Amiodarone or Dronedarone for Atrial Fibrillation
Too Early to Know the Winner?*

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Atrial fibrillation (AF) is estimated to affect >10 million patients by 2050 in the U.S. (1) and is associated with significant rates of morbidity and an increased risk of mortality. Health care costs due to AF are enormous at >$2 billion annually. Restoration of sinus rhythm in patients with AF has been demonstrated to improve left ventricular ejection fraction, left atrial size, and quality of life both in patients with congestive heart failure and normal ejection fraction, even when optimal ventricular rate control during AF has been achieved (2–4). Furthermore, many patients with AF are troubled by symptoms that persist despite adequate rate control. Therefore, maintenance of sinus rhythm often is desirable in patients with AF.

In the most recent American College of Cardiology/American Heart Association guidelines, an antiarrhythmic agent is recommended as first-line therapy to maintain sinus rhythm (5). However, the risk of proarrhythmia, only modest efficacy, and the risk of organ toxicity (amiodarone) have complicated antiarrhythmic drug therapy. In a recent meta-analysis (6), Vaughan-Williams Class 1A antiarrhythmic agents like quinidine and disopyramide were associated with a >2-fold increased risk for all-cause mortality when compared with placebo, and sotalol was associated with a strong trend toward a greater risk of mortality. Although there were insufficient mortality data for Class 1C antiarrhythmic agents, propafenone and flecainide have been linked to worse outcomes in patients with ischemic heart disease or cardiomyopathy (7). Furthermore, a post hoc analysis of the AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) study suggested that the beneficial effects of sinus rhythm on survival were negated by the negative effect of antiarrhythmic drug therapy on survival (8).

Dofetilide has been recommended as an alternative to amiodarone in patients with a reduced ejection fraction and can also be considered in patients with coronary artery disease or for second-line therapy in patients without structural heart disease (5). Because of the risk of proarrhythmia, however, dofetilide requires inpatient initiation of therapy under electrocardiogram monitoring and only by certified providers.

Although amiodarone is associated with organ toxicity, it appears to have a lower risk of proarrhythmia than other agents. Amiodarone has been one of the few and sometimes is the only agent recommended in patients with structural heart disease. For example, in patients with substantial left ventricular hypertrophy, it is the only agent recommended in the American College of Cardiology/American Heart Association guidelines (5). However, to date, only 4 small randomized trials involving 669 patients have been performed comparing amiodarone with placebo for patients with AF (6). This is one reason why currently approved indications by the Food and Drug Administration do not include AF (9). Yet, >2 million prescriptions for amiodarone are filled annually, with >80% of these related to off-label uses like AF (10). Importantly, the use of amiodarone is not without serious side effects resulting from its high iodine content.

For these reasons, there has been great interest in dronedarone, a novel compound that shares many structural similarities with amiodarone but without the iodine. In recent trials, dronedarone has generated substantial interest by demonstrating a reduction in recurrence of AF without serious side effects (11). In the ATHENA (A Trial With Dronedarone to Prevent Hospitalization or Death in Patients With Atrial Fibrillation) trial (12), dronedarone was found to reduce the rate of the primary end point of cardiovascular hospitalization and cardiovascular mortality by 24% (31.9% vs. 39.4%; hazard ratio [HR]: 0.76; 95% confidence interval [CI]: 0.69 to 0.84; p < 0.001) and of cardiovascular mortality alone by 29% (2.7% vs. 3.9%; HR: 0.71; 95% CI: 0.51 to 0.98; p = 0.03). To date, this is the first antiarrhythmic treatment of AF that has been shown to improve a composite end point of cardiovascular morbidity and mortality. However, it should be noted that freedom from recurrent AF was not an end point in the ATHENA trial.

It is with these issues in mind that the indirect meta-analysis by Piccini et al. (13) in this issue of the Journal, in

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which they compared amiodarone with dronedarone in AF, takes on a larger significance. Because adequately powered clinical trials comparing these 2 agents are not available, indirect meta-analysis remains the only means of comparing their relative effectiveness and safety by extrapolating results from individual trials comparing each against placebo. The authors found in their meta-analysis that patients treated with amiodarone, compared with dronedarone, were twice as likely to remain in sinus rhythm (for recurrent AF: odds ratio [OR]: 0.49; 95% CI: 0.37 to 0.63; p < 0.001). However, amiodarone was associated with a trend toward greater all-cause mortality (OR: 1.61; 95% CI: 0.97 to 2.68; p = 0.07) and was associated with greater rates of adverse events requiring drug discontinuation (OR: 1.81; 95% CI: 1.33 to 2.46; p < 0.001).

There are 2 important aspects of this study. First, the authors used a novel meta-analytical approach to compare 2 drugs that have not been studied in a head-to-head randomized controlled trial. Second, by using this technique, they have been able to address the important clinical question of whether dronedarone should be preferred as initial therapy over amiodarone in patients with AF who need an effective but also safer antiarrhythmic agent.

However, given the large number of patients with AF and the major public health implications, their findings need to be interpreted carefully and in the proper context. First, indirect meta-analysis has significant limitations beyond those associated with meta-analyses in general, even when applied appropriately as in this study. Results from indirect meta-analyses may overestimate the relative effectiveness of the compared treatments because of the assumption that there is no interaction between different study populations across trials. For example, an indirect meta-analysis in which the authors compared sulfamethoxazole/trimethoprim with dapsone/pyrimethamine found the former to be associated with a 63% reduction (risk ratio: 0.37; 95% CI: 0.21 to 0.65) in Pneumocystis carinii pneumonia but with a more modest 36% reduction (risk ratio: 0.64; 95% CI: 0.45 to 0.90) during direct meta-analysis because of the different types of patients studied across these trials (14).

It is noteworthy that all 4 dronedarone studies excluded patients with permanent AF, whereas 2 of the 4 amiodarone studies excluded patients with paroxysmal AF. Differences in study populations and treatments (as was observed with warfarin use) between these trials could lead to biased estimates with indirect meta-analysis. It is likely that amiodarone studies were more likely to include patients with structural heart disease and also persistent/permanent forms of AF.

Second, it is noteworthy that there were almost 9 times as many patients in the trials evaluating dronedarone (n = 5,967) than in those evaluating amiodarone (n = 669), largely because of the ATHENA trial. Sensitivity analyses were not performed (specifically with the ATHENA trial for dronedarone), which would have been helpful, especially given several of the marginal findings. In addition, the authors could have considered including patients from other AF trials such as AFFIRM (15), in sensitivity analyses for amiodarone, because amiodarone was used in the majority of these patients. If inclusion of the AFFIRM trial attenuated the relative mortality risk for amiodarone, additional caution would be needed in interpreting the mortality estimates from this indirect meta-analysis.

Third, although the authors of this study were primarily interested in examining the effect of these drugs in AF, it remains a concern that dronedarone has been shown to result in a >2-fold increased mortality risk in patients with left ventricular systolic dysfunction (3.8% vs. 8.1%; HR: 2.13; 95% CI: 1.07 to 4.25; p = 0.03) (16). The presence of left ventricular systolic dysfunction is common among patients with AF, which has implications for the ultimate role of these agents in clinical practice.

Fourth, it is important to note that only 1 of the 4 amiodarone trials and none of the dronedarone trials enrolled patients with highly symptomatic AF. However, elimination of symptoms due to AF is often the primary reason to attempt to restore and maintain sinus rhythm in patients with AF. Given that only 1 of the 8 trials included in this indirect meta-analysis explicitly enrolled symptomatic patients in their study inclusion criteria, we need to question whether the indications for chronic antiarrhythmic therapy in the patients evaluated in this meta-analysis are relevant to contemporary practice.

Finally, this meta-analysis was unable to evaluate the role of amiodarone or dronedarone on quality of life. Previous studies (17,18) have not shown that a rhythm control strategy using an antiarrhythmic drug improves quality of life in patients with stable symptoms. However, sinus rhythm may not have been maintained in a majority of patients in these studies. This finding is particularly important when considering that patients with symptomatic AF are primarily interested in treatments that will improve their health status and reduce symptom burden. Radiofrequency catheter ablation therapy has been shown to markedly improve quality of life and left ventricular function in patients with symptomatic AF by achieving greater rates of sinus rhythm maintenance (2,3). Should ongoing clinical trials of ablation therapy also demonstrate reductions in rates of stroke or death, the role of chronic antiarrhythmic therapy in treating AF would have to be reassessed in comparison to nonpharmacologic therapy (19).

In summary, although this study by Piccini et al. (13) does raise provocative questions regarding the effectiveness and safety of dronedarone versus amiodarone, the results are hypothesis generating and require confirmation from direct comparisons in adequately powered clinical trials. In the meantime, clinicians will need to balance whether the use of dronedarone, a less efficacious but possibly safer antiarrhythmic drug than amiodarone (in patients with-
out reduced ejection fraction), is justified for their patients with AF.

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