

## ORIGINAL ARTICLE

# Increased Mortality after Dronedarone Therapy for Severe Heart Failure

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## ABSTRACT

**BACKGROUND**

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Dronedarone is a novel antiarrhythmic drug with electrophysiological properties that are similar to those of amiodarone, but it does not contain iodine and thus does not cause iodine-related adverse reactions. Therefore, it may be of value in the treatment of patients with heart failure.

**METHODS**

In a multicenter study with a double-blind design, we planned to randomly assign 1000 patients who were hospitalized with symptomatic heart failure and severe left ventricular systolic dysfunction to receive 400 mg of dronedarone twice a day or placebo. The primary end point was the composite of death from any cause or hospitalization for heart failure.

**RESULTS**

After inclusion of 627 patients (310 in the dronedarone group and 317 in the placebo group), the trial was prematurely terminated for safety reasons, at the recommendation of the data and safety monitoring board, in accordance with the board's predefined rules for termination of the study. During a median follow-up of 2 months, 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% confidence interval [CI], 1.07 to 4.25;  $P=0.03$ ). The excess mortality was predominantly related to worsening of heart failure — 10 deaths in the dronedarone group and 2 in the placebo group. The primary end point 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;  $P=0.12$ ). More increases in the creatinine concentration were reported as serious adverse events in the dronedarone group than in the placebo group.

**CONCLUSIONS**

In patients with severe heart failure and left ventricular systolic dysfunction, treatment with dronedarone was associated with increased early mortality related to the worsening of heart failure. (ClinicalTrials.gov number, NCT00543699.)

**A**TRIAL AND VENTRICULAR ARRHYTHMIAS contribute to the morbidity and mortality associated with heart failure.<sup>1-3</sup> Class III antiarrhythmic agents reduce the likelihood of the development of atrial fibrillation in patients with heart failure and also increase the rate of conversion from atrial fibrillation to sinus rhythm, which may reduce the risk of acute decompensation. In a previous randomized trial involving patients with heart failure, use of one agent in this class, dofetilide, was associated with fewer hospitalizations for worsening heart failure.<sup>4</sup>

Ventricular arrhythmias are also common in patients with heart failure and reduced systolic function and frequently lead to sudden death. Class III antiarrhythmic drugs reduce the occurrence of these arrhythmias, and although these agents should, at least in theory, also reduce the risk of sudden death, this benefit has not been observed.<sup>5</sup> The reasons for this finding are uncertain, but proarrhythmic effects and other toxicity may be important contributing factors. Notably, of the drugs that are currently recommended for the treatment of ventricular arrhythmias, amiodarone is associated with serious noncardiac adverse effects, and both amiodarone and, in particular, dofetilide increase the risk of torsades de pointes.<sup>4,6</sup>

Dronedarone is a multichannel blocker with electrophysiological properties similar to those of amiodarone; it was developed for the treatment of atrial fibrillation. The drug has very little effect on the QT interval, and proarrhythmia has not been observed. Among patients with persistent atrial fibrillation, dronedarone has been shown to reduce the risk of recurrent atrial fibrillation after cardioversion by 25%, as compared with placebo.<sup>7,8</sup> Given these properties, we anticipated that dronedarone would reduce the rate of hospitalization due to heart failure and possibly also reduce mortality by reducing the incidence of death due to arrhythmia. We tested this hypothesis in the Antiarrhythmic Trial with Dronedarone in Moderate to Severe CHF Evaluating Morbidity Decrease (ANDROMEDA) study.

## METHODS

### PATIENTS

We screened for entry into the study consecutive patients 18 years of age or older who were hospitalized with new or worsening heart failure and

who had had at least one episode of shortness of breath on minimal exertion or at rest (New York Heart Association [NYHA] functional class III or IV) or paroxysmal nocturnal dyspnea within the month before admission. At screening, an echocardiogram was recorded on videotape and was evaluated in a central laboratory within one working day. Wall-motion index was measured as described previously, with use of a 16-segment model of the left ventricle.<sup>9,10</sup> Patients were eligible for the study if they had a wall-motion index of no more than 1.2 (approximating an ejection fraction of no more than 35%) and provided written informed consent. Exclusion criteria were acute myocardial infarction within 7 days before screening; a heart rate of less than 50 beats per minute; a PR interval longer than 0.28 second; sinoatrial block or second- or third-degree atrioventricular block that was not treated with a pacemaker; a history of torsades de pointes; a corrected QT interval (calculated with Bazett's formula as the QT interval divided by the square root of the RR interval in seconds) exceeding 500 msec; a serum potassium level of less than 3.5 mmol per liter; use of class I or III antiarrhythmic drugs, drugs known to cause torsades de pointes, or potent inhibitors of the P450 CYP3A4 cytochrome system; other serious disease; acute myocarditis; constrictive pericarditis; planned or recent (within the preceding month) cardiac surgery or angioplasty; clinically significant obstructive heart disease; acute pulmonary edema within 12 hours before randomization; pregnancy or lactation; expected poor compliance; participation in another clinical trial; and previous treatment with dronedarone. There was no restriction related to renal function.

The estimated glomerular filtration rate was calculated with the use of the following equation:  $186 \times (\text{serum creatinine [in milligrams per deciliter]})^{-1.154} \times (\text{age [in years]})^{-0.203}$ . For women and nonwhites, the product of this equation was multiplied by a correction factor of 0.742 and 1.21, respectively.<sup>11</sup>

### DESIGN AND ORGANIZATION OF THE STUDY

The study was designed as a double-blind, placebo-controlled, randomized, parallel-group trial comparing treatment with 400 mg of dronedarone twice daily with administration of matching placebo. The trial was conducted at 72 hospitals in Denmark, Sweden, Norway, Poland, the Netherlands, and Hungary.

The study was conducted in accordance with the Declaration of Helsinki II and the Guideline for Good Clinical Practice of the European Union. The study was led by a steering committee, and the ethics committee of each participating center or region approved the protocol. A treatment-blinded critical events committee classified deaths as due to cardiovascular or noncardiovascular causes, with deaths from cardiovascular causes further classified as sudden death or death due to arrhythmia, or death due to other cardiovascular causes. This committee classified all hospitalizations as either cardiovascular (subclassified as due to worsening of heart failure or not) or noncardiovascular. The study was designed by the steering committee (see the Appendix) in collaboration with the sponsor. Data management and statistical analyses were performed by the sponsor.

When the study was prematurely terminated in early 2003, many analyses were performed by the sponsor in an attempt to explain the findings. The academic authors allowed this process to continue because dronedarone was not on the market and no other major study with this drug was published. When other data on dronedarone were published in late 2007 and regulatory submissions were considered, the academic authors wrote a report on our data and submitted it for publication as quickly as possible. The first draft was written by the principal investigator, and subsequent drafts were revised and edited by all authors, who vouch for the accuracy and completeness of the data.

#### RANDOMIZATION AND STUDY TREATMENT

Eligible patients were randomly assigned in a 1:1 ratio to double-blind treatment with either dronedarone or placebo.

**Table 1. Baseline Characteristics of the Patients.\***

Characteristic	Dronedarone Group (N=310)	Placebo Group (N=317)
Mean duration of heart failure — mo	20	2.3
Age — yr		
Median	71	72
Range	33–90	27–96
Male sex — no. (%)	230 (74.2)	242 (76.3)
Current smoker — no. (%)	74 (23.9)	76 (24.0)
Medical history — no. (%)		
Previous myocardial infarction	167 (53.9)	158 (49.8)
Ischemic heart disease	206 (66.5)	201 (63.4)
Diabetes	73 (23.5)	62 (19.6)
Hypertension	123 (39.7)	107 (33.8)
Dilated cardiomyopathy	79 (25.5)	103 (32.5)
Atrial fibrillation or flutter	114 (36.8)	126 (39.7)
Body-mass index — no./total no. (%) †		
<30	261/307 (85.0)	244/313 (78.0)
≥30	46/307 (15.0)	69/313 (22.0)
Height — cm	172	172
Weight — kg	78	79
Estimated glomerular filtration rate — ml/min		
Mean	50.0	52.8
Range	16–104	6–99
Wall-motion index		
Median	0.9	0.9
Range	0.3–1.2	0.3–1.2

**Table 1. (Continued.)**

Characteristic	Dronedarone Group (N=310)	Placebo Group (N=317)
QTc — msec		
Mean	446	442
Range	328–351	292–632
Mean blood pressure — mm Hg		
Systolic	120	122
Diastolic	73	74
Mean heart rate — beats/min	78	81
Atrial fibrillation at randomization — no. (%)	72 (23.2)	85 (26.8)
Medications at randomization — no. (%)		
ACE inhibitor or angiotensin-receptor blocker	274 (88.4)	267 (84.2)
Beta-blocker	192 (61.9)	192 (60.6)
Spironolactone	131 (42.3)	124 (39.1)
Diuretic (other than spironolactone)	288 (92.9)	302 (95.3)
Digitalis	96 (31.0)	101 (31.9)
Anticoagulant	92 (29.7)	102 (32.2)
Treatment with ICD — no. (%)	4 (1.3)	6 (1.9)
NYHA functional class — no. (%)		
I	0	0
II	131 (42.3)	121 (38.2)
III	173 (55.8)	183 (57.7)
IV	6 (1.9)	13 (4.1)

\* ACE denotes angiotensin-converting enzyme, ICD implantable cardioverter–defibrillator, and NYHA New York Heart Association.

† Body-mass index is the weight in kilograms divided by the square of the height in meters.

darone or matching placebo. Patients were assigned no later than day 7 after hospital admission. Inclusion could be postponed if the patient was on a respirator, in cardiogenic shock, or receiving inotropic drugs. All patients were assigned during their hospital stay. Patients were seen on day 5 (plus or minus 2 days) after randomization and again after 1 and 3 months. Subsequent visits were scheduled every 3 months. Treatment with dronedarone could be temporarily interrupted at the discretion of the investigator. Compliance was estimated by a pill count at each study visit. Safety evaluations included the recording of all adverse events, laboratory measurements, vital signs, electrocardiographic results, and heart-failure status. Laboratory measurements were obtained at each planned visit, except for the day 5 visit, and included blood chemical studies, electrolyte levels, and serum creatinine levels. The

serum creatinine level was measured as soon as possible after the patient stopped taking the study drug.

#### END POINTS

The primary end point was death from any cause or hospitalization for worsening heart failure. Secondary end points included death from all causes, hospitalization for cardiovascular causes, hospitalization for worsening heart failure, occurrence of atrial fibrillation or flutter, death from arrhythmia, or sudden death. End points were considered to be cardiovascular unless an unequivocal non-cardiovascular cause was established. All end points were assessed up to the day active treatment was stopped, 1 month after the date of cessation of the active-treatment phase, and at the end of a 6-month follow-up phase after the end of the study.

**SAFETY MONITORING AND EARLY TERMINATION OF STUDY**

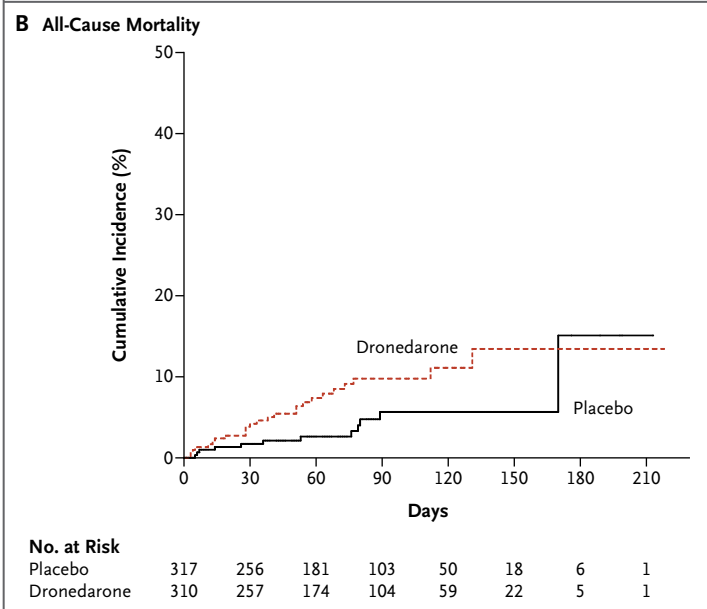
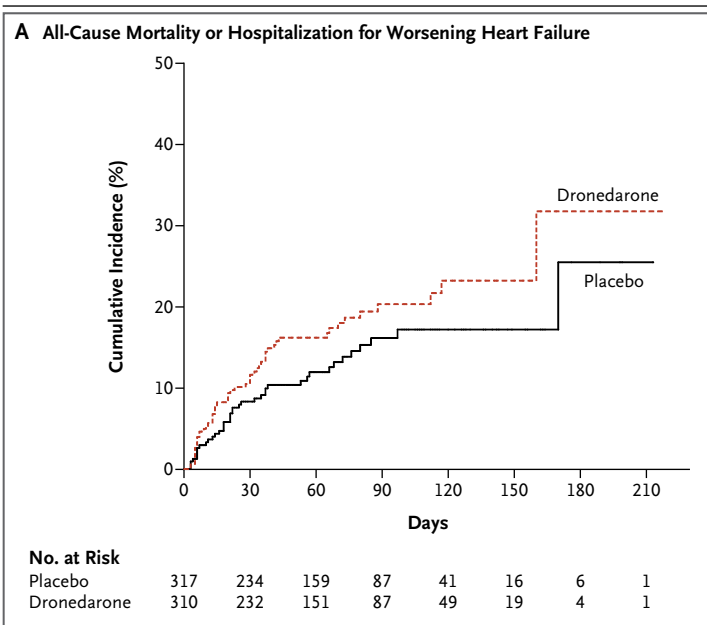
An independent data and safety monitoring board reviewed the results of the trial on a regular basis, with two yearly meetings planned. The trial was

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, 7 months after the first patient was assigned to a study group, enrollment and study treatment were discontinued for safety reasons on the recommendation of the data and safety monitoring board because of an increased number of deaths among patients who were assigned to the active treatment as compared with those assigned to the placebo group. Mortality was the primary safety measure considered by the board, and termination of the trial for safety reasons was pre-specified at a nominal P value of <0.05 for the difference in mortality between the two study groups. Findings with respect to this excess mortality were available at the first meeting of the data and safety monitoring board, in early January 2003, and also in late January 2003, when additional data became available. After discontinuation of the study treatment, all patients were followed for an additional 6 months, during which both they and the investigators remained unaware of the original treatment assignment.

**STATISTICAL ANALYSIS**

A sample size of 1000 patients had been planned on the basis of an expected event rate of 50% in the placebo group, a relative reduction in the event rate of 20% in the dronedarone group, a two-sided type 2 error of 5%, and a power of 90%. The times to various events were analyzed with the use of a two-sided log-rank test, and the Kaplan–Meier method was used to construct life-table plots.

Exploratory analyses included Cox proportional-hazards models to determine prognostic factors and interactions between study drug effect and baseline subgroups. Originally, subgroup analyses were planned for five prespecified variables for the primary end point, but after the trial was stopped, the steering committee decided to perform post hoc subgroup analyses of the mortality end point for eight variables.



**Figure 1. Kaplan–Meier Cumulative Incidence of All-Cause Mortality or Hospitalization for Worsening Heart Failure.**

Panel A shows the Kaplan–Meier cumulative incidence of all-cause mortality or hospitalization for worsening heart failure among patients in the dronedarone and placebo groups. Panel B shows the Kaplan–Meier cumulative incidence of all-cause mortality among patients in the dronedarone and placebo groups.

**RESULTS**

**STUDY CONDUCT**

The study began on June 12, 2002. In January 2003, the data and safety monitoring board recommended that the trial be terminated for safety reasons, owing to an excess of deaths in the dronedarone group. The steering committee followed

the advice of the data and safety monitoring board and terminated the trial on January 16, 2003, 7 months after the study began. Follow-up was continued until at least 6 months after withdrawal of the study drug.

#### STUDY POPULATION

By the day of termination of the double-blind treatment phase, 2402 patients with heart failure had been screened. Of these patients, 1146 were not eligible because they had a wall-motion index of more than 1.2, and 603 were not eligible owing to other exclusion criteria or because they did not give informed consent. Of 653 patients randomly assigned to a study group, 3 patients in the placebo group did not receive any study drug at their own request. Of the remaining 650 patients, 23 from one center (12 in the placebo group and 11 in the dronedarone group) were excluded before analysis owing to major violations of Good Clinical Practice guidelines concerning study documents, raising doubt about the integrity of the data provided by this center. Of the remaining 627 patients who made up the study population, 317 received placebo and 310 received 400 mg of dronedarone twice daily. Follow-up was complete for all patients, and the median follow-up time was approximately 2 months.

The baseline characteristics of the two study groups were similar (Table 1). A history of atrial fibrillation (chronic, persistent, or paroxysmal) was reported frequently (by almost 40% of the patients), whereas atrial fibrillation at the time of randomization (as detected on an electrocardiogram) was present in 23.2% of the patients in the dronedarone group and 26.8% in the placebo group. Of the patients with atrial fibrillation at the time of randomization, 76.4% in the dronedarone group and 67.1% in the placebo group received anticoagulant therapy.

#### ALL-CAUSE MORTALITY

A total of 37 patients, 25 in the dronedarone group and 12 in the placebo group, died during the double-blind, randomized study period (hazard ratio in the dronedarone group, 2.13; 95% confidence interval [CI], 1.07 to 4.25;  $P=0.03$ ) (Fig. 1B); few patients reached 180 days of follow-up, so the small number of events at this time resulted in large steps in the Kaplan–Meier curves (e.g., the death of 1 patient resulted in a change in mortality of nearly 10%). The causes of death are shown

**Table 2. Cause of Death.**

Cause	Dronedarone Group (N=310)	Placebo Group (N=317)
	no. (%)	
Cardiovascular	24 (7.7)	9 (2.8)
Myocardial infarction	0	2 (0.6)
Progressive heart failure	10 (3.2)	2 (0.6)
Documented arrhythmia	6 (1.9)	2 (0.6)
Other cardiovascular cause	3 (1.0)	0
Presumed cardiovascular cause	5 (1.6)	3 (0.9)
Arrhythmia or sudden death*	10 (3.2)	6 (1.9)
Noncardiovascular	1 (0.3)	3 (0.9)
Total	25 (8.1)	12 (3.8)

\* Sudden death was defined by time and is also included in the other reported cardiovascular causes of death.

in Table 2. The number of deaths that were attributed to arrhythmia or sudden death did not differ significantly between the two groups (10 in the dronedarone group and 6 in the placebo group). A total of 10 patients in the dronedarone group had worsening heart failure when they died, as compared with 2 patients in the placebo group. After an additional 6 months without study treatment, 42 patients in the dronedarone group (13.5%) and 39 patients in the placebo group (12.3%) had died (hazard ratio, 1.13; 95% CI, 0.73 to 1.74;  $P=0.60$ ).

Subgroup analyses showed that the risk of death associated with dronedarone was increased among patients who had a lower wall-motion index as compared with those who had a higher wall-motion index (Table 3). After adjustment for other risk factors, the most powerful predictor of death was treatment with dronedarone (hazard ratio, 2.19; 95% CI, 1.06 to 4.52;  $P=0.03$ ).

#### PRIMARY COMPOSITE END POINT

The primary combined end point of all-cause mortality or hospitalization for worsening heart failure was not significantly different between the two groups; there were 53 events in the dronedarone group (crude estimate, 17.1%) and 40 events in the placebo group (crude estimate, 12.6%) (hazard ratio in the dronedarone group, 1.38; 95% CI, 0.92 to 2.09;  $P=0.12$ ) (Fig. 1A). After an additional 6 months of follow-up after treatment with the study drug was discontinued, 74 patients in the dronedarone group (23.9%) and 72 patients in the placebo group (22.7%) had reached the primary

**Table 3. Incidence of Death According to Subgroup.\***

Subgroup	Dronedaronone Group (N=310)	Placebo Group (N=317)	Hazard Ratio for Death in the Dronedaronone Group (95% CI)	P Value for Interaction
<i>no. of deaths/total no. of patients</i>				
Baseline estimated GFR (ml/ min/1.73 m <sup>2</sup> )†				0.09
<50	20/148	5/130	3.32 (1.25–8.87)‡	
≥50	4/155	6/180	0.89 (0.25–3.20)	
Baselinewall-motionindex§				0.04
<1.0	15/144	4/180	4.61 (1.53–13.9)‡	
≥1.0	10/165	8/136	1.05 (0.42–2.67)	
Baseline NYHA class				0.33
II	7/131	5/121	1.28 (0.41–4.03)	
>II	18/179	7/196	2.77 (1.16–6.63)‡	
ACE inhibitor or ARB				0.52
Yes	18/274	9/267	1.96 (0.88–4.37)	
No	7/36	3/50	3.40 (0.88–13.2)	
Beta-blocker (excluding sotalol)				0.72
Yes	16/192	7/191	2.36 (0.97–5.75)	
No	9/118	5/126	1.82 (0.61–5.44)	
Digitalis				0.13
Yes	13/96	3/101	4.25 (1.21–14.9)‡	
No	12/214	9/216	1.34 (0.57–3.19)	
Spironolactone				0.93
Yes	12/131	5/124	2.19 (0.77–6.22)	
No	13/179	7/193	2.01 (0.80–5.04)	
Ischemic heart disease				0.23
Yes	17/206	10/201	1.61 (0.74–3.72)	
No	8/104	2/116	9.03 (1.13–72.2)‡	

\* Hazard ratios are for the dronedaronone group. Hazard ratios and confidence intervals were estimated with the Cox proportional-hazards model. ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, GFR glomerular filtration rate, and NYHA New York Heart Association.

† Data on estimated GFR were missing for 14 patients (7 patients in each group).

‡ P<0.05.

§ Data on wall-motion index were missing for 2 patients (1 patient in each group).

end point (hazard ratio, 1.09; 95% CI, 0.79 to 1.51; P=0.60).

#### OTHER OUTCOMES

During the study, the total number of patients who had a first hospitalization for an acute cardiovascular cause was higher in the dronedaronone group (71 patients) than in the placebo group (50 patients) (P=0.02). The main reason for hospitalization for a cardiovascular cause, as determined by central adjudication, was worsening heart fail-

ure, which occurred in 35 patients (49.3%) in the dronedaronone group and in 30 patients (60.0%) in the placebo group. Other cardiovascular events requiring a first hospitalization, according to the central adjudication, were myocardial ischemia, in 13 patients (18.3%) and 8 patients (16.0%) in the dronedaronone group and the placebo group, respectively; ventricular arrhythmia, in 3 (4.2%) and 2 (4.0%); supraventricular arrhythmia, in 4 (5.6%) and 1 (2.0%); stroke, in 4 (5.6%) and 3 (6.0%); other cardiovascular events, in 9 (12.7%) and 4 (8.0%);

and presumed cardiovascular events, in 3 (4.2%) and 2 (4.0%). Serious adverse events, excluding events resulting in death, are shown in Table 4. There were no significant differences between the two groups, except for increases in the serum creatinine concentration, which were observed more frequently in the dronedarone group than in the placebo group. A decrease in the estimated glomerular filtration rate was found early after study treatment was started in patients who received dronedarone. The mean estimated glomerular filtration rate was 7 ml per minute per 1.73 m<sup>2</sup> 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, the estimated glomerular filtration rate returned to baseline values. At the 1-month visit, 21.4% of the patients in the dronedarone group had atrial fibrillation, as compared with 24.8% of the patients in the placebo group (a nonsignificant difference between the two groups). No cases of torsades de pointes were observed in either group.

## DISCUSSION

Our study shows that treatment with dronedarone in patients with severe heart failure and depressed left ventricular systolic function resulted in an early increase in mortality. The explanation for this early excess mortality is uncertain. Three findings, however, seem relevant. First, the excess deaths related to dronedarone were largely deaths due to heart failure. Second, the risk of death with dronedarone was greatest among patients with the most severely reduced left ventricular systolic function. Third, treatment with dronedarone led to a small increase in hospitalizations for heart failure. These findings raise the possibility that dronedarone directly or indirectly causes worsening heart failure, particularly in patients who have poor systolic function, although this interpretation must be treated with caution since it is based on a post hoc subgroup analysis. In addition, since there was a difference of only 13 deaths in total between the two groups, it is possible that this finding resulted from chance and that the trial was stopped too early to allow valid conclusions to be drawn with respect to treatment effects.

The decrease in the estimated glomerular filtration rate in patients who were treated with dronedarone is of potential concern, but the fall in the estimated glomerular filtration rate may not

**Table 4. Patients with Serious Adverse Events, Excluding Events Resulting in Death, during the Treatment Period.\***

Adverse Event	Dronedarone Group (N=310)	Placebo Group (N=317)
	no (%)	
Any event	115 (37.1)	109 (34.4)
Any cardiac event	68 (21.9)	52 (16.4)
Cardiac failure	31 (10.0)	26 (8.2)
Angina pectoris	7 (2.3)	7 (2.2)
Myocardial infarction	2 (0.6)	4 (1.3)
Ventricular fibrillation	1 (0.3)	3 (0.9)
Ventricular tachycardia	6 (1.9)	2 (0.6)
Noncardiac events		
Increase in serum creatinine	8 (2.6)	0†
Any infection	9 (2.9)	9 (2.8)
Any gastrointestinal event	8 (2.6)	7 (2.2)
Any respiratory event	14 (4.5)	14 (4.4)
Surgical procedures		
Coronary-artery bypass	0	6 (1.9)
Coronary angioplasty	0	1 (0.3)
ICD placement	0	1 (0.3)

\* The treatment period was considered to be the period between the first and last drug administration plus 10 days. ICD denotes implantable cardioverter-defibrillator.

† P=0.01.

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) glomerular filtration rate, suggesting that dronedarone causes a specific partial inhibition of tubular organic cation transporters.<sup>12</sup> Nevertheless, for any future use of dronedarone, it will be important to establish whether it interferes with the renal clearance of other drugs and whether there is a threshold glomerular filtration rate below which it is dangerous to administer the drug.

How do our findings compare with those of prior studies? Three other class III antiarrhythmic drugs have been tested in patients with left ventricular systolic dysfunction. Treatment with D-sotalol after myocardial infarction increased mortality,<sup>13</sup> and although dofetilide did not increase overall mortality among patients with acute myocardial infarction or heart failure, its use was associated with an excess risk of torsades de pointes.<sup>4,14</sup> Amiodarone has not been associated with an increase in mortality,<sup>5,15,16</sup> but subgroup

analyses from the Sudden Cardiac Death in Heart Failure Trial suggested that amiodarone was associated with an excess mortality among patients with NYHA class III heart failure, a finding that is consistent with that in the present study.<sup>17</sup> Amiodarone has well known adverse effects, but renal dysfunction has not been reported in humans. Nevertheless, an increase in the creatinine concentration may be associated with amiodarone in humans, and amiodarone may have acute renal toxic effects in rats.<sup>18,19</sup>

The outstanding question is whether dronedarone is safe in populations that are at lower risk than the patients in this trial. Although increased mortality has not been observed in other dronedarone trials, the small number of events in those studies does not allow for a definitive answer to this question.<sup>7,8</sup> Therefore, the effect of dronedarone on cardiovascular events in patients with atrial fibrillation and additional risk factors, in-

cluding structural heart disease, is being evaluated in a large placebo-controlled trial.<sup>20</sup> This trial may establish whether dronedarone is safe in such patients.

The implication of the findings in the ANDROMEDA study is that dronedarone should not be used in patients with heart failure and reduced left ventricular systolic function. Further studies are necessary to establish the safety of dronedarone in other patients and to clarify the effect of this agent on renal function, including its effect on renal excretion of other drugs.

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Dr. Torp-Pedersen reports receiving a research grant and consulting fees from Sanofi-Aventis. Dr. McMurray reports that Glasgow University receives compensation for his time spent on a clinical trial with an agent other than dronedarone, sponsored by Bristol-Myers Squibb in collaboration with Sanofi-Aventis. Drs. Crijns and Lévy report receiving consulting fees from Sanofi-Aventis. No other potential conflict of interest relevant to this article was reported.

#### APPENDIX

The following authors and investigators participated in the trial: **Steering Committee** — S. Levy (chair), J. Aldershvile (deceased), J. Amlie, J. Carlsen, H.J.G.M. Crijns, O. Gøtzsche, A.L. Hansen (secretary), K. Hedegaard (contract research organization), L. Køber (principal investigator), J.J.V. McMurray, C. Torp-Pedersen; **Critical Events Committee** — K. Egstrup (chair), E. Myhre, U. Nässtrand, K. Skagen; **Data and Safety Monitoring Board** — A. Leizorovicz (chair), J. Camm, L. Erhardt, G. Jensen, K. Rasmussen; **Echo Central Readers** — L. Køber (principal investigator), C. Hassager, B. Holmgaard, C. Torp-Pedersen; **Investigators: Denmark** — E. Agner, M. Askund, J. Berning, J. Böttzauw, A. Brandes, M. Brøns, J. Buhl, A.N. Davidson, K. Egstrup, P. Eliassen, L. Gøtzsche, O. Gøtzsche, T. Haghfelt, C. Hassager, K.K. Klarlund, L. Køber, K. Kristensen, J. Launbjerg, S. Lind Rasmussen, H. Madsen, H. Nielsen, I. Nielsen, T. Nielsen, A. MacNair, J. Markensvard, O. Nyvad, J. Petersen, H. Rickers, J. Rokkedal, M. Scheibel, H. Sejersen, K. Skagen, J. Svanegaard, R. Sykulski, C. Torp-Pedersen, H. Ulriksen, E. Vigholt, P. Wiggers; **Hungary** — T. Forster, H.K. Simon, J. Tenczer; **the Netherlands** — A.M.W. Alings, D.J.A. Lok, P.E.J. Van Denderen Van Pol; **Norway** — J.P. Amlie, T. Graven, T. Indrebo, T. Nerdrum, V. Tuseth; **Poland** — M. Dlużniowski, P. Ponikowski, D. Wojciechowski; **Sweden** — P.L. Ågren, S. Bandh, P. Blomström, K. Boman, K. Broms, P. Cherfan, C. Cline, J. Herlitz, U. Hurtig, S. Jensen, J.E. Karlsson, L. Klintberg, P. Kozak, L.E. Larsson, J.O. Magnusson, T. Mooe, U. Naslund, H. Öhlin, A. Ohlsson-Onerud, H. Persson, P. Smedgård.

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