

## ORIGINAL ARTICLE

# Dronedaronone for Maintenance of Sinus Rhythm in Atrial Fibrillation or Flutter

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## ABSTRACT

**BACKGROUND**

Amiodarone is effective in maintaining sinus rhythm in atrial fibrillation but is associated with potentially serious toxic effects. Dronedaronone is a new antiarrhythmic agent pharmacologically related to amiodarone but developed to reduce the risk of side effects.

**METHODS**

In two identical multicenter, double-blind, randomized trials, one conducted in Europe (ClinicalTrials.gov number, NCT00259428) and one conducted in the United States, Canada, Australia, South Africa, and Argentina (termed the non-European trial, NCT00259376), we evaluated the efficacy of dronedaronone, with 828 patients receiving 400 mg of the drug twice daily and 409 patients receiving placebo. Rhythm was monitored transtelephonically on days 2, 3, and 5; at 3, 5, 7, and 10 months; during recurrence of arrhythmia; and at nine scheduled visits during a 12-month period. The primary end point was the time to the first recurrence of atrial fibrillation or flutter.

**RESULTS**

In the European trial, the median times to the recurrence of arrhythmia were 41 days in the placebo group and 96 days in the dronedaronone group ( $P=0.01$ ). The corresponding durations in the non-European trial were 59 and 158 days ( $P=0.002$ ). At the recurrence of arrhythmia in the European trial, the mean ( $\pm$ SD) ventricular rate was  $117.5\pm 29.1$  beats per minute in the placebo group and  $102.3\pm 24.7$  beats per minute in the dronedaronone group ( $P<0.001$ ); the corresponding rates in the non-European trial were  $116.6\pm 31.9$  and  $104.6\pm 27.1$  beats per minute ( $P<0.001$ ). Rates of pulmonary toxic effects and of thyroid and liver dysfunction were not significantly increased in the dronedaronone group.

**CONCLUSIONS**

Dronedaronone was significantly more effective than placebo in maintaining sinus rhythm and in reducing the ventricular rate during recurrence of arrhythmia.

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N Engl J Med 2007;357:987-99.  
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**A**TRIAL FIBRILLATION IS THE MOST common arrhythmia requiring hospitalization.<sup>1,2</sup> Although arrhythmia-related symptoms and thromboembolic strokes are significantly reduced by anticoagulation therapy and rate control, sinus rhythm is often associated with improvement in exercise capacity and quality of life.<sup>3</sup> Therefore, restoration and maintenance of sinus rhythm remain major therapeutic goals for patients with atrial fibrillation.<sup>3-6</sup>

Amiodarone is an especially potent atrial antiarrhythmic agent,<sup>7</sup> but it induces potentially serious side effects in some patients.<sup>7-10</sup> Thus, compounds that are devoid of such effects but that retain the antiarrhythmic potential of amiodarone are therapeutically desirable.<sup>7,11</sup> Dronedaron is a benzofuran derivative with an electropharmacologic profile closely resembling that of amiodarone<sup>12-20</sup> but with structural differences intended to eliminate the effects of amiodarone on thyroid and pulmonary functions.<sup>17,18</sup> In addition, the elimination half-life of dronedaron is 1 to 2 days, as compared with 30 to 55 days for amiodarone.<sup>20</sup> We investigated the hypothesis that dronedaron is superior to placebo for maintaining sinus rhythm after electrical, pharmacologic, or spontaneous conversion from atrial fibrillation or atrial flutter.

## METHODS

### STUDY DESIGN

The European Trial in Atrial Fibrillation or Flutter Patients Receiving Dronedaron for the Maintenance of Sinus Rhythm (EURIDIS, NCT00259428) and the American–Australian–African Trial with Dronedaron in Atrial Fibrillation or Flutter Patients for the Maintenance of Sinus Rhythm (ADONIS, NCT00259376) were two identical, placebo-controlled, multicenter, double-blind, parallel-group trials sponsored by Sanofi-Aventis. The European trial was conducted in 12 European countries, and the non-European trial was conducted in the United States, Canada, Australia, South Africa, and Argentina.

The study protocols were approved by the human-research review boards at each participating institution. A single common steering committee designed the studies and the data analysis plans in collaboration with the sponsor. An independent data and safety monitoring board oversaw the

safety of patients. All data-management activities were the responsibility of the sponsor. Data entry, verification, and validation were performed with the use of standard computer software (Clintrial 4.3), and data were stored in an Oracle database on a Sun Solaris computer. At study termination, the database was locked and transferred to the biostatistics department at Sanofi-Aventis for analysis. The academic investigators had independent access to the raw data. Dr. Singh, who wrote the manuscript with input from the other steering-committee members and from Sanofi-Aventis personnel, vouches for the accuracy and completeness of the data and the analysis.

### PATIENTS

Patients qualifying for enrollment were of either sex and at least 21 years of age, had had at least one episode of atrial fibrillation (as seen on electrocardiography) in the preceding 3 months, and were in sinus rhythm for at least 1 hour before randomization. Excluded from the study were patients with permanent atrial fibrillation (i.e., a duration of at least 12 months); women who could become pregnant and who were not using birth control; patients who had had torsades de pointes; patients with persistent bradycardia of less than 50 beats per minute, a PR interval of 0.28 second or more on electrocardiography, second-degree (or higher) atrioventricular block, and clinically significant sinus-node disease without an implanted pacemaker; patients who were taking class I or III antiarrhythmic agents; patients with New York Heart Association class III or IV congestive heart failure; and patients with a serum creatinine level of 1.7 mg per deciliter (150  $\mu$ mol per liter) or more, severe electrolyte abnormalities, and clinically significant hepatic, pulmonary, endocrine, or other disorders associated with atrial fibrillation. Previous treatment with amiodarone was permitted, and patients who had received the drug could be enrolled immediately after its discontinuation. Written informed consent was obtained from all patients.

### BASELINE EVALUATION, RANDOMIZATION, AND THERAPY

All study patients underwent a baseline evaluation that included a medical history, symptom review, cardiovascular examination, assessment of vital signs, 12-lead electrocardiography, chest radiog-

raphy, and laboratory tests, including a complete blood count and tests of serum electrolytes, urea, creatinine, and cholesterol and thyroid and liver function. Left atrial size and left ventricular ejection fraction were determined by two-dimensional echocardiography. Eligible patients who were not in sinus rhythm during screening could be enrolled if they underwent successful cardioversion and remained in sinus rhythm for at least 1 hour.

After a 7-day screening period, eligible patients were randomly assigned in a 2:1 ratio to receive either 400 mg of oral dronedarone twice daily or a matching placebo. A stochastic randomization procedure suggested by Pocock and Simon<sup>21</sup> and revised by Freedman and White<sup>22</sup> was used. On the first day of the study, symptoms were evaluated, vital signs were assessed, the assigned study drug was administered, and 12-lead electrocardiography was performed.

#### FOLLOW-UP

We scheduled follow-up visits that included a 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 above-mentioned blood tests were repeated on day 21 and at months 4, 9, and 12. Chest radiography was repeated in the case of pulmonary symptoms.

All enrolled patients were given a transtelephonic electrocardiographic monitor and were instructed in its use. Patients transmitted electrocardiograms on days 2, 3, and 5; at months 3, 5, 7, and 10; and whenever they had symptoms. On each occasion, two electrocardiograms were recorded approximately 10 minutes apart and were evaluated at a central core laboratory (MDS Pharma Services, Paris) by investigators who were unaware of study-group assignments to confirm the recurrence of atrial fibrillation. Each time an electrocardiogram was recorded, the patient was contacted to confirm the occurrence of one or more of the following symptoms: palpitations, dizziness, fatigue, chest pain, and dyspnea. Reported symptoms were taken into account if they were accompanied by atrial fibrillation. If oral anticoagulation therapy was administered, the international normalized ratio was monitored locally.

#### STUDY END POINTS

The primary end point was the time from randomization to the first documented recurrence of atrial

fibrillation, defined as an episode lasting for at least 10 minutes and confirmed by two consecutive recordings taken 10 minutes apart on 12-lead electrocardiography or transtelephonic monitoring. The main secondary end points were symptoms related to atrial fibrillation during recordings of 12-lead electrocardiography or transtelephonic monitoring and the mean ventricular rate during the first recurrence.

#### STATISTICAL ANALYSIS

The hypothesis for determining the number of patients needed for the study was derived from data from efficacy trials of antiarrhythmic drugs for the treatment of atrial fibrillation.<sup>23-25</sup> It was presumed that 60% of patients in the placebo group would have a recurrence of arrhythmia within 12 months; a relative decrease in this rate of at least 25% was expected in the dronedarone group (i.e., a 45% recurrence rate).

With a sample size of 552 patients (368 in the dronedarone group and 184 in the placebo group), each trial would have a power of 90% to detect a between-group difference, assuming a 20% dropout rate and a 1-year follow-up period. The primary analysis was performed according to a modified intention-to-treat principle, with all randomized patients who received at least one dose of a study drug included. A secondary on-treatment analysis was also performed. A two-sided Fisher's exact test was used for qualitative measures. The event-free probability curves were estimated by the nonparametric Kaplan-Meier technique, with 95% confidence intervals. A standard log-rank technique was used to test the null hypothesis of identical Kaplan-Meier curves in the two study groups. All reported P values are two-sided, and P values of less than 0.05 were considered to indicate statistical significance.

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## RESULTS

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#### PATIENTS

In the European trial, 680 patients were screened, and 612 were randomly assigned to study groups to receive treatment (411 to the dronedarone group and 201 to the placebo group). In the non-European trial, 731 patients were screened, and 625 were randomly assigned to receive treatment (417 to the dronedarone group and 208 to the placebo group). Three patients in the European trial and

four in the non-European trial did not receive a study drug (Fig. 1).

Table 1 presents the baseline characteristics of the patients in the European and non-European trials, individually and combined. The mean age of all patients was 63 years, and 69% were men; 41% had structural heart disease. There were 60 patients (10%) with atrial flutter in the European trial and 71 (11%) in the non-European trial. In the European trial, 67 patients in the dronedarone group and 25 in the placebo group discontinued the study prematurely; in the non-European trial, the corresponding numbers were 81 and 36.

#### PRIMARY END POINT

In the European trial, according to the modified intention-to-treat analysis, the median times from randomization to a documented recurrence of atrial fibrillation were 96 days in the dronedarone group and 41 days in the placebo group. At 12 months, 67.1% of patients in the dronedarone group and 77.5% of patients in the placebo group had had a recurrence of atrial fibrillation (hazard ratio for the dronedarone group, 0.78; 95% confidence interval [CI], 0.64 to 0.96;  $P=0.01$ ) (Table 2). On-treatment analysis of the same population had similar results ( $P=0.01$ ).

In the non-European trial, according to a modified intention-to-treat analysis, the median times from randomization to a documented recurrence of atrial fibrillation were 158 days in the dronedarone group and 59 days in the placebo group. At 12 months, 61.1% of patients in the dronedarone group and 72.8% of patients in the placebo group had had a recurrence of atrial fibrillation (hazard ratio, 0.73; 95% CI, 0.59 to 0.89;  $P=0.002$ ) (Table 2). The results of on-treatment analysis were confirmatory ( $P=0.002$ ).

For the two trials combined, the median times to a documented recurrence of atrial fibrillation were 116 days in the dronedarone group and 53 days in the placebo group. 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;  $P<0.001$ ) (Table 2). Figure 2 shows the Kaplan–Meier cumulative incidence curves for the adjudicated first recurrence in patients in the European trial and the non-European trial, separately and combined. The association of dronedarone with a reduction in the risk of recurrence of atrial fibrillation, as compared

with placebo, was consistent for a series of clinically important subgroups (Fig. 3).

A separate preplanned analysis excluded patients with a study-drug exposure of less than 5 days before the occurrence of the primary end point (either because the patient discontinued treatment within 5 days or because atrial fibrillation recurred within 5 days). In the European trial, this analysis showed that patients in the dronedarone group had a reduction in the risk of adjudicated recurrence of 29% from day 5 to 12 months after randomization, as compared with those in the placebo group ( $P=0.006$  by the log-rank test). In the non-European trial, the reduction was 26% ( $P=0.02$  by the log-rank test) (Table 2).

#### HEART RATE AND QT INTERVAL IN SINUS RHYTHM

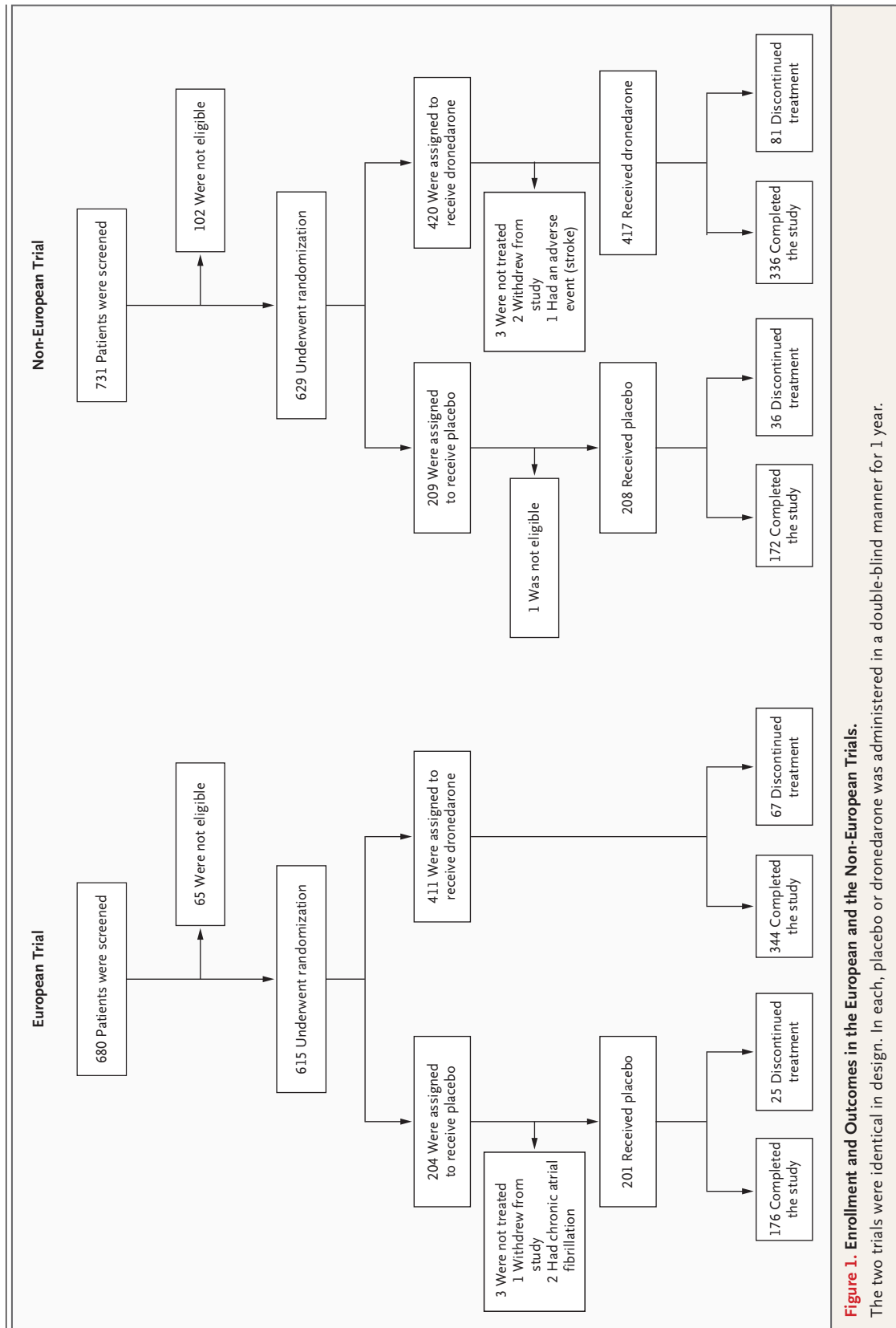
In the combined European and non-European trials, the effects of dronedarone, as compared with those of placebo, on the mean heart rate, QT interval, and QT interval corrected for heart rate (QTc) were investigated in preplanned analyses (see the Supplementary Appendix, available with the full text of this article at [www.nejm.org](http://www.nejm.org)). As compared with baseline values, in the dronedarone group, heart rate was reduced by 6.8%, the QT interval was prolonged by 23.4 msec, and the QTc interval was prolonged by 9.0 msec ( $P<0.001$  for all comparisons with the placebo group), without significant effects on the QRS duration.

#### VENTRICULAR RATE AT FIRST RECURRENCE

In both trials, ventricular rates during the recurrence of atrial fibrillation were evaluated in preplanned analyses. In the European trial, the mean ( $\pm$ SD) ventricular rate during the first adjudicated recurrence was  $102.3\pm 24.7$  beats per minute in the dronedarone group and  $117.5\pm 29.1$  beats per minute in the placebo group ( $P<0.001$ ). The corresponding numbers for the non-European trial were  $104.6\pm 27.1$  beats per minute in the dronedarone group and  $116.6\pm 31.9$  beats per minute in the placebo group ( $P<0.001$ ) (Table 2).

#### SYMPTOMATIC FIRST RECURRENCE

In another preplanned analysis, the rates of symptomatic recurrence of atrial fibrillation were compared between the study groups in each trial. The majority of documented first recurrences were symptomatic, and the pattern of symptoms did not differ between the dronedarone group and the pla-



**Figure 1. Enrollment and Outcomes in the European and the Non-European Trials.**

The two trials were identical in design. In each, placebo or dronedarone was administered in a double-blind manner for 1 year.

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

Characteristic	European Trial		Non-European Trial		Combined Trials	
	Placebo (N=201)	Dronedaron (N=411)	Placebo (N=208)	Dronedaron (N=417)	Placebo (N=409)	Dronedaron (N=828)
Sex — no. (%)						
Female	61 (30.3)	126 (30.7)	68 (32.7)	124 (29.7)	129 (31.5)	250 (30.2)
Male	140 (69.7)	285 (69.3)	140 (67.3)	293 (70.3)	280 (68.5)	578 (69.8)
Age — yr	61.3±10.7	62.3±10	63±11.4	64.6±11.3	62.2±11.1	63.5±10.7
Race — no. (%)†						
White	201 (100)	409 (99.5)	199 (95.7)	391 (93.8)	400 (97.8)	800 (96.6)
Black	0	0	3 (1.4)	9 (2.2)	3 (0.7)	9 (1.1)
Asian	0	2 (0.5)	0	4 (1.0)	0	6 (0.7)
Other	0	0	6 (2.9)	13 (3.1)	6 (1.5)	13 (1.6)
Body-mass index — no. (%)‡						
<30	143 (73.3)	287 (70.9)	130 (63.7)	251 (61.2)	273 (68.4)	538 (66.0)
≥30	52 (26.7)	118 (29.1)	74 (36.3)	159 (38.8)	126 (31.6)	277 (34.0)
Weight — kg	86.43±14.78	83.84±14.39	87.81±19.27	88.61±19.88	87.14±17.22	86.25±17.53
Cardiovascular history — no. (%)						
Structural heart disease§	65 (33.3)	149 (36.3)	94 (45.6)	199 (48.5)	159 (39.7)	348 (42.4)
Hypertension	108 (53.7)	255 (62.0)	97 (46.6)	242 (58.0)	205 (50.1)	497 (60.0)
Coronary artery disease¶	31 (15.4)	91 (22.1)	44 (21.2)	104 (24.9)	75 (18.3)	195 (23.6)
Cardiac valvular disease	19 (9.5)	50 (12.2)	42 (20.2)	86 (20.6)	61 (14.9)	136 (16.4)
Nonischemic cardiomyopathy	11 (5.5)	16 (3.9)	19 (9.1)	34 (8.2)	30 (7.3)	50 (6.0)
Implanted pacemaker	7 (3.5)	33 (8.0)	13 (6.2)	31 (7.4)	20 (4.9)	64 (7.7)
Implanted cardioverter–defibrillator	3 (1.5)	0	2 (1.0)	6 (1.4)	5 (1.2)	6 (0.7)
Rheumatic heart disease	6 (3.0)	7 (1.7)	8 (3.8)	18 (4.3)	14 (3.4)	25 (3.0)
Hypertrophic cardiomyopathy	8 (4.0)	10 (2.4)	4 (1.9)	13 (3.1)	12 (2.9)	23 (2.8)
Congenital heart disease	2 (1.0)	9 (2.2)	1 (0.5)	4 (1.0)	3 (0.7)	13 (1.6)
Left ventricular ejection fraction — %	59.83±9.37	59.57±10.25	57.21±12.24	57.91±11.23	58.5±10.98	58.75±10.77
Left atrial anteroposterior diameter — mm	42.7±6.7	42.4±6.6	42.0±6.9	42.9±7.4	42.4±6.8	42.6±7.0
Congestive heart failure — no. (%)						
Any disease	37 (18.4)	65 (15.8)	36 (17.3)	78 (18.7)	73 (17.8)	143 (17.3)
NYHA class I	16 (8.0)	19 (4.6)	10 (4.8)	28 (6.7)	26 (6.4)	47 (5.7)
NYHA class II	21 (10.4)	46 (11.2)	26 (12.5)	50 (12.0)	47 (11.5)	96 (11.6)
Symptoms of atrial fibrillation in the 3 months before randomization — no. (%)	175 (87.1)	352 (85.6)	180 (86.5)	374 (89.7)	355 (86.8)	726 (87.7)
Recent cardioversion (within 5 days before randomization) — no. (%)	75 (37.3)	153 (37.2)	46 (22.1)	90 (21.6)	121 (29.6)	243 (29.3)

cebo group. In the European trial, 37.1% of patients in the dronedarone group and 47.5% of those in the placebo group had symptomatic recurrences (P=0.006 by the log-rank test). In the non-European trial, symptomatic recurrences occurred in 38.3% of patients in the dronedarone group and 44.5% of those in the placebo group (P=0.02 by the log-rank test). The corresponding numbers for the pooled data were 37.7% and 46.0% (P<0.001 by the log-rank test) (Table 2). The Prentice cumu-

**Table 1. (Continued.)**

Characteristic	European Trial		Non-European Trial		Combined Trials	
	Placebo (N=201)	Dronedarone (N=411)	Placebo (N=208)	Dronedarone (N=417)	Placebo (N=409)	Dronedarone (N=828)
Concomitant cardiovascular therapy — no. (%)						
Digoxin	42 (20.9)	51 (12.4)	53 (25.5)	94 (22.5)	95 (23.2)	145 (17.5)
Calcium-channel blocker (rate-lowering)	23 (11.4)	36 (8.8)	55 (26.4)	103 (24.7)	78 (19.1)	139 (16.8)
Beta-blocker (except sotalol)	124 (61.7)	245 (59.6)	114 (54.8)	208 (49.9)	238 (58.2)	453 (54.7)
Oral anticoagulant	142 (70.6)	273 (66.4)	149 (71.6)	298 (71.5)	291 (71.1)	571 (69.0)
Long-term antiplatelet therapy	64 (31.8)	135 (32.8)	88 (42.3)	191 (45.8)	152 (37.2)	326 (39.4)
Statin	52 (25.9)	95 (23.1)	79 (38.0)	168 (40.3)	131 (32.0)	263 (31.8)
ACE inhibitor	79 (39.3)	176 (42.8)	80 (38.5)	151 (36.2)	159 (38.9)	327 (39.5)
Previous antiarrhythmic treatment — no. (%)						
Class IA	19 (9.5)	39 (9.5)	21 (10.1)	43 (10.3)	40 (9.8)	82 (9.9)
Class IB	0	3 (0.7)	0	3 (0.7)	0	6 (0.7)
Class IC	69 (34.3)	120 (29.2)	39 (18.8)	70 (16.8)	108 (26.4)	190 (22.9)
Class II	61 (30.3)	137 (33.3)	6 (2.9)	22 (5.3)	67 (16.4)	159 (19.2)
Class III	8 (4.0)	31 (7.5)	19 (9.1)	55 (13.2)	27 (6.6)	86 (10.4)
Class IV	22 (10.9)	43 (10.5)	16 (7.7)	29 (7.0)	38 (9.3)	72 (8.7)
Amiodarone	56 (27.9)	101 (24.6)	70 (33.7)	142 (34.1)	126 (30.8)	243 (29.3)
Sotalol	59 (29.4)	129 (31.4)	53 (25.5)	85 (20.4)	112 (27.4)	214 (25.8)

\* Plus-minus values are means ±SD. NYHA denotes New York Heart Association, and ACE angiotensin-converting enzyme.

† Race was determined by the investigators on the basis of hospital records.

‡ The body-mass index was calculated as the weight in kilograms divided by the square of the height in meters. In the European trial, data were missing for six subjects in the placebo group and six in the dronedarone group; in the non-European trial, data were missing for four subjects in the placebo group and seven in the dronedarone group.

§ In the European trial, data were missing for six subjects in the placebo group and one in the dronedarone group; in the non-European trial, data were missing for two subjects in the placebo group and seven in the dronedarone group.

¶ The diagnosis of coronary artery disease was made on the basis of the clinical history and the results of investigational tests.

|| The diagnosis of congestive heart failure (NYHA class I and II) was made on clinical grounds. Patients who were classified as having NYHA class I congestive heart failure had received a diagnosis of the disease but had no symptoms.

lative incidence curves<sup>26</sup> for a symptomatic first recurrence for the pooled data are shown in the Supplementary Appendix.

(hazard ratio, 0.73; 95% CI, 0.57 to 0.93; P=0.01) (Table 2).

**HOSPITALIZATION OR DEATH**

In the European Trial, a post hoc analysis revealed that 21.2% of patients in the dronedarone group had been hospitalized or had died at 12 months, as compared with 32.0% of those in the placebo group (hazard ratio, 0.66; 95% CI, 0.47 to 0.93; P=0.02). In the non-European trial, 24.5% of patients in the dronedarone group had been hospitalized or had died, as compared with 29.8% of those in the placebo group (hazard ratio, 0.80; 95% CI, 0.56 to 1.14; P=0.22). The corresponding numbers in the combined analysis were 22.8% and 30.9%

**ADVERSE EVENTS**

Table 3 shows the incidence of selected adverse events in the two study groups. Most of these specific adverse events are shown because they include many of the known side effects of amiodarone. 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).

In addition to the events listed in Table 3, one patient in the dronedarone group received the diagnosis of interstitial lung disease, which was reported after the patient had completed the 1-year

**Table 2. Study End Points.\***

Variable	European Trial				Non-European Trial				Combined Trials			
	Placebo	Dronedarone	Hazard Ratio (95% CI)	P Value	Placebo	Dronedarone	Hazard Ratio (95% CI)	P Value	Placebo	Dronedarone	Hazard Ratio (95% CI)	P Value
Time to first recurrence of atrial fibrillation												
No. of patients	201	411			208	417			409	828		
Median (days)	41	96			59	158			53	116		
Recurrence rate at 12 mo (%)	77.5	67.1	0.78 (0.64–0.96)	0.01	72.8	61.1	0.73 (0.59–0.89)	0.002	75.2	64.1	0.75 (0.65–0.87)	<0.001
Recurrence rate at treatment analysis (%)	76.5	65.5	0.78 (0.64–0.95)	0.01	72.7	58.8	0.71 (0.57–0.88)	0.002	74.7	62.3	0.74 (0.64–0.86)	<0.001
Recurrence at 12 mo												
No. of patients	148	307			146	327			294	634		
Analysis excluding drug exposure of <5 days (%)	69.5	56.4	0.71 (0.56–0.91)	0.006	62.6	51.3	0.74 (0.57–0.96)	0.02	66.2	53.8	0.72 (0.60–0.86)	<0.001
First symptomatic atrial fibrillation	47.5	37.1	0.70 (0.54–0.90)	0.006	44.5	38.3	0.74 (0.57–0.96)	0.02	46.0	37.7	0.71 (0.60–0.86)	<0.001
Ventricular rate at first recurrence (with TTM)												
No. of patients	117	199			102	188			219	387		
Mean rate (bpm)	117.5±29.1	102.3±24.7		<0.001	116.6±31.9	104.6±27.1		<0.001	117.1±30.4	103.4±25.9		<0.001
Hospitalization or death (%)	32.0	21.2	0.66 (0.47–0.93)	0.02	29.8	24.5	0.80 (0.56–1.14)	0.22	30.9	22.8	0.73 (0.57–0.93)	0.01

\* Plus-minus values are means ±SD. TTM denotes transtelephonic monitoring.

**Figure 2. Kaplan–Meier Cumulative Incidence of the Adjudicated First Recurrence of Atrial Fibrillation or Flutter.**

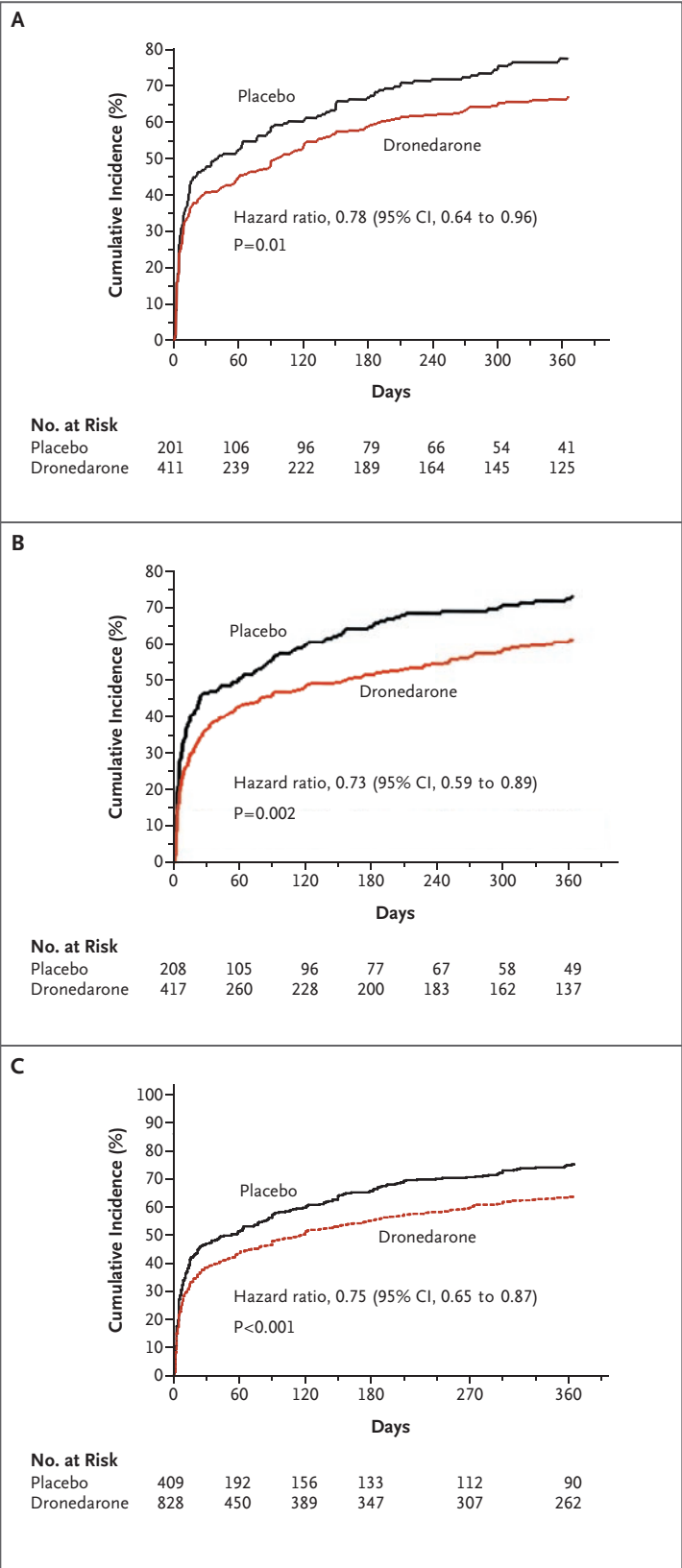
The times to recurrence of atrial fibrillation or flutter are shown for the European trial (Panel A), the non-European trial (Panel B), and the two trials combined (Panel C). The hazard ratios were determined for the dronedarone group as compared with the placebo group. CI denotes confidence interval.

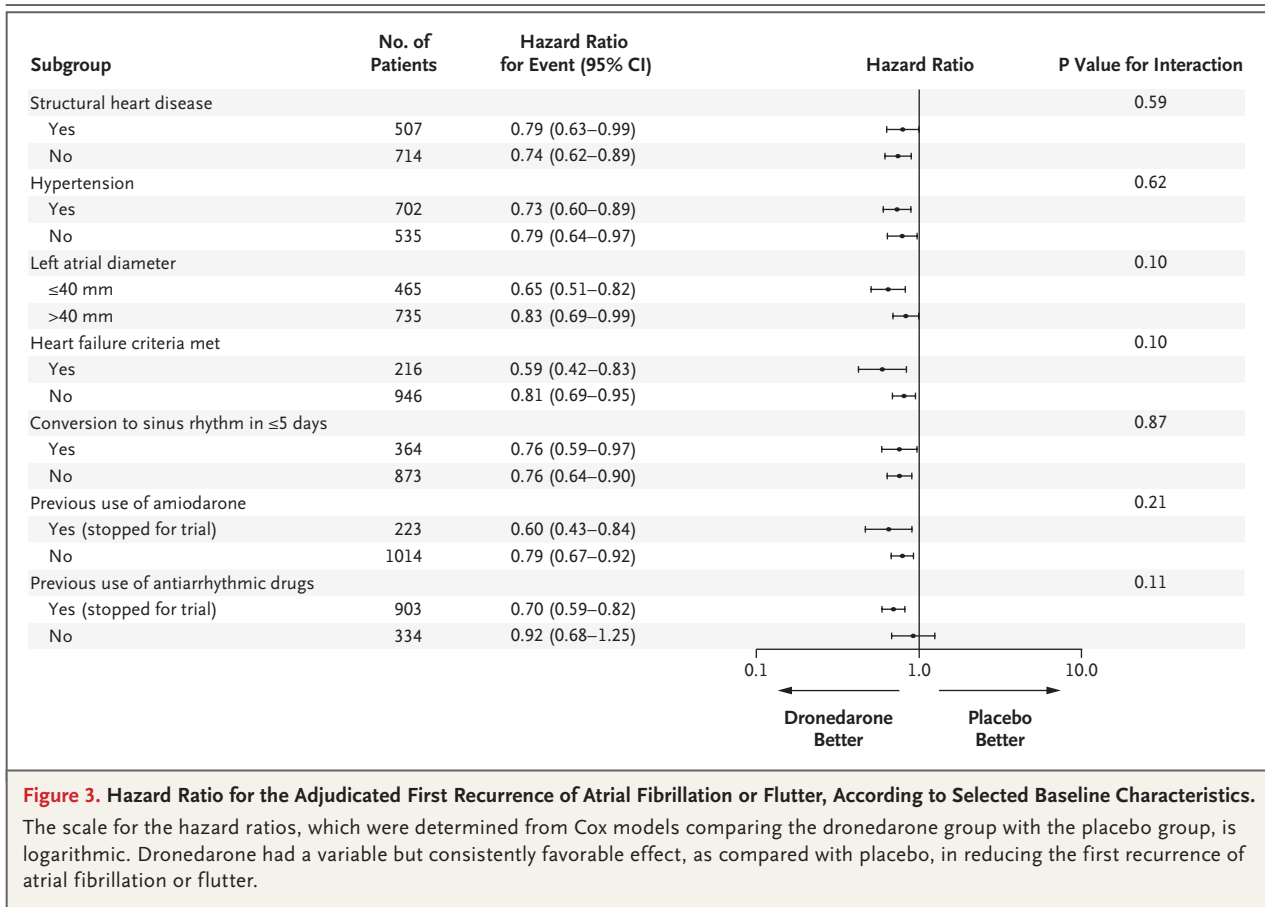
follow-up. This patient also had mitral-valve disease and a history of congestive heart failure and had had a viral infection during the week preceding the report of the diagnosis. The pulmonary findings subsequently resolved without sequelae. A second patient in the dronedarone group was reported to have pulmonary fibrosis, which on further investigation and blinded radiologic review had been present on chest radiography at baseline. Ventricular arrhythmias occurred infrequently in both study groups; no episodes of torsades de pointes were reported.

DISCUSSION

The European trial and the non-European trial were large, double-blind, placebo-controlled trials, each comparing the efficacy of dronedarone with that of placebo for the maintenance of sinus rhythm in patients with atrial fibrillation. We found that dronedarone reduced the incidence of a first recurrence, as well as a symptomatic first recurrence, within 12 months after randomization. Dronedarone also significantly reduced the ventricular rate during the recurrence of arrhythmia. In addition, in a post hoc analysis, dronedarone significantly reduced the rate of hospitalization or death.

In both the European and non-European trials, dronedarone prolonged the time to the recurrence of atrial fibrillation by a factor of more than 2, as compared with placebo. This finding is consistent with the drug’s propensity for markedly prolonging the atrial effective refractory period<sup>18,27</sup> by inducing multiple ion-channel blockade.<sup>15</sup> However, the effectiveness of dronedarone in maintaining sinus rhythm in atrial fibrillation cannot be reliably compared with that of amiodarone or sotalolol on the basis of these data. The latter agents have been evaluated in studies that may have differed markedly from our trials with respect to the trial design, study population, and pattern of atrial fibrillation (paroxysmal or persistent).<sup>3,24,28,29</sup> In our





**Figure 3. Hazard Ratio for the Adjudicated First Recurrence of Atrial Fibrillation or Flutter, According to Selected Baseline Characteristics.**

The scale for the hazard ratios, which were determined from Cox models comparing the dronedarone group with the placebo group, is logarithmic. Dronedaron had a variable but consistently favorable effect, as compared with placebo, in reducing the first recurrence of atrial fibrillation or flutter.

trials, patients were in sinus rhythm at the time of randomization, but the trial design did not permit a clear distinction between patients who had persistent atrial fibrillation and those with paroxysmal atrial fibrillation. It is likely that most of the patients in our trials who did not require direct-current cardioversion during the 5 days preceding randomization (71%) had paroxysmal atrial fibrillation or flutter. The results of the subgroup analyses underscore the consistent effectiveness of dronedarone in maintaining sinus rhythm in patients with atrial fibrillation encompassing a wide range of covariates.

In our trials, the effectiveness of 400 mg of dronedarone twice daily in maintaining sinus rhythm without major prolongation of either the QT or the QTc interval suggests a measure of atrial selectivity of the drug action, as reported in studies involving rabbit ventricular and atrial cells.<sup>17,18</sup> Amiodarone and dronedarone both limit the risk of torsades de pointes by attenuating after-depolarization activity in the M cell and Pur-

kinje fiber activity<sup>30–38</sup> in the ventricular myocardium. In the case of amiodarone, torsades de pointes is rare,<sup>32,33</sup> and to date an unequivocal case of torsades induced by dronedarone has not been noted despite the lengthening of the QT and QTc intervals by 23 and 9 msec, respectively, in our combined trials.

In neither of the trials did we directly compare dronedarone with amiodarone. Therefore, we cannot be certain that the efficacy of dronedarone is similar to that of amiodarone, nor can we state with certainty that the rate of adverse events is significantly lower. On the basis of experience with amiodarone in other trials, our findings suggest these conclusions, but a definitive answer will require a trial that directly compares the two drugs. Furthermore, the low rate of adverse events (especially pulmonary toxic effects) may be explained in part by the relatively short duration of our trials and by the fact that chest radiography and assessment of pulmonary function were not performed unless symptoms were present.

**Table 3. Selected Adverse Events and Laboratory Abnormalities.\***

Event	Treatment Group		P Value†
	Dronedarone (N=828)	Placebo (N=409)	
Death — no. (%)			
Any cause	8 (1.0)	3 (0.7)	1.00
Sudden death	4 (0.5)	1 (0.2)	1.00
Stroke — no. (%)‡	4 (0.5)	3 (0.7)	0.69
Pulmonary event — no. (%)§			
Cough	19 (2.3)	7 (1.7)	0.67
Dyspnea	27 (3.3)	15 (3.7)	0.74
Endocrine event — no./total no. (%)¶			
Hyperthyroidism	67/801 (8.4)	56/396 (14.1)	0.002
Hypothyroidism	44/801 (5.5)	14/396 (3.5)	0.15
Cardiac event — no. (%)			
Bradycardia or conduction block			
Any event	22 (2.7)	8 (2.0)	0.56
Serious event	8 (1.0)	3 (0.7)	1.00
Heart failure or shock**			
Any event	20 (2.4)	4 (1.0)	0.12
Serious event	13 (1.6)	3 (0.7)	0.29
Ventricular arrhythmia††	6 (0.7)	2 (0.5)	1.00
Neurologic event — no. (%)			
Insomnia or other sleep disorder	12 (1.4)	6 (1.5)	1.00
Memory impairment	1 (0.1)	0	1.00
Peripheral neuropathy	0	1 (0.2)	0.33
Paresthesia	11 (1.3)	4 (1.0)	0.78
Tremor	6 (0.7)	2 (0.5)	1.00
Gastrointestinal or hepatic event			
Diarrhea — no. (%)	59 (7.1)	20 (4.9)	0.14
Nausea — no. (%)	36 (4.3)	14 (3.4)	0.54
Abnormality of liver function — no./total no. (%)‡‡	100/822 (12.2)	55/405 (13.6)	0.52
Dermatologic event — no. (%)			
Photosensitivity or skin discoloration§§	6 (0.7)	1 (0.2)	0.44
Other			
Elevation of serum creatinine — no. (%)	20 (2.4)	1 (0.2)	0.004

\* Adverse events were defined as those occurring between the first administration of a study drug and the last administration plus 10 days.

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

‡ Stroke includes cerebral-artery embolism, cerebrovascular accident, cerebral infarction, and transient ischemic attack.

§ Dyspnea includes exacerbated, exertional, and nocturnal dyspnea.

¶ Hyperthyroidism was defined as a free triiodothyronine or free thyroxine level above the normal range or a thyrotropin level below the normal range. Hypothyroidism was defined as a free triiodothyronine or free thyroxine level below the normal range or a thyrotropin level above the normal range. Patients with inconsistent changes in these measures were excluded from the analysis.

|| Bradycardia or conduction block includes complete atrioventricular block. Serious adverse events include complete atrioventricular block, sinus bradycardia, first-degree atrioventricular block, and nodal arrhythmia.

\*\* Heart failure or shock includes congestive cardiac failure, cardiac failure, left ventricular failure, and right ventricular failure. Serious adverse events include congestive cardiac failure, cardiac failure, left ventricular failure, cardiogenic shock, and ventricular dysfunction.

†† Ventricular arrhythmia includes ventricular tachycardia, ventricular extrasystoles, and ventricular fibrillation.

‡‡ An abnormality of liver function was defined as a level of alanine aminotransferase or aspartate aminotransferase of more than 2 times the upper limit of the normal range, an alkaline phosphatase level of more than 1.5 times the upper limit of the normal range, a  $\gamma$ -glutamyltransferase level of 3 times the upper limit of the normal range or more, or a total bilirubin level of 2 mg per deciliter (34  $\mu$ mol per liter) or more. Patients with no abnormality and with at least one missing measurement of liver function were excluded.

§§ Photosensitivity or skin discoloration includes photosensitive rash and photosensitivity reaction.

As in many other trials examining the efficacy of treatments for atrial fibrillation, it is likely that we were not able to detect every episode of recurrent arrhythmia in our study patients. Follow-up electrocardiograms were obtained at frequent intervals and in the case of symptoms. The fact that the majority of first documented recurrences were symptomatic strongly suggests that not all episodes were detected, since the majority of episodes of atrial fibrillation in the general population may be asymptomatic. Continuous monitoring of all study patients over the long term was beyond the scope of these trials and typically has not been considered essential for the interpretation of such studies.

A previous study, the Antiarrhythmic Trial with Dronedaron in Moderate to Severe Congestive Heart Failure Evaluating Morbidity Decrease (ANDROMEDA), was discontinued early because an interim safety analysis suggested a potential increase in the risk of death with dronedarone therapy. The discontinued trial involved patients with moderate-to-severe congestive heart failure and ventricular dysfunction, and thus investigated a different (and higher-risk) population than the patients we studied. In our trials, the rates of death from any cause and sudden death in the dronedarone group did not differ significantly from those in the placebo group. Nonetheless, the experience with the ANDROMEDA trial indicates that dronedarone may be associated with an increased risk

of death in patients with advanced congestive heart failure and that the drug should not be used in such patients until appropriate data are gathered.

In conclusion, our trials showed that the rates of the first recurrence of atrial fibrillation and of the first symptomatic recurrence at 1 year were significantly reduced with dronedarone, as compared with placebo. Dronedarone also reduced the ventricular rate in atrial fibrillation during recurrences of arrhythmia. The available data are not directive with respect to the rates of adverse effects, as compared with those of amiodarone.

Supported by Sanofi-Aventis.

Dr. Singh reports receiving consulting and lecture fees from CV Therapeutics, Sanofi-Aventis, GlaxoSmithKline, Astellas, and Procter & Gamble Pharmaceuticals; Dr. Hohnloser, consulting fees from Sanofi-Aventis, St. Jude Medical, Boehringer Ingelheim, Procter & Gamble Pharmaceuticals, and Solvay Pharmaceuticals and lecture fees from Sanofi-Aventis and St. Jude Medical; Dr. Connolly, consulting and lecture fees from Sanofi-Aventis and grant support from Sanofi-Aventis, Boehringer Ingelheim, and St. Jude Medical; Dr. Crijns, consulting fees from Sanofi-Aventis, AstraZeneca, Cardiome, and Meda Pharma, lecture fees from Sanofi-Aventis, AstraZeneca, St. Jude Medical, and Meda Pharma, and grant support from Medtronic, St. Jude Medical, and Sanofi-Aventis; Dr. Roy, consulting and lecture fees from Sanofi-Aventis, Astellas, and Cardiome and grant support from the Canadian Institutes of Health Research; Dr. Kowey, consulting fees from Sanofi-Aventis, Reliant, Cardiome, Astellas, Procter & Gamble Pharmaceuticals, and Solvay Pharmaceuticals and lecture fees from Sanofi-Aventis; Dr. Capucci, consulting fees from CV Therapeutics and St. Jude Medical and lecture fees from Sanofi-Aventis, Meda Pharma, and Pfizer; Dr. Radzik, being employed by Sanofi-Aventis and having equity interest in the company; and Dr. Aliot, consulting and lecture fees from Sanofi-Aventis, Meda Pharma, and Sorin-Ela. No other potential conflict of interest relevant to this article was reported.

#### APPENDIX

The following authors and other investigators participated in the European trial and the non-European trial: **Steering Committee:** B.N. Singh (chair), E. Aliot, A. Capucci, S.J. Connolly, H.J.G.M. Crijns, S. Hohnloser, P. Kowey, L.D. Roy, and D. Radzik. **Data and Safety Monitoring Board:** Lyon, France — A. Leizorovicz (chair); London — J. Camm; Miami — R. Myerburg.

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