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EDITORIAL COMMENT

Rate Control Versus Rhythm Control in the ORBIT-AF Registry

The Beat Goes On*

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For most patients, atrial fibrillation (AF) is a chronic, progressive problem with widely varying patterns of recurrence, persistence, symptoms, and major clinical morbidity. Accordingly, it is a condition that is "managed" over an extended period of time. There are 3 distinct, minimally overlapping aspects to the management of AF: prevention of stroke/systemic embolus; antiarrhythmia management; and identification and optimal management of all treatable medical conditions contributing to progressive atrial remodeling (substrate) or the risks of AF. Given the multidisciplinary needs for optimal management, perhaps the preferred management model is shared care, coordinated through specialty clinics staffed with nurse clinicians (1,2).

In the case of treatment for stroke/systemic embolus prevention, there has been a great deal of progress in the past 2 decades (3). Less progress has been evident for antiarrhythmia management, the main purview of the cardiologist and the subject of the current analysis of ORBIT-AF (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation) (4) in this issue of *JACC: Clinical Electrophysiology*.

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With respect to antiarrhythmia management of AF, between the years 2000 and 2009, at least 9 randomized, controlled trials comparing the 2 strategies, merely controlling the heart rate (rate control) or attempting to restore and maintain sinus rhythm (rhythm control), have been reported. The first patients entering these trials were enrolled in 1995, a little more than 20 years ago. The 3 major and largest of these trials, enrolling a total of ~6,000 patients were AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) (5), RACE (Rate Control Versus Electrical Cardioversion for Persistent Atrial Fibrillation) (6), and AF-CHF (Atrial Fibrillation and Congestive Heart Failure) (7). Simply stated, these 9 trials showed no important advantage of either strategy with respect to major clinical outcomes, such as death, stroke, and worsening heart failure. Attempting to restore and maintain sinus rhythm is better for symptom control in highly symptomatic patients, and controlling the heart rate is less expensive.

AS THESE RESULTS ARE BASED ON CLINICAL PRACTICE PATTERNS AND KNOWLEDGE THAT IS 2 DECADES OLD, COULD THE SITUATION HAVE CHANGED?

On a theoretical basis, several benefits are expected to accrue from restoring atrioventricular synchrony, which also controls heart rate and bestows regularity. The lingering hypothesis that restoration and maintenance of sinus rhythm is superior to simply controlling the heart rate has been bolstered by a number of contemporary cohort studies. Such cohort studies typically compare 2 subgroups constructed from administrative databases of retrospectively collected data. They try to mimic randomized, controlled trials through matching for comorbidities and other potentially important covariates between the subgroups (8,9). The subgroups are often badly mismatched for important covariates affecting clinical

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outcomes until after the statistical adjustment. Of course that level of evidence cannot overturn the results of well-done randomized, controlled trials because of inherent flaws in the study design, mostly because all the potentially important covariates are not available and perhaps not even known (10). Such studies also often have a limited scope because retrospective administrative databases were not designed to study AF and included only selected samples of patients (e.g., those older than 65 years of age or those with a hospital admission for AF). Finally, there is rarely adjustment for important time-dependent covariates (those only evident after study entry). The pitfall is that the "new data" cachet can be seductive, leading some to neglect results from earlier randomized, controlled clinical trials considered to be "old" and "passé."

ORBIT-AF is a comparative cohort study of similar design, but with the major advantage that it is a prospectively designed database specifically intended to study patients presenting with AF in a variety of encounters. In this particular analysis (4), the ORBIT-AF investigators compare clinical outcomes using contemporary therapies in those initially managed with rate control versus those initially managed with rhythm control. In matching the 2 cohorts, the ORBIT-AF investigators used the arguably best statistical method of adjustment for imbalance of baseline covariates, propensity scores. The limitation of matching only for differences evident at baseline remains. Nevertheless, it is reassuring that this study of contemporary, physician-selected, antiarrhythmia management supports the "no major difference" result of the earlier randomized, controlled trials.

ASIDE FROM TRIAL DESIGN, WHAT ELSE NEW AND DIFFERENT WITH RESPECT TO CONTEMPORARY ANTIARRHYTHMIA MANAGEMENT MAKES THIS ORBIT-AF ANALYSIS IMPORTANT?

Since the original randomized, controlled trials were completed, there has been a dearth of new antiarrhythmic drugs approved for management of AF. Probably the only new antiarrhythmic drug in wide use since the original 9 trials were conducted is dronedarone, and drugs like quinidine and procainamide have virtually disappeared. Dronedarone use has largely been confined to paroxysmal AF or persistent AF after conversion to sinus rhythm in patients with well-preserved left ventricular systolic function (11,12). The current paper did not list use of individual antiarrhythmic drugs (4). We are told that 23.6% of rhythm control patients were on amiodarone and 49.0% were on other antiarrhythmic drugs (a total of ~73% on drugs). Presumably the remaining 27% were treated after conversion without starting an antiarrhythmic drug. A recent U.S. report focused on patients younger than 65 years of age without structural heart disease found that only 7% of such patients treated with antiarrhythmic agents were treated with dronedarone (13). Thus, although we do not know for sure, it can be deduced that use of dronedarone was low In ORBIT-AF (median age ~75 years). Therefore, it seems unlikely that dronedarone had much impact on the outcomes.

COULD NONPHARMACOLOGICAL THERAPIES HAVE MADE AN IMPACT NOT SEEN IN THE EARLIER RANDOMIZED, CONTROLLED TRIALS?

Since the major rate versus rhythm trials were done and beginning in about 1998, there has been an explosion of research on nonpharmacological alternatives for AF antiarrhythmia management. To say that ablation, particularly catheter-based techniques, have dominated the AF antiarrhythmia management literature for the past decade is no exaggeration. For the most part, this research has focused on procedural techniques or has compared a nonpharmacological treatment with antiarrhythmic drug therapy, often after drug therapy had already failed. In the case of catheter-based techniques, some of these studies have been randomized, controlled trials of a rather modest size, often with surrogate outcome measures, such as recurrence of AF. I am not aware of any completed randomized, controlled trials of any note with respect to surgical procedures using an important clinical outcome measure. Nevertheless, both catheter-based and surgical therapies are now part of the AF antiarrhythmia management armamentarium used in the developed world. Of the previous major randomized rate versus rhythm trials, AFFIRM was the only one that reported these kinds of therapies. Their use in AFFIRM was vanishingly small. Among the 2,033 patients randomized to rhythm control, 14 had a catheter-based ablation for AF or atrial flutter, 4 had a surgical maze procedure, and 1 had a catheter-based maze procedure (5). The current "big question" is whether these nonpharmacological therapies may have shifted the "no-difference" paradigm.

In this ORBIT-AF report, we are not specifically told how many were treated initially with catheter- or surgery-based ablation procedures, but we are told that 13.1% had AF ablation procedures during the course of the study (4). We can see from Table 3 that

after initial therapy, 5.4% had a subsequent ablation procedure aimed at maintaining sinus rhythm and 0.7% had an AV junction ablation, so we can deduce that ~7.0% had an ablation procedure as their initial antiarrhythmia therapy (4). Although the exact proportion among all patients with AF currently receiving this type of nonpharmacological therapy is not accurately known, these data suggest that it is a small percentage.

We know that these procedures are used more in patients with paroxysmal AF. Earlier randomized, controlled trials of rate versus rhythm were dominated by persistent AF. In this ORBIT-AF report, only recurrent AF was subclassified into paroxysmal or persistent AF. First-detected/new-onset AF was not subclassified (4). Overall, paroxysmal AF was more common (at least 70%) in ORBIT-AF (4) than in the previous randomized, controlled trials of rate versus rhythm.

Thus, in ORBIT-AF, a higher proportion of paroxysmal AF and nonpharmacological antiarrhythmia procedures appears to have had no substantial impact on the "no difference" outcome found in the earlier randomized, controlled trials. One potential inference is that so far, catheter-based and surgical procedures to restore and maintain sinus rhythm have made little impact on the "no difference" paradigm compared with rate control in the general population with AF. Of course, the caveat is that this result does not answer the question of whether, in the patients specifically eligible for these procedures, nonpharmacological approaches are superior to pharmacological therapies with respect to important clinical outcomes. The ORBIT-AF investigators are appropriately cautious on this point, noting that in selected patients, their impact may be different (4). The answer to that question is not in sight for surgical procedures and, as they correctly point out, for catheter-based techniques awaits the results of ongoing trials, such as EAST (Early Treatment of Atrial Fibrillation for Stroke Prevention Trial) (14), CABANA (Catheter Ablation vs Anti-arrhythmic Drug Therapy for Atrial Fibrillation Trial) (15), and RAFT-AF (Rhythm Control-Catheter Ablation With or Without Anti-arrhythmic Drug Control of Maintaining Sinus Rhythm Versus Rate Control With Medical Therapy and/or Atrio-ventricular Junction and Pacemaker Treatment for Atrial Fibrillation) (16).

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