

Efficacy of Dofetilide in the Treatment of Atrial Fibrillation-Flutter in Patients With Reduced Left Ventricular Function

A Danish Investigations of Arrhythmia and Mortality ON Dofetilide (DIAMOND) Substudy

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Background—In patients with left ventricular dysfunction, atrial fibrillation and flutter (AF and AFL, respectively) are common arrhythmias associated with increased morbidity and mortality. The present study investigated the potential of dofetilide in AF-AFL patients with left ventricular dysfunction to restore and maintain sinus rhythm, which might reduce mortality and hospitalizations.

Methods and Results—In the Danish Investigations of Arrhythmia and Mortality ON Dofetilide (DIAMOND) studies, 506 patients were in AF-AFL at baseline. Over the course of study, cardioversion occurred in 148 (59%) dofetilide- and 86 (34%) placebo-treated patients. In these patients, the probability of maintaining sinus rhythm for 1 year was 79% with dofetilide versus 42% with placebo ($P < 0.001$). Dofetilide had no effect on all-cause mortality, but restoration and maintenance of sinus rhythm was associated with significant reduction in mortality (risk ratio [RR], 0.44; 95% CI, 0.30 to 0.64; $P < 0.0001$). In addition, dofetilide therapy was associated with a significantly lower risk ratio versus placebo for either all-cause (RR, 0.70; 95% CI, 0.56 to 0.89; $P \leq 0.005$) or congestive heart failure (RR, 0.69; 95% CI, 0.51 to 0.93; $P \leq 0.02$) rehospitalization.

Conclusions—Dofetilide is safe and increases the probability of obtaining and maintaining sinus rhythm in patients with structural heart disease. The present study suggests that restoration of sinus rhythm is associated with improved survival. (*Circulation*. 2001;104:292-296.)

Key Words: antiarrhythmia agents ■ arrhythmia ■ heart failure ■ fibrillation ■ tachyarrhythmias

Atrial fibrillation (AF) is a common arrhythmia in patients with left ventricular (LV) dysfunction often associated with worsening of the clinical condition.^{1,2} Presence of AF is associated with increased risk of death in a consecutive series of patients with LV dysfunction and congestive heart failure (CHF).³ Therefore, effective treatment of AF could save lives. Dofetilide is a new class III antiarrhythmic drug that has been demonstrated to be effective for treatment of AF⁴⁻⁶ and safe to use in patients with CHF.⁷ In the Danish Investigations of Arrhythmia and Mortality ON Dofetilide (DIAMOND) CHF and acute myocardial infarction (MI) studies, dofetilide was effective for conversion of AF to sinus rhythm (SR) and for maintaining SR after conversion.^{7,8} Nevertheless, dofetilide had no effect on overall mortality of patients with AF at baseline in either study. Despite this result, dofetilide could be beneficial in

cases in which SR is achieved, because the benefit to the overall treatment group is diluted by patients who did not convert to SR and those who quickly relapsed to AF. To study further the potential benefit of SR in patients with LV dysfunction and AF, we pooled subgroups of patients with AF enrolled in the 2 DIAMOND studies. This group of patients consists of patients with reduced LV function and either CHF or recent acute MI, and the present study is the largest to date of the benefit of restoring and maintaining SR in patients with LV dysfunction.

Methods

Study Design and Population

DIAMOND investigations consisted of 2 separate randomized, double-blind, placebo-controlled, parallel-group, multicenter studies

Received November 1, 2000; revision received April 6, 2001; accepted April 16, 2001.

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Dr Marchant is an employee of Pfizer Central Research, Sandwich, UK, which provided a grant in support of the present study.

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TABLE 1. Demographic Characteristics at Baseline

	Patients	
	Dofetilide (n=249) DIAMOND CHF/MI (n=190/59)	Placebo (n=257) DIAMOND CHF/MI (n=201/56)
Age, mean (range), y	72 (40–92)	72 (36–89)
Weight, mean (range), kg	77 (40–134)	77 (38–127)
Sex (M/F), n	188/61	201/56
Ischemic heart disease, n (%)	140 (56.2)	152 (59.1)
Prior cardiac arrest, n (%)	9 (3.6)	12 (4.7)
WMI, n (%)		
<0.8	53 (21.3)	62 (24.1)
≥0.8	196 (78.7)	195 (75.9)
Thrombolytic treatment, n (%)	18 (7.2)	29 (11.3)
NYHA class at baseline, n (%)		
I and II	105 (43.2)	110 (43.1)
III and IV	138 (56.8)	145 (56.9)
Not available	6	2
Mean creatinine clearance rate, mL/s*	57.2	56.9
Angiotensin-converting enzyme inhibitor use at baseline, %	67	63
β-blocker use at baseline, %	12	13
Digoxin use at baseline, %	92	89

*To convert to conventional units (mL/min), divide SI units by factor of 0.01667.

of safety and efficacy of oral dofetilide in patients with CHF or recent MI.^{7,8} Studies were conducted simultaneously at 37 hospitals in Denmark. Protocol was approved by Danish Board of Health and Central Danish Research Ethics Committee.

Qualifying diagnosis of CHF required ≥1 episode within the preceding month of shortness of breath either on minimal exertion or at rest (New York Heart Association [NYHA] functional class III or IV) or paroxysmal nocturnal dyspnea.⁷ Diagnosis of an MI required symptoms or ECG changes compatible with MI and confirmed by an increase in cardiac enzymes to >2 times upper limit of normal.⁸

At screening, an echocardiogram was recorded on videotape and evaluated in a central laboratory within 1 working day to ensure consistency and determine eligibility. To be eligible, the patient had to have a wall-motion index (WMI) of ≤1.2 (corresponding roughly to an ejection fraction of ≤35%), to be ≥18 years old, to have no childbearing potential, and to provide written, informed consent. Major exclusion criteria were heart rate of <50 bpm when awake; sinoatrial block or second- or third-degree atrioventricular block not treated with a pacemaker; history of drug-induced proarrhythmia; corrected QT interval that exceeded 460 ms (500 ms in cases of bundle-branch block), or diastolic or systolic blood pressures >115 or <80 mm Hg. Patients also were excluded who were likely to die from other causes during the study; had serum potassium levels of <3.6 mEq/L (<3.6 mmol/L) or >5.5 mEq/L (>5.5 mmol/L); treatment with class I or III antiarrhythmic drugs or had participated in experimental drug studies in the previous 3 months; had been treated previously with dofetilide; were unable to cooperate in the study; or had creatinine clearance rates of <20 mL/min (<0.33 mL/s) calculated by the method of Cockcroft and Gault.⁹

Eligible patients were enrolled within 3 to 7 days of hospitalization and were monitored by continuous telemetry during the initial 72 hours of study treatment to ensure that proarrhythmic events would be recognized and treated immediately. Patients with AF and atrial flutter (AFL) at baseline were included in the present analysis. AF was defined as having absence of P waves, coarse or fine fibrillatory waves, and completely irregular RR intervals; AFL, presence of regular P waves occurring at a rate of 250 to 350 per minute and regular or irregular RR intervals.

Patients with AF were randomized to receive either oral dofetilide 250 μg BID or placebo. This dosage was reduced to 250 μg once daily for patients with creatinine clearance rates of <40 mL/min. Dofetilide was discontinued if creatinine clearance was <20 mL/min. Further adjustments were made as necessary to reduce excessive corrected QT interval prolongation (>550 ms or >20% increase from baseline). Patients were required to receive anticoagulation treatment before scheduled direct-current (DC) conversion.

Patients were evaluated 1 and 3 months after hospital discharge and at 3-month intervals until study closure (12 months after randomization of final patient). At each of these visits, a 12-lead ECG was recorded and presence of AF was noted.

At the first outpatient visit after 1 month, the investigator was encouraged to schedule DC conversion for patients with persistent AF. The final decision as to who should be considered for DC conversion was left to the discretion of the local investigator. After cardioversion by any method and at any time during the study, SR was considered to be maintained unless AF-AFL was documented subsequently on a 12-lead ECG. No patient was lost to follow up.

Statistical Analysis

End points were analyzed on an intention-to-treat basis. Baseline characteristics were compared with the use of χ^2 or Fisher's Exact Test. Kaplan-Meier plots were used to present data on survival. Relative hazard ratios (denoted risk ratio) of dofetilide to placebo were obtained using Cox's proportional hazards model. Because restoration of SR and relapse to AF occurred at different times, the effect of being in SR was estimated by introducing a time-dependent variable, which assumed a value of 0 until SR was achieved. At that time, the variable assumed a value of 1. If an AF relapse occurred, the value would revert to 0. After a first relapse, the value remained 0 throughout the study.

Results

Study Population

Of 3028 patients with severe CHF or recent MI, 506 (17%) had AF-AFL. Of these, 249 were randomized to treatment

with dofetilide and 257 to treatment with placebo. Table 1 summarizes baseline characteristics. Treatment groups were well balanced and constituted a relative high-risk population, with 283 patients (56%) in NYHA class III or IV.

Cardioversion

After 1 month of treatment, SR had been restored pharmacologically in 31 (12%) dofetilide-treated compared with 5 (2%) placebo-treated patients ($P<0.001$). Over the course of the study, pharmacological or spontaneous cardioversion occurred in 112 (44%) dofetilide- and 35 (14%) placebo-treated patients ($P<0.001$). Cox's regression analysis was performed and included treatment group, age, sex, baseline medications, coexisting cardiovascular diseases, NYHA class, and WMI. As expected, dofetilide treatment was a strong predictor of pharmacological conversion; (risk ratio [RR], 4.24; 95% CI, 2.89 to 6.21; $P<0.001$). WMI >0.8 was also associated with improved conversion (RR, 1.62; 95% CI, 1.02 to 2.56; $P<0.05$), as was increase in heart rate (RR, 1.14; 95% CI, 1.05 to 1.24; $P<0.01$). An additional 36 dofetilide- and 51 placebo-treated patients underwent successful DC cardioversion. In total, 148 dofetilide-treated patients (59%) and 86 placebo-treated patients (34%) were restored successfully to SR. Minor differences occurred between patients who converted to SR and those who did not. When comparing patients converting to SR with patients not converting to SR, the groups were similar with respect to mean age (71 years among converters versus 72 years among nonconverters); use of β -blocker (12% versus 13%), angiotensin-converting enzyme inhibitor (89% versus 88%), or digoxin (89% versus 92%) at baseline; creatinine clearance (59 versus 56 mL/min); and male sex (78% versus 76%), whereas they differed slightly with respect to previous MI (2% versus 6%), ischemic heart disease (53% versus 62%), NYHA class III and IV (53% versus 59%), and WMI <0.8 (20% versus 24%) at baseline.

Maintenance of SR

Of those converting to SR, life-table analysis demonstrated a 1-year probability of 79% for maintaining SR in patients who received dofetilide compared with 42% in patients who received placebo ($P<0.001$). This advantage of dofetilide therapy persisted >1 year. Dofetilide was a predictor of successful maintenance (RR, 0.30; 95% CI, 0.19 to 0.48; $P<0.001$), whereas use of angiotensin-converting enzyme inhibitors at baseline was associated with increased risk of relapse (RR, 1.88; 95% CI, 1.11 to 3.17; $P<0.05$).

Mortality

Overall, mortality of patients with AF was similar in patients who received dofetilide or placebo (Figure 1). After adjusting for age, sex, WMI, NYHA class, ischemic heart disease, creatinine clearance, history of previous MI, angiotensin-converting enzyme inhibitor usage, and β -blocker usage in proportional hazards model, adjusted hazard ratio associated with dofetilide treatment was as follows: RR, 1.03; 95% CI, 0.79 to 1.35; $P=0.93$.

When the focus was SR, unadjusted mortality rate was significantly lower in patients who converted to SR versus

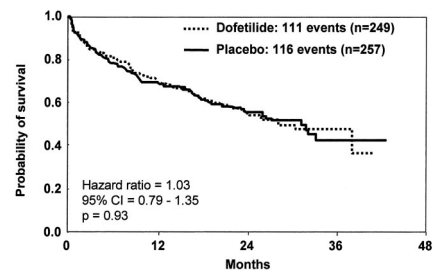


Figure 1. Probability of survival during treatment and follow-up periods in 506 patients with LV dysfunction and AF-AFI at baseline treated with dofetilide or placebo.

those who did not (Figure 2). To study further the importance of SR, the introduction of a time-dependent variable was necessary: both restoration of SR and relapse to AF occurred at variable time points. This variable assumed a value of 1 during SR; a value of 0 during AF was added in a multivariate proportional hazard model that also included age, sex, WMI, NYHA class, ischemic heart disease, creatinine clearance, history of previous MI, angiotensin-converting enzyme inhibitor usage, and β -blocker usage as covariates. Presence of SR was associated with a significantly lower mortality rate (RR, 0.44; 95% CI, 0.30 to 0.64; $P<0.0001$), as shown in Table 2. This lower mortality rate was similar for the placebo-treated (RR, 0.38; 95% CI, 0.20 to 0.73; $P<0.004$) and dofetilide-treated (RR, 0.43; 95% CI, 0.27 to 0.68; $P<0.001$) groups. Also, no difference was seen in mortality reduction in either treatment group that depended on whether SR was obtained by electrical conversion or occurred spontaneously or pharmacologically.

Hospitalization

Both all-cause hospitalization and hospitalization for worsening CHF were delayed significantly by dofetilide therapy.

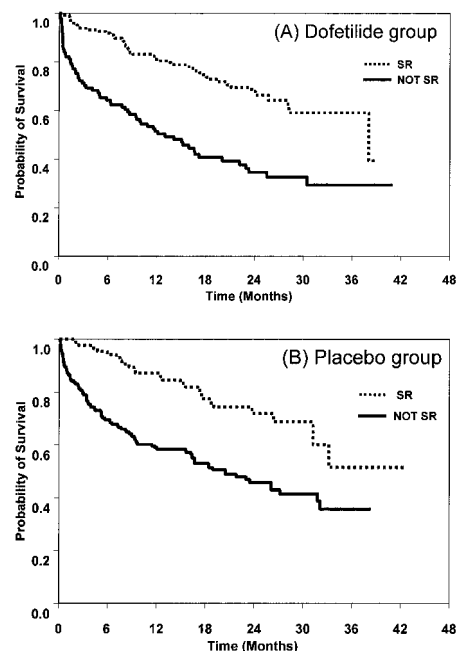


Figure 2. Survival rates of patients treated with dofetilide (A) or placebo (B) who converted or did not convert to SR.

TABLE 2. Mortality Reduction (RR) of Being in SR in All Patients or According to Treatment Groups (Placebo/Dofetilide) and Whether SR Was Achieved Spontaneously or Pharmacologically or by DC Cardioversion

Treatment Group/Type of Cardioversion	RR (95% CI)
All patients	0.44 (0.30–0.64)
All placebo patients	0.38 (0.20–0.73)
All dofetilide patients	0.43 (0.27–0.68)
Placebo patients/spontaneous	0.32 (0.13–0.79)
Dofetilide patients/pharmacological	0.54 (0.33–0.88)
Placebo patients/DC cardioversion	0.36 (0.15–0.88)
Dofetilide patients/DC cardioversion	0.41 (0.15–1.15)

For this analysis, the time in SR was entered as a time-dependent variable in the Cox regression analysis.

Overall, 73 of 249 patients (29%) given dofetilide and 102 of 257 patients (40%) given placebo were hospitalized for worsening CHF. After adjusting for WMI, relative hazard of CHF hospitalization for dofetilide versus placebo was RR, 0.69; 95% CI, 0.51 to 0.93; $P \leq 0.02$. Overall, 125 of 249 patients (50%) given dofetilide and 156 of 257 patients given placebo (61%) were hospitalized for any reason. After adjusting for WMI, relative hazard of all-cause hospitalization for dofetilide versus placebo was (RR, 0.70; 95% CI, 0.56 to 0.89; $P \leq 0.005$). Dofetilide treatment also had an effect on the combined end point of first hospitalization for worsening CHF or death (RR, 0.77; 95% CI, 0.59 to 0.99; $P \leq 0.05$).

Adverse Events

Except for proarrhythmia, adverse events in the 2 treatment groups were well balanced. Torsade de pointes occurred in 4 dofetilide-treated patients (1.6%), and treatment was stopped. Two patients (1 man, 1 woman) experienced torsade de pointes on day 2 of dofetilide treatment, 1 on day 8, and 1 on day 13. All cases were successfully treated, and no deaths occurred.

Discussion

This retrospective analysis of patients with AF-AFL at baseline in the DIAMOND studies demonstrates that dofetilide is effective for restoration and maintenance of SR in patients with LV dysfunction. When treatment was initiated carefully, dofetilide had no adverse effect on survival. Conversion to and maintenance of SR was associated with a lower mortality.

This result was obtained in the largest cohort ever studied of AF-AFL patients ($n=506$) with LV dysfunction. Few studies (all nonrandomized) have previously addressed the issue of conversion and maintenance of SR in patients with LV dysfunction.^{10–12} Dofetilide was effective for restoration and maintenance of SR in this group of patients. During the course of study, restoration of SR occurred in 148 (59%) dofetilide- and 86 (34%) placebo-treated patients. In pharmacologically or DC-converted patients, probability of maintaining SR for 1 year was 79% for those treated with dofetilide versus 42% for those treated with placebo. In general, the 1-year maintenance rate of SR in previous studies of antiarrhythmic drugs is 40% to 60%,^{13,14} but it is difficult to draw comparisons with other studies, given that study

designs and patient populations are inevitably different. Specifically, the patients in DIAMOND have more severe underlying cardiac disease than do patients in most studies of AF, as evidenced by the high 1-year mortality rate in the DIAMOND AF study. Dofetilide compare favorably with this maintenance rate and even slightly better in the present study. However, the 1-year maintenance rate in the placebo group was 42%, which is higher than in previous studies.^{13,14} The high placebo response could be explained by selection bias, because only patients who converted to SR could enter the maintenance period. Also, the high mortality rate could have caused fewer patients to relapse to AF (ie, death eliminated opportunity for relapse in both treatment groups).

Despite these limitations, the results of the present study indicate that dofetilide is effective for restoration and maintenance of SR in heart failure patients. Multivariate analysis that included such variables as treatment group, age, sex, baseline medications, coexisting cardiovascular diseases, NYHA class, and WMI identified 3 predictors for successful pharmacological conversion to SR. As expected, treatment with dofetilide was a strong predictor of pharmacological conversion and long-term maintenance of SR. In addition, patients with better LV function had greater efficacy in conversion to SR and also patients with high heart rate. A similar analysis in the Congestive Heart Failure Survival Trial of Antiarrhythmic Therapy (CHF-STAT) trial was unable to identify any predictors of conversion.¹⁰ Except for dofetilide treatment, the present study was unable to identify any other predictors of maintenance of SR. These results indicate an influence of LV function on ability to obtain SR but not on maintenance of SR. However, important variables such as duration of AF and left atrial size were not assessed, which could influence conversion and maintenance of SR. Nonetheless, the results indicate that the degree of LV dysfunction should not be an obstacle to attempting conversion to SR.

Dofetilide had a neutral effect on overall mortality, which indicates that dofetilide caused no harm to the patients (Figure 1). Dofetilide was initiated in hospital, and patients were monitored by continuous telemetry for the first 72 hours of study to detect and treat possible proarrhythmia as well as excessive QT prolongation.

An important finding is that patients who converted to SR successfully had a lower mortality rate than nonconverters (Figure 2). This association was even more pronounced when the time of being in SR was included in the multivariate analysis and was independent of either treatment with dofetilide or placebo, which indicated an effect primarily of SR rather than of drug treatment (Table 2). The fact that SR obtained with dofetilide was as beneficial as SR obtained on placebo although nearly twice as many conversions were obtained on dofetilide further substantiates the claim that obtaining SR is more important than using SR as a marker of good health. This observation confirms and extends the finding in the CHF-STAT trial,¹⁰ in which 16 patients with AF who converted to SR on amiodarone had a better survival rate than 35 patients treated with amiodarone who did not convert to SR. In addition, dofetilide also significantly reduced rate of hospitalization for worsening of CHF and for any reason, a result that was not shown in the CHF-STAT trial. A possible explanation for these findings is that the

reduction in mortality by restoration of SR may be related to improved LV function that occurs after conversion to SR.^{15–17}

Study Limitations

A possible limitation of the study concerns the fact that patients enrolled in DIAMOND were not stratified by rhythm before randomization. However, the 506 AF-AFL patients were randomized as a part of the DIAMOND studies, and baseline characteristics of the dofetilide- and placebo-treated AF-AFL patients were very similar (Table 1). Prevalence of AF-AFL at baseline in DIAMOND studies (17%), an approximate average of previous studies,^{18–22} indicates that the study population is representative of patients with LV dysfunction. The entry criteria ensured that the present study investigated patients with significant LV dysfunction. Most of the patients had WMI between 0.8 and 1.2, which corresponds approximately to LV ejection fraction between 20% to 35%. Also, the result of a better outcome in patients converting to SR may be influenced by differences in covariates versus patients who did not convert to SR. Minor differences were observed between those who did and did not convert to SR. Although we adjusted for these differences in the Cox regression analysis, differences in the populations could have influenced the result. Other factors, such as left atrial size, LV diastolic function, and mitral regurgitation, were not determined in the present study and could have influenced the results.

Conclusions

The findings in the present study demonstrate that dofetilide is superior to placebo for restoration and maintenance of SR in patients with significant LV dysfunction and AF-AFL. Dofetilide has few side effects and thus is an alternative to amiodarone in treatment of AF in patients with LV dysfunction. The present study also shows a reduction in morbidity by dofetilide treatment in terms of hospitalization. Perhaps the most important finding is the association between a lower mortality and being in SR. Overall mortality was not reduced by treatment with dofetilide versus placebo (Figure 1). However, the sample size in the present study is probably too small and the follow up too short to investigate this issue. Although AF is a major problem in heart failure patients, only limited evidence exists to support a clinical benefit of restoration of SR.²³ Therefore, further studies are needed to assess the potential benefit of conversion to and maintenance of SR, as indicated by the results of the present study.

Acknowledgments

The present study was supported by a grant from Pfizer Central Research, Sandwich, UK.

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Circulation. 2001;104:292-296

doi: 10.1161/01.CIR.104.3.292

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:

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