DOFETILIDE IN PATIENTS WITH CONGESTIVE HEART FAILURE AND LEFT VENTRICULAR DYSFUNCTION

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ABSTRACT

Background   Atrial fibrillation occurs frequently in patients with congestive heart failure and commonly results in clinical deterioration and hospitalization. Sinus rhythm may be maintained with antiarrhythmic drugs, but some of these drugs increase the risk of death.

Methods   We studied 1518 patients with symptomatic congestive heart failure and severe left ventricular dysfunction at 34 Danish hospitals. We randomly assigned 762 patients to receive dofetilide, a novel class III antiarrhythmic agent, and 756 to receive placebo in a double-blind study. Treatment was initiated in the hospital and included three days of cardiac monitoring and dose adjustment. The primary end point was death from any cause.

Results   During a median follow-up of 18 months, 311 patients in the dofetilide group (41 percent) and 317 patients in the placebo group (42 percent) died (hazard ratio, 0.95; 95 percent confidence interval, 0.81 to 1.11). Treatment with dofetilide significantly reduced the risk of hospitalization for worsening congestive heart failure (risk ratio, 0.75; 95 percent confidence interval, 0.63 to 0.89). Dofetilide was effective in converting atrial fibrillation to sinus rhythm. After one month, 22 of 190 patients with atrial fibrillation at base line (12 percent) had sinus rhythm restored with dofetilide, as compared with only 3 of 201 patients (1 percent) given placebo. Once sinus rhythm was restored, dofetilide was significantly more effective than placebo in maintaining sinus rhythm (hazard ratio for the recurrence of atrial fibrillation, 0.35; 95 percent confidence interval, 0.22 to 0.57; P<0.001). There were 25 cases of torsade de pointes in the dofetilide group (3.3 percent) as compared with none in the placebo group.

Conclusions   In patients with congestive heart failure and reduced left ventricular function, dofetilide was effective in converting atrial fibrillation, preventing its recurrence, and reducing the risk of hospitalization for worsening heart failure. Dofetilide had no effect on mortality. (N Engl J Med 1999;341:857-65.)
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CONGESTIVE heart failure is a serious disease that can be exacerbated by many factors unrelated to ventricular dysfunction. One important factor in determining the symptoms and clinical course of patients with severe congestive heart failure is the maintenance of sinus rhythm. Unfortunately, atrial fibrillation is common in patients with heart failure and can impair exercise tolerance, exacerbate symptoms, and have hemodynamic and thromboembolic consequences.[1-4] Although digitalis can attenuate the ventricular response in patients at rest, it fails to do so during exercise and thus does not eliminate the effect of atrial fibrillation on exercise tolerance.[5] In addition, previous studies have shown that atrial fibrillation increases the risk of cardiovascular morbidity among patients with heart failure.[6] Hence, prevention or conversion of atrial fibrillation is a worthwhile goal in patients with congestive heart failure.

Currently available drug therapy to prevent or convert atrial fibrillation can have adverse effects in patients with heart failure, including an increase in the risk of death.[7] Patients with heart failure who were receiving class I drugs for atrial fibrillation had an increase by a factor of three in the risk of both death and death from arrhythmia.[7] Quinidine therapy has also been associated with a threefold increase in the risk of death.[8] The only exception has been the class

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III drug amiodarone[9,10]; however, this drug is frequently associated with serious noncardiac side effects and is poorly tolerated.[11]

Dofetilide is a novel class III antiarrhythmic drug that selectively inhibits the rapid component of the delayed rectifier potassium current and prolongs the refractory period.[12-14] As a pure class III agent, it has no negative inotropic effects, even in patients with markedly reduced left ventricular function.[15] In addition, dofetilide does not affect cardiac conduction or sinus-node function in patients with preexisting cardiac disease.[15,16] In patients with atrial fibrillation, dofetilide has been shown to restore and maintain sinus rhythm.[17,18,24]

We designed the Danish Investigations of Arrhythmia and Mortality on Dofetilide in Congestive Heart Failure (DIAMOND-CHF) Study to evaluate whether dofetilide affects survival or morbidity among patients with reduced left ventricular function and congestive heart failure. At the time the study was initiated, we anticipated that the drug would be effective in treating both atrial and ventricular arrhythmias. However, the results of clinical trials indicated that dofetilide was primarily effective in patients with atrial fibrillation,[18,24] and this paper focuses on the use of dofetilide for that condition.

METHODS

Study Population

The design of the study has been described previously.[19] It was conducted at 34 hospitals in Denmark. Consecutive patients who were hospitalized with new or worsening congestive heart failure and who within the preceding month 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 were screened for entry. At screening, an echocardiogram was recorded on videotape and evaluated in a central laboratory within one working day to ensure consistency of screening methods and determine eligibility. The wall-motion index was measured as described previously,[20] with use of a 16-segment model[21] of the left ventricle. Patients were eligible for the study if they had a wall-motion index of no more than 1.2 (corresponding roughly to an ejection fraction of no more than 35 percent), were at least 18 years old, were postmenopausal or were using a reliable means of contraception, and provided written informed consent. Patients with acute myocardial infarction within seven days before screening were excluded from the study. Other exclusion criteria were a heart rate of less than 50 beats per minute during waking hours, sinoatrial block or second- or third-degree atrioventricular block that was not treated with a pacemaker, a history of drug-induced proarrhythmia, a corrected QT interval exceeding 460 msec (500 msec in patients with bundle-branch block), a diastolic blood pressure of more than 115 mm Hg, a systolic blood pressure of less than 80 mm Hg, a serum potassium level of less than 3.6 mmol per liter or more than 5.5 mmol per liter, recent use of class I or III antiarrhythmic drugs, a calculated creatinine clearance rate of less than 20 ml per minute,[22] serious liver dysfunction, acute myocarditis, planned cardiac surgery or angioplasty, aortic stenosis, cardiac surgery within the preceding four weeks, and the presence of an implantable cardioverter–defibrillator.

Organization and Design of the Study

The Danish Board of Health and the Central Danish Ethics Committee approved the protocol, which was conducted in accordance with the Declaration of Helsinki II and Guidelines for Good Clinical Practice in the European Union. The study was led by a steering committee. Members of an events committee reviewed available data on a blinded basis and classified deaths as being of cardiac origin unless specific evidence of a noncardiac origin was present. Deaths from cardiac causes were further classified as due to documented arrhythmia, presumed arrhythmia, or other causes according to previously published criteria,[23] except that successful resuscitation after cardiac arrest was not included. Members of the arrhythmia committee classified episodes of arrhythmia when electrocardiograms were available. An episode of polymorphic ventricular tachycardia was classified as torsade de pointes if any of the following was present: a heart rate of no more than 50 beats per minute before the episode, a QT interval of more than 0.45 second, an abnormal and shifting T-wave configuration, ventricular extrasystoles with a long–short coupling interval, or a typical twisting QRS axis.

Eligible patients were randomly assigned to double-blind treatment that was stratified according to center and the degree of left ventricular dysfunction (a wall-motion index of less than 0.8 or of 0.8 or more). All patients were hospitalized and monitored continuously for the first 72 hours of treatment to ensure that any early arrhythmic events were immediately recognized and treated.

Initially, a 500-μg dose of dofetilide was given twice daily to patients who did not have atrial fibrillation, and a 250-μg dose was given twice daily to patients who did have atrial fibrillation. After 288 patients had been enrolled, the dose was changed on the basis of data from other clinical trials of dofetilide. Thereafter, the initial dose for all patients was selected on the basis of calculated creatinine clearance.[22] Patients with a creatinine clearance of 40 to less than 60 ml per minute were given 250 μg of dofetilide twice daily, and those with a creatinine clearance of 20 to less than 40 ml per minute were given 250 μg of dofetilide once daily. The minimal dose was 250 μg once daily, and further adjustments were made as necessary in patients with excessive prolongation of the QT or corrected QT interval (more than 20 percent longer than base-line values or longer than 550 msec) or adverse effects. If a reduction was required at the lowest possible dose, dofetilide was discontinued. The dose could also be reduced at the discretion of the investigator. A proarrhythmic event always triggered discontinuation of treatment. Patients' compliance was estimated by a pill count at each visit.

Patients were seen one month and three months after the initiation of therapy and every three months thereafter. The study continued as scheduled until one year after the last patient had been enrolled. Vital status was monitored through the Danish Central Person Registry, in which all deaths in the country are registered within two weeks of their occurrence. Follow-up was complete for all patients.

Members of an independent data and safety monitoring board reviewed the results of four preplanned interim analyses during the course of the study and on each occasion recommended that the study be continued.

End Points

The primary end point was death from any cause. Secondary end points included death from cardiac causes, death from arrhythmia, death from cardiac causes or successful resuscitation after cardiac arrest, arrhythmias requiring treatment, worsening congestive heart failure, and myocardial infarction. In patients with atrial fibrillation at base line, the total numbers of deaths, strokes, and systemic embolisms were also analyzed. Mortality was reanalyzed after the exclusion of data obtained before the protocol was amended to allow a reduction in the dose according to creatinine clearance. Worsening congestive heart failure was defined as the need for both hospitalization for congestive heart failure and an increase in the dose of medication for congestive heart failure or a change of medication. The incidence of conversion to and maintenance of sinus rhythm in patients with atrial fibrillation at base line was analyzed as part of a predefined substudy.

TABLE 1. CHARACTERISTICS OF THE PATIENTS
AT BASE LINE.*

CHARACTERISTIC	DOFETILIDE (N=762)	PLACEBO (N=756)
Median duration of heart failure — mo	12	12
Age — yr		
Mean	70	70
Range	26–94	32–92
Male sex — no. (%)	546 (72)	568 (75)
Current smoker — no. (%)	254 (33)	268 (35)
Medical history — no. (%)		
Myocardial infarction	389 (51)	390 (52)
Ischemic heart disease	509 (67)	508 (67)
Diabetes	152 (20)	140 (19)
Hypertension	111 (15)	115 (15)
Creatinine clearance — ml/min	57±23	57±25
Atrial fibrillation — no. (%)	190 (25)	201 (27)
Wall-motion index		
Median	0.9	0.9
Range	0.3–1.2	0.3–1.2
Medications at randomization — no. (%)		
Beta-blocker	72 (9)	80 (11)
ACE inhibitor	552 (72)	571 (76)
Calcium-channel blocker	153 (20)	170 (22)
NYHA functional class — no. (%)		
I	16 (2)	17 (2)
II	268 (35)	297 (39)
III	423 (56)	385 (51)
IV	49 (6)	52 (7)
Not available	6 (<1)	5 (<1)

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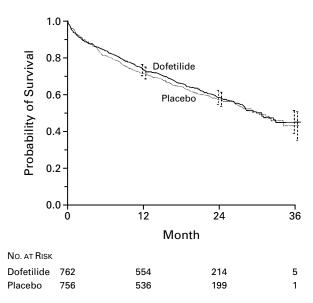
Statistical Analysis

The times to various events were analyzed by a two-sided logrank test, which was stratified according to center and wall-motion index. The Kaplan–Meier method was used to construct life-table plots. Hazard ratios were obtained from Cox's proportional-hazard models, after adjustment for center and wall-motion index.

RESULTS

Characteristics of the Patients

A total of 5548 patients with congestive heart failure were screened, and 2531 (46 percent) had a wall-motion index of no more than 1.2 and were therefore eligible for the study. Approximately 4 percent of this population was screened more than once, resulting in 5812 screenings. Twenty-seven percent of the screened population (1518 patients) underwent randomization: 762 patients were assigned to receive dofetilide, and 756 patients to placebo. The baseline characteristics of the two groups were similar (Table 1). Among the patients who were alive at one year, 421 patients (76 percent of the survivors) were still receiving dofetilide and 397 (74 percent of the survivors) were still receiving placebo. The median duration of therapy was 383 days in the dofetilide

Figure 1. Kaplan–Meier Estimates of the Probability of Survival, According to the Intention to Treat.

I bars indicate 95 percent confidence intervals. The hazard ratio for the dofetilide group was 0.95 (95 percent confidence interval, 0.81 to 1.11).

group and 371 days in the placebo group. The median follow-up was 18 months. No patient was lost to follow-up.

Survival

A total of 628 patients in the study died: 311 in the dofetilide group (41 percent) and 317 in the placebo group (42 percent). Survival in the two groups did not differ significantly (Fig. 1). The survival rate at one year among the patients who were still receiving their assigned treatment (on-treatment analysis) was 89 percent in each group, and when the rates were compared for the entire duration of the study, no significant difference was found between the two groups (P=0.54). Similarly, there were no significant differences in survival when the analysis included only the patients who were enrolled after the change in the protocol, which allowed a reduction in the dose according to creatinine clearance (P=0.49).

Table 2 shows the causes of death in both groups, and Table 3 shows the relative risk of death in the dofetilide group as compared with the placebo group in predefined subgroups. There was no significant difference in the risk of death in all subgroup analyses, including an analysis of subgroups classified according to the presence or absence of atrial fibrillation or flutter at base line (Fig. 2A and 2B).

Other Clinical Outcomes

As compared with the placebo group, the dofetilide group had a lower rate of hospitalization for worsen-

TABLE 2. CAUSES OF DEATH.

CAUSE OF DEATH	DOFETILIDE (N=762)	PLACEBO (N=756)
	number (percent)	
Cardiac	255 (33)	251 (33)
Arrhythmia	156 (20)	151 (20)
Presumed	111 (15)	101 (13)
Documented	28 (4)	28 (4)
Unclassified*	17 (2)	22 (3)
Noncardiac	56 (7)	66 (9)
Total	311 (41)	317 (42)

*Unclassified deaths were analyzed as deaths that were presumed to be due to arrhythmia.

ing heart failure (30 percent vs. 38 percent) and a lower incidence of hospitalizations for worsening heart failure (352 events vs. 422 events). The percentage of patients with an improvement in NYHA class was similar in the dofetilide group and the placebo group (35 percent vs. 30 percent, P=0.18). Figures 2C and 2D show the time to hospitalization for worsening heart failure according to the presence or absence of atrial fibrillation at base line. Treatment with dofetilide significantly reduced the overall risk of hospitalization for worsening heart failure (P<0.001; risk ratio, 0.75; 95 percent confidence interval, 0.63 to 0.89) regardless of whether atrial fibrillation was present or absent at base line. There were no other significant differences between groups with respect to secondary end points (the hazard ratios ranged from 0.66 to 1.62).

Patients with atrial fibrillation at base line more often had conversion to sinus rhythm after one month of treatment with dofetilide (spontaneous cardioversion in 12 percent [22 of 190] and electrical cardioversion in 2 percent [3 of 190]) than after one month of treatment with placebo (1 percent and 1 percent [3 of 201 and 2 of 202], respectively). The overall rates of cardioversion at 12 months were also higher in the dofetilide group than in the placebo group (spontaneous cardioversion, 44 percent vs. 13 percent; electrical cardioversion, 17 percent vs. 20 percent). These differences were statistically significant at 1 month (P<0.001) and 12 months (P<0.001) for pharmacologic cardioversion but not for electrical cardioversion (P=0.68 and P=0.37, respectively). Once cardioversion had occurred by either pharmacologic or electrical means, the likelihood that sinus rhythm would be maintained was significantly higher (P<0.001) in the dofetilide group than in the placebo group (Fig. 3). Similarly, among the patients who were known to be in sinus rhythm at base line, atrial fibrillation developed less often with dofetilide therapy than with placebo (11 of 556 patients vs. 35

of 534 patients, P<0.001). The incidence of the composite end point of a first event of death, stroke, or arterial embolism among patients with atrial fibrillation at base line was similar in the two groups, representing 52 of 190 events in the dofetilide group and 54 of 201 events in the placebo group (P=0.85).

Adverse Events

The overall rates of adverse events and discontinuation of treatment did not differ significantly between the two groups. However, prolongation of the corrected QT interval was a more frequent reason for discontinuation in the dofetilide group than in the placebo group (14 patients vs. 3 patients, 2 percent vs. 0.4 percent). The peak increase in the corrected QT interval occurred within the first two days of treatment.

Using predefined criteria, the members of the arrhythmia committee identified 25 cases of torsade de pointes in the dofetilide group and no cases in the placebo group (Table 4). Of these episodes, 15 required electrical cardioversion and 2 resulted in death. Nineteen of the 25 episodes (76 percent, including the 2 that were fatal) occurred within three days after the initiation of therapy. Cardiac monitoring during the first three days of treatment showed that there were five additional episodes of cardiac arrest followed by resuscitation in the dofetilide group and three in the placebo group in the absence of torsade de pointes. Of the 146 patients who were assigned to receive dofetilide before the protocol was amended, 7 had torsade de pointes (4.8 percent), as compared with 18 in the group of 616 patients (2.9 percent) who underwent randomization after the protocol was amended. Adjusting the dose according to renal function and continuous cardiac monitoring during the first three days of treatment reduced the risk of torsade de pointes. The frequency of other ventricular arrhythmias was similar in the two groups (Table 4). A linear logistic-regression analysis revealed that only female sex (odds ratio, 3.2) and a NYHA class of III or IV at base line (odds ratio, 3.9 for the comparison with a NYHA class of I or II) were significantly associated with the occurrence of torsade de pointes once the dose of dofetilide had been adjusted according to creatinine clearance.

DISCUSSION

Our study demonstrates that long-term use of dofetilide, with the dose adjusted according to renal function, is not associated with an increased risk of death among patients with congestive heart failure and reduced left ventricular function. The finding was the same in all subgroups studied, including patients with atrial fibrillation at base line and those without it.

Dofetilide, however, effectively restored and maintained sinus rhythm in patients with atrial fibrillation.

TABLE 3. INCIDENCE OF DEATH FROM ANY CAUSE, THE PRIMARY END POINT.*

VARIABLE	DOFETILIDE (N=762)	PLACEBO (N=756)	HAZARD RATIO (95% CI)†
	no. with ≥1 event/no. randomized (%)		
Median age			
≤71 yr	128/401 (31.9)	138/388 (35.6)	0.88 (0.69–1.12)
>71 yr	183/361 (50.7)	179/368 (48.6)	1.03 (0.83–1.26)
Sex			
Male	228/546 (41.8)	237/568 (41.7)	1.00 (0.83–1.20)
Female	83/216 (38.4)	80/188 (42.6)	0.85 (0.62–1.15)
NYHA class‡			
I	5/16 (31.2)	6/17 (35.3)	0.88 (0.27–2.88)
II	86/268 (32.1)	108/297 (36.4)	0.84 (0.63–1.12)
III	186/423 (44.0)	169/385 (43.9)	0.98 (0.79–1.20)
IV	32/49 (65.3)	34/52 (65.4)	1.13 (0.70–1.84)
Previous myocardial infarction			
No	138/373 (37.0)	137/366 (37.4)	1.02 (0.81–1.30)
Yes	173/389 (44.5)	180/390 (46.2)	0.90 (0.73–1.11)
Smoking status§			
Formerly or never smoked	213/505 (42.2)	212/486 (43.6)	0.95 (0.79–1.15)
Currently smokes	96/254 (37.8)	104/268 (38.8)	0.94 (0.71–1.24)
Diabetes			
No	239/610 (39.2)	243/616 (39.4)	0.97 (0.81–1.16)
Yes	72/152 (47.4)	74/140 (52.9)	0.88 (0.64–1.22)
Hypertension			
No	265/651 (40.7)	274/641 (42.7)	0.92 (0.78–1.09)
Yes	46/111 (41.4)	43/115 (37.4)	1.19 (0.78–1.81)
Median wall-motion index			
≤0.9	197/445 (44.3)	195/413 (47.2)	0.87 (0.72–1.06)
>0.9	114/317 (36.0)	122/343 (35.6)	1.06 (0.82–1.36)
Presence of ischemia¶			
No	88/253 (34.8)	80/248 (32.3)	1.18 (0.87–1.59)
Yes	223/509 (43.8)	237/508 (46.7)	0.87 (0.73–1.05)
Creatinine clearance rate‖			
≤52.85 ml/min	192/383 (50.1)	196/372 (52.7)	0.93 (0.77–1.14)
>52.85 ml/min	116/375 (30.9)	118/379 (31.1)	0.97 (0.75–1.25)
Treatment with beta-blocker			
No	282/690 (40.9)	295/676 (43.6)	0.91 (0.77–1.07)
Yes	29/72 (40.3)	22/80 (27.5)	1.55 (0.89–2.70)
Treatment with ACE inhibitor			
No	90/210 (42.9)	85/185 (45.9)	0.88 (0.65–1.18)
Yes	221/552 (40.0)	232/571 (40.6)	0.98 (0.81–1.18)
Treatment with calcium-channel blocker			
No	246/609 (40.4)	248/586 (42.3)	0.93 (0.78–1.11)
Yes	65/153 (42.5)	69/170 (40.6)	1.06 (0.76–1.49)
Atrial fibrillation or flutter			
No	227/572 (39.7)	229/555 (41.3)	0.94 (0.78–1.13)
Yes	84/190 (44.2)	88/201 (43.8)	1.00 (0.74–1.35)

*NYHA denotes New York Heart Association, and ACE angiotensin-converting enzyme.

†Hazard ratios are for the dofetilide group. Hazard ratios and confidence intervals (CIs) were estimated with the Cox proportional-hazards model. There was no evidence of an interaction between treatment group and any variable, nor was there any significant difference in results between the two groups.

‡Data were missing for six patients in the dofetilide group and five in the placebo group.

§Data were missing for three patients in the dofetilide group and two in the placebo group.

¶The presence of ischemia was determined on the basis of the patient's history, symptoms, and electrocardiographic findings.

‖Data were missing for four patients in the dofetilide group and five in the placebo group.
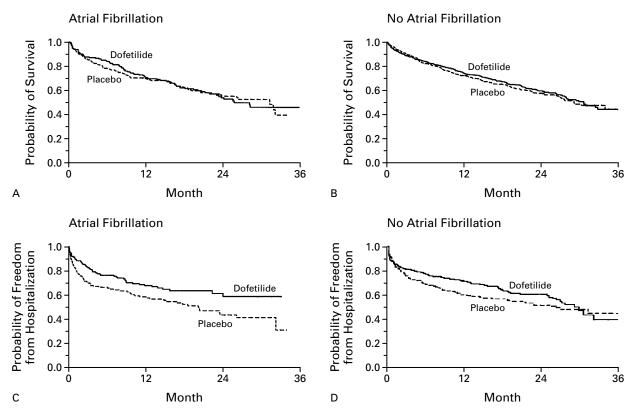
Figure 2. Kaplan–Meier Estimates of the Probability of Survival and of Freedom from Hospitalization for Worsening Congestive Heart Failure, According to the Presence or Absence of Atrial Fibrillation at Base Line.

Panel A shows the probability of survival among patients with atrial fibrillation at base line (hazard ratio for the dofetilide group, 1.01; 95 percent confidence interval, 0.75 to 1.36). Panel B shows the probability of survival among patients without atrial fibrillation at base line (hazard ratio, 0.94; 95 percent confidence interval, 0.78 to 1.13). Panel C shows the probability of freedom from hospitalization for worsening congestive heart failure among patients with atrial fibrillation at base line (hazard ratio, 0.64; 95 percent confidence interval, 0.46 to 0.91). Panel D shows the probability of freedom from hospitalization for worsening congestive heart failure among patients without atrial fibrillation at base line (hazard ratio, 0.80; 95 percent confidence interval, 0.65 to 0.98).

This finding is similar to that of two other double-blind, placebo-controlled studies,[18,24] which reported that oral dofetilide converted atrial fibrillation to sinus rhythm in 29 percent and 30 percent of patients and was associated with a probability of continued sinus rhythm at six months of 62 percent and 71 percent. Therefore, if initiated in the hospital together with continuous cardiac monitoring, dofetilide therapy can be used to treat patients with congestive heart failure and atrial fibrillation. This conclusion is similar to that reached in the recent analysis of the effect of amiodarone on atrial fibrillation in patients with heart failure.[25] In our study, dofetilide also reduced the risk of atrial fibrillation in patients with congestive heart failure who were in sinus rhythm at enrollment.

Among the secondary end points in our study, the risk of hospitalization for worsening congestive heart failure was significantly reduced among patients who received dofetilide. Although no definitive explanation can be provided for this result, the beneficial effect of dofetilide on atrial fibrillation may have had a role.

Overall, 76 percent of the episodes of torsade de pointes occurred within the first three days of dofetilide therapy, consistent with our observation that the peak increase in the corrected QT interval occurred within the first two days of treatment with dofetilide. These observations support the importance of initiating dofetilide therapy in the hospital together with three days of cardiac monitoring. Episodes of torsade de pointes may have been overlooked after the first three days of monitoring, but any further episodes that may have occurred were not associated with an increase in the mortality rate.

In addition to reducing the risk of hospitalization for worsening congestive heart failure and increasing the incidence of conversion to and maintenance of sinus rhythm, treatment with dofetilide did not in-
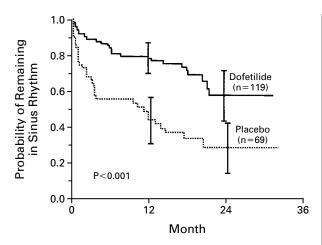
Figure 3. Kaplan–Meier Estimate of the Probability of Remaining in Sinus Rhythm among Patients Who Had Atrial Fibrillation or Flutter at Base Line That Was Successfully Pharmacologically or Electrically Cardioverted to Sinus Rhythm.

I bars indicate 95 percent confidence intervals. The hazard ratio for the dofetilide group was 0.35 (95 percent confidence interval, 0.22 to 0.57).

TABLE 4. CLASSIFICATION OF VENTRICULAR ARRHYTHMIAS BY THE ARRHYTHMIA EVENTS COMMITTEE.

EVENT	DOFETILIDE (N=762)	PLACEBO (N=756)
	number (percent)	
Torsade de pointes	25 (3.3)	0
Before change in dosing protocol	7 (4.8)*	—
After change in dosing protocol	18 (2.9)†	—
Polymorphic ventricular tachycardia	3 (0.4)	4 (0.5)
Monomorphic ventricular tachycardia	12 (1.6)	13 (1.7)
Ventricular fibrillation	13 (1.7)	12 (1.6)

*A total of 146 patients were enrolled and treated according to the original protocol.

†A total of 616 patients were enrolled and treated with dofetilide according to the amended protocol.

crease the risk of secondary end points, including death from presumed or documented arrhythmia. Thus unlike some class IA, class IC, and class III drugs, dofetilide does not affect survival adversely.[26,27] To date, no convincing evidence has been found that any antiarrhythmic drug decreases the risk of death among patients with advanced ventricular dysfunction. Although two studies reported that amiodarone reduced the risk of death or sudden death,[9,28] these results were not confirmed in other, larger trials.[10,29,30]

The characteristics of the patients who are enrolled in clinical trials and selection biases influence the study end points. The Trandolapril Cardiac Evaluation Study[31,32] used strict methods of screening and enrollment of consecutive patients to maximize the number of eligible patients. We used the same overall strategy of recruiting a substantial number of high-risk patients from a limited number of centers in this study. The overall mortality rate in our study was similar to that in one study of amiodarone[9] but much higher than that in another such study.[10]

The mortality rate in the Survival with Oral *d*-Sotalol (SWORD) study[27] was much lower than in our study. The difference may be explained by important differences in study design that preclude a direct comparison between the two studies. For example, patients in the SWORD study were less acutely ill, were not selected consecutively, and were not hospitalized when treatment was begun. The greatest reduction in the risk of death in the SWORD study was in the patients with a remote history of myocardial infarction and an ejection fraction of 31 to 40 percent,[33] a group that we did not evaluate.

Important differences between the available class III agents, however, should be considered. Dofetilide blocks a single potassium channel — the delayed rectifier potassium current — whereas amiodarone affects potassium channels, calcium channels, sodium channels, and a beta-adrenergic receptor.[34] Sotalol is also less selective than dofetilide, because it affects three ion channels, inhibits acetylcholinesterase, and has residual beta-blocking actions.[13] The extent to which these differences in action influence the clinical effect of these agents is unknown. The specificity of the action of dofetilide results in good long-term tolerability, allowing patients — even those with clinically significant structural heart disease and reduced left ventricular function — to continue treatment.

In conclusion, dofetilide did not increase the risk of death among patients with congestive heart failure and reduced left ventricular function, was effective for the treatment of atrial fibrillation, and significantly reduced the risk of hospitalization for worsening congestive heart failure. The dose of dofetilide must be titrated carefully according to renal function, and treatment must be initiated together with a minimum of 72 hours of cardiac monitoring.

APPENDIX

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