Dronedarone for the control of ventricular rate in permanent atrial fibrillation: The Efficacy and safety of dRonedArone for The cOntrol of ventricular rate during atrial fibrillation (ERATO) study

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Background Dronedarone is a new multichannel blocker for atrial fibrillation (AF) previously demonstrated to have both rhythm and rate control properties in paroxysmal and persistent AF. 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 therapy.

Methods In this randomized, double-blind, multinational trial, dronedarone, 400 mg twice a day (n = 85), or matching placebo (n = 89) was administered for 6 months to adult patients with permanent AF, in addition to standard therapy. The primary end point 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.

Results Dronedarone significantly decreased mean 24-hour ventricular rate. Compared with placebo, the mean treatment effect at day 14 was a reduction of 11.7 beats per minute (beat/min; $P < .0001$). Comparable reductions were sustained throughout the 6-month trial. During maximal exercise and compared to placebo, there was a mean reduction of 24.5 beat/min ($P < .0001$), 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 β-blockers, calcium antagonists, and digoxin. Dronedarone was well tolerated, with no organ toxicities or proarrhythmia.

Conclusion In addition to its reported rhythm-targeting and rate-targeting therapeutic actions in paroxysmal and persistent AF, dronedarone improves ventricular rate control in patients with permanent AF. Dronedarone was well tolerated with no evidence of organ toxicities or proarrhythmias in this short-term study. (Am Heart J 2008;156:527.e1-527.e9.)

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, with a prevalence of 5% to 6% in people aged 65 years and rising to 10% in those aged ≥80 years.[1] It is associated with significant impairment of quality of life, a significantly increased risk of stroke, including a greater incidence of fatal and incapacitating strokes than non-AF patients, and death.[2] Early management of AF generally focuses on the restoration and maintenance of sinus rhythm, alongside curative interventions including ablation therapy and surgery in selected patients.[3] For most patients, however, pharmacological treatment remains central to long-term management.

The available pharmacological interventions for AF can broadly be divided into rhythm-based and rate-based approaches, although some agents, such as amiodarone and sotalol, have therapeutic benefits for both rhythm and rate.[3] Safe and effective control of atrial rhythm remains a therapeutic ideal for most patients, but rate control is especially useful in older patients with persistent or permanent AF. Established pharmacological therapies include digoxin, β-blockers, and the nondihydropyridine calcium-channel blockers verapamil and diltiazem.[3] Recently, 5 comparative studies, including the

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large multicenter Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial,[4] found that AF management based on rate control was at least as effective as rhythm-based management for outcomes, as related in 2 subsequent meta-analysis.[5-6] This parity is likely to reflect limitations in the efficacy, safety, and/or tolerability of some of the older rhythm-control agents used in these studies. However, despite its palliative use, optimal rate control is not achieved in a significant proportion of patients, either because the targeted heart rate (HR) is not obtained with usual doses or because side effects tend to restrict the use of high doses of β-blockers and calcium-channel blockers. Thus, adequate rate control at rest and exercise was only achieved in 64% of patients assigned to rate control in AFFIRM.[4] Additional techniques for further controlling ventricular rate would therefore be advantageous in AF management.

Dronedarone is a novel, noniodinated benzofuran derivative with class I, II, III, and IV antiarrhythmic properties.[7] A number of clinical trials have shown that dronedarone, 400 mg twice a day, is effective in the prevention of AF relapses and the long-term maintenance of sinus rhythm.[8,9] These studies also reported dronedarone to be well tolerated, with none of the organ toxicities associated with amiodarone, or proarrhythmic effects associated with many other antiarrhythmic drugs. Importantly, alongside its rhythm-related therapeutic effects, a rate-reducing effect was anticipated on the basis of its class II and IV activity. Studies in paroxysmal and persistent AF, including the EURIDIS-ADONIS trial program, reported that dronedarone significantly reduced ventricular rate.[9] The combination of rhythm and rate control properties with good tolerability and a lack of proarrhythmic effects together suggest that dronedarone may address several of the shortcomings of current rhythm and pharmacologically based management therapies. However, the rate-controlling properties of dronedarone have not hitherto been characterized in patients with permanent AF in whom they would be of greatest clinical use.

To characterize the therapeutic action of dronedarone in the management of ventricular rate in permanent AF, we conducted the multicenter Efficacy and safety of dRonedArone for The cOntrol of ventricular rate during atrial fibrillation (ERATO) study. The primary objective was to assess the efficacy of dronedarone in the control of mean 24-hour ventricular rate in patients with permanent AF. Secondary objectives included assessment of the effects of dronedarone on HR during exercise, the impact of treatment on exercise tolerance, and the tolerability of dronedarone.

Methods

Study design

ERATO was a randomized, double-blind, placebo-controlled, parallel-group study conducted at 38 centers in 9 European countries. The design of the study is summarized in Figure 1. After a 2-week screening period, patients were randomly assigned to receive dronedarone, 400 mg twice a day, or matching placebo, in addition to their standard therapy for AF. The effect of dronedarone on mean 24-hour ventricular rate was documented at day 14 (D14) (primary end point) and 4 months. Treatment with the study drug was continued for a total of 6 months to assess tolerability.

The study was carried out in accordance with the ethical principles of the current Declaration of Helsinki and all applicable guidelines in each participating country. Prior ethics committee and/or institutional review board approval was given at all participating centers. The Data Safety Monitoring Board (Appendix A) was created and patients gave written informed consent before study enrolment.

Patients

The study was conducted in adult patients (≥21 years) with documented, symptomatic permanent AF, for which cardioversion was not considered an option. *Symptomatic AF* was defined as the presence of any AF-related symptoms including palpitations. *Permanent AF* was defined as AF of >6 months of duration.

To be eligible for inclusion, patients had to have a resting ventricular rate of ≥80 beat/min as measured on a 6-second rhythm strip. Patients were excluded if they had a history of unstable angina pectoris, a history of torsades de pointe, baseline (D0) plasma potassium <3.5 mmol/L, third-degree atrioventricular block or significant sinus node disease, New York Heart Association (NYHA) class III or IV congestive heart failure (CHF), or clinically relevant hematological, hepatic, gastrointestinal, renal, endocrinological, or psychiatric disease.

Patients taking other antiarrhythmic agents or any potent inhibitor of CYP3A4 were ineligible. A 2-month washout period was required before patients on chronic amiodarone therapy could enter the study. Concomitant use of other standard rate control agents including calcium antagonists, β-blockers (except sotalol), and digoxin was permitted, provided administration was carried out with caution. It was recommended that the dose of concomitant drugs that can slow HR was not changed until after D14 (time of the primary end point assessment) unless necessary for safety reasons.

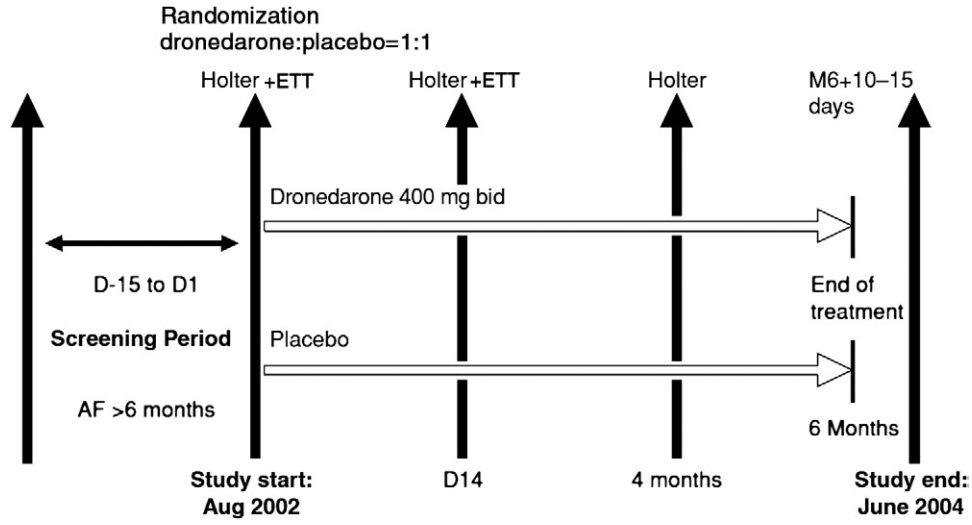
Study interventions and blinding

Patients meeting the eligibility criteria were randomized 1:1 to 6 months of treatment with either dronedarone, 400 mg twice a day, or matching placebo on an outpatient basis. Study medication was taken orally as a single tablet in the morning during or shortly after breakfast and again in the evening during or shortly after dinner. Dronedarone and placebo medications were identical in appearance to ensure blinding.

Investigative procedures

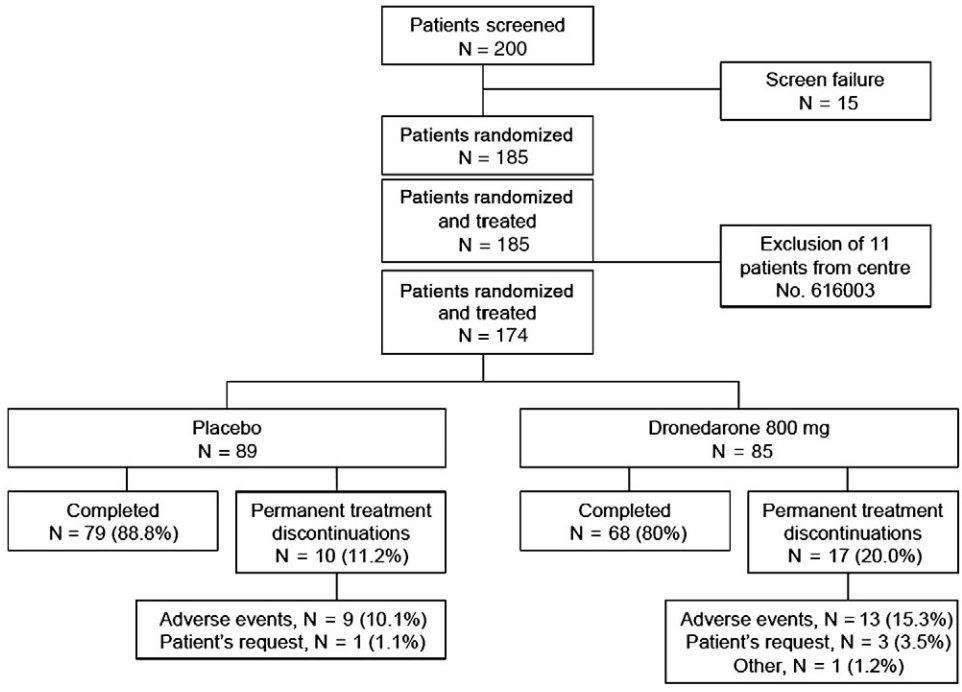
Heart rate measurements were made at D0, D14, and 4 months using 24-hour Holter monitoring. For the primary efficacy variable, results were expressed as mean HR for a 24-hour period. To assess whether dronedarone was effective in controlling ventricular rate during exercise and to

Figure 1



Design of the ERATO study.

Figure 2



Patient disposition.

determine whether any such effects compromised exercise tolerance, exercise tests were performed at D0 and on D14. The exercise tests were symptom-limited, with standard criteria for discontinuation, that is, a fall in systolic blood pressure (SBP), anginal pain, central nervous system symptoms (eg, ataxia, dizziness), signs of poor perfusion (eg, pallor, cyanosis), serious arrhythmia, or patient's request. Heart rate and SBP were measured at rest, at submaximal exercise (50%

of the maximum workload of the D0 exercise test), and at maximal exercise. The *maximal exercise duration* was defined as the time elapsed between the start and end of exercise. After maximal exercise, patients were monitored until HR, ECG, and SBP returned to D0 levels.

Outcome parameters

The primary efficacy end point was the change in mean ventricular rate measured by 24-hour Holter recording on D14, as compared to D0, expressed as beats per minute.

Secondary efficacy variables included the change in mean ventricular rate during submaximal and maximal exercise at D14 compared with D0; the change in maximal exercise duration at D14 compared with D0; and the change in mean ventricular rate measured by 24-hour Holter after 4 months as compared to D0. A prespecified subgroup analysis stratified the results of the primary efficacy end point according to the concomitant use of other rate-lowering drugs in background therapy. Further secondary variables assessed safety and tolerability.

Statistical analysis

Sample size estimation was based on data from the Dronedarone Atrial Fibrillation Study After Electrical Cardioversion (DAFNE) trial[7] and assumed a 10 beat/min decrease in D14 HR compared to D0 from the addition of dronedarone to standard background therapy. To achieve 90% power to detect such a difference, assuming an SD of 18 beat/min and using a 2-group Student *t* test with a 2-sided 0.05 significance level, at least 70 patients were needed in each treatment arm. With further allowance for 10% lost data for the primary efficacy end point, a total study population of at least 160 patients was required.

Analyses were carried out on the all-randomized patient population and the per protocol population, which included all those randomized to treatment and with a primary end point evaluation and no major protocol deviations. Primary efficacy analysis was performed on change at D14 from D0 as follows: dronedarone, 400 mg twice a day, and placebo groups were compared using an analysis of covariance model, adjusting for the following covariates: age, D0 medications (β-blockers, calcium antagonists [diltiazem, verapamil], digoxin), each taken separately, and D0 Holter-monitored HR values. There was no analysis according to D0 HR. Missing data were imputed using a multiple imputation technique to provide treatment effect assessment based on all randomized patients. The same analysis on changes at D14 from D0 was performed, on all secondary efficacy end points, but without multiple imputations for missing data with the exception of the main secondary end point, that is, maximal exercise duration. Here, a sequential approach was used—maximal exercise duration was tested at a level of 5% only if the primary end point was significant.

Results

Patient disposition

The disposition of patients through the course of the study is summarized in Figure 2. A total of 200 patients were screened, of whom 174 met inclusion criteria and were randomized. In total, 85 and 89 patients received dronedarone, 400 mg twice a day, and placebo, respectively. All data from one center were excluded from the randomized patient population because of major protocol violations (11 patients).

Table I. Patient characteristics at D0

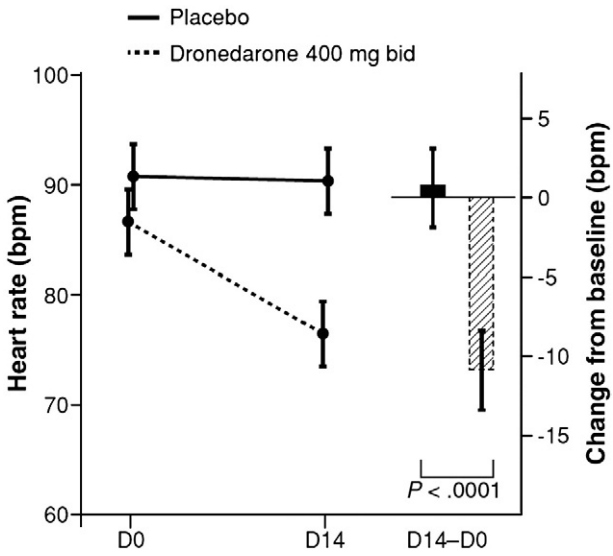
	Dronedarone, 400 mg twice a day (n = 85)	Placebo (n = 89)
Demographics		
Male/Female (%)	58/27 (68/32)	62/27 (70/30)
White (%)	84 (99)	88 (99)
Mean age (range), (y)	65.2 (31-86)	66.4 (39-86)
Mean weight (range), (kg)	83.3 (48.0-122.0)	85.1 (54.0-133.2)
Cardiovascular history		
Hypertension (%)	44 (52)	41 (46)
Structural heart disease (%)	31/82 (38)	34/85 (40)
Congestive heart failure (%)	37 (44)	32 (36)
NYHA class I (potential) (%)	12 (14)	8 (9)
NYHA class II (mild) (%)	25 (29)	24 (27)
Valvular heart disease including mitral valve prolapse (%)	14 (17)	16 (18)
Coronary heart disease (%)	16 (19)	14 (16)
Dilated cardiomyopathy (%)	8 (9)	10 (11)
Concomitant medication use at D0		
Oral anticoagulants (%)	73 (86)	80 (90)
β-Blockers (except sotalol) (%)	46 (54)	44 (50)
ACEI or AIIRA (%)	43 (51)	43 (48)
ACEI (%)	32 (38)	35 (39)
AIIRA (%)	11 (13)	8 (9)
Diuretics (%)	43 (51)	34 (38)
Digoxin (%)	34 (40)	41 (46)
Calcium antagonists with HR-lowering effects (%)	25 (29)	15 (17)
Statins (%)	19 (22)	20 (23)
Chronic antiplatelet therapy (%)	17 (20)	10 (11)
NSAIDs (%)	5 (6)	5 (6)

ACEI, Angiotensin-converting enzyme inhibitors; *AIIRA*, angiotensin II receptor antagonists; *NSAIDs*, nonsteroidal antiinflammatory drugs.

Baseline characteristics

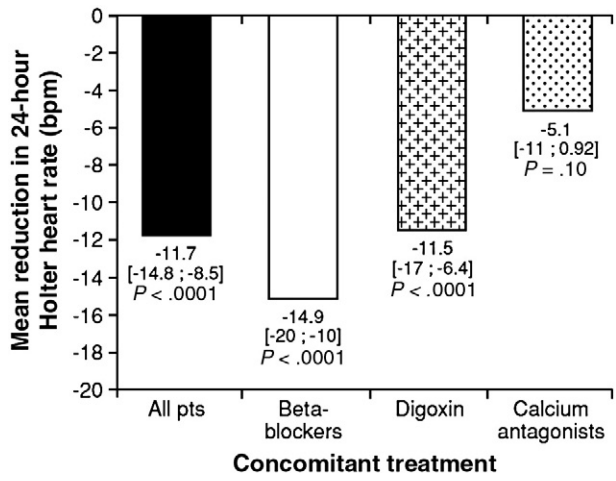
The D0 demographic and clinical characteristics, including concomitant medication use, were similar in the 2 treatment arms (Table I). There was no statistically significant difference in the proportion of patients receiving a conventional HR-lowering drug. The study population consisted primarily of elderly (>65 years)

Figure 3



Effect of dronedarone on resting HR: mean (±SEM) ventricular rate at D0 and D14 and mean change from D0 to D14 (95% CI).

Figure 4



Effect of dronedarone on mean 24-hour HR when added to standard rate-lowering therapies: mean change from D0 to D14 (95% CI).

male patients. Overall, 49% had hypertension, 39% had structural heart disease, and 40% had class I or II NYHA CHF. With regard to concomitant medications, 52% of participants were receiving β-blockers (excluding sotalol), 43% were receiving digoxin, and 23% were receiving calcium-channel blockers with HR-lowering effects. For the 6 months of the study, exposure to study medication was similar in the 2 treatment arms as follows: mean treatment exposure was 156.5 days in the dronedarone treatment arm and 168.6 days in the placebo arm.

Effects on HR

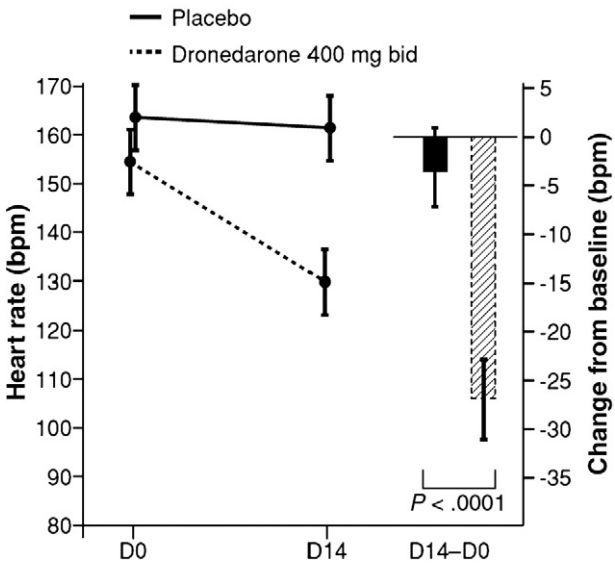
Effect on mean ventricular rate. Dronedarone treatment was associated with a significant reduction in ventricular rate. With regard to the primary efficacy end point, there was a mean reduction in mean 24-hour ventricular rate of 11.0 beat/min in the dronedarone group at D14 in comparison with D0, as opposed to an increase of 0.7 beat/min in the placebo group, a treatment effect of −11.7 beat/min ($P < .0001$; Figure 3). When the results were stratified according to the presence or absence of other concomitant rate-lowering drugs in background therapy including β-blockers, calcium antagonists, and digoxin, there was no significant effect on the primary analysis. The prespecified subgroup analysis by concomitant rate-lowering medication revealed that HR was, in addition, lowered by dronedarone in patients receiving each of these classes of medication, with mean reductions in ventricular rate versus placebo of −14.9, −11.5, and −5.1 beat/min in patients receiving concomitant β-blockers, digoxin, and calcium antagonists, respectively (Figure 4).

Effects during exercise. The reductions in ventricular rate observed with dronedarone were of a greater absolute magnitude during exercise than during the mean 24-hour ventricular rate measurement. During submaximal exercise, there was a reduction in mean HR from D0 of 25.6 beat/min in the dronedarone group, compared with 2.2 beat/min in the placebo group ($P < .0001$). At maximal exercise, there was a reduction in mean HR of 27.4 beat/min in the dronedarone group, compared with 2.9 beat/min in the placebo group ($P < .0001$) (Figure 5)—a treatment effect of 24.5 beat/min.

The reduction in HR in the dronedarone group was not associated with any reduction in exercise tolerance. Between D0 and D14, there was a mean increase in maximal exercise duration of 0.14 minutes and 0.26 minutes in the dronedarone and placebo groups, respectively ($P = .514$).

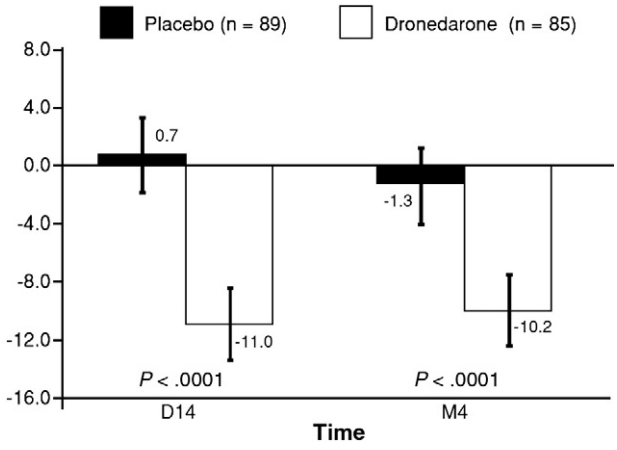
Long-term efficacy. The decrease in HR with dronedarone observed at D14 was sustained during long-term treatment. At 4 months, the mean change from D0 in 24-hour Holter-monitored ventricular HR was again significantly greater among dronedarone-treated patients compared with those receiving placebo (−10.1 beat/min vs −1.3 beat/min, respectively; treatment effect −8.8 beat/min, $P < .001$) (Figure 6). As with the primary end point, dronedarone's effect on mean 24-hour HR was always present, whatever the presence of standard background therapy (calcium antagonists, β-blockers, or digoxin), indicating that the long-term rate-lowering effects of dronedarone were additional to those of other standard agents.

Figure 5



Effect of dronedarone on HR during maximal exercise: mean (±SEM) ventricular rate at D0 and D14 and mean change from D0 (95% CI).

Figure 6



Long-term efficacy of dronedarone in reducing mean 24-hour ventricular rate (M4 = 4 months).

Per protocol analysis. Efficacy analyses carried out on the per protocol population were similar to those of the all-randomized patient population. Mean 24-hour ventricular rate in the dronedarone group was reduced from 88.8 ± 1.6 beat/min at D0 to 76.5 ± 1.4 beat/min at D14, a change of −12.3 beat/min (95% CI −14.6 to −10.0). This reduction was significantly different ($P < .001$) to that seen in the placebo group—from 92.3 ± 1.7 beat/min at D0 to 91.1 ± 1.7 beat/min at D14; mean change 0.4 beat/min (95% CI −2.2 to 2.9).

Safety and tolerability

Dronedarone was well tolerated during the course of the study, and no notable safety issues arose. No cases of torsades de pointe or sustained ventricular tachycardia were reported in either treatment group. One sudden death was reported during treatment. This was a female patient in the dronedarone group who had a personal history of congenital heart disease and a family history of sudden death and Steinert's disease. This patient had major ECG abnormalities at D0 that were not detected at the inclusion and should therefore not have been included in the study. Two further deaths were reported after completion of the trial (one in the dronedarone and one in the placebo group). Neither of these deaths involved cardiovascular disease (ie, malignant lung neoplasm and diverticular perforation), and both were considered unrelated to trial participation.

The incidence of treatment-emergent adverse events is summarized in Table II. Overall, the incidence of treatment-emergent adverse events was slightly higher in the dronedarone treatment arm in comparison with placebo, whereas the proportion of patients with serious adverse events and premature discontinuations for adverse events was similar in the 2 groups. Serious adverse cardiovascular events were rare and included 3 cases of myocardial infarction (1 dronedarone vs 2 placebo), 1 case of heart failure in the dronedarone group, and 1 case of unstable angina in the placebo group.

Infections were the most frequently reported adverse events but occurred at a similar frequency in the placebo group (Table II). Gastrointestinal disturbances were also common in both groups occurring in 20% of patients receiving dronedarone versus 13.5% of those receiving placebo. Respiratory, thoracic and mediastinal disorders, and mild nervous system disorders such as headache and dizziness were also common in both groups. Adverse events were in general mild or moderate in severity.

With regard to clinical laboratory values, the most notable observation was a mild increase in mean serum creatinine levels in the dronedarone group. This difference was already observed on the first blood sample after treatment initiation drawn on D14 and remained stable during the treatment period (mean 10.6 μmol/L) and persisted for the duration of the study.

With regard to drug interactions, there was a mean 41.4% increase in digoxin levels in patients taking concomitant dronedarone, but no significant difference between the treatment groups with regard to the

Table II. Frequency of treatment-emergent adverse events >3.0%, serious treatment-emergent adverse events, and deaths during the period from first study drug intake to last study drug intake plus 10 days (all randomized patients)

	Dronedarone, 400 mg twice a day (n = 85 [%])	Placebo (n = 89 [%])
Any TEAE	65 (77)	53 (60)
Serious TEAEs	14 (17)	12 (14)
Deaths	1 (1)*	0 (0)
Permanent discontinuations for any TEAE	13 (15)	9 (10)
Infections and infestations		
Any event	26 (31)	22 (25)
Nasopharyngitis	15 (18)	9 (10)
Influenza	8 (9)	4 (5)
Gastrointestinal disorders		
Any event	17 (20)	12 (14)
Diarrhea	5 (6)	1 (1)
Abdominal pain	3 (4)	1 (1)
Respiratory, thoracic, and mediastinal disorders		
Any event	16 (19)	6 (7)
Dyspnea	5 (6)	2 (2)
Cough	3 (4)	1 (1)
Dyspnea exertional	3 (4)	0
Nervous system disorders		
Any event	14 (17)	11 (12)
Dizziness	4 (5)	4 (5)
Headache	4 (5)	3 (3)
Somnolence	3 (4)	0
Other		
Fatigue	4 (5)	2 (2)
Noncardiac chest pain	3 (4)	0

TEAE, Treatment-emergent adverse events.
*Sudden death in patient with a history of congenital heart disease and a family history of sudden death and of Steinert's disease.

number of patients with an increase in digoxin outside normal ranges (4.5% in the dronedarone group vs 2.8% in the placebo group). Dronedarone had no effect on international normalized ratio in patients taking oral anticoagulants.

Discussion

The results of the ERATO trial demonstrate that the addition of dronedarone to standard therapy results in a significant decrease in mean 24-hour ventricular rate in patients with permanent AF. The mean treatment effect at D14 was a reduction in ventricular rate of 11.7 beat/min —an effect sustained thereafter for the duration of the trial (−8.8 beat/min at month 4). During exercise, the magnitude of the reduction in HR was greater, with a mean reduction of 24.5 beat/min relative to the placebo group response during maximal exercise at D14. These reductions in HR were not associated with any reduction in exercise tolerance as measured by maximal exercise duration. Furthermore, the effects of dronedarone in reducing ventricular rate were additional to those of other rate-control agents, including β-blockers, calcium antagonists, and digoxin. Finally, a long-term efficacy on the control of HR was documented.

Several details of these results warrant technical discussion. Firstly, the timing of the primary efficacy end point, at D14 of the study, was selected on the basis of previous pharmacokinetic studies, which indicated that concentrations of dronedarone and its major metabolite SR35021 reached steady state within 14 days of drug administration.[7] Consistent with these previous studies, pharmacokinetic assessments conducted during ERATO showed plasma levels of dronedarone had reached steady state by D14 when the first blood sample after treatment initiation was drawn. This observation is likely to reflect good observance of the requirement for study medications to be taken during or after meal.

With respect to the additive effects of dronedarone to the rate-lowering effects of other drugs, it should be pointed out that there was a moderate interaction between dronedarone and digoxin, such that digoxin levels were raised by a mean of 41.4%, although the dronedarone and placebo groups did not differ significantly in the number of patients in whom digoxin was outside the normal range. Digoxin is eliminated mainly by renal excretion, a process that is known to be affected by a number of established drugs including quinidine, verapamil, and amiodarone[10]; as all of these drugs have been used extensively in the management of AF in the past without major problems, then the dronedarone-induced digoxinemia reported here is also likely to be of little clinical consequence. The relatively more modest reduction in HR in the patients taking calcium antagonist is suspected to be a random consequence of the small size of this subgroup. Finally, the analysis of both primary and secondary end points was adjusted for D0 HR value, age, and type of D0 standard treatment (β-blocker, HR-lowering calcium antagonist, or digitalis) so possible differences in D0 characteristics should not have contributed to any treatment effects.

The results from ERATO in permanent AF complement the findings from the EURIDIS and ADONIS studies in paroxysmal and persistent AF and flutter.[9] In these 2 large randomized studies of identical protocol, dronedarone significantly reduced the risk of AF recurrence but, in addition, proved effective in controlling ventricular rate. Mean HR recorded by transtelephonic ECG monitoring during the first arrhythmia recurrence was 102.3 ± 24.7 beat/min and 104.6 ± 27.1 beat/min in the dronedarone treatment arms of EURIDIS and ADONIS, respectively, compared to 117.5 ± 29.1 and 116.6 ± 31.9 beat/min in the placebo arms ($P < .001$ in both cases). Taken together, the EURIDIS-ADONIS and ERATO studies therefore demonstrate that dronedarone is effective both in maintaining sinus rhythm in

paroxysmal and persistent AF and in controlling ventricular rate across the spectrum from paroxysmal and persistent to permanent AF. Agents that combine rhythm-control and rate-control properties without increasing proarrhythmic risk have the potential to provide the backbone of an integrated pharmacological management approach across the spectrum from paroxysmal to permanent AF.

The addition of dronedarone to standard therapy was well tolerated by patients in the ERATO study, as reflected by high rates of study completion and low rates of premature withdrawal, notwithstanding the greater numerical incidence of side effects and study discontinuations in the dronedarone group. The most significant adverse events with dronedarone were gastrointestinal. Importantly, dronedarone displayed good long-term cardiac tolerability, with no evidence of proarrythmia or torsades de pointe, and no increase in heart failure episodes after 6 months of continuous treatment. It is notable that one sudden death was reported in the dronedarone group—this patient had a family history of cardiac rhythm disorder not detected at the inclusion and was erroneously included in the study; in any case, this event has to be considered in the context that sudden cardiac deaths are common in a population at risk for cardiovascular events. There was no evidence of thyroid or pulmonary fibrosis with dronedarone, in contrast to amiodarone, whose combined efficacy in rhythm and rate control can be compromised in long-term management by these extracardiac effects.[11,12] Overall, these findings are consistent with pooled safety data from the EURIDIS and ADONIS studies, in which no proarrhythmic episodes or signs of extracardiac organ toxicity were reported.[9] With regard to clinical laboratory values in ERATO, there was a slight sustained increase in mean serum creatinine levels in the dronedarone group. This is a recognized side effect of dronedarone treatment that normalizes if treatment is discontinued, is related to changes in creatinine tubular secretion, and is not associated with any renal toxicity or impairment of kidney function.[13]

Based on its safety and tolerability profile, dronedarone would appear to be suitable for management in the outpatient setting and for treatment initiation outside the hospital, with no loading or titration and no need for cardiac monitoring when prescribed in a similar patient population. A morbi-mortality trial with dronedarone in AF has just been reported.[14]

In conclusion, the ERATO trial has demonstrated for the first time that dronedarone controls ventricular rate in patients with permanent AF already treated with standard therapies. Dronedarone was well tolerated with no evidence of organ toxicities or proarrhythmias. This significant effect on rate control in permanent AF complements dronedarone's proven efficacy in maintaining sinus rhythm and controlling ventricular rate in paroxysmal and persistent AF.

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