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EDITORIAL COMMENT

Dronedarone

"Real-World" Data Vis-à-Vis Data From Randomized Clinical Trials*

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Dronedarone is an antiarrhythmic drug developed for therapy of atrial fibrillation (AF) that is structurally related to amiodarone but has been the object of several molecular modifications in an attempt to reduce its toxicity and improve its pharmacokinetic properties (1,2). The most significant structural changes are the removal of iodine and the addition of a methane-sulfonyl group. The removal of iodine should result in freedom from the iodine-related organ toxicity of amiodarone, and the second molecular change is thought to decrease lipophilicity, thus shortening the half-life of the drug and reducing its accumulation in tissue. The compound shares the class I to IV antiarrhythmic properties of amiodarone and has been explored for the treatment of a broad range of patients with AF (3,4). In fact, more than 9,600

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AF patients have been enrolled in randomized controlled trials of dronedarone (5), which have confirmed good tolerability and a lack of significant proarrhythmic effects of the compound. The ATHENA trial (A Trial With Dronedarone to Prevent Hospitalization or Death in Patients With Atrial Fibrillation) randomized patients with paroxysmal or persistent AF to dronedarone or placebo and represents the largest AF trial (4,628 patients) ever conducted with an antiarrhythmic drug (6). It demonstrated a significant reduction in cardiovascular-related hospital stays or death. Mainly on the basis of the results of this trial, the drug was approved by authorities in various jurisdictions and became part of the algorithms of major guidelines for the treatment of AF (7,8). Contraindications for the use of dronedarone were based on the observations made in 2 large studies: The ANDROMEDA study (Antiarrhythmic Trial with Dronedarone in Moderate to Severe CHF Evaluating Morbidity Decrease) (9) in patients with recently decompensated heart failure (and without a requirement that the patients have AF at baseline) and the PALLAS trial (Permanent Atrial fibriLLAtion Outcome Study Using Dronedarone on Top of Standard Therapy) (10) in patients with permanent AF (who have never before been the focus of a prospective study using antiarrhythmic drugs). Both of these trials had to be terminated because of increased mortality and cardiovascular events associated with dronedarone (9,10). In addition, after drug approval, there were 2 reports about severe hepatocellular liver injury in patients exposed to dronedarone (11), which resulted in new regulatory labeling of the drug that was more restrictive in Europe than in the United States.

These diverging trial results and safety concerns led to extensive debates about the clinical utility of dronedarone. Today, more than 1 million patients have been exposed to dronedarone worldwide, which probably reflects the need for new antiarrhythmic drugs to treat the increasing number of patients afflicted with symptomatic AF.

In this issue of the *Journal*, Friberg (12) reports data from 4,856 Swedish patients with symptomatic, nonpermanent AF who were exposed to dronedarone. They were compared with 170,139 control patients with AF who had not received the drug during the period from May 2010 to December 2012. The analyses were based on the previously validated Swedish National Patient Register and the Swedish Prescribed Drug Register. By linking these 2 registries, exposure times to dronedarone and other antiarrhythmic drugs were estimated and mortality/morbidity data were calculated over a mean follow-up period of 1.6 years. Patients exposed to dronedarone were younger and healthier than AF patients in the control group, had tried more antiarrhythmic drugs previously, and more often used anticoagulation therapy. There was an annual mortality rate of 1.3% in dronedarone patients compared with 14% in the control group. Even after adjustment for many pertinent baseline variables and after propensity score matching, mortality with dronedarone remained lower than that of other AF patients (hazard ratio: 0.41; 95% confidence interval: 0.33 to 0.51). The selection of truly low-risk AF patients for therapy with dronedarone is further indicated by a lower mortality than expected from the general population (standardized mortality ratio: 0.67; 95% confidence interval: 0.55 to 0.78). Finally, the risk of severe liver disease was not increased in the dronedarone group.

The results of this study need to be interpreted in the light of the results of the aforementioned randomized clinical trials, with special emphasis on 3 questions: Are the results valid? What is the main message? What are the clinical implications of the findings?

First, the results of the study appear valid. The analyses are based on data from previously validated national registries that included a large number of patients who were treated with dronedarone according to current

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guidelines (7,8). More than 170,000 AF patients receiving other often-used antiarrhythmic drugs served as a control population. The data were analyzed by appropriate statistical methodology aimed at accounting for as many confounders as possible, for instance, by performing propensity score matching. Important limitations of the data were addressed adequately. Among those, uncertainties about discontinuation of dronedarone and hidden confounders that could not be corrected for are the most important.

Second, there is a clear message provided to physicians taking care of patients with AF. The main message is that "dronedarone, as prescribed to AF patients in Sweden, has not exposed patients to increased risks of death or liver disease" (12). The author should be complimented for undertaking the effort to pinpoint the safety of dronedarone in everyday clinical practice when used according to current recommendations (7,8). In this respect, these "real-world" data are a valuable addition to those stemming from the randomized controlled clinical trials, particularly after the conclusion of a clinical drug development program. In accordance with a previous meta-analysis (13), the present findings put the mortality risk of dronedarone in some perspective compared with that of patients exposed to other antiarrhythmic drugs. Although comparisons of survival rates with various drugs on the basis of registry data are of somewhat limited value because of the nonrandomized selection of patients, it is reassuring that the survival rate of patients treated with dronedarone was, at the very least, not inferior to rates observed in subjects treated with sotalol or propafenone, that is, drugs that are also administered predominantly to patients with preserved left ventricular function.

Third, the present observations can be viewed as an important endorsement of defining the target population for which there appears to be the most favorable risk-benefit ratio for dronedarone (7,8): Patients with non-permanent AF who are younger, live an active life, and have only little to moderate structural heart disease and hence preserved left ventricular function. Although amiodarone is clearly superior with respect to maintaining sinus rhythm compared with dronedarone (14), amiodarone was associated with the worst survival rate in the present analysis, most likely because amiodarone is usually reserved for therapy in patients with advanced structural heart disease, but certainly also because of its organ toxicity. It appears reasonable, therefore, to use dronedarone in this population as a first-line drug, particularly because the compound has been shown to reduce rates of AF-related hospital stays significantly in this population (6).

Finally, can we expect to see more data on dronedarone from controlled clinical trials? There is evidence from the basic laboratory that the combination of low-dose dronedarone and ranolazine, a drug originally developed as an antianginal drug, significantly improves the antiarrhythmic efficacy of either drug alone (15). Currently, HARMONY (A Study to Evaluate the Effect of Ranolazine and Dronedarone When Given Alone and in Combination in Patients With Paroxysmal Atrial Fibrillation) is evaluating the clinical efficacy of this combination in pacemaker patients with AF (16). In summary, therefore, there is more to learn about the ultimate role of dronedarone in treating patients with AF, both from randomized controlled trials and probably from real-world data as well.

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