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 (ClCr). 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 ClCr are necessary to minimize a small but nonnegligible proarrhythmic risk. (Circulation. 2000;102:2385-2390.)

Key Words: antiarrhythmia agents □ arrhythmia □ fibrillation □ atrial flutter
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 endpoints—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 atioventricular block, unless treated with a properly functioning pacemaker; ECG intervals exceeding the specified limits during the study; 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; systolic 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 >2.21 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 >1.25 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 the specified limits), antihistamines, tricyclic antidepressants, anticonvulsants or phenothiazines, digoxin (allowed if the dosage was constant during the study), cimetidine (after the April 5, 1994, protocol amendment), and amiodarone (if blood levels of amiodarone >0.3 mg/mL); history of polymorphic ventricular tachycardia associated with antiarrhythmic drugs or other drugs known to prolong the QT interval; history of substance dependency or abuse; any experimental medication concomitantly 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.

Safety Monitoring

Safety was evaluated by physical examination, cardiopulmonary examination, multiple-lead ECG analysis, blood tests, and urinalysis. All adverse events and reactions (observed or volunteered by the patient) were recorded. Adverse electrophysiological events were considered separately from other adverse events. Patients who had a proarrhythmic event were withdrawn from the study and, if appropriate, followed up until the event subsided.

Statistical Analysis

The Cochran-Mantel-Haenszel test, adjusting for center, was used to compare the proportion of randomized patients pharmacologically converting to SR in each dofetilide-treated group with that in the placebo-treated group. Pharmacological conversion was considered successful when SR was maintained for a minimum of 24 hours. Time to conversion was determined by the number of hours from first dose and displayed graphically by means of the Kaplan-Meier (product-limit) method. Patients failing to convert were censored at the time of electrical cardioversion or time of last ECG before discontinuation.

The maintenance phase analysis included Kaplan-Meier estimates in each treatment group for the probability of maintaining SR for 6, 9, and 12 months after pharmacological or electrical cardioversion. Time in SR was defined as the time from conversion to documented recurrence of AF or AFl lasting >24 hours or last study visit. To examine efficacy of conversion to SR and maintenance of SR, 2 populations were analyzed. In one analysis, which included the intention-to-treat population (all randomized patients), patients whose rhythm could not be converted were considered to have had a relapse at time 0 of the maintenance phase. The other analysis included only patients who were successfully cardioverted, either pharmacologically or electrically, and entered the maintenance phase.

Log-rank tests stratified by center and hazard ratios from the Cox proportional hazards model compared each dofetilide-treated group with the placebo-treated group. The effects of covariates, including age, sex, primary diagnosis, and comorbidity, on the treatment comparisons were assessed by the proportional hazards model analysis.

Twelve-month survival data were presented as raw proportions and analyzed for the combined dofetilide-treated groups versus the placebo-treated group with the Kaplan-Meier method. The hazard ratio with 95% confidence intervals was estimated from the Cox proportional hazards model.

Results

Throughout this section, numbers separated by commas that are enclosed by parentheses refer to data from the 4 random-
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. At baseline, 277 patients (85%) had AF and 48 patients (15%) had AFl. Eighty-four percent of patients had AF/AFl for 1 or 2 weeks to 26 weeks. Seventy-two percent of the patients were in New York Heart Association classes II

<table>
<thead>
<tr>
<th>TABLE 1. Patient Demographics, Characteristics, and Other Diseases at Baseline</th>
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<tbody>
<tr>
<td>Characteristic</td>
</tr>
<tr>
<td>Sex (male/female), n</td>
</tr>
<tr>
<td>Age range (mean), y</td>
</tr>
<tr>
<td>Primary diagnosis, n (%)</td>
</tr>
<tr>
<td>AF</td>
</tr>
<tr>
<td>AFl</td>
</tr>
<tr>
<td>NYHA class, n (%)*</td>
</tr>
<tr>
<td>I</td>
</tr>
<tr>
<td>II</td>
</tr>
<tr>
<td>III</td>
</tr>
<tr>
<td>ClCr, n (%)†</td>
</tr>
<tr>
<td>&gt;1.0 mL/s (&gt;60 mL/min)</td>
</tr>
<tr>
<td>0.67–1.0 mL/s (40–60 mL/min)</td>
</tr>
<tr>
<td>0.33–0.67 mL/s (20–40 mL/min)</td>
</tr>
<tr>
<td>Structural heart disease, n (%)‡</td>
</tr>
<tr>
<td>Hypertensive disease, n (%)</td>
</tr>
<tr>
<td>No antiarrhythmics previous 6 mo, n (%)</td>
</tr>
<tr>
<td>Concomitant medications at entry, n (%)</td>
</tr>
<tr>
<td>Anticoagulants</td>
</tr>
<tr>
<td>Cardiac glycosides</td>
</tr>
<tr>
<td>Antihypertensives</td>
</tr>
<tr>
<td>Electrolyte/water replacement</td>
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<tr>
<td>Diuretics</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
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</tbody>
</table>

*Data missing for 2 patients in the dofetilide 125 μg BID treatment group.
†Data missing for 1 patient in all treatment groups.
‡Structural heart disease indicates history of heart failure, myocardial infarction, ischemic or valvular heart disease, or dilated or obstructive cardiomyopathy.

<table>
<thead>
<tr>
<th>TABLE 2. Successful Pharmacological Cardioversions</th>
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<tbody>
<tr>
<td>Characteristic</td>
</tr>
<tr>
<td>No. of patients pharmacologically converted/total randomized (%)</td>
</tr>
<tr>
<td>P vs placebo*</td>
</tr>
<tr>
<td>No. of patients converted (pharmacological or electric)/total randomized (%)</td>
</tr>
<tr>
<td>No. of patients pharmacologically converted/total converted (%)</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 Cardiioversion**

<table>
<thead>
<tr>
<th>Time point, d</th>
<th>AF</th>
<th>AFI</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>180</td>
<td>0.38</td>
<td>0.53</td>
<td>0.43</td>
</tr>
<tr>
<td>270</td>
<td>0.36</td>
<td>0.44</td>
<td>0.43</td>
</tr>
<tr>
<td>360</td>
<td>0.36</td>
<td>0.44</td>
<td>0.43</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 µg group apparently provides a more consistent dose response with respect to separation of the efficacy of the 125 and 250 µg dofetilide groups.

The effect of the dosing algorithm on maintenance of SR was examined. Of the 77 patients in the 500 µg 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 µg, 250 µg, and 500 µg 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 points. One of these occurred in a 66-year-old white woman randomized to treatment with 250 µg BID dofetilide. After 1 dose, her dosage was reduced to 125 µg BID because of QT interval prolongation. On day 2, after 3 dofetilide doses, torsade de points 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 µg BID, had torsade de points 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 µg 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 µg BID dofetilide was 30%. The 10% pharmacological conversion rate for patients randomized to 250 µg BID is similar to the 12% conversion rate of DIAMOND-CHF, in which 250 µg BID was the maximum dose evaluated in patients with AF.7 In patients given 500 µg 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.8 Without drug therapy, AF recurs in ~75% of patients within 1 year after conversion.9 Prophylactic drug therapy has been shown to decrease the probability of recurrence of AF to 50%.9 This finding was strongly reinforced by our results, in which a randomized dosage of 500 µg 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 µg BID dofetilide group was >365 days, compared with 27 days observed in the placebo group. Although maintenance of SR for 1 year was higher (~80%) in the DIAMOND-CHF study, most of these patients (88%) were pharmacologically converted on dofetilide and thus would be more likely to maintain SR on continued dofetilide therapy.7 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.10 Unfortunately, currently available drug therapies to prevent or convert AF have adverse effects11,12 or may increase mortality rates or worsen heart failure.13

In this study, 3 (1.2%) proarrhythmic events were considered to be related to dofetilide. In the DIAMOND-CHF7 study, the incidence of torsade de points was substantially reduced by adjusting the dose for renal function. The DIAMOND-CHF7 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 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 AFI and subsequent maintenance of SR.

Highly symptomatic AF or AFI of >1 week’s duration should benefit from dofetilide as primary therapy provided that (1) patients have a ClCr ≥20 mL/min; (2) starting doses 500, 250, and 125 μg 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 AFI 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 AFI.

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 Bhal, 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, Foothills Hospital, Calgary, Alberta, Canada; Michael Giudici, MD, Saint Lukes Regional Heart Center, and Cardiovascular Medicine PC, Davenport, Iowa; Frank Gold, MD, Illinois Heart Institute, and Low-dose amiodarone. Ann Intern Med. 1994;120:449–457.

References
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