Efficacy and Safety of Oral Dofetilide in Converting to and Maintaining Sinus Rhythm in Patients With Chronic Atrial Fibrillation or Atrial Flutter

The Symptomatic Atrial Fibrillation Investigative Research on Dofetilide (SAFIRE-D) Study

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Background—This double-blind, multicenter, placebo-controlled study determined the efficacy and safety of dofetilide in converting atrial fibrillation (AF) or atrial flutter (AFL) to sinus rhythm (SR) and maintaining SR for 1 year.

Methods and Results—Patients with AF or AFL (n = 325) were randomized to 125, 250, or 500 μg dofetilide or placebo twice daily. Dosages were adjusted for QTc response and, after 105 patients were enrolled, for calculated creatinine clearance (CrCl). Pharmacological cardioversion rates for 125, 250, and 500 μg dofetilide were 6.1%, 9.8%, and 29.9%, respectively, versus 1.2% for placebo (250 and 500 μg versus placebo; P = 0.015 and P < 0.001, respectively). Seventy percent of pharmacological cardioversions with dofetilide were achieved in 24 hours and 91% in 36 hours. For the 250 patients who successfully cardioverted pharmacologically or electrically, the probability of remaining in SR at 1 year was 0.40, 0.37, 0.58 for 125, 250, and 500 μg dofetilide, respectively, and 0.25 for placebo (500 μg versus placebo, P = 0.001). Two cases of torsade de pointes occurred, 1 on day 2 and the other on day 3 (0.8% of all patients given active drug); 1 sudden cardiac death, classified as proarrhythmic, occurred on day 8 (0.4% of all patients given active drug).

Conclusions—Dofetilide, a new class III antiarrhythmic agent, is moderately effective in cardioverting AF or AFL to SR and significantly effective in maintaining SR for 1 year. In-hospital initiation and dosage adjustment based on QTc and CrCl are necessary to minimize a small but nonnegligible proarrhythmic risk. (Circulation. 2000;102:2385-2390.)

Key Words: antiarrhythmia agents ▪ arrhythmia ▪ fibrillation ▪ atrial flutter

Atrial fibrillation (AF), one of the most common arrhythmias, is associated with symptomatic impairment and decreased quality of life, and it carries a substantial risk of stroke in patients with risk factors.1,2

Dofetilide, a new class III antiarrhythmic agent, selectively blocks the rapid component of the delayed rectifier potassium channel (Ikr) in cardiac cells,3 producing dose-dependent increases in atrial and ventricular refractory periods4 and QT intervals.5,6 The Danish Investigations of Arrhythmia and Mortality on Dofetilide–Congestive Heart Failure (DIAMOND-CHF) showed that dofetilide has no adverse effect on mortality rates in severely ill patients with left ventricular dysfunction and advanced heart failure.7 The Symptomatic Atrial Fibrillation Investigative Research on Dofetilide (SAFIRE-D) study measured the efficacy and safety of dofetilide in the conversion to and the maintenance of sinus rhythm (SR). The study also assessed the effect of SR on symptoms and cardiac function. These data will be presented separately.

Methods

Study Design and Patient Population

This double-blind, multicenter, placebo-controlled, dose-ranging study began with an in-hospital conversion phase of 3 days or 5 doses, followed by a 12-month maintenance phase. During the conversion phase, the effects of 3 dosages of dofetilide and placebo on conversion of AF/AFL to SR were compared. During the maintenance phase, the times to first relapse to AF/AFL with dofetilide and placebo were compared. The institutional review board in each study center approved the protocol. After providing informed consent, patients 18 to 85 years
of age with AF/AFl for 2 to 26 weeks, confirmed by ECG, were screened. Exclusion criteria are listed below.

Patients were admitted to telemetry for a minimum of 3 days. In patients who received a minimum of 5 doses of study drug without converting pharmacologically, electrical cardioversion was attempted. Converted patients were monitored for an additional 24 hours after conversion and then entered the outpatient maintenance phase. Patients whose SR could not be restored or maintained for 24 hours after conversion were withdrawn from the study. Anticoagulation therapy was initiated before conversion and continued for a minimum of 3 to 4 weeks after SR was established but could be continued throughout the trial, depending on local practice. Patients with contraindications to warfarin therapy were treated according to local practice.

Follow-up clinic visits were scheduled at 2 weeks, 1, 2, and 3 months, and at 3-month intervals thereafter until 1 of the study end points—relapse to AF or AFl for at least 24 hours, as documented by ECG, or maintenance of SR for a full year—was reached. Twelve-month survival data were collected for all randomized patients irrespective of treatment duration.

Exclusion Criteria

Patients with the following characteristics were excluded from participating in the cardioversion phase of the trial: women of childbearing potential, inability to tolerate withdrawal from current antiarrhythmic therapy; syncope of unknown origin in the preceding 6 months; active thyrotoxicosis, AF, or AFl from reversible noncardiac diseases; uncompensated or rapidly progressive congestive heart failure; myocardial infarction or unstable angina pectoris within the preceding month or percutaneous transluminal coronary angioplasty within the preceding 3 months; heart surgery in the preceding 2 months; significant sinus node abnormalities, including sick sinus syndrome, or greater than first-degree atrioventricular block, unless treated with a properly functioning pacemaker; ECG intervals exceeding the following limits in the drug-free state and in the absence of preexcitation syndrome and bundle-branch block: QRS of >180 ms, QT interval of >440 ms, or both; in the case of bundle-branch-block, the QT or QTc was not to exceed 500 ms; R-R interval of >3.5 seconds; ventricular rate of <50 bpm on 12-lead ECG;ystolic blood pressure of <90 mm Hg or diastolic blood pressure of >110 mm Hg (>105 mm Hg at Canadian centers after the January 1994 protocol amendment); major hematological, pulmonary, hepatic, or renal disease (serum creatinine of >221 μmol/L or, after the April 1994 protocol amendment, calculated ClCr of <0.3334 mL/s); serum potassium of <4.0 or >5.5 mmol/L and serum magnesium of <0.75 or >2.5 mmol/L at screening, 1 week before entry, and immediately before entry into study; concomitant therapy with other antiarrhythmic agents, verapamil, diltiazem, diuretics (if serum potassium was out of specified limits), antihistamines, tricyclic antidepressants, anticonvulsants or phenothiazines, digoxin (allowed if the dosage was constant during the trial), and amiodarone (if blood levels of amiodarone >0.3 mg/mL); history of polymorphic ventricular tachycardia associated with arrhythmic drugs or other drugs known to prolong the QT interval; history of substance dependency or abuse; any experimental medication concurrently or within the 4 weeks of the study; and participation in a previous dofetilide study.

Dosing Algorithm

The initial dosage of dofetilide (125, 250, or 500 μg BID) was determined by randomization. After the first 105 patients had been enrolled, the protocol was amended to adjust the randomized dosage of dofetilide for renal function as indicated by each patient’s baseline calculated creatinine clearance (ClCr) (Figure 1). Patients whose ClCr was <20 mL/min were excluded from the study. Additionally, if the QTc interval increased by >15% over baseline, dosage was halved. Dosages could be adjusted only once for prolongation of QTc intervals, and patients with QT or QTc intervals that exceeded 550 ms or increased >25% over baseline values were withdrawn. Treatment comparisons were made with respect to randomized group, regardless of adjustments or actual dosage administered.
ized treatment groups in the following sequence: 125, 250, and 500 μg BID dofetilide, and placebo.

**Patient Characteristics**

In total, 325 patients at 37 centers were randomized and distributed similarly between all groups (Table 1). All randomized patients were included in the intention-to-treat analyses for both conversion and maintenance phases. Of these, 250 (60, 61, 61, 68, for dofetilide 125, 250, and 500 μg BID groups and placebo group, respectively) patients entered the maintenance phase and were included in the efficacy analyses for this phase. All patients were included in the safety analysis. A total of 218 (54, 51, 50, 63) patients reached a study end point or completed 12 months of follow-up.

**TABLE 2. Successful Pharmacological Cardioversions**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dofetilide</th>
<th>Plac-boe</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>125 μg BID (n=82)</td>
<td>250 μg BID (n=82)</td>
</tr>
<tr>
<td>No. of patients pharmacologically converted/total randomized (%)</td>
<td>5/82 (6.1)</td>
<td>8/82 (9.8)</td>
</tr>
<tr>
<td>P vs placebo*</td>
<td>0.098</td>
<td>0.015</td>
</tr>
<tr>
<td>No. of patients converted (pharmacological or electric)/total randomized (%)</td>
<td>60 (73)</td>
<td>61 (74)</td>
</tr>
<tr>
<td>No. of patients pharmacologically converted/total converted (%)</td>
<td>5/60 (8.3)</td>
<td>8/61 (13.1)</td>
</tr>
</tbody>
</table>

*Cochran-Mantel-Haenszel test.
and III. Structural heart disease (including myocardial infarction, congestive heart failure, ischemic heart disease, valvular heart disease, and dilated and obstructive cardiomyopathy) was present in >50% of patients.

Efficacy of Conversion and Maintenance of SR
Dofetilide restored SR in a dose-dependent manner (Table 2). Significantly more patients treated with 250 and 500 μg dofetilide than placebo-treated patients converted to SR (P=0.015 and P<0.001, respectively). Of the patients who converted pharmacologically, 70% did so within 24 hours and 91% within the initial 36 hours (Figure 2). Analysis of pharmacological conversion by primary diagnosis for the 500 μg BID dofetilide group showed a 21.6% rate for the AF subgroup and 66.7% for the AFI subgroup. However, both of these subgroups were highly statistically significant with respect to the conversion rate for placebo.

Electrical cardioversion was attempted for patients who did not cardiovert pharmacologically. The rate of successful conversion, defined as maintenance of SR for 24 hours, with either study drug or electrical cardioversion was similar in all treatment groups (Table 2).

Dofetilide showed a dose-response relation in maintaining SR. The probabilities of maintaining SR at 12 months in patients who converted and entered the maintenance phase were 40%, 37%, and 58% for the dofetilide groups and 25% for placebo (Table 3 and Figure 3). The log-rank test revealed a significant difference between the 500 μg BID dofetilide and placebo groups (P=0.001).

The median time to relapse was also analyzed. In the placebo-treated group, the median time to relapse to AF was 27 days, whereas a dose-response relation of 31, 179, and 365 days was obtained for the dofetilide-treated groups.

Analysis of the probability of achieving and maintaining SR for all randomized (intention-to-treat) patients showed a dose-response pattern similar to that of the maintenance group, except that all 4 groups’ probabilities were ≈20% lower. This reflects the addition of classifying patients who failed initially to convert to SR as having relapsed at the onset of the maintenance period. The log-rank test demonstrated a significant difference between the 500 μg BID dofetilide and placebo groups (P=0.008).

### TABLE 3. Probability* of Maintaining SR During Maintenance Period in Patients With Successful Cardioversion

<table>
<thead>
<tr>
<th>Time point, d</th>
<th>125 μg BID (n=48)</th>
<th>250 μg BID (n=54)</th>
<th>500 μg BID (n=50)</th>
<th>Placebo (n=52)</th>
<th>125 μg BID (n=12)</th>
<th>250 μg BID (n=7)</th>
<th>500 μg BID (n=11)</th>
<th>Placebo (n=16)</th>
<th>125 μg BID (n=60)</th>
<th>250 μg BID (n=61)</th>
<th>500 μg BID (n=61)</th>
<th>Placebo (n=68)</th>
</tr>
</thead>
<tbody>
<tr>
<td>180</td>
<td>0.38</td>
<td>0.49</td>
<td>0.58</td>
<td>0.28</td>
<td>0.65</td>
<td>0.57</td>
<td>0.80</td>
<td>0.67</td>
<td>0.44</td>
<td>0.50</td>
<td>0.62</td>
<td>0.37</td>
</tr>
<tr>
<td>270</td>
<td>0.36</td>
<td>0.44</td>
<td>0.55</td>
<td>0.19</td>
<td>0.65</td>
<td>0.57</td>
<td>0.80</td>
<td>0.59</td>
<td>0.42</td>
<td>0.46</td>
<td>0.60</td>
<td>0.28</td>
</tr>
<tr>
<td>360</td>
<td>0.36</td>
<td>0.38</td>
<td>0.53</td>
<td>0.15</td>
<td>0.49</td>
<td>0.38</td>
<td>0.80</td>
<td>0.59</td>
<td>0.40</td>
<td>0.37</td>
<td>0.58</td>
<td>0.25</td>
</tr>
<tr>
<td>Hazard ratio vs placebo (95% CI)</td>
<td>(0.44, 1.20)</td>
<td>(0.33, 0.85)</td>
<td>(0.25, 0.75)</td>
<td>...</td>
<td>(0.32, 1.20)</td>
<td>(0.36, 0.85)</td>
<td>(0.09, 0.75)</td>
<td>...</td>
<td>(0.48, 1.20)</td>
<td>(0.44, 0.85)</td>
<td>(0.26, 0.75)</td>
<td>...</td>
</tr>
<tr>
<td>P vs placebo</td>
<td>0.209</td>
<td>0.008</td>
<td>0.002</td>
<td>...</td>
<td>0.837</td>
<td>0.553</td>
<td>0.427</td>
<td>...</td>
<td>0.208</td>
<td>0.104</td>
<td>0.001</td>
<td>...</td>
</tr>
<tr>
<td>Patients completing ≥350 d in SR, n (%)</td>
<td>13 (27)</td>
<td>13 (24)</td>
<td>20 (40)</td>
<td>7 (14)</td>
<td>6 (50)</td>
<td>2 (29)</td>
<td>8 (73)</td>
<td>8 (50)</td>
<td>13 (31)</td>
<td>19 (24)</td>
<td>28 (46)</td>
<td>15 (22)</td>
</tr>
</tbody>
</table>

*Kaplan-Meier estimate.
In the examination of the effects of baseline covariates by the Cox proportional hazards model, the only significant factor other than treatment group was primary diagnosis (AF or AFl). In a model including terms for treatment, center, and primary diagnosis, the effect of primary diagnosis was highly significant ($P=0.0004$), indicating that patients with AFl maintained SR better than patients with AF. The correction for the baseline imbalance of fewer patients with AFl in the 250 $\mu$g group apparently provides a more consistent dose response with respect to separation of the efficacy of the 125 and 250 $\mu$g dofetilide groups.

The effect of the dosing algorithm on maintenance of SR was examined. Of the 77 patients in the 500 $\mu$g group, 37 (48%) had their dosage adjusted, 20 for reduced ClCr and 17 for $>15\%$ change from baseline in QT or QTc. Efficacy in those patients was maintained.

**Effect of Dofetilide on Mortality Rates**

Although this study was not designed to provide robust statistical evidence of the benefits of conversion and maintenance of SR with respect to all-cause mortality, survival was similar among all 4 groups. By 12 months, 2.5% of dofetilide-treated patients and 3.5% of placebo-treated patients had died (2, 2, 2, 3 in each group, respectively). The mortality hazard ratio (dofetilide/placebo) was 0.70 (range, 0.17 to 2.78).

**Adverse Events**

Eleven patients were withdrawn because of adverse events potentially related to treatment. Prolongation of QT or QTc interval accounted for 10 of the withdrawals (2, 2, 5, 1); 7 occurred during the first 3 days. One sudden death occurred. Dosages were adjusted in 79 (33%) patients treated with dofetilide for either ClCr or prolonged QT or QTc.

The incidence of serious adverse events was comparable in all 4 groups. Serious adverse events potentially related to treatment were reported in 7 patients (2.9%) in the dofetilide-treated groups and in 2 patients (2.3%) in the placebo-treated group. There was no evidence of a dose-response relation for serious adverse events, with 2, 2, and 3 events occurring in patients receiving 125 $\mu$g, 250 $\mu$g, and 500 $\mu$g dofetilide, respectively.

There were 7 proarrhythmic events, 3 of which were considered treatment related and 4 secondary to other illnesses. Two of the treatment-related events were torsade de pointes. One of these occurred in a 66-year-old white woman randomized to treatment with 250 $\mu$g BID dofetilide. After 1 dose, her dosage was reduced to 125 $\mu$g BID because of QT interval prolongation. On day 2, after 3 dofetilide doses, torsade de pointes and ventricular fibrillation developed, which degenerated to ventricular fibrillation. She was successfully defibrillated. The other patient, a 38-year-old white man with a history of dilated cardiomyopathy and heart failure, randomized to treatment with 500 $\mu$g BID, had torsade de pointes and ventricular fibrillation on day 3 after 5 doses. He underwent electrical defibrillation that subsequently produced AF with frequent ventricular ectopy. Magnesium was infused, and the event resolved. Both of these patients had calculated ClCr of $>60$ mL/min.

The third treatment-related proarrhythmic event occurred in a 69-year-old black man in the 500 $\mu$g dofetilide group who died on day 8 of treatment; the death was unwitnessed and presumed to be a sudden cardiac death.

**Discussion**

This study showed that oral dofetilide is moderately effective in converting AF and AFl to SR. The conversion rate for those randomized to treatment with 500 $\mu$g BID dofetilide was 30%. The 10% pharmacological conversion rate for patients randomized to 250 $\mu$g BID is similar to the 12% conversion rate of DIAMOND-CHF, in which 250 $\mu$g BID was the maximum dose evaluated in patients with AF. In patients given 500 $\mu$g dofetilide in the current study, 70% of the pharmacological conversions occurred within 24 hours and 91% within 36 hours. This suggests that electrical cardioversion should be considered if the patient does not convert within 24 to 36 hours of the start of dofetilide therapy.

Preventing recurrence of AF during antiarrhythmic therapy should not be the only measure of drug success. Rather, the frequency of recurrence may be a more appropriate measure of efficacy. Without drug therapy, AF recurs in $\approx75\%$ of patients within 1 year after conversion. Prophylactic drug therapy has been shown to decrease the probability of recurrence of AF to $50\%$. This finding was strongly reinforced by our results, in which a randomized dosage of 500 $\mu$g BID dofetilide was significantly more effective than placebo (58% versus 25%) at maintaining SR for 1 year. In addition, analysis of the median time to relapse of AF for the 500 $\mu$g BID dofetilide group was $>365$ days, compared with 27 days observed in the placebo group. Although maintenance of SR for 1 year was higher ($\approx80\%$) in the DIAMOND-CHF study, most of these patients (88%) were pharmacoologically converted on dofetilide and thus would be more likely to maintain SR on continued dofetilide therapy. The results of both of these trials, however, indicate that dofetilide favorably affects the time to recurrence of AF.

The dose adjustment for renal function attempted to provide equivalent serum concentrations in patients with different degrees of renal function within each randomized-dosage group. The dosing algorithm also allowed dose adjustment for QT/QTc prolongation. Efficacy was maintained in both dosage-adjusted and dosage-unadjusted subgroups.

**Implications for Therapy of AF**

The goal of antiarrhythmic therapy should be either to reduce symptoms or to improve mortality or both. The treatment should not be worse than the disease itself. Unfortunately, currently available drug therapies to prevent or convert AF have adverse effects or may increase mortality rates or worsen heart failure.

In this study, 3 (1.2%) proarrhythmic events were considered to be related to dofetilide. In the DIAMOND-CHF study, the incidence of torsade de pointes was substantially reduced by adjusting the dose for renal function. The DIAMOND-CHF study of patients with ventricular dysfunction and congestive heart failure showed that treatment with dofetilide does not increase mortality when it is initiated in the hospital with dosage determined on the basis of renal function and QTc response to therapy.
The low incidence of proarrhythmia and sudden death in the current study along with its neutral effect on mortality in DIAMOND-CHF\(^{2}\) suggest that when initiated in a monitored setting and dosed according to renal function and QT response to therapy, dofetilide is a safe therapy for conversion of AF or AFl and subsequent maintenance of SR.

Highly symptomatic AF or AFl of $>1$ week’s duration should benefit from dofetilide as primary therapy provided that (1) patients have a ClCr $\geq 20$ mL/min; (2) starting doses 500, 250, and 125 $\mu$g BID are used for ClCr $>60$, 40 to 60, and 20 to $<40$ mL/min; (3) dosing is halved if corrected QT increases $>15$% versus baseline or is $>500$ ms (550 ms if ventricular conduction abnormalities exist) 2 to 3 hours after the first dose. Because of the small nonnegligible risk of proarrhythmia, dofetilide should be initiated in the hospital with continuous ECG monitoring.

Conclusions

Dofetilide, a new class III antiarrhythmic agent, is moderately effective in cardioverting AF or AFl to SR and significantly effective in maintaining SR for 1 year once patients are pharmacologically or electrically converted. In-hospital initiation and dosage adjustment based on QTc and ClCr are necessary to minimize a small but nonnegligible risk of proarrhythmic or sudden death. Withdrawal from treatment during maintenance of SR is low. Dofetilide should be considered an important new treatment option for patients with AF or AFl.

Appendix

In addition to the authors, the following Dofetilide Atrial Fibrillation Investigators also participated in the study: Jeffrey Anderson, MD, LDS Hospital, Salt Lake City, Utah; John Atwood, MD, Department of Veterans Affairs Medical Center, Cardiology Medical Service, Palo Alto, Calif; Lawrence Baruch, MD, Veterans Affairs Medical Center, Bronx, NY; Rajinder Bhalla, MD, Saint John Hospital, Nassau Bay, Tex; Benoit Coutu, MD, Hospital Notre Dame, Montreal, Quebec, Canada; Mark Eaton, MD, David Grant United States Air Force Medical Center, Travis Air Force Base, Calif; Kenneth Ellenbogen, MD, Virginia Commonwealth University, Medical College of Virginia Hospitals, Richmond, Va; Jack Farahi, MD, Daniel Freeman Memorial Hospital, Inglewood, Calif; Anne Gillis, MD, LDS Hospital, Salt Lake City, Utah; Udipi Shettigar, MD, Bay Medical Corporation, Encinitas, Calif; Jeffrey Shanes, MD, Gottlieb Memorial Hospital, Melrose Park, Ill; Udipi Shettigar, MD, Bay Pines Veterans Affairs Medical Center, Bay Pines, Fla; Nicholas Stamato, MD, Cardiology Associates PC, Johnson City, NY; Vilma Torres, MD, Loma Linda University Medical Center, and International Heart Institute, Loma Linda, Calif; Dennis Unks, MD, Keesler Medical Center, Keesler Air Force Base, Biloxi, Miss; Dennis Unks, MD, Department of Veterans Affairs Medical Center, Long Beach, Calif; Jule Wetherbee, MD, Saint Lukes Medical Center, Milwaukee, Wis; Michael Weber, MD, Department of Veterans Affairs Medical Center, Long Beach, Calif; Jule Wetherbee, MD, Saint Lukes Medical Center, Milwaukee, Wis; Bruce Wilkoff, MD, The Cleveland Clinic Foundation, Cleveland, Ohio; and David Wyse, MD, Foothills Hospital, Calgary, and the University of Calgary Medical Clinic, North Calgary, Alberta, Canada.

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References

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