Comparative Efficacy of Dronedarone and Amiodarone for the Maintenance of Sinus Rhythm in Patients With Atrial Fibrillation

In ATHENA (A Trial With Dronedarone to Prevent Hospitalization or Death in Patients With Atrial Fibrillation), dronedarone was shown to reduce morbidity and cardiovascular mortality in patients with atrial fibrillation (AF) who had additional risk factors for death (1). Available antiarrhythmic drugs are limited by a lack of effect on reducing morbidity and their potential for serious proarrhythmia or extracardiac toxic effects. However, no morbidity and mortality end point trial is available for a direct comparison.

Every effort to quantify the relative efficacy and safety of dronedarone is welcome to define its role in improving the prognosis of patients with AF. In the September 15 issue of the *Journal*, (2), a meta-analysis was published showing that dronedarone is less effective than amiodarone in maintaining sinus rhythm while showing a trend toward reduced mortality and fewer adverse events.

A careful exploration, however, reveals a number of inconsistencies:

1. Particularly evident is the reported lack of efficacy of dronedarone for the prevention of recurrent AF (odds ratio: 0.79; 95% confidence interval: 0.33 to 1.87). This result is largely based on EURIDIS (EUROpean trial In atrial fibrillation or flutter patients receiving Dronedarone for the maintenance of Sinus rhythm)/ADONIS (American-Australasian trial with DronedarOne In atrial fibrillation or flutter patients for the maintenance of Sinus rhythm) trials (3) for which Piccini et al. (2) reported a trend for an increased recurrence with dronedarone (Fig. 2A of their paper [2]; odds ratio: >1). However, this is not consistent with the original publication (hazard ratio: 0.75; 95% confidence interval: 0.65 to 0.87). Piccini et al. (2), in recalculating the results, obviously falsely used the number of patients at 12 months, excluding those with a drug exposure of <5 days. This error has a direct impact on the overall reported relative efficacy of dronedarone and amiodarone, resulting in a more favorable odds ratio for amiodarone and a lower number of AF recurrences.

2. In DAFNE (Dronedarone Atrial FibrillationN study after Electrical Cardioversion) (4), 90% of 48 patients receiving placebo and 65% of 54 patients receiving dronedarone (800 mg) had recurrence of AF at 6 months. Piccini et al. (2) extrapolated these numbers to the group size of the safety population (placebo n = 66, dronedarone 800 mg n = 76), which is not feasible.

3. In ATHENA, 290 of 2,291 patients taking dronedarone and 187 of 2,313 patients taking placebo discontinued treatment because of adverse events. Piccini et al. (2) related these discontinuations to the 2,301 and 2,327 patients of the intention-to-treat population. However, 10 patients randomized to dronedarone and 14 randomized to amiodarone never received the study drug.

4. Piccini et al. (2) restricted data of GEFACA (Grupo de Estudio de Fibrilación Auricular Con Amiodarona) (5) to patients with successful cardioversion only, whereas all patients including those with unsuccessful cardioversion were considered for DAFNE.

5. In SAFE-T (Sotalol Amiodarone Atrial Fibrillation Efficacy Trial) (6), patients were not considered in whom AF recurred within the first 28 days. Therefore, the data used for the meta-analysis are likely to overestimate the effect of amiodarone on reducing the recurrence of AF.

Further to these obvious discrepancies, the Methods section fails to report whether important variables like the mean duration of follow-up; differences in the proportion of paroxysmal, persistent, and permanent atrial fibrillation; and anticoagulation use have been accounted for in the analyses.

Taken together, false aggregation of available randomized clinical trials has led to an underestimation of the true antiarrhythmic effect of dronedarone and should be corrected. However, it cannot be overemphasized that sinus rhythm maintenance in patients with AF might not translate into better outcomes and survival as demonstrated in trials like the PIAF (Pharmacological Intervention in Atrial Fibrillation) trial (7), CTAF (Canadian Trial of Atrial Fibrillation) (8), and AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) (9). Therefore, it is time for a reappraisal of end points in the treatment of AF that should focus on true patient-related benefits like hospital stays and cardiovascular and cerebrovascular events (10).

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References:
I read with interest the study by Piccini et al. (1) that evaluated presenting these data as percentages (1). It is also possible that the number of patients in line 2 also is a denominator, and absolute represents the denominator for the analysis that follows, much like the trial’s publication (3). The numerators are supposed to represent the patient population, but it is inconsistent with the results of EURIDIS to assume that they represent the number of patients with recurrent AF. The same number sources are used for ADONIS. This artificially makes dronedarone seem the same as placebo in terms of AF recurrence rate at 1 year, a finding that significantly differs from the data in Table 2 and the Kaplan-Meier plots in Figure 2 (3).

While awaiting clarification from the authors of EURIDIS and ADONIS, there seems to be an error here that creates an overly negative conclusion as to the effect of dronedarone. After all, dronedarone has already been demonstrated in several studies to be superior to placebo (3,4) and not equal to it, as is suggested by the article by Piccini et al. (1).

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doi:10.1016/j.jacc.2009.11.045


Dronedarone Is Superior to Placebo
The Case for Optimism

I read with interest the study by Piccini et al. (1) that evaluated dronedarone for treating atrial fibrillation (AF). I agree with the primary conclusion that amiodarone is more effective than dronedarone for maintenance of sinus rhythm, as would be expected on the basis of the DIONYSOS (Efficacy and Safety of Dronedarone versus Amiodarone for the Maintenance of Sinus Rhythm in Patients with Atrial Fibrillation) trial (2). However, I have concern about the dronedarone data that might have mistakenly led to an overly negative appraisal of its effect.

In Figure 2A of the paper (1), the authors present an odds ratio plot for EURIDIS (EUROpean trial In atrial fibrillation or flutter patients receiving Dronedarone for the maintenance of Sinus rhythm) and ADONIS (American-Australasian trial with Dronedarone In atrial fibrillation or flutter patients for the maintenance of Sinus rhythm) (3). The data as presented suggest that placebo had efficacy comparable to dronedarone in these studies, which directly contradicts the studies’ conclusions. The answer to this inconsistency lies in the supporting data to the right of the odds ratio plot. For EURIDIS, the denominators of 411 and 201 patients/treatment arm come from the second line of Table 2 of the trial’s publication (3). The numerators are supposed to represent the number of patients with recurrent AF and are also taken from Table 2, 5th line of data (1).

These numbers do not make sense as representing the number of patients with recurrent AF at 1 year. They would correspond to 74.7% (307 of 411) and 73.6% (148 of 201) with recurrent AF at 1 year for dronedarone and placebo, respectively, and thus would show no difference between the 2 treatments. The actual reported recurrence rates of AF at 1 year (Table 2, line 3 [1]) are 67.1% and 77.5% for dronedarone and placebo, respectively. Instead, I believe that the number of patients presented in line 5 of the table likely represents the denominator for the analysis that follows, much like the number of patients in line 2 also is a denominator, and absolute numbers of patients with recurrent AF are not specified, favoring presenting these data as percentages (1). It is also possible that the numbers in line 5 present some other subselection of the total patient population, but it is inconsistent with the results of EURIDIS to assume that they represent the number of patients with recurrent AF. The same number sources are used for ADONIS. This artificially makes dronedarone seem the same as placebo in terms of AF recurrence rate at 1 year, a finding that significantly differs from the data in Table 2 and the Kaplan-Meier plots in Figure 2 (3).

While awaiting clarification from the authors of EURIDIS and ADONIS, there seems to be an error here that creates an overly negative conclusion as to the effect of dronedarone. After all, dronedarone has already been demonstrated in several studies to be superior to placebo (3,4) and not equal to it, as is suggested by the article by Piccini et al. (1).

REFERENCES

Reply

We appreciate the opinions of Dr. Lewalter regarding our methodology (1), particularly the use of intention-to-treat populations. The meta-analysis was constructed with conservative assumptions to reduce the risk of type I error. From this perspective, when estimating potential differences among treatments, biases that make the treatments seem more similar (including crossovers or failure to receive treatment) are conservative assumptions. Intention-to-treat provides the best pragmatic estimate of a given therapeutic strategy (in this case, therapy with dronedarone vs. amiodarone) (2). Often disagreement arises over the exact definition of intention-to-treat in an individual trial. In our meta-analysis we attempted to include patients in the denominator according to treatment allocation at the time of randomization.

Although the primary end point in EURIDIS (EUROpean trial In atrial fibrillation or flutter patients receiving Dronedarone for the maintenance of Sinus rhythm) and ADONIS (American-Australasian trial with Dronedarone In atrial fibrillation or flutter patients for the maintenance of Sinus rhythm) (3) was the time to recurrence of atrial fibrillation (AF), in our analysis the primary efficacy end point was recurrent AF at follow-up. This approach was...