Effect of Dronedarone on Cardiovascular Events in Atrial Fibrillation

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BACKGROUND
Dronedarone is a new antiarrhythmic drug that is being developed for the treatment of patients with atrial fibrillation.

METHODS
We conducted a multicenter trial to evaluate the use of dronedarone in 4628 patients with atrial fibrillation who had additional risk factors for death. Patients were randomly assigned to receive dronedarone, 400 mg twice a day, or placebo. The primary outcome was the first hospitalization due to cardiovascular events or death. Secondary outcomes were death from any cause, death from cardiovascular causes, and hospitalization due to cardiovascular events.

RESULTS
The mean follow-up period was 21±5 months, with the study drug discontinued prematurely in 696 of the 2301 patients (30.2%) receiving dronedarone and in 716 of the 2327 patients (30.8%) receiving placebo, mostly because of adverse events. The primary outcome occurred in 734 patients (31.9%) in the dronedarone group and in 917 patients (39.4%) in the placebo group, with a hazard ratio for dronedarone of 0.76 (95% confidence interval [CI], 0.69 to 0.84; P<0.001). There were 116 deaths (5.0%) in the dronedarone group and 139 (6.0%) in the placebo group (hazard ratio, 0.84; 95% CI, 0.66 to 1.08; P=0.18). There were 63 deaths from cardiovascular causes (2.7%) in the dronedarone group and 90 (3.9%) in the placebo group (hazard ratio, 0.71; 95% CI, 0.51 to 0.98; P=0.03), largely due to a reduction in the rate of death from arrhythmia with dronedarone. The dronedarone group had higher rates of bradycardia, QT-interval prolongation, nausea, diarrhea, rash, and an increased serum creatinine level than the placebo group. Rates of thyroid- and pulmonary-related adverse events were not significantly different between the two groups.

CONCLUSION
Dronedarone reduced the incidence of hospitalization due to cardiovascular events or death in patients with atrial fibrillation. (ClinicalTrials.gov number, NCT00174785.)
Atrial Fibrillation is the most common type of cardiac arrhythmia requiring medical care, with a prevalence of almost 1% in the adult population in the United States.\(^1\) Its prevalence increases with age, affecting 3.8% of the U.S. population over 60 years of age and 9.0% of the population older than 80 years. Over the past two decades, hospitalizations for atrial fibrillation in the United States have increased by a factor of two to three, resulting in a substantial public health burden.\(^2\) Despite advances in nonpharmacologic therapy,\(^3\) many symptomatic patients receive medical treatment for rhythm control. Currently available antiarrhythmic agents are limited by either their modest efficacy or their potential for serious ventricular proarrhythmia or extracardiac toxic effects. Furthermore, no currently available antiarrhythmic treatment has been shown to reduce the rate of hospitalization due to cardiovascular events in patients with atrial fibrillation.

Dronedarone is a benzofuran derivative with an electropharmacologic profile resembling that of amiodarone but with different relative effects on individual ion channels.\(^4\)–\(^7\) The structural changes made to amiodarone to produce dronedarone include the removal of iodine and the addition of a methane–sulfonyl group.\(^8\) The latter change decreases lipophilicity, thus shortening the half-life (to approximately 24 hours) and reducing accumulation in tissue. These molecular changes were made with the intention of reducing the risk of amiodarone-associated thyroid-related and pulmonary disease.\(^7\)–\(^8\) Dronedarone is hepatically metabolized and excreted in the feces.

In two randomized, controlled trials involving 1,237 patients with atrial fibrillation or flutter, dronedarone was shown to be more effective than placebo in maintaining sinus rhythm and in controlling the ventricular rate during recurrences of atrial fibrillation.\(^9\) At 12 months of follow-up, rates of pulmonary, thyroid-related, and hepatic adverse effects were not significantly greater with dronedarone than with placebo. However, another study of dronedarone in patients with advanced symptomatic congestive heart failure, but without atrial fibrillation, was prematurely terminated because of an excess of deaths among patients taking dronedarone.\(^10\)

ATHENA (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) was designed to determine whether dronedarone would reduce the rate of the composite outcome of hospitalization due to cardiovascular events or death in patients with atrial fibrillation.

**Methods**

Details of the study protocol have been published previously.\(^11\) ATHENA was a randomized, double-blind, placebo-controlled trial conducted according to the Declaration of Helsinki at 551 centers in 37 countries. The institutional review board at each site approved the study, and all patients gave written informed consent. Enrollment of patients commenced in June 2005 and was completed on December 30, 2006.

The trial was sponsored by Sanofi-Aventis and designed by the steering committee (see the Supplementary Appendix, available with the full text of this article at NEJM.org) in collaboration with the sponsor. Data collection and management and statistical analysis were performed by the sponsor. The first draft of the report was written by the principal investigator (an academic author), and subsequent drafts were revised and edited by all the authors, who vouch for the accuracy and completeness of the data.

**Study Population**

Patients with paroxysmal or persistent atrial fibrillation or flutter were eligible if they met at least one of the following requirements: age of at least 70 years; arterial hypertension (with ongoing therapy involving at least two antihypertensive drugs of different classes); diabetes mellitus; previous stroke, transient ischemic attack, or systemic embolism; left atrial diameter greater than or equal to 50 mm, as measured on M-mode echocardiography; and left ventricular ejection fraction less than or equal to 40%. For each patient, a 12-lead electrocardiogram (ECG) showing atrial fibrillation or flutter and obtained within 6 months before randomization had to be available. A second 12-lead ECG within the same period had to show sinus rhythm.

During the course of the trial, overall mortality figures were lower than expected. Therefore, the steering committee elected to change the inclusion criteria to enrich the risk profile of the overall study population. On the basis of the re-
vised criteria, patients 75 years of age or older were eligible, whether or not they had any previously specified risk factors, but patients 70 years of age or older were eligible only if they had one or more of the other risk factors. Patients younger than 70 years of age were no longer eligible. This protocol amendment was implemented on March 8, 2006.

EXCLUSION CRITERIA

Patients were ineligible for participation in the trial if they had any of the following cardiac conditions: permanent atrial fibrillation; an unstable hemodynamic condition (i.e., decompensated heart failure within the previous 4 weeks); New York Heart Association (NYHA) class IV congestive heart failure; planned major surgery; acute myocarditis; bradycardia with a heart rate of less than 50 beats per minute or a PR interval of more than 0.28 second; or previous clinically significant sinus-node disease, if the patient was not currently being treated with a pacemaker. General (noncardiac) exclusion criteria were as follows: any severe noncardiac illness limiting life expectancy; pregnancy, breast-feeding, or lack of adequate birth control among women of childbearing potential; a calculated glomerular filtration rate at baseline of less than 10 ml per minute; a potassium level of less than 3.5 mmol per liter, if not currently being corrected; and a requirement for concomitant medication that was prohibited (i.e., other class I or III antiarrhythmic drugs).

ENROLLMENT AND FOLLOW-UP

Patients could be enrolled while in sinus rhythm (if conversion had occurred either spontaneously or after electrical or pharmacologic cardioversion). Patients also could be enrolled while in atrial fibrillation or flutter, in which case they would be expected to undergo cardioversion after appropriate anticoagulation. Patients were randomly assigned, in a 1:1 ratio, to receive dronedarone, 400 mg twice a day, or placebo. Randomization was stratified according to center and by the presence or absence of atrial fibrillation or flutter at the time of randomization.

The follow-up schedule called for clinical evaluations at days 7 and 14 and at months 1, 3, 6, 9, and 12 and every 3 months thereafter. The trial was planned to have a minimum follow-up duration of 12 months; all patients were followed until the common end date of December 30, 2007.

STUDY OUTCOMES

The primary study outcome was the first hospitalization due to cardiovascular events or death from any cause. Any unplanned hospitalization (i.e., admission with an overnight stay in the hospital) was classified by the investigator as a hospitalization due to either cardiovascular or noncardiovascular causes.11 Deaths were categorized by means of blinded adjudication, according to a modified Hinkle and Thaler classification,12 into four categories: death from cardiac arrhythmia, death from nonarrhythmic cardiac causes, death from noncardiac vascular causes, and death from noncardiovascular causes. This classification scheme has been validated previously.13-15 Secondary study outcomes were death from any cause, death from cardiovascular causes, and first hospitalization due to cardiovascular events.

STATISTICAL ANALYSIS

On the basis of two large efficacy trials of dronedarone in patients with atrial fibrillation,8 the 1-year rate of hospitalization due to cardiovascular events in the placebo group was estimated to be 20%, a figure also reported in the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study.16 In order to have a statistical power of 80% to detect a 15% reduction with dronedarone in the rate of the primary outcome (under the exponential model at a two-sided alpha level of 0.05), 970 primary outcome events were estimated to be required. We aimed to observe approximately 260 deaths, which would allow for the estimate of the relative risk of death to be made with a precision of ±0.13 within an inclusion period of 1.5 years. To achieve these objectives, we anticipated that a minimum follow-up period of 1 year and a maximum follow-up period of 2.5 years (mean, 1.7), with enrollment of 2150 patients per group (4300 in total), would be necessary.

Prespecified analyses were performed according to the intention-to-treat principle. The times to the primary outcome of hospitalization due to cardiovascular events or death and to secondary outcomes were estimated with the use of the Kaplan–Meier method and compared by means of the log-rank test. All P values were two-tailed.

An independent data and safety monitoring board reviewed the study data regularly. One formal interim analysis was performed when half the
originally expected primary outcome events had occurred.

RESULTS

A total of 4628 patients were enrolled, of whom 2301 were randomly assigned to receive dronedarone and 2327 to receive placebo (Fig. 1). The two groups were well matched with respect to baseline characteristics (Table 1). Overall, the mean age was 71.6 years, and 46.9% of participants were female. Twenty-five percent of patients had atrial fibrillation at randomization. The predominant underlying cardiovascular disease was hypertension, and there was evidence of structural heart disease in the majority of patients (59.6%) for whom the data were available. The left ventricular ejection fraction was quantified in 4544 patients, of whom 179 (3.9%) and 540 (11.9%) had an ejection fraction of less than 35% and less than 45%, respectively. There was a history of NYHA heart failure in 979 patients (21.2%): class II failure in 779 (17.1%) and class III in 200 (4.4%).

The mean (±SD) duration of follow-up among all patients was 21±5 months. The minimum follow-up duration was 1 year, and the maximum 2.5 years.

PRIMARY OUTCOME

Among patients assigned to receive dronedarone, 734 (31.9%) had a primary outcome event, including 675 (29.3%) with a hospitalization due to cardiovascular events and 59 (2.6%) who died. In the placebo group, 917 patients (39.4%) had a primary outcome event. These included 859 (36.9%) with a first hospitalization due to cardiovascular events and 58 (2.5%) who died before hospitalization. The hazard ratio for the primary outcome in the dronedarone group was 0.76 (95% confidence interval [CI], 0.69 to 0.84; P<0.001) (Table 2 and Fig. 2A). Figure 3 shows that the effect of dronedarone on the primary outcome was consistent across a variety of important subgroups (which were not prespecified).

FATAL OUTCOMES

Death from any cause was one of the three prespecified secondary outcomes. There were 116 deaths (in 5.0% of patients) in the dronedarone group and 139 (in 6.0%) in the placebo group.
(hazard ratio, 0.84; 95% CI, 0.66 to 1.08; P = 0.18) (Table 2 and Fig. 2B). Death was classified, on the basis of blinded adjudication, as being cardiovascular in origin in 63 patients (2.7%) in the dronedarone group and 90 (3.9%) in the placebo group (hazard ratio, 0.71; 95% CI, 0.51 to 0.98; P = 0.03) (Table 2 and Fig. 2C). There were 26 deaths from cardiac arrhythmia (in 1.1% of patients) in the dronedarone group and 48 (in 2.1%) in the placebo group (hazard ratio, 0.55; 95% CI, 0.34 to 0.88; P = 0.01) (Table 2).

**HOSPITALIZATION DUE TO CARDIOVASCULAR EVENTS**

In the dronedarone group, 675 patients (29.3%) had a first hospitalization due to cardiovascular...
events, as compared with 859 patients (36.9%) in the placebo group (hazard ratio, 0.74; 95% CI, 0.67 to 0.82; <0.001) (Table 2 and Fig. 2D). This reduction in the rate of hospitalization due to cardiovascular events was driven mainly by a reduction in the number of hospitalizations for atrial fibrillation. There were no significant differences between the two groups in the number of hospitalizations for heart failure or for ventricular arrhythmia or nonfatal cardiac arrest. There were also significantly fewer hospitalizations for an acute coronary syndrome in the dronedarone group (Table 2). When all outcome events (hospitalization due to any cardiovascular event or death from any cause) during the study period were considered, the effect of dronedarone was consistent: 1253 patients (54.5%) had an event in the dronedarone group, as compared with 1668 (71.7%) in the placebo group (hazard ratio, 0.76; 95% CI, 0.68 to 0.84; <0.001).

**Study Discontinuation and Adverse Events**

The study drug was prematurely discontinued in 696 (30.2%) of patients receiving dronedarone, as compared with 716 (30.8%) of those receiving placebo. The main reasons were adverse events (in 12.7% of patients in the dronedarone group vs. 8.1% in the placebo group), subject’s request (7.5% in each group), and other reasons (9.4% in the dronedarone group vs. 14.4% in the placebo group).

The incidence of important treatment-emergent adverse events and laboratory abnormalities is shown in Table 3. Bradycardia, QT-interval prolongation, diarrhea, nausea, rash, and an increase in the serum creatinine level were significantly more common in the dronedarone group than in the placebo group. Pulmonary symptoms, interstitial lung disease, and abnormalities of thyroid function were not significantly more common with dronedarone than with placebo.

One case of torsades de pointes tachycardia was reported in a 66-year-old female patient receiving dronedarone. After she had been resuscitated from out-of-hospital ventricular fibrillation, an episode of torsades de pointes was documented in the in-
In this trial, the use of dronedarone significantly reduced the risk of hospitalization due to cardiovascular events or death in patients with paroxysmal or persistent atrial fibrillation or flutter. A significant reduction in death from any cause was not demonstrated (hazard ratio for dronedarone vs. placebo, 0.84; P = 0.18). However, there was a significant reduction in the rate of the prespecified secondary outcome of death from cardiovascular causes. The rate of death from cardiac arrhythmia was also significantly reduced with dronedarone.
In two previous randomized studies, dronedarone was reported to be more effective than placebo for maintenance of sinus rhythm. Specifically, the time to first recurrence of atrial fibrillation was increased from a median of 53 days in the control group to 116 days in the dronedarone group. Also, the drug decreased the mean ventricular rate during the recurrence of atrial fibrillation, from 117 to 103 beats per minute (P<0.001). It is likely that both prevention of recurrent atrial fibrillation and rate control during the arrhythmia were responsible for reducing the rate of hospitalization due to cardiovascular events in the present trial.

Another previous study, the Anti-arrhythmic Trial with Dronedarone in Moderate to Severe CHF Evaluating Morbidity Decrease (ANDROMEDA), was terminated prematurely because of increased mortality with dronedarone. Patients enrolled in ANDROMEDA had symptomatic congestive heart failure, a left ventricular ejection fraction of 35% or less, and recent hospitalization with new or worsening heart failure. The excess mortality was predominantly related to congestive heart failure.

The difference in outcome between ATHENA and ANDROMEDA may be a consequence of the fact that ANDROMEDA enrolled only patients with advanced heart failure and recent decompensation leading to hospitalization. In contrast, ATHENA specifically excluded patients who had either hemodynamic instability or severe (NYHA class IV) heart failure. It is therefore possible that dronedarone...
Table 3. Selected Adverse Events and Laboratory Abnormalities in Patients Who Received the Study Drug.

<table>
<thead>
<tr>
<th>Event*</th>
<th>Dronedarone (N=2291)</th>
<th>Placebo (N=2313)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any TEAE</td>
<td>1649 (72.0)</td>
<td>1603 (69.3)</td>
<td>0.048</td>
</tr>
<tr>
<td>Cardiac events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>260 (11.3)</td>
<td>221 (9.6)</td>
<td>0.048</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>81 (3.5)</td>
<td>28 (1.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>QT-interval prolongation</td>
<td>40 (1.7)</td>
<td>14 (0.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Respiratory events</td>
<td>332 (14.5)</td>
<td>337 (14.6)</td>
<td>0.97</td>
</tr>
<tr>
<td>Cough</td>
<td>83 (3.6)</td>
<td>83 (3.6)</td>
<td>1.00</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>120 (5.2)</td>
<td>97 (4.2)</td>
<td>0.10</td>
</tr>
<tr>
<td>Interstitial lung disease‡</td>
<td>5 (0.2)</td>
<td>5 (0.2)</td>
<td>1.00</td>
</tr>
<tr>
<td>Gastrointestinal events</td>
<td>600 (26.2)</td>
<td>508 (22.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>223 (9.7)</td>
<td>144 (6.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nausea</td>
<td>122 (5.3)</td>
<td>72 (3.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Abnormal liver-function test§</td>
<td>12 (0.5)</td>
<td>14 (0.6)</td>
<td>0.84</td>
</tr>
<tr>
<td>Endocrine events</td>
<td>25 (1.1)</td>
<td>25 (1.1)</td>
<td>1.00</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>11 (0.5)</td>
<td>6 (0.3)</td>
<td>0.23</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>6 (0.3)</td>
<td>7 (0.3)</td>
<td>1.00</td>
</tr>
<tr>
<td>Neurologic events</td>
<td>373 (16.3)</td>
<td>381 (16.5)</td>
<td>0.87</td>
</tr>
<tr>
<td>Dizziness</td>
<td>169 (7.4)</td>
<td>152 (6.6)</td>
<td>0.30</td>
</tr>
<tr>
<td>Headache</td>
<td>70 (3.1)</td>
<td>87 (3.8)</td>
<td>0.19</td>
</tr>
<tr>
<td>Skin-related events</td>
<td>237 (10.3)</td>
<td>176 (7.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>Rash</td>
<td>77 (3.4)</td>
<td>47 (2.0)</td>
<td>0.006</td>
</tr>
<tr>
<td>Urticaria</td>
<td>11 (0.5)</td>
<td>9 (0.4)</td>
<td>0.66</td>
</tr>
<tr>
<td>Serum creatinine increase</td>
<td>108 (4.7)</td>
<td>31 (1.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any serious TEAE</td>
<td>456 (19.9)</td>
<td>489 (21.1)</td>
<td>0.31</td>
</tr>
<tr>
<td>Cardiac events</td>
<td>15 (0.7)</td>
<td>15 (0.6)</td>
<td>1.00</td>
</tr>
<tr>
<td>Respiratory events</td>
<td>41 (1.8)</td>
<td>45 (1.9)</td>
<td>0.74</td>
</tr>
<tr>
<td>Gastrointestinal events</td>
<td>81 (3.5)</td>
<td>68 (2.9)</td>
<td>0.28</td>
</tr>
<tr>
<td>Endocrine events</td>
<td>4 (0.2)</td>
<td>5 (0.2)</td>
<td>1.00</td>
</tr>
<tr>
<td>Neurologic events</td>
<td>21 (0.9)</td>
<td>27 (1.2)</td>
<td>0.47</td>
</tr>
<tr>
<td>Skin-related events</td>
<td>7 (0.3)</td>
<td>6 (0.3)</td>
<td>0.79</td>
</tr>
<tr>
<td>Increase in serum creatinine</td>
<td>5 (0.2)</td>
<td>1 (&lt;0.1)</td>
<td>0.12</td>
</tr>
<tr>
<td>Premature discontinuation of study drug because of an adverse event</td>
<td>290 (12.7)</td>
<td>187 (8.1)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* A treatment-emergent adverse event (TEAE) was defined as an adverse event occurring between first dose of the study drug and 10 days after the last dose. A serious TEAE was one that resulted in death; was life-threatening; required or prolonged hospitalization; was a medically important event; resulted in persistent, clinically significant disability or incapacity; or was a congenital anomaly or birth defect. Any adverse event was an adverse event occurring before 10 days after the last dose of the study drug.

† P values were calculated with the use of Fisher’s exact test.

‡ Interstitial lung disease includes the following preferred terms according to the Medical Dictionary for Regulatory Activities: interstitial lung disease, pneumonitis, pulmonary fibrosis, lung infiltration, and pulmonary toxicity.

§ Results of liver-function tests were coded with the use of hepatobiliary-investigation high-level group terms in the adverse-event database. No scheduled liver-function tests were performed in this study.
dronedarone increases cardiovascular mortality among patients with advanced and recently decompensated congestive heart failure but reduces cardiovascular mortality in patients with less severe heart failure. In the present trial, 21% of patients did have a history of congestive heart failure with NYHA class II or III symptoms, and 12% had a left ventricular ejection fraction less than 45%. Subgroup analysis indicated that patients receiving dronedarone who had congestive heart failure had a benefit similar to that of the entire group. However, given the results of ANDROMEDA, dronedarone should not be initiated in patients with severe heart failure and left ventricular dysfunction.

Adverse events occurring significantly more frequently with dronedarone than with placebo included bradycardia, QT-interval prolongation, diarrhea, nausea, rash, and an increase in the serum creatinine level. The increase in creatinine level, which was also noted in ANDROMEDA, may not reflect a deterioration in renal function. Dronedarone reduces renal creatinine clearance by about 18%, without evidence of an effect on glomerular filtration rate, apparently as a result of a specific partial inhibition of tubular organic-cation transporters.17 Trial investigators were informed that a small rise in the creatinine level was expected with dronedarone and did not necessarily indicate a decline in renal function.

In this trial, no significant increase in the rates of thyroid or pulmonary disorders was seen with dronedarone. This observation may suggest that dronedarone has a more benign side-effect profile than amiodarone and that the intended benefits of the modifications in the benzofuran chemical structure were achieved. However, it is important to note that the mean follow-up for patients in the trial was only 21 months and that in many cases patients treated with amiodarone have such side effects (especially pulmonary toxic effects) later than 2 years after initiating therapy.

Another limitation of this trial is that the rate of premature discontinuation of the study drug was very high (30.2% in the dronedarone group). This may have resulted in an underestimate of the benefit of dronedarone, but it also may have limited the likelihood of demonstrating an increase in the rate of adverse events.

No antiarrhythmic agent other than dronedarone has been evaluated in a large trial involving patients with atrial fibrillation for the prevention of hospitalization due to cardiovascular events or death. Therefore, it is not possible to know the relative efficacy or safety of dronedarone as compared with other drugs for this outcome. The efficacy and tolerability of dronedarone and amiodarone as used to prevent the recurrence of atrial fibrillation are currently being evaluated in an ongoing randomized trial. In conclusion, among patients with atrial fibrillation, dronedarone was associated with a significant reduction in the rate of hospitalization due to cardiovascular events or death, as compared with placebo.

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