

## New Pharmacological Options for Patients With Atrial Fibrillation: The ATHENA Trial

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Atrial fibrillation is a growing epidemic in Western countries with an estimated prevalence of 3.8% of the population over 60 years of age and 9% over 80 years.<sup>1</sup> Arrhythmia not only carries prognostic implications,<sup>2</sup> but also represents a significant economic burden. For instance, hospitalizations for atrial fibrillation in the United States of America have increased 2- to 3-fold over the past 2 decades.<sup>3</sup> Despite advances in nonpharmacological treatment of atrial fibrillation, notably catheter ablation, pharmacological therapy continues to be the mainstay of treatment. Because catheter ablation is an invasive, time-consuming procedure which carries a significant risk, particularly in elderly patients with or without concomitant structural heart disease,<sup>4</sup> most elderly and older patients with atrial fibrillation are not suitable for this procedure. On the other hand, currently available antiarrhythmic drugs are limited by lack of efficacy or by adverse effects in many instances. For instance, class I antiarrhythmic drugs are suitable for treatment of atrial fibrillation in patients with minimal or no structural heart disease. However, in individuals with significant underlying heart disease, particularly coronary disease, these drugs are not allowed due to potential proarrhythmic drug effects. Current guidelines also discourage their use in patients with left ventricular hypertrophy. In contrast, amiodarone is highly effective in maintaining sinus rhythm after cardioversion and has few cardiac adverse effects. The use of this compound, however, is associated with the frequent occurrence of extracardiac (ie, thyroid, pulmonary, or cutaneous) adverse effects, which limits its use in many patients. Accordingly, there is a need for safer, more efficacious antiarrhythmic drugs.

Dronedarone is one of these new compounds developed for treatment of atrial fibrillation. The drug is a benzofuran derivative structurally related to amiodarone but free of iodine and with a sulfonamide group placed on the benzofuran ring. The electrophysiologic properties of dronedarone are very similar to those of amiodarone, which is presently the most effective drug to maintain sinus rhythm (SR) in patients with atrial fibrillation. Similar to amiodarone, dronedarone demonstrates electrophysiologic characteristics belonging to all 4 Vaughan-Williams classes: it blocks sodium channels, shows noncompetitive antiadrenergic activity, prolongs action potential and refractory periods, and has calcium antagonist properties.<sup>5,6</sup> However, the level and the composition of ion-channel blockade are somewhat different from its parent compound. Dronedarone is effective in experimental models of atrial fibrillation, ventricular tachycardia, and ventricular fibrillation. Its terminal half-life is approximately 20 to 25 hours, making handling the drug much easier compared to amiodarone. Dronedarone has been subjected to a careful clinical evaluation program<sup>7</sup> based upon which a large outcome trial has been designed, the ATHENA trial (A placebo-controlled, double-blind, parallel arm Trial to assess the efficacy of dronedarone 400 mg bid for the prevention of cardiovascular Hospitalization or death from any cause in patiENTs with Atrial fibrillation/atrial flutter). ATHENA is a new type of atrial fibrillation trial and its results have been recently published.<sup>8</sup>

ATHENA is the first large atrial fibrillation trial which does not use any "conventional" endpoint directly related to atrial fibrillation, such as prevention of recurrent atrial fibrillation, time to first atrial fibrillation recurrence, atrial fibrillation burden, or others. This randomized clinical trial uses, for the first time, only the combined endpoint of all-cause mortality and rehospitalization for cardiovascular causes. The reason to choose this endpoint is due to the fact that atrial fibrillation represents an increasing socioeconomic burden to Western societies, particularly as a consequence of repeated requirement of arrhythmia-related hospitalizations. Moreover, rehospitalization is one of the major reasons for a significant impairment

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in quality of life in these patients. Because it has been shown that dronedarone is not only capable of maintaining SR in many patients,<sup>9</sup> but also of controlling heart rate in case of atrial fibrillation relapses,<sup>10</sup> it was expected that treatment with this compound would result in a significant reduction in the need for rehospitalizations for cardiovascular reasons.

As of today, ATHENA is the largest study ever conducted to evaluate the efficacy and safety of a single antiarrhythmic compound in a typical atrial fibrillation population.<sup>8</sup> The study enrolled 4628 patients with paroxysmal or persistent atrial fibrillation and additional cardiovascular risk factors and randomized them to dronedarone 400 mg twice daily or to matching placebo on top of standard medical care. The mean age of the population was 72 years, half the patients were women, and the majority of patients suffered from structural heart disease. There was a high usage of angiotensin receptor blockers, beta-blockers, and statins, indicating that investigators adhered to current therapeutic guidelines. Thus, the patient population represents a typical atrial fibrillation population at increased risk for major arrhythmia-related morbidity and mortality. The average study duration was 21 months, resulting in approximately 4000 patient-years of observation.

The main result of ATHENA consisted of a highly significant substantial reduction in the primary trial outcome, time to first cardiovascular hospitalization or death (hazard ratio [HR]=0.76; 95% confidence interval [CI], 0.69-0.84;  $P<.001$ ). Moreover, all secondary outcome measures were reduced in the dronedarone compared to the placebo group. There were 139 deaths on placebo and 116 on dronedarone (HR=0.84; 95% CI, 0.66-1.08,  $P=.18$ ); there were fewer cardiac arrhythmic deaths ( $n=26$ ) in the dronedarone group compared to the placebo group ( $n=48$ ; HR=0.55; 95% CI, 0.34-0.88;  $P=.01$ ); and there were 859 cardiovascular hospitalizations on placebo compared to 675 in the dronedarone group (HR=0.75; 95% CI, 0.67-0.82;  $P<.001$ ). The dramatic reduction in the need for repeated hospitalizations for cardiovascular events was due to fewer hospital admissions for atrial fibrillation treatment and for therapy of acute coronary syndromes. The latter may be due to a number of dronedarone-induced effects, such as rate control in case of atrial fibrillation recurrence, a drug-associated reduction in blood pressure, and some vasodilating capability which the drug is known to have (similar to amiodarone).

Dronedarone was well tolerated and premature study drug discontinuation rates were similar in the groups receiving active therapy and placebo. Gastrointestinal adverse effects were more common in dronedarone patients relative to the control

group. Cardiac adverse effects were few, and only one female patient was reported to have suffered from a proarrhythmic effect (torsade de pointes tachycardia). Overall, therefore, there was a good tolerability of the drug, a finding of particular importance because subjects were treated as outpatients. A separate analysis of important patient subgroups revealed consistent beneficial effects of dronedarone for all subgroups evaluated including that of patients with a history of class II or III heart failure (979 patients).

The latter finding is of particular importance because an earlier study in patients with recently decompensated heart failure and depressed left ventricular function (ANDROMEDA; Antiarrhythmic trial with DRonedarone in Moderate to severe congestive heart failure Evaluating morbidity DecreAse) was prematurely terminated due to an excess mortality in patients receiving dronedarone.<sup>11</sup> The reasons for the discrepancy between the 2 studies are not fully elucidated. However, it seems that the different patient characteristics (stable heart failure in ATHENA, recently decompensated heart failure leading to hospitalization in ANDROMEDA) are of major importance. It has been recently demonstrated that the prognosis of patients admitted to hospital for decompensated heart failure remains poor after discharge.<sup>12</sup> Particularly in the first few weeks after discharge, mortality from heart failure remains high,<sup>12</sup> and this may be reflected by the results of ANDROMEDA. Another issue—perhaps of less importance—is the fact that dronedarone interferes with the tubular secretion of creatinine, thus leading to a slight increase in serum creatinine in approximately 15% to 20% of patients. Whereas it has been shown that the drug does not impair renal function,<sup>13</sup> the increase in serum creatinine might have led to discontinuation of angiotensin-converting enzyme inhibitors in some patients in ANDROMEDA, thereby further increasing the risk for heart failure decompensation.

What are the lessons to be learned from ATHENA? This trial is the first to prove that an antiarrhythmic drug, dronedarone, is able to reduce the incidence of major cardiovascular events, including cardiovascular mortality and stroke, in patients with paroxysmal or persistent atrial fibrillation. Virtually no other antiarrhythmic drug currently used for rhythm control has similarly well-documented safety and mortality data. At the same time, the study shows a reduction in the need for repeated hospitalization which should translate in a reduced public health care burden in the future. Given the favorable overall profile of dronedarone, the drug may be considered for first-line treatment of many patients with atrial fibrillation, for instance, patients with arterial hypertension, coronary artery

disease, or stable class II/III heart failure. In patients with unstable hemodynamic status, however, dronedarone should not be administered.

Finally, ATHENA is a unique study because of its primary outcome. AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) and the AF-CHF (The Atrial Fibrillation and Congestive Heart Failure) trial were pivotal studies because they showed that prevention of atrial fibrillation is not necessarily beneficial.<sup>14,15</sup> In both trials, reduction of atrial fibrillation did not reduce mortality or stroke. This indicates that for a new antiarrhythmic drug to gain acceptance it must show benefits beyond merely reducing atrial fibrillation recurrences. In ATHENA, dronedarone has been clearly shown to reduce an important outcome of major relevance to patient well-being, cardiovascular hospitalization. In doing so, ATHENA has clearly established a new paradigm for antiarrhythmic drug development.

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