

# Dronedarone for atrial fibrillation: a new therapeutic agent

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**Abstract:** Atrial fibrillation is the most common of the serious cardiac rhythm disturbances and is responsible for substantial morbidity and mortality. Amiodarone is currently one of the most widely used and most effective antiarrhythmic agents for atrial fibrillation. But during chronic usage amiodarone can cause some serious extra cardiac adverse effects, including effects on the thyroid. Dronedarone is a newer therapeutic agent with a structural resemblance to amiodarone, with two molecular changes, and with a better side effect profile. Dronedarone is a multichannel blocker and, like amiodarone, possesses both a rhythm and a rate control property in atrial fibrillation. The US Food and Drug Administration approved dronedarone for atrial fibrillation on July 2, 2009. In this review, we discuss the role of dronedarone in atrial fibrillation.

**Keywords:** dronedarone, amiodarone, atrial fibrillation

## Introduction

Atrial fibrillation (AF) is the most common of the serious cardiac rhythm disturbances and is responsible for substantial morbidity and mortality. The prevalence of AF is almost 1% and it is estimated that by the year 2050, approximately 5 million subjects will have AF in the United States.<sup>1</sup> Currently, there are two major treatment strategies for AF: rate control and rhythm control. Sustained sinus rhythm is associated with an improved quality of life and improved exercise performance.<sup>2</sup>

## Rationale for dronedarone

Currently amiodarone is one of the most widely used and most effective antiarrhythmic agents<sup>2</sup> with little proarrhythmic potential.<sup>3</sup> But during chronic usage amiodarone and its active metabolite desethylamiodarone can cause some serious extra cardiac adverse effects, including effects on the thyroid.<sup>2</sup> Therefore there is a need for the development of safer and effective antiarrhythmics agents. Amiodarone is an iodinated benzofuran derivative and contains 37% of organic iodine by weight. Amiodarone itself and its high iodine content can cause subclinical to overt thyroid dysfunction, manifesting either amiodarone-induced hypothyroidism or amiodarone-induced thyrotoxicosis. About 15% to 28% of patients develop thyroid dysfunction after 2 to 3 years of therapy, a risk that increases with higher doses. Moreover, amiodarone is lipophilic because of its iodine content, thus accumulates in adipose tissue and highly perfused organs like the liver, lung, cornea, and skin. In addition, because of its long half-life of up to 100 days, high iodine levels persist for >6 months after discontinuation of the drug.<sup>4</sup>

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Dronedarone is a newer benzofuran derivative with a structural resemblance to amiodarone, with two molecular changes: it lacks the iodine moiety and it has a methane sulfonyl group that decreases lipophilicity, resulting in a shorter half-life and lower tissue accumulation. In vitro the amiodarone metabolite N-desethylamiodarone (DEA) strongly inhibited  $T_3$  binding to thyroid hormone receptor (TR), both  $TR\alpha_1$  and  $TR\beta_1$ , within the same order of magnitude, whereas the active metabolite of dronedarone N-debutyl-dronedarone (DBD) was shown to inhibit  $T_3$  binding to  $TR\alpha_1$  but much less so to  $TR\beta_1$ . This isoform selectivity may explain the effects of dronedarone on the heart (a mainly  $TR\alpha_1$  organ) and the lack of effect on the liver (a mainly  $TR\beta_1$  organ) with little effect on plasma thyroid hormone.<sup>5</sup> The steady-state serum level of dronedarone is achieved in 5 to 7 days. The elimination half-life of dronedarone is 24 hours. It is cleared by nonrenal mechanism. Like amiodarone, oral bioavailability is increased 2- to 3-fold when taken with food. It is well absorbed after oral administration (70% to 100%). The bioavailability is relatively low (15%) because of extensive hepatic first-pass metabolism by cytochrome P450 (CYP) 3A4 and CYP2D6, thus requiring twice-daily dosing to achieve steady-state serum levels.<sup>4</sup>

Dronedarone has been shown to exhibit even less reverse use-dependency of repolarization than that found with amiodarone, which may provide better cardiac safety.<sup>6</sup> In patch-clamp experiments in canine ventricular myocytes, 10  $\mu$ M dronedarone markedly reduced the rapid component of the delayed rectifier potassium current (97%,  $P < 0.05$ ) and the L-type calcium current (76.5%,  $P < 0.05$ ). In the same experimental study on dog myocytes, acute superfusion of dronedarone shortened the APD in Purkinje fibres (at 1 Hz from  $309.6 \pm 11.8$  to  $287.1 \pm 10.8$  ms,  $P < 0.05$ ) and reduced the incidence of early and delayed after depolarizations induced by dofetilide and strophantidine in Purkinje fibers. Chronic treatment with dronedarone for 4 weeks, unlike chronic administration of amiodarone, did not lengthen significantly the QTc interval of the electrocardiogram.<sup>7</sup>

In multicellular preparations of guinea pig ventricular cells, dronedarone (3, 10, and 30  $\mu$ M) decreased maximum rate of rise of action potential (dV/dt max) with a concentration- and frequency-dependent relationship.<sup>8</sup> Similarly, under whole-cell patch clamp on human atrial myocytes, amiodarone inhibited I (Na) by only 41% at 3  $\mu$ M while dronedarone inhibited I (Na) almost completely, by 97% at 3  $\mu$ M.<sup>9</sup> Thus dronedarone inhibits I (Na) significantly in single human atrial cells and exhibits class I antiarrhythmic properties.

In patch-clamp technique guinea pig atrial cell, dronedarone inhibited the muscarinic acetylcholine receptor-operated  $K^+$  current ( $I_{K(ACh)}$ ) either by depressing the function of  $K_{ACh}$  channel itself or associated with GTP-binding proteins. Compared with amiodarone, dronedarone is an approximately 100 times more potent inhibitor on  $I_{K(ACh)}$ . This property may be involved, at least in part, in the antiarrhythmic action of dronedarone against AF, as vagal activation plays a role in the pathophysiology of AF.<sup>10</sup>

Dronedarone is a multichannel blocker, as it decreases delayed-rectifier  $K^+$  current I (Kr), slowly activating delayed-rectifier  $K^+$  current I (Ks), and inward rectifier potassium current I (K1), L-type  $Ca^{2+}$  current I (Ca (L)) and maximum rate of rise of action potential (dV/dt max) with a concentration- and frequency-dependent relationship (I (Na)).<sup>7,8</sup> Thus dronedarone, like amiodarone, possesses both rhythm and a rate-control properties as it has class I to IV antiarrhythmic activity.

## Antiadrenergic property

In anesthetized, atropinized dogs, both amiodarone and dronedarone were shown to inhibit alpha-adrenoceptor (adrenaline)-induced increase in blood pressure to similar extents. In the same study, inhibition of beta 1-adrenoceptor (isoprenaline)-induced increase in heart rate was less marked in dronedarone than amiodarone, whereas dronedarone was more potent than amiodarone in inhibiting beta 2-adrenoceptor (isoprenaline)-induced increase in blood pressure. However, in conscious dogs, both dronedarone and amiodarone inhibited isoprenaline-induced increases in heart rate by approximately the same amount. Thus, like amiodarone, dronedarone can partially inhibit the effects of stimulation of the adrenoceptor system that may play a pivotal role in the onset of severe ventricular rhythm disturbances.<sup>11</sup> In a study on conscious dogs with healed myocardial infarction, dronedarone displayed antiadrenergic actions comparable to those of amiodarone. Both dronedarone and amiodarone significantly reduced the exercise-induced tachycardia and, at the highest dose, decreased the isoproterenol-induced tachycardia and did not impair the resting left ventricular function.<sup>12</sup>

Preclinical studies suggest that dronedarone is more efficacious in reducing ventricular arrhythmias. In a rat model, during a 20-minute period of ischemia, dronedarone significantly reduced the incidence of ventricular fibrillation (VF) from 80% to 30% ( $P < 0.05$ ) at 3 mg/kg and eliminated VF and mortality at 10 mg/kg. In contrast, amiodarone at 10 mg/kg reduced significantly only the incidence of mortality during ischemia (from 60% to 0%,  $P < 0.01$ ),

while having no significant effect on 3 mg/kg. On reperfusion (after a 5-minute period of ischemia), dronedarone reduced significantly the incidence of mortality (from 90 to 20%,  $P < 0.01$ ) at 1 mg/kg and eliminated VF and mortality when administered at 3 and 10 mg/kg. Amiodarone (10 mg/kg iv) eliminated completely reperfusion-induced VF and mortality while having no significant effect at 1 and 3 mg/kg.<sup>13</sup> Similarly in anesthetized pigs, dronedarone was more potent than amiodarone in reducing ischemia-induced ventricular arrhythmias.<sup>14</sup>

## Clinical studies (Table I)

### DAFNE trial

The Dronedarone Atrial Fibrillation study after Electrical Cardioversion (DAFNE) was the first double-blind, randomized, placebo controlled trial designed to evaluate the efficacy and safety of dronedarone.<sup>15</sup> 270 patients with persistent AF were randomly allocated to 800, 1200, 1600 mg daily doses of dronedarone or placebo in 50 centres and 11 countries. The main

analysis was conducted on 199/270 patients, who entered the maintenance phase following pharmacological cardioversion or, if unsuccessful, DC cardioversion. The primary outcome was time to first documented AF recurrence. Secondary study endpoints were spontaneous conversion of AF following randomization, heart rate in case of AF recurrence and the incidence of side effects. 6-month follow-up showed that treatment with dronedarone 800 mg significantly prolonged the time to AF recurrence with a median time to recurrence of 60 days vs 5.3 days in the placebo group (relative risk reduction 55% [95% CI, 28% to 72%]  $P = 0.001$ ).

The incidence of spontaneous conversion to sinus rhythm was associated with a significant dose-effect relationship ( $P = 0.0261$ ). Patients in the dronedarone 800, 1200, and 1600 mg groups exhibited 5.8%, 8.2%, and 14.8% conversion rates respectively, vs 3.1% on placebo. At the time of first AF recurrence, dronedarone appeared to slow the ventricular response in a dose-dependent fashion. Patients receiving 800, 1200, or 1600 mg dronedarone had their ventricular rate

**Table I** Summary of clinical trials

Trial	Subjects enrolled	Follow-up period	Main outcome	Common side effects
DAFNE <sup>15</sup>	270	6 months	First AF recurrence was 5.8% with 800 mg, 8.2% with 1200 mg and 14.8% with 1600 mg dronedarone vs 3.1% in placebo ( $P = 0.0261$ )	Gastrointestinal
EURIDIS and ADONIS <sup>16</sup>	612 in EURIDIS and 625 in ADONIS	12 months	First recurrence of AF/AFL was 64.1% with dronedarone vs 75.2% with placebo ( $P < 0.001$ )	Gastrointestinal (diarrhea)
ERATO <sup>17</sup>	174	6 months	Reduction of 11.7 beats per minute in ventricular rate at day 14 ( $P < 0.0001$ ) – this effect was sustained for the duration of trial (–8.8 beat/minute at 4 months) ( $P < 0.001$ )	Infections Mild increase in serum creatinine levels
ANDROMEDA <sup>18</sup>	627	13 months (including additional 6 months after premature discontinuation of study)	Premature termination of trial due to excess mortality related to the worsening of heart failure in dronedarone group (hazard ratio of 2.13; 95% CI 1.07 to 4.25; $P = 0.03$ )	Worsening heart failure Increase in serum creatinine levels
ATHENA <sup>21</sup>	4628	21 months	First hospitalization due to cardiovascular events or death was 31.9% in dronedarone group vs 39.4% in placebo group (hazard ratio of 0.76; 95% CI 0.69 to 0.84; $P < 0.001$ )	Gastrointestinal (diarrhea, nausea) Increase in serum creatinine levels Rash Bradycardia

**Abbreviations:** AF, atrial fibrillation; AFL, atrial flutter; CI, confidence interval.

reduced by 13.2, 19.2, and 17.8 bpm on average, respectively, compared to those on placebo ( $P = 0.0001$ ). Twenty-two (10.8%) dronedarone patients discontinued treatment due to adverse events. In the 800 mg, 1200 mg and 1600 mg dronedarone groups, the discontinuation rates were 3.9%, 7.6% and 22.6%, respectively. The most common cause of drug discontinuation was gastrointestinal side effects. Importantly no evidence of thyroid, ocular, or pulmonary toxicity was observed. There were no proarrhythmic reactions. Drug-induced QT prolongation was noticed only in the 1600 mg group and the effect of dronedarone on the QT interval remained modest. Dronedarone also proved to be hemodynamically well tolerated. Thus the DAFNE trial showed that dronedarone, at an 800 mg daily dose, appears to be effective and safe for the prevention of AF relapses after cardioversion at a 6-month follow-up.

## EURIDIS and ADONIS trials

The results of DAFNE provided promising role of dronedarone (400 mg bid) in prevention of AF recurrence and later it was evaluated by two similar double-blind, placebo-controlled, multicenter, multinational, pivotal phase III studies with similar study protocols to determine the efficacy of dronedarone (400 mg bid) for the maintenance of normal sinus rhythm after electrical, pharmacological, or spontaneous conversion of AF or AFL (atrial flutter). The European Trial in Atrial Fibrillation or Flutter Patients Receiving Dronedarone for the Maintenance of Sinus Rhythm (EURIDIS) was carried out at 65 centers in 12 European countries and the American-Australian-African Trial with Dronedarone in Atrial Fibrillation/Flutter Patients for the Maintenance of Sinus Rhythm (ADONIS) at 101 centers in USA, Canada, Australia, South Africa and Argentina.<sup>16</sup>

Male and female patients over 21 years of age were enrolled provided they had at least one episode of AF (as seen on electrocardiography) in the preceding 3 months, and were in sinus rhythm for at least 1 hour before randomization. Patients previously treated with amiodarone were permitted, and were enrolled immediately after its discontinuation. Eligible patients ( $n = 612$  in EURIDIS and  $n = 625$  in ADONIS) were randomly assigned in a 2:1 ratio to receive either 400 mg of oral dronedarone twice daily or a matching placebo for 1 year. Follow-up visits were scheduled for review of symptoms, assessment of vital signs, and performance of electrocardiography on days 7, 14, and 21 and at 2, 4, 6, 9, and 12 months. The primary endpoint was the time to the first documented recurrence of AF/AFL, defined as an episode lasting for at least 10 minutes and confirmed by

two consecutive recordings on 12-lead electrocardiography or Tran telephonic monitoring. The secondary endpoints were severity of symptoms related to AF/AFL during recordings of 12-lead electrocardiography or Tran telephonic monitoring and the mean ventricular rate during the first recurrence.

In EURIDIS, the median time to relapse was 96 days in the dronedarone group and 41 days in the placebo group and in ADONIS it was 158 days in the dronedarone group and 59 days in the placebo group. For the two trials combined, the median times to recurrence were 116 days in the dronedarone group and 53 days in the placebo group. Combining data for the two trials, at 12 months, the rates of recurrence were 64.1% in the dronedarone group and 75.2% in the placebo group (hazard ratio, 0.75; 95% CI, 0.65 to 0.87;  $P < 0.001$ ). When the data for the two trials were analyzed separately, the results were similar with reductions in the risk of AF/AFL recurrence over 1 year by 29% ( $P = 0.0059$ ) and 26% ( $P = 0.0244$ ) in EURIDIS and ADONIS, respectively. Mean ventricular rate during first AF/AFL recurrence was 102 and 104 bpm in the dronedarone group of EURIDIS and ADONIS, respectively, whereas the the corresponding rates in the placebo groups were 117 and 116 bpm, respectively ( $P < 0.001$  and  $P < 0.001$ , respectively). Combining the pooled data from trials, 37.7% of patients in the dronedarone group and 46.0% of patients in the placebo group had symptomatic recurrences ( $P < 0.001$  by the log-rank test). In both trials, dronedarone was superior to placebo in variety of patient subgroups including hypertension, structural heart disease, and previous amiodarone use.

There was no evidence of pulmonary or thyroid toxicity in dronedarone group. The incidence of hyperthyroidism in dronedarone group (8.4%) was significantly lower than in placebo group (14.1%) ( $P = 0.002$ ), and the incidence of hypothyroidism (5.5%) in dronedarone group was slightly higher than in placebo group (3.5%) but not significantly ( $P = 0.15$ ). The incidence of photosensitive rash and reaction was not significant (0.7% in dronedarone group vs 0.2% in placebo group [ $P = 0.44$ ]). The main side effect of dronedarone group was diarrhea at high doses. In addition, there was a higher incidence of elevated serum creatinine levels in the dronedarone group than in the placebo group (2.4% vs 0.2%,  $P = 0.004$ ). Serious side effects were rare and were reported with similar frequency in both groups (16.5% dronedarone vs 13.5% placebo). In the combined European and non-European trials, dronedarone was safe in maintaining sinus rhythm without major prolongation of either the QT or the QTc interval (lengthening by 23 and 9 msec, respectively, without significant effects on the QRS

duration) with no reports of torsades. When analyzed separately or in combination, dronedarone proved to be superior in maintaining sinus rhythm with an excellent safety and tolerability profile.

### ERATO trial

The Efficacy and safety of dRonedArone for The cOntrol of ventricular rate during atrial fibrillation (ERATO) trial assessed the efficacy of dronedarone in the control of ventricular rate in patients with permanent AF, when added to standard rate-control therapy.<sup>17</sup> In this prospective, multinational, double-blind, randomized study, 174 elderly patients with permanent AF were randomized to 6 months' treatment with dronedarone, 400 mg twice a day ( $n = 85$ ) or matching placebo ( $n = 89$ ). All patients were receiving standard rate-control therapy beta-blockers, calcium antagonists, and digoxin. In this study, 38.9% had structural heart disease and 39.7% had NYHA class I or II heart failure. The primary endpoint was the change in mean ventricular rate between baseline and day 14, as assessed by 24-hour Holter. Ventricular rate was also assessed during submaximal and maximal exercise.

At day 14, mean reduction in mean 24-hour ventricular rate in the dronedarone group was 11.0 bpm as opposed to an increase of 0.7 bpm in the placebo group, a treatment effect of  $-11.7$  bpm ( $P < 0.0001$ ). Comparable reductions were sustained throughout the 6-month trial. During maximal exercise and compared to placebo, there was a mean reduction of 24.5 bpm ( $P < 0.0001$ ), without any reduction in exercise tolerance as measured by maximal exercise duration. The effects of dronedarone were additive to those of other rate-control agents, including beta-blockers, calcium antagonists, and digoxin. Thus, dronedarone appears to improve ventricular rate control in patients with permanent AF without any organ toxicity or proarrhythmia.

In the ERATO study, there was a mean 41.4% increase in digoxin levels in patients taking concomitant dronedarone, but without significant difference between the treatment groups in number of patients with an increase in digoxin outside the normal range (4.5% in the dronedarone group vs 2.8% in the placebo group). Also dronedarone had no effect on international normalized ratio in patients taking oral anticoagulants.

### ANDROMEDA trial

In the EURIDIS and ADONIS trials, patients with NYHA class III and IV were excluded. The Antiarrhythmic Trial with Dronedarone in Moderate to Severe congestive heart

failure Evaluating Morbidity Decrease (ANDROMEDA) study was double-blind, placebo-controlled, randomized in 1:1 ratio, parallel-group trial comparing treatment with 400 mg of dronedarone twice daily with administration of matching placebo to assess the rate of hospitalization and mortality in patients with heart failure.<sup>18</sup> Patients with symptomatic heart failure (NYHA class III or IV) requiring diuretic treatment, or paroxysmal nocturnal dyspnea within the month before admission with a left ventricular ejection fraction of  $<35\%$  were enrolled. The study began in June 2002 and was originally scheduled to last for 2 years, and each patient was to be treated with dronedarone or matching placebo for a minimum of 12 months. However, in January 2003, the trial was terminated owing to an excess of deaths in the dronedarone group. Follow-up was continued until at least 6 months after withdrawal of the study drug. 627 patients had been enrolled (310 in dronedarone group and 317 in placebo group) and treated by the time the trial was stopped at a median follow-up of 2 months. During this period, 25 patients in the dronedarone group (8.1%) and 12 patients in the placebo group (3.8%) died (hazard ratio in the dronedarone group, 2.13; 95% CI 1.07 to 4.25;  $P = 0.03$ ). The excess mortality was predominantly due to worsening of heart failure (10 deaths in the dronedarone group and 2 in the placebo group). After 6 months of discontinuation of treatment, the mortality rates were comparable in both groups, 42 patients in the dronedarone group (13.5%) and 39 patients in the placebo group (12.3%) (hazard ratio, 1.13; 95% CI, 0.73 to 1.74;  $P = 0.60$ ). The primary endpoint (death from any cause or hospitalization for worsening heart failure) did not differ significantly between the two groups; there were 53 events in the dronedarone group (17.1%) and 40 events in the placebo group (12.6%) (hazard ratio, 1.38; 95% CI, 0.92 to 2.09;  $P = 0.12$ ).

In the ANDROMEDA trial, the estimated glomerular filtration rate (EGFR) was decreased early after study treatment was started in patients who received dronedarone. Mean EGFR was 7 mL per minute per  $1.73 \text{ m}^2$  of body-surface area lower in the dronedarone group than in the placebo group ( $P = 0.009$ ). After treatment with the study drug was terminated, EGFR returned to baseline values. However, the fall in EGFR may not reflect a deterioration of renal function. Dronedarone has been shown to reduce creatinine clearance by about 18%, with no evidence of an effect on the measured (as opposed to estimated) GFR, suggesting that dronedarone causes a specific partial inhibition of tubular organic cation transporters.<sup>19</sup>



There was no evidence of proarrhythmia or an increased incidence of sudden death in the dronedarone group. Retrospective analysis of ANDROMEDA revealed an inappropriate discontinuation of angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB) in the dronedarone group after transient rise in serum creatinine levels early after the initiation of dronedarone. It is suspected that inappropriate discontinuation of ACEI/ARB with subsequent pump failure may be a contributing factor for excess mortality. Other proposed explanations included negative inotropic effect or the play of chance but the precise explanation is still not clear.

Of note, ANDROMEDA was not an AF study. A history or the presence of AF was not an inclusion criterion for this study. A history of AF (chronic, persistent, or paroxysmal) was reported in almost 40% of the patients, whereas AF at the time of randomization was present in 23.2% of the patients in the dronedarone group and 26.8% in the placebo group. Given the results of ANDROMEDA, dronedarone is not recommended for patients with NYHA class IV symptoms or cardiogenic shock.

## ATHENA trial

Post hoc analysis from the EURIDIS and ADONIS trial showed that dronedarone reduced the risk of all-cause hospitalization or death by 27% compared to placebo (95% CI 7% to 43%;  $P = 0.01$ ).<sup>20</sup> To elucidate this potential clinical benefit, the ATHENA (A Trial to Assess the Efficacy of Dronedarone for the Prevention of Cardiovascular Hospitalization or Death from any cause in Patients with Atrial Fibrillation/Atrial Flutter) was conducted recently.<sup>21</sup> It was a prospective, randomized, placebo-controlled, double-blind, multi-national, multi-center, parallel-group trial evaluating the effects of dronedarone 400 mg bid versus placebo (ratio 1:1) in patients with paroxysmal or persistent AF/AFL who had additional risk factors for death. 4628 patients were enrolled, 2301 received dronedarone and 2327 received placebo. The mean follow-up period was 21 months.

ATHENA was the landmark study that evaluated for the first time a treatment on the top of standard background therapy for the management of AF in reducing morbidity and mortality by preventing cardiovascular hospitalizations or death from any cause. It was the largest study ever conducted in a typical AF population (4628 patients were enrolled). The primary outcome was the first hospitalization due to cardiovascular events or death. This was the first large trial where a rhythm-control agent was studied with this primary endpoint in patients with AF/AFL. Secondary outcomes were

death from any cause, death from cardiovascular causes, and hospitalization due to cardiovascular events. Patients enrolled in this study had one of the following risk factors: age over 70 years; arterial hypertension; diabetes mellitus; previous stroke or systemic embolism; left atrial enlargement; or left ventricular ejection fraction  $\leq 40\%$ . Therefore, the patients enrolled in ATHENA represent the largest group of individuals seeking medical attention for treatment of AF. Patients were ineligible for participation in ATHENA if they had one of the following cardiac conditions: permanent AF, unstable hemodynamic situation (ie, recently decompensated heart failure), or congestive heart failure NYHA class IV.

In the dronedarone group 734 (31.9%) had a primary outcome event and in the placebo group, 917 patients (39.4%) had a primary outcome event. The hazard ratio for the primary outcome in the dronedarone group was 0.76 (95% 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;  $P = 0.18$ ). In the dronedarone group 63 patients died from cardiovascular causes (2.7%) while 90 (3.9%) patients died 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. 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;  $P = 0.01$ ).

675 patients (29.3%) in the dronedarone group had a first hospitalization due to cardiovascular events compared with 859 patients (36.9%) in the placebo group (hazard ratio, 0.74; 95% CI, 0.67 to 0.82;  $P < 0.001$ ). This reduction in the rate of hospitalization due to cardiovascular events was mainly due to reduction in the number of hospitalizations for AF. Also hospitalization due to any cardiovascular event or death from any cause was less in the dronedarone group (1253 patients (54.5%)) vs 1668 patients (71.7%) in the placebo group (hazard ratio, 0.76; 95% CI, 0.68 to 0.84;  $P < 0.001$ ). Total hospital nights spent by the patients in the dronedarone group were significantly less than in the placebo group (9995 vs 13986;  $P < 0.001$ ). This reduction of almost 4000 hospital days translates to a decrease of 1.26 hospitalization days per patient per year. In patients with permanent AF there was 26% drop in risk of cardiovascular hospitalization or death. They had a similar hazard ratio for the primary endpoint to the overall study population.<sup>22</sup>

The study drug was prematurely discontinued in 696 (30.2%) of patients receiving dronedarone and in 716 (30.8%)

of those receiving placebo. The main reasons were adverse events. 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. No significant increase in the rates of thyroid or pulmonary disorders was seen with dronedarone. The most frequently reported adverse events were gastrointestinal: 26% in dronedarone vs 22% in placebo.

The ATHENA trial concluded that treatment with dronedarone significantly reduces the incidence of hospitalization due to cardiovascular events or death in patients with paroxysmal or persistent AF/AFL. In a post-hoc analysis of the ATHENA trial, dronedarone was associated with a 34% decrease in adjusted risk of stroke compared with placebo over a follow-up averaging 21 months (1.19% per year in dronedarone group vs 1.79% per year in placebo group) (hazard ratio, 0.66; 95% CI, 0.46 to 0;  $P = 0.027$ ).<sup>23</sup>

The ANDROMEDA study enrolled only patients with advanced heart failure and recent decompensation leading to hospitalization while patients with severe (NYHA class IV) heart failure were excluded in ATHENA. Given the results of both trials it is postulated that 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.

On the basis of ANDROMEDA study, dronedarone failed in its first appearance before the US Food and Drug Administration (FDA) committee in August 2006. However, after the results of ATHENA study, dronedarone was resubmitted to the FDA and the European Medicines Agency for regulatory panel. On March 18, 2009 it was recommended by an Advisory Committee of the US FDA for approval in the management of AF. The FDA approved dronedarone 400 mg tablets on July 2, 2009 for AF/AFL (Multaq®; sanofi-aventis) with a boxed warning that the drug should not be used in severe heart failure patients.

## DIONYSUS trial

In the Efficacy and Safety of Dronedarone vs Amiodarone for the maintenance of Sinus Rhythm in Patients with AF (DIONYSUS) trial, dronedarone was compared with amiodarone for the safety and efficacy in the maintenance of sinus rhythm in patients with AF (not AFL). 500 patients were involved in the study and had a follow-up of 6 months. Dronedarone was less effective for the maintenance of sinus rhythm. Rate of recurrent AF was 63% with dronedarone and 42% with amiodarone. But the use of dronedarone

was associated with fewer side effects and less premature discontinuation of drug treatment.<sup>24</sup>

## Conclusions

Dronedarone is a newer benzofuran derivative structurally similar to amiodarone except it lacks the iodine moiety and there is an addition of a methane sulfonyl group. It does not significantly prolong the QTc and no significant pulmonary, hepatic, ocular, or neurologic toxic effects have been observed in the studies done to date. Dronedarone, in addition to its benefits for rate and rhythm control, may reduce all-cause hospitalization or death in patients with AF. Dronedarone may be a viable, uniformly effective, and safer treatment option for patients with AF.

## Disclosures

The authors declare no conflicts of interest.

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