Safety of Oral Dofetilide for Rhythm Control of Atrial Fibrillation and Atrial Flutter

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Background—Although dofetilide is widely used in the United States for rhythm control of atrial fibrillation, there is limited postapproval safety data in the atrial fibrillation population despite its known risk of Torsade de pointes (TdP).

Methods and Results—We conducted a retrospective chart review of all patients admitted to the Cleveland Clinic from 2008 to 2012 to evaluate the incidence and risk factors for in-hospital adverse events and the long-term safety of continued use. Of the 17 patients with TdP during loading (1.2%), 10 had a cardiac arrest requiring resuscitation (1 death), 5 had syncope/presyncope, and 2 were asymptomatic. Dofetilide loading was stopped for 105 patients (7.5%) because of QTc prolongation or TdP. Variables correlated with TdP were (1) female sex, (2) 500-μg dose, (3) reduced ejection fraction, and (4) increase in QTc from baseline. One-year all-cause mortality was higher in patients who continued dofetilide compared with those who discontinued use (hazard ratio, 2.48; 95% confidence interval, 1.08–5.71; P=0.03). Those patients who had a TdP event had higher one-year all-cause mortality than those who did not (17.6% versus 3% at 1 year; P<0.001).

Conclusions—Dofetilide loading has a low but finite risk of TdP and other adverse events that warrant the current Food and Drug Administration–mandated practice of inpatient monitoring during drug loading. In this cohort, all-cause mortality was higher at 1 year in those patients continued on dofetilide and in those patients who experienced TdP while loading. (Circ Arrhythm Electrophysiol. 2015;8:772-776. DOI: 10.1161/CIRCEP.114.002339.)

Key Words: anti-arrhythmic drugs • atrial fibrillation • atrial flutter • dofetilide • Torsade de pointes
WHAT IS KNOWN
• Dofetilide requires inpatient initiation because of the known risk of Torsade de pointes.
• There is limited postapproval safety data in the AF population despite its known risk of Torsade de pointes.

WHAT THE STUDY ADDS
• Risks of dofetilide are reported for a large single-center series
• One-year all-cause mortality was higher in patients who continued dofetilide compared with those who discontinued use.
• Patients who had a Torsade de pointes had greater 1-year all-cause mortality (17.6% versus 3%) than those who did not, suggesting that a Torsade de pointes event may be predictive of a proarrhythmic substrate warranting consideration of further risk stratification in addition to counseling to avoid other QTc-prolonging agents.
• The study underscores the importance of cautious use and careful monitoring of this drug.

Statistical Analysis
Clinical characteristics are presented as percentages (%) for categorial variables, means±SD for normally distributed continuous variables and medians with 1st and 3rd quartiles for variables with a non-normal distribution. The χ² test or Fisher exact test was used to test categorial variables. Continuous data were tested with either the Student t test for normally distributed data or the Wilcoxon signed-rank test for non-normally distributed data. A multivariable logistic model was used to determine factors related to Torsade. Bootstrap sampling methods were used to identify candidate variables for inclusion into the final logistic model. Variables retained at α=0.20 level in at least 50% of the samples were included in the model. Given the low number of TdP events, a penalized likelihood method was used, and Firth bias-adjusted estimates are reported. A Cox proportional hazards model was used to estimate the risk of continued versus discontinued use of dofetilide on all-cause mortality after controlling for age and congestive heart failure; 2 factors known to increase mortality risk. Dofetilide usage was modeled as a time-varying covariate. All statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC).

Results
Patients
One thousand four hundred four patients (92% whites) were loaded on dofetilide at the Cleveland Clinic between 2008 and 2012. The patient population demographics are largely as expected for a cohort of patients with AF at a tertiary care center (Table 1). One thousand three hundred fifty-nine of the cohort had AF (359 of whom carried a concomitant diagnosis of atrial flutter), 41 patients had atrial flutter alone, and 4 patients had atrial tachycardia as the sole diagnosis. Of the 1404 patients, 165 (12%) stopped the drug at some point during the inpatient load, the most common reason being asymptomatic QTc prolongation (n=88; 6.3%; Table 2). Although the drug was stopped for 28 (2%) because of inefficacy, 70 (5%) patients were discharged on the drug despite failure to maintain sinus rhythm during the initial hospitalization (data subcohort is published elsewhere).

Short-Term Safety
Of the 17 patients who experienced TdP during inpatient loading (1.2%), 10 had a cardiac arrest requiring resuscitation (of whom 1 died), 5 had syncope/presyncope with no required resuscitation, and 2 were asymptomatic. There were 3 in-hospital deaths (0.2%) because of (1) TdP in a patient with critical aortic stenosis, (2) pulseless electric activity secondary to cardiac amyloidosis (no longer on drug at the time), and (3) acute bowel ischemia causing lactic acidosis. The 2 other major inpatient adverse events were a transient ischemic attack and a sinus/asystolic arrest. The combined rate of major adverse events was 1.5% (21/1401).

Long-Term Safety
At the time of chart review, 693 patients (56% of those discharged on treatment) were still on dofetilide (mean follow-up time, 1186±526 days) and 546 patients (44% of those discharged on treatment) had discontinued dofetilide (mean follow-up time, 1382±505 days). There was a significant interaction between continued dofetilide use and time (P<0.001), suggesting the risk of mortality with continued dofetilide usage varied across time. Within the first year, the risk of death was greater for those with continued dofetilide use compared with those who discontinued the drug (hazard ratio [HR], 2.48; 95% confidence interval [CI], 1.08–5.71; P=0.03). For patients surviving the first year, the risk of death with continued dofetilide use was lower compared with those who discontinued use (HR, 0.51; 95% CI, 0.32–0.82; P=0.005). Patients who had TdP event during loading had significantly higher all-cause mortality at 1 year than those who did not experience TdP despite discontinuing the drug (17.6% versus 3%; P≤0.001).

Correlates of TdP
By univariate analysis, patients with TdP were more likely to have a history of heart failure, a significantly lower
postmarketing safety data in a large AF cohort beyond the heart failure and MI populations of the DIAMOND trials.

In terms of risk factors for the known finite risk for TdP with dofetilide use, our analysis yielded similar findings to those published in previous studies. The dofetilide FDA approval meta-analysis revealed several factors that were associated with TdP by univariate analysis: baseline QTc>450 ms, maximum QTc increase of ≥15% compared with baseline, presence of structural heart disease, primary diagnosis of ventricular tachycardia, and female sex (this held up in multiple logistic regression analysis; \( P=0.0135 \)). The investigators for the DIAMOND trials performed a subanalysis to determine the risk factors for TdP (overall rate, 32/1511 or 2.1%) and found that risk factors for developing TdP were female sex (OR, 2.2; 95% CI, 1.0–5.0), MI within 8 weeks (decreased risk in this population; OR, 0.3; 95% CI, 0.1–0.7), New York Heart Association class III or IV (OR, 3.2; 95% CI, 1.2–8.6), and baseline QTc duration (OR, 1.14; 95% CI, 1.00–1.30) per 10-ms increase. The findings of our analysis yielded similar results such that female sex, increasing QTc, worsening ejection fraction, and higher end dose of dofetilide were all associated with increased risk of TdP. In our cohort, the presence of left ventricular hypertrophy was not associated with increased risk of TdP, which provides some evidence that it may be possible to safely use dofetilide in this population, despite recommendations to the contrary in the national guidelines for AF management.

Our review of the literature on dofetilide safety in the AF population found that to date there have been no studies for which the primary end point is safety of dofetilide use in a relatively healthier population with AF (Table 4). The FDA dofetilide approval documentation indicates that although they initially requested a study powered for safety in the AF population, they eventually accepted a meta-analysis of pooled data. Their meta-analysis of patients enrolled in a phase II or III, placebo controlled, supraventricular arrhythmia study of oral dofetilide use demonstrated a 1.7% rate of TdP in the Dofetilide Development Program (59/3452 patients) in those given dofetilide and none in those given placebo. There was a

Table 1. Characteristics of Patients in Relation to Occurrence of TdP

<table>
<thead>
<tr>
<th>Variable</th>
<th>TdP, n=17</th>
<th>No TdP, n=1387</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, sex</td>
<td>9 (53%)</td>
<td>472 (34%)</td>
<td>0.10</td>
</tr>
<tr>
<td>Age, mean±SD</td>
<td>68±11.8</td>
<td>66.5±10.6</td>
<td>0.19</td>
</tr>
<tr>
<td>Length of follow-up, d, median (Q1, Q3)</td>
<td>903 (515, 1229)</td>
<td>1225 (841, 1674)</td>
<td>0.007</td>
</tr>
<tr>
<td>Paroxysmal AF</td>
<td>3 (18%)</td>
<td>442 (32%)</td>
<td>0.21</td>
</tr>
<tr>
<td>Previous antiarrhythmic drugs</td>
<td>7 (46%)</td>
<td>647 (47%)</td>
<td>0.65</td>
</tr>
<tr>
<td>Previous AF ablation (percutaneous or surgical)</td>
<td>4 (24%)</td>
<td>386 (28%)</td>
<td>0.69</td>
</tr>
<tr>
<td>Baseline ventricular rate, median±SD</td>
<td>94±32</td>
<td>79±22</td>
<td>0.10</td>
</tr>
<tr>
<td>Congestive heart failure history</td>
<td>14 (82%)</td>
<td>654 (47%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Ejection fraction (%), median (IQR, MD N)</td>
<td>35 (20, 45), (0)</td>
<td>55 (40, 55), (19)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left ventricular hypertrophy (MD N)</td>
<td>(8.3%), (5)</td>
<td>(25.5%) (424)</td>
<td>0.31</td>
</tr>
<tr>
<td>Hypertension</td>
<td>16 (94%)</td>
<td>1363 (98%)</td>
<td>0.26</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>6 (35%)</td>
<td>418 (30%)</td>
<td>0.65</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>11 (65%)</td>
<td>635 (46%)</td>
<td>0.12</td>
</tr>
<tr>
<td>CHADS2 score, median (IQR)</td>
<td>3 (2, 3)</td>
<td>1 (1, 3)</td>
<td>0.012</td>
</tr>
<tr>
<td>GFR (MDRD), mL/min, median (IQR, MD N)</td>
<td>66 (49, 76), (2)</td>
<td>74 (61, 87), (18)</td>
<td>0.07</td>
</tr>
<tr>
<td>Electric cardioversion</td>
<td>7 (41%)</td>
<td>530 (38%)</td>
<td>0.80</td>
</tr>
<tr>
<td>ORS duration, ms, median (IQR)</td>
<td>94 (88, 128)</td>
<td>98 (88, 116)</td>
<td>0.90</td>
</tr>
<tr>
<td>Preload QTc, ms, median (IQR)</td>
<td>384 (364, 440)</td>
<td>396 (360, 432)</td>
<td>0.85</td>
</tr>
<tr>
<td>( \Delta )QTc, ms, median (IQR)</td>
<td>54 (−3.7, 125)</td>
<td>17 (−6.7, 39)</td>
<td>0.01</td>
</tr>
<tr>
<td>( \Delta )QTc, %, median (IQR)</td>
<td>12 (−1.27)</td>
<td>4 (−1, 9)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; CHADS2, combined stroke risk score: congestive heart failure, hypertension, age>75 years, diabetes, prior stroke/transient ischemic attack, vascular disease; GFR, glomerular filtration rate; IQR, interquartile range; MD, missing data; MD N, number of missing data; MDRD, modification of diet in renal disease; and TdP, Torsade de points.

ejection fraction, a higher CHADS2 (combined stroke risk score: congestive heart failure, hypertension, age>75 years, diabetes, prior stroke/transient ischemic attack, vascular disease) score, and a greater increase in QTc from baseline (Table 1). In multivariable modeling, female sex, increase in QTc (treated as a continuous variable), lower ejection fraction (treated as a continuous variable), and final dofetilide dose of 500 μg BID were associated with TdP (Table 3; \( c\)-statistic=0.87).

**Discussion**

In this retrospective cohort study of 1404 patients loaded on dofetilide for a 5-year period at a single institution, we found a 1.2% incidence of TdP, which was more common in women, those with lower ejection fractions, those with greater QTc prolongation, and in patients taking the 500-μg BID dose of dofetilide. We found an increase in all-cause mortality through 1 year in those taking dofetilide when compared with those who stopped the drug. This analysis provides the first

Table 2. Causes for Dofetilide Discontinuation During Loading

<table>
<thead>
<tr>
<th>Cause</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic QTc prolongation</td>
<td>88</td>
</tr>
<tr>
<td>Ineffective</td>
<td>28</td>
</tr>
<tr>
<td>TdP (1 event resulting in death)</td>
<td>17</td>
</tr>
<tr>
<td>Change in treatment plan</td>
<td>7</td>
</tr>
<tr>
<td>Ventricular ectopy</td>
<td>7</td>
</tr>
<tr>
<td>Sinus node dysfunction</td>
<td>7</td>
</tr>
<tr>
<td>Renal failure</td>
<td>3</td>
</tr>
<tr>
<td>Medication interaction</td>
<td>3</td>
</tr>
<tr>
<td>Thrombus on transesophageal echocardiogram</td>
<td>2</td>
</tr>
<tr>
<td>Intolerance (headache and nausea)</td>
<td>2</td>
</tr>
<tr>
<td>Bowel ischemia (progressed to lactic acidosis and death)</td>
<td>1</td>
</tr>
<tr>
<td>Transient ischemic attack after cardioversion</td>
<td>1</td>
</tr>
<tr>
<td>Medication cost</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>165</td>
</tr>
</tbody>
</table>

TdP indicates Torsade de points.
0.7% (12/1776) sudden unexplained cardiac death rate in the dofetilide group versus 0.4% (3/759) in the placebo group. 9 There was a 0.9% (12/1346) all-cause mortality rate in the dofetilide group versus 0.4% (3/677) in the placebo group (HR, 1.4; 95% CI, 0.4–5.1),9 and according to their interpretation of the data, excess mortality (and arrhythmias) occurred with dofetilide although the studies carefully selected patients and routinely discontinued dofetilide or lowered the dose if prolonged QT/QTc interval was observed.9 The EMERALD trial was one of the 2 major efficacy trials for dofetilide use in AF that were not powered for safety.7 Although there were 4 TdP events in 397 patients on dofetilide (1.0%) and 1 presumed cardiac death in the dofetilide group, there are many gaps in the safety data available for review (it was only published in abstract form, and because the safety data for the FDA review was pooled, no specific information is available on the nature of the adverse events that occurred and the reasons for premature withdrawal). However, all-cause mortality at 1 year was not different between the dofetilide and placebo-treated groups (1.5% versus 2.2%; HR, 0.69; 95% CI, 0.17–2.75).6 In the SAFFIRE-D trial, the other major efficacy trial for dofetilide use in AF, there were 3 TdP events in 241 patients on dofetilide (1.2%) and no significant difference in all-cause mortality compared with placebo (1.8% versus 2.4%; HR, 0.7; 95% CI, 0.17–2.78).1 The DIAMOND trials were conducted to evaluate safety with the primary end point of all-cause mortality in a heart failure and post–MI population (maximum dose of 250 μg BID for patients with AF, which was 10% of the cohort of 3028 patients). They found that dofetilide use did not increase all-cause mortality compared with placebo in either group although absolute all-cause mortality was quite elevated in both populations (41% versus 42% mortality, respectively, at a median of 18 months for the heart failure cohort and 31% versus 32% mortality, respectively, at a median of 15 months for the MI cohort).3,4 To evaluate mortality with dofetilide use in the AF population, we compared patients who continued on the drug with those who discontinued the drug at any point during follow-up, and in addition, we evaluated whether the patient was taking the medication at the time of death. We found that within the first year, all-cause mortality for the patients who continued dofetilide was more than twice as high as those patients who discontinued the drug (HR, 2.48; 95% CI, 1.08–5.71; P=0.03). Interestingly though, for patients surviving the first year, the risk of death with continued dofetilide was not statistically different than those who discontinued use. The reason for this temporal discrepancy is unclear although these findings suggest that more prospective studies of the safety of dofetilide for rhythm control in the AF population would be important and that close monitoring of patients on dofetilide is particularly important in the first year.

Another unexpected finding from our analysis was that patients who had TdP had a higher all-cause mortality rate at 1 year than those who did not have TdP (17.6% versus 3%)

### Table 3. Multivariable Model for Factors Associated With Torsade De Pointes

<table>
<thead>
<tr>
<th>Parameter</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, sex</td>
<td>5.2 (1.9–14.4)</td>
<td>0.002</td>
</tr>
<tr>
<td>Delta QTc</td>
<td>1.02 (1.01–1.04)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>0.93 (0.90–0.96)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>End dose, 500 μg</td>
<td>4.0 (1.5–10.8)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

C-statistic=0.87. CI indicates confidence interval; and OR, odds ratio.

### Table 4. Dofetilide Safety Data

<table>
<thead>
<tr>
<th>Study (Date)</th>
<th>Population</th>
<th>n on Dofetilide</th>
<th>Primary End point</th>
<th>Incidence of TdP</th>
<th>All-Cause Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA Meta-analysis (1999)⁹</td>
<td>Phase II or III placebo controlled dofetilide supraventricular arrhythmia trials</td>
<td>3452</td>
<td>Meta-analysis of the rates of TdP and all-cause mortality</td>
<td>1.7% (n=59)</td>
<td>0.9% (12/1346) vs 0.4% (3/677) for controls</td>
</tr>
<tr>
<td>DIAMOND-HF (1999)⁴</td>
<td>Symptoms of heart failure and left ventricular dysfunction (25% with AF)</td>
<td>762 (vs 756 controls)</td>
<td>All-cause mortality</td>
<td>3.3% (n=25)</td>
<td>41% vs 42% for controls (median follow-up of 18 mo)</td>
</tr>
<tr>
<td>DIAMOND-MI (2000)³</td>
<td>Recent MI, EF≤35% (8% with AF)</td>
<td>749 (vs 761 controls)</td>
<td>All-cause mortality</td>
<td>0.9% (n=7)</td>
<td>31% vs 32% for controls (median follow-up of 15 mo)</td>
</tr>
<tr>
<td>DIAMOND-AF (2001)²</td>
<td>EF≤35%, AF/AFL</td>
<td>249 (vs 257 controls)</td>
<td>Secondary analysis evaluating efficacy of rhythm control and chemical cardioversion</td>
<td>1.6% (n=4)</td>
<td>=30% at 1 y (same for controls)</td>
</tr>
<tr>
<td>DIAMOND-TdP (2007)¹⁰</td>
<td>One of the DIAMOND trials and given dofetilide (16% with AF)</td>
<td>1511 (total)</td>
<td>Secondary analysis evaluating TdP predictors</td>
<td>2.1% (n=32)</td>
<td>Not reported</td>
</tr>
<tr>
<td>EMERALD (1999, abstracts)⁶,⁷</td>
<td>Persistent AF</td>
<td>397 (vs 137 controls)</td>
<td>Probability of sinus rhythm at 1 yr</td>
<td>1.0% (4/397)</td>
<td>1.5% (6/397) vs 2.2% (3/137) for controls (at 12 mo)</td>
</tr>
<tr>
<td>SAFIRE-D (2000)⁶</td>
<td>Persistent AF and AFL</td>
<td>241 (vs 84 controls)</td>
<td>Probability of sinus rhythm at 1 yr; % pharmacological cardioversion</td>
<td>1.2% (3/241)</td>
<td>2.4% (2/84) vs 1.8% (6/325) for controls (at 12 mo)</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; AFL, atrial flutter; DIAMOND, Danish Investigations of Arrhythmia and Mortality on Dofetilide; FDA, Food and Drug Administration; EF, ejection fraction; EMERALD, European and Australian Multicenter Evaluative Research on Atrial Fibrillation Dofetilide; HF, heart failure; MI, myocardial infarction; SAFIRE-D, Symptomatic Atrial Fibrillation Investigative Research on Dofetilide; and TdP, Torsade de pointes.
at 1 year; \( P<0.001 \). This finding is hypothesis-generating to the extent that it suggests that a TdP event may be predictive of a proarrhythmic substrate and may warrant consideration of further risk stratification in addition to counseling to avoid other QTc-prolonging agents.

Limitations

This was a single-center, retrospective cohort study, and hence, no definitive conclusions can be made on the causal relationship between dofetilide use and either TdP or all-cause mortality. Given the relatively small number of TdP events (n=17), positive associations from the multivariable logistic model could be spurious and should be interpreted with caution. In addition, the cohort was 92% of whites, which may limit the generalizability of this result to other ethnic groups. Furthermore, the mortality analysis was constructed by comparing patients who continued the drug with those who stopped it, and our study did not have a separate control group. Nonetheless, all-cause mortality in our cohort was similar to previous studies, such as the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial that found 4% all-cause mortality at 1 year for both the rhythm and rate control groups.12

Conclusions

Dofetilide loading has a low but finite risk of TdP, and other adverse events that warrant the current FDA-mandated practice of inpatient monitoring for the first 6 doses. TdP is more common in women, patients prescribed the 500 μg BID doses, patients with reduced ejection fraction, and in those who have a greater increase in QTc from baseline, and the risk is not increased in patients with left ventricular hypertrophy. All-cause mortality within the first year was greater in patients who continued dofetilide compared with those who discontinued it. Future studies focusing prospectively on this issue in the AF population are warranted.

Acknowledgments

We thank Kia Afsar, MD, for his assistance with the initiation and conceptualization of this project.

Disclosures

None.

References

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_Circ Arrhythm Electrophysiol._ 2015;8:772-776; originally published online June 10, 2015;
doi: 10.1161/CIRCEP.114.002339
_Circulation: Arrhythmia and Electrophysiology_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3149. Online ISSN: 1941-3084

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