “arrhythmic,” which at first glance raises the worrisome hypothesis that class I drugs, even taken for a relatively brief period, cause long-term consequences that may lead to death after the drug is discontinued. However, it is important to note that of the 69 deaths that occurred over the duration of the study, 24 patients were taking amiodarone at the time of death, 10 patients were taking class I drugs, 8 patients were taking sotalol, and 27 patients were not taking antiarrhythmic drugs.

What does all this mean for the practicing clinician? Medicine is still an art. Subjective, patient-perceived quality of life, as well as the patient’s own perceptions of the risk of antiarrhythmic therapy compared with its potential benefits, needs to be individually assessed in each and every patient with AF. Although the AFFIRM parent study has reported, in abstract form, equivalent quality-of-life outcomes in the rate-control arm versus rhythm-control arm, there were clearly many patients with AF who have unexpectedly severe symptoms that can only be substantially improved if sinus rhythm is restored. Additionally, as mentioned previously, physicians were likely to have an enrollment bias toward recruiting patients who were mildly or minimally symptomatic, making the results of this study less generalizable to the patient with disabling symptoms during AF. As was done in the setting of this substudy, clinicians need to carefully establish, before antiarrhythmic therapy is contemplated, explicit criteria of drug efficacy (for the particular patient) and persist with therapy only if these criteria are fulfilled.

There are options in the restoration and maintenance of sinus rhythm that were not a part of the AFFIRM drug substudy. For example, there is intriguing and plausible evidence that impeding the actions of angiotensin II on the heart may reduce the burden of AF. In a randomized, blinded study, the combination of amiodarone plus irbesartan led to a lower rate of AF recurrence than amiodarone plus placebo (4). In the Trandolapril Cardiac Evaluation (TRACE) study, treatment with trandolapril led to a lower incidence of new-onset AF (defined as an outpatient electrocardiogram documenting the presence of AF) in patients with reduced left ventricular function after myocardial infarction, compared with placebo (5). Furthermore, beta-blocker therapy may have independent “antiarrhythmic” effects in AF. Metoprolol led to a lower risk of AF recurrence after cardioversion, as compared with placebo, in a randomized, controlled study (6), and beta-blockers plus amiodarone may have synergistic effects on arrhythmia prevention, at least for ventricular arrhythmias (7). Additionally, it cannot be overemphasized that blood pressure control is extremely important in patients with AF, and it is possible that some of the beneficial effect of beta-blockers or medications that affect the renin-angiotensin system may be related to their effect on blood pressure.

It is important to remember that neither the AFFIRM study nor the current drug substudy attempted to discern the difference in outcome between those AF patients who achieve and maintain sinus rhythm and those who do not. These studies are merely assessing some of the currently available clinical strategies that are used for the treatment of AF, and they have clearly answered some very important, clinically relevant questions. However, given the large number of patients with refractory, exceedingly symptomatic AF, there is still a role for the development and utilization of new methods that may be more effective in the long-term maintenance of sinus rhythm, including novel atrial selective antiarrhythmic drugs and various nonpharmacologic approaches.

Despite substantial progress in the understanding of the electrophysiologic mechanisms of AF (8), as well as a plethora of pharmacologic, electrical pacing-based, and ablative strategies to manage AF, its management continues to be a very considerable challenge. For most patients with AF, the heart is not only a pump but also a metaphor. Therefore, cardiac symptoms occupy a larger section of our patients’ consciousness than objective abnormalities in cardiac function would warrant, and the dilemma of rate versus rhythm will continue to be with us.

Based on this substudy data, the parent AFFIRM study, as well as other recent, large trials in AF—Pharmacological Intervention in Atrial Fibrillation (PIAF) (9) and Rate Control versus Electrical Cardioversion (RACE) (10)—it is very clear that all patients with AF not due to a reversible cause and with risk factors for stroke should be permanently anticoagulated with warfarin. It seems reasonable for all of them to be treated with a drug that will reduce the rapid ventricular rates expected with AF (among those with normal atrioventricular node function), in the case of recurrence of AF or as a primary strategy. Beyond that, a thorough discussion with the patient of the anticipated benefits and risks of sinus rhythm maintenance using cardioversion, as necessary, and antiarrhythmic drug therapy is warranted. If drug efficacy is the primary and most important goal, then amiodarone is clearly the most effective agent available. However, a strategy of beginning with an alternative drug and changing to amiodarone only if the initial therapy is ineffective is also quite reasonable. This is particularly true for sotalol, because class I agents as initial therapy are fraught with a relatively high risk of adverse effects, early inefficacy, and a hypothetical but potentially worrisome future risk of death. The AFFIRM First Antiarrhythmic Drug Substudy investigators have done the
cardiology community a considerable service with their careful and comprehensive investigation.

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