Dofetilide dose reductions and discontinuations in women compared with men

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BACKGROUND Compared with men, women have longer corrected QT (QTc) intervals, lower clearance of dofetilide, and higher rates of drug-induced torsades de pointes, but the dofetilide dosing algorithm is the same for men and women.

OBJECTIVE The purpose of this study was to evaluate the tolerability of the 500 μg twice daily dose of dofetilide for men and women.

METHODS Men and women admitted to Duke University Medical Center (January 1, 2006, to October 19, 2012) for the initiation of dofetilide 500 μg twice daily were matched 1:1 on age and estimated creatinine clearance. Electrocardiograms throughout dosing were analyzed, and rates of dofetilide discontinuations and dose reductions were compared in unadjusted and adjusted analyses.

RESULTS For 220 matched men and women, the median age was 62.5 years (interquartile range 55–69 years) and the median eCrCl was 98.1 mL/min (interquartile range 77.6–126.2 mL/min). Women were less likely than men to have hypertension and interventricular conduction delay but were otherwise similar. During dofetilide initiation, women were more likely than men to have their dofetilide dose discontinued or reduced (55% vs 32%; P < .001). In most women (82%) and men (69%), the reason for dose adjustment was significant QTc prolongation. In the adjusted analysis, female sex was associated with higher rates of dofetilide dose discontinuations or reductions (odds ratio 3.01; 95% confidence interval 1.58–5.71; P < .01).

CONCLUSION More than half of women who initiated on 500 μg twice daily of dofetilide required medication discontinuations or dose reductions, mostly because of QTc prolongation. Additional studies are needed to evaluate the optimal dosing algorithm of dofetilide in women.

KEYWORDS Atrial fibrillation; Dofetilide; QT prolongation; Rhythm control; Women

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Introduction

Professional society guidelines for atrial fibrillation (AF) recommend antiarrhythmic drug therapy for patients with symptomatic recurrent paroxysmal AF and recurrent persistent AF despite rate control. Dofetilide has been shown to be effective in cardioversion of AF and maintenance of sinus rhythm in 2 randomized controlled clinical trials, and as a result, dofetilide is the only antiarrhythmic agent that is recommended as a first line therapy for a wide range of patients with AF—those with and those without structural heart disease (coronary artery disease or heart failure). Dofetilide is a Vaughan Williams class III antiarrhythmic medication that blocks the rapid-delayed outward rectifier potassium current (I_{Kr}) during repolarization, which can result in a dose-related prolongation of the action potential duration and corrected QT (QTc) interval on an electrocardiogram (ECG). Dofetilide is primarily excreted by the kidneys (70%–80%). The Food and Drug Administration—
approved dose selection algorithm for dofetilide is based on the estimated creatinine clearance (eCrCl; as determined using the Cockcroft-Gault equation). Lower initiation doses are selected for those with poorer renal function with the intent of minimizing the risk of QTc prolongation and torsades de pointes. Women have a longer baseline QTc interval than do men, and female sex has been associated with at least a 2-fold higher rate of torsades de pointes with class III antiarrhythmic drugs; however, no differential dosing adjustment is recommended for women with the same eCrCl as men.

The purpose of this analysis was to explore the tolerability of the 500 μg twice daily dose of dofetilide that is the recommended initiation dose for both men and women with eCrCl >60 mL/min by comparing changes in QTc interval, adverse events, and rates of dose discontinuations or reductions between men and women.

Methods
Study population

This retrospective study included adult patients at Duke University Medical Center, initiating dofetilide for treatment of AF for the first time between January 1, 2006, and October 19, 2012, with a dose of 500 μg twice daily. Patients were identified through the Duke Enterprise Data Unified Content Explorer (DEDUCE), which is a research database of data collected through patient care at Duke University Medical Center. Manual chart abstraction was used to collect comorbid conditions, actual body weight, baseline QTc intervals, and QTc intervals after each of the first 5 doses of dofetilide, dofetilide discontinuations, dofetilide dose reductions, reasons in the chart for dofetilide dose discontinuations or reductions, adverse drug reactions, and electrophysiology procedures performed. Patients were excluded for the following reasons: previous treatment with dofetilide, reinitiation of dofetilide, or initiation of dofetilide at a dose less than 500 μg twice daily. As per hospital policy, all patients were monitored for at least the first 5 doses of dofetilide on continuous telemetry with daily electrolyte and renal function monitoring, as well as ECGs before the first dose of dofetilide and 2–3 hours after each dose. Patients were monitored by cardiologists or electrophysiologists who were certified dofetilide prescribers.

All women initiated on dofetilide for the first time at a dose of 500 μg twice daily during the study period were included in the analysis. These women were matched 1:1—on age and eCrCl—with men who were admitted during the study period for initiation of 500 μg twice daily of dofetilide for the first time. Serum creatinine on the day of or day before the initiation of dofetilide and actual body weight on admission were used to calculate the eCrCl by using the Cockcroft-Gault equation. Patients in the analysis had eCrCl > 60 mL/min, so they were dosed appropriately with the 500 μg twice daily dose.

End points

Measurements of baseline QTc intervals and the QTc intervals after each dose of dofetilide were performed manually using the Bazett formula by a single cardiologist (S.D.P.). The ECG reader was blinded to patient sex, whether the ECG was taken at baseline or after one of the dofetilide doses, previous and future QTc interval values for a given patient, and patient outcomes (adverse events, dose modifications, or medication discontinuation). Measurements of QTc intervals were retrospective and independent of clinical care measurements. The QT interval was measured from the onset of the QRS complex to the intersection of the line of the maximal slope of the t wave and the TP baseline. The QTc interval measurement for an ECG in AF was based on the average of 3 QTc interval measurements, including the shortest R-R interval in any lead, the longest R-R interval in any lead, and an intermediate R-R interval in the limb leads.

Dofetilide discontinuations or dose reductions were determined through manual chart review. Dofetilide discontinuation was defined as initiation of the dofetilide 500 μg twice daily dose with subsequent discharge off dofetilide. Dofetilide dose reductions were defined as initiations of the dofetilide 500 μg twice daily dose with subsequent discharges on a dose less than 500 μg twice daily. Dofetilide discontinuations were defined as initiations of the dofetilide 500 μg twice daily dose with subsequent discharges off dofetilide. Decisions to modify the doses of dofetilide, either by medication discontinuations or by dose reductions, were made by the certified dofetilide prescriber who were clinically caring for the patients. Adverse events such as torsades de pointes, bradycardia-requiring pacemaker implantation, and in-hospital death were determined through chart abstraction. Recurrence of AF was evaluated 1 year after dofetilide initiation, and AF recurrence was defined as patient reported symptomatic recurrence of AF, ECG documented AF, or AF documented on Holter monitor.

Statistical methods

Men were identified for the analysis by matching them 1:1 to women on age and eCrCl. Patients were first matched on age with the goal of obtaining an exact match whenever possible. Patients were then matched on eCrCl, and women and men were a match if their eCrCl were within 10% of each other. If there were no matches based on eCrCl for patients of the same age, a match was then pursued for women and men with ages with a maximum of 5-year difference while maintaining the 10% difference in eCrCl; if there was still no match, the unmatched women (n = 2) were excluded from the analysis. If more than 1 match was identified, the matched pair with the closest eCrCl was used.

Baseline characteristics were compared between men and women. Categorical variables were summarized as counts and percentages and were compared using the Pearson χ² test. Continuous variables were summarized as medians and interquartile ranges and were compared using the Kruskal-Wallis test. The unadjusted number and prevalence of dofetilide discontinuations or dose reductions by sex during in-hospital initiation were reported. Logistic regression modeling assessed the adjusted association between sex and dofetilide
dose modifications (discontinuations or dose reductions). The covariates in the model included age, race, sex, actual body weight, hypertension, diabetes, heart failure, coronary artery disease, obstructive sleep apnea, chronic obstructive pulmonary disease, eCrCl, and baseline QTc interval.

All analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC). The study was approved by the Duke University’s Institutional Review Board.

Results

Baseline characteristics

There were 110 female patients and 110 male patients matched and included in the analysis with the median age of 62.5 years (interquartile range 55–69 years) and the median eCrCl of 98.1 mL/min (interquartile range 77.6–126.2 mL/min). The median age and eCrCl were similar for male and female patients (Table 1). The actual body weight in men was significantly higher than that in women (median 95.5 kg vs 84.1 kg; P < .001). β-Blockers or diltiazem were present at baseline (Table 2) and included in the analysis with the median age of 62 (55–69) years and the median eCrCl of 98.1 mL/min (interquartile range 77.6–126.2 mL/min). There was an association between female sex and dofetilide discontinuations (OR 2.92; 95% CI 1.13–7.54) (Table 3). There was also an association between female sex and QTc prolongation in women (n = 49 [82%]) and men (n = 24 [69%]) (Table 2 and Supplemental Appendix 1).

Dofetilide dose changes or discontinuations

Forty-one women (37%) initiated on dofetilide 500 µg twice daily and had their dofetilide dose reduced during in-hospital initiation. Fewer men (n = 27 [25%]) of similar age and eCrCl had dose reductions in comparison to women (P = .042) (Figure 1). A greater number of women initiated on 500 µg twice daily of dofetilide had the medication discontinued during hospitalization in comparison to men (17% vs 7%; P = .024). Overall, women were more likely than men to have discontinuations or dose reductions (55% vs 32%; P < .001), and the most common dose reduction was down to 250 µg twice daily (Figure 2).

Most discontinuations or dose reductions were due to QTc prolongation in women (n = 49 [82%]) and men (n = 24 [69%]) (Table 2 and Supplemental Appendix 1). Bradycardia (5 women [8%] and 8 men [23%]) was the second most common reason for dose modification, and 4 women and 7 men who developed bradycardia were on β-blockers or calcium channel blockers at baseline (Table 2). There were 2 women (2%) and 1 man (1%) who developed profound sinus bradycardia on dofetilide requiring pacemaker implantation during the dofetilide initiation hospitalization in order to safely continue dofetilide.

After adjustment, female sex was associated with dofetilide discontinuations or dose reductions (odds ratio [OR] 3.01; 95% confidence interval [CI] 1.58–5.71) (Table 3). There was also an association between female sex and dofetilide discontinuations (OR 2.92; 95% CI 1.13–7.54) and a trend toward an association between female sex and dose reductions (OR 1.93; 95% CI 1.00–3.74) (Table 3).

There were no cases of torsades de pointes or in-hospital death among women or men.

AF 1-year follow-up data

There were 91 female (83%) and 102 male (93%) patients discharged on dofetilide, while 84 women (76%) and 88

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Women (n = 110)</th>
<th>Men (n = 110)</th>
<th>P</th>
</tr>
</thead>
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<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Age (y)</td>
<td>62 (55–69)</td>
<td>63 (55–69)</td>
<td>.92</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>84.1 (72.7–101.4)</td>
<td>95.5 (86.0–110.0)</td>
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<td>Black race</td>
<td>7 (6)</td>
<td>8 (7)</td>
<td>.79</td>
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<tr>
<td>Medical history</td>
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<td>17 (15)</td>
<td>17 (15)</td>
<td>1.00</td>
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<tr>
<td>Hypertension</td>
<td>59 (54)</td>
<td>75 (68)</td>
<td>.027</td>
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<td>19 (17)</td>
<td>29 (26)</td>
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<td>Diabetes</td>
<td>20 (18)</td>
<td>15 (14)</td>
<td>.36</td>
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<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>5 (5)</td>
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<td>.73</td>
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<tr>
<td>Obstructive sleep apnea</td>
<td>23 (21)</td>
<td>23 (21)</td>
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<td>eCrCl (mL/min)</td>
<td>99.0 (74.9–123.0)</td>
<td>98.1 (78.3–127.1)</td>
<td>.57</td>
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<td>Baseline medications</td>
<td></td>
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</tr>
<tr>
<td>β-Blockers or diltiazem</td>
<td>86 (78)</td>
<td>89 (81)</td>
<td>.62</td>
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<tr>
<td>Baseline electrocardiographic findings</td>
<td></td>
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<tr>
<td>Atrial fibrillation at initiation</td>
<td>45 (41)</td>
<td>52 (47)</td>
<td>.34</td>
</tr>
<tr>
<td>QRS duration (ms)</td>
<td>90 (80–100)</td>
<td>100 (90–110)</td>
<td>&lt;.001</td>
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<tr>
<td>QRS duration &gt; 120 ms</td>
<td>10 (9)</td>
<td>18 (16)</td>
<td>.032</td>
</tr>
<tr>
<td>QTc interval (ms)</td>
<td>435 (417–456)</td>
<td>430 (405–458)</td>
<td>.41</td>
</tr>
</tbody>
</table>

Values are presented as median (interquartile range) or n (%).

eCrCl = estimated creatinine clearance; QTc = corrected QT.

*Men and women were matched on age and eCrCl.
†eCrCl is defined by Cockroft-Gault.

Table 1: Patient characteristics
men (80%) had follow-up data at 1 year (6 women lost to follow-up and 1 died; 13 men lost to follow-up and 1 had cardiac transplant). Rates of any AF recurrence at 1 year were higher for male (n = 56 of 88 [64%]) than for female (n = 41 of 84 [49%]) patients (P < .001). Rates of AF recurrence were similar for men discharged on 500 mg twice daily (n = 67) vs 250 mg twice daily (n = 10) (64% vs 70%, respectively), as well as for women discharged on 500 mg twice daily (n = 46) vs 250 μg twice daily (n = 31) (50% vs 48%, respectively).

**Subgroup analysis**

Of the 10 women with QRS duration ≥120 ms, 7 had dofetilide discontinuations or dose reductions, while 7 of the 18 men with QRS duration ≥120 ms had dofetilide discontinuations or dose reductions. Among patients with
Table 2  Events resulting in discontinuations or dose reductions*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Women (n = 60)</th>
<th>Men (n = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTc prolongation</td>
<td>49 (82)</td>
<td>24 (69)</td>
</tr>
<tr>
<td>Angioedema</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Atrioventricular block</td>
<td>1 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Sinus bradycardia</td>
<td>5 (8)</td>
<td>8 (23)</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (2)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Torsades de pointes</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Nonsustained ventricular tachycardia</td>
<td>4 (7)</td>
<td>2 (6)</td>
</tr>
</tbody>
</table>

Values are presented as n (%).

*Based on documentation identified in the medical records.

QRS duration <120 ms, 53% of women (n = 53 of 100) and 32% of men (n = 28 of 92) had dofetilide discontinuations or dose reductions (P < .001).

At baseline, 14 women (13%) and 29 men (26%) had QTc interval >440 ms with a narrow QRS complex or QTc interval >500 ms with QRS duration >120 ms. Nearly all (n = 13 [93%]) of these women had dofetilide discontinuations (n = 6 [43%]) or dose reductions (n = 7 [50%]), while fewer than half (n = 13 [45%]) of these men had dofetilide discontinuations (n = 3 [10%]) or dose reductions (n = 10 [34%]). Among 96 women (87%) and 81 men (74%) with QTc interval ≤440 ms with a narrow QRS complex or QTc interval ≤500 ms with QRS duration ≥120 ms, women still tended to have more dofetilide discontinuations (n = 13 [14%]) or dose reductions (n = 34 [35%]) as compared with dofetilide discontinuations (n = 5 [6%]) or dose reductions (n = 17 [21%]) in men.

Discussion

The recommended initiation dose of dofetilide for women and men with eCrCl >60 mL/min by Cockroft-Gault is 500 μg twice daily. Despite following this dosing recommendation, more than 50% of women who were initiated on the 500 μg twice daily dose of dofetilide had medication discontinuations or dose reductions during in-hospital monitored initiation. Prolongation of the QTc interval was the most common reason for dose modification and occurred in more than two-thirds of women and men. Female sex was associated with medication discontinuations or dose reductions in unadjusted and adjusted analyses when compared with men of matched age and eCrCl.

Data from the dofetilide clinical trials demonstrated that dose reductions of dofetilide for QTc prolongation occurred in 5% and 7% of Danish Investigation of Arrhythmia and Mortality ON Dofetilide (DIAMOND) CHF and DIAMOND MI patients, respectively. Data from 2 cardioversion trials found that 3% of patients had their dofetilide dose reduced because of QTc prolongation. The rates of dofetilide discontinuations across all 4 trials were 2%–3%. The rates of discontinuations and dose reductions were meaningfully higher in our analysis, with 32% of male patients and 55% of female patients unable to complete the initiation with 500 μg of dofetilide twice daily. Compared with those in clinical trials, dose reduction rates in women were 5- to 12-fold higher in this analysis, while dofetilide discontinuation rates in women in this analysis were 6- to 9-fold higher than those in clinical trials. However, this analysis evaluated only patients with eCrCl >60 mL/min who were initiated on the 500 μg twice daily dose. The data in this analysis were in line with reports from other clinical practices in which the rates of discontinuations during dofetilide initiation were also meaningfully higher than those in the trials, ranging from 7% to 12%, while the rates of dofetilide dose reductions ranged from 17% to 29%. Rates of QTc prolongation may be even higher in patients who chemically cardiovert with the initiation of dofetilide.

Prolongation of the QTc interval was the reason that dofetilide was discontinued or dose reduced in more than 2 of 3 men and women patients in this analysis. It is known that women have longer baseline QTc intervals than do men, which may make them more prone to drug-induced QT prolongation. This difference in QTc interval arises after puberty when men experience shortening of their QTc intervals while women do not. A proposed mechanism for this is the effect of sex hormones on cardiac repolarization. In animal studies, testosterone was protective against action potential prolongation, including with infusion of QTc-prolonging cardiovascular medications. Animal models have also found a higher prevalence of early afterdepolarizations in adult female patients exposed to dofetilide. A difference in baseline QTc intervals between women and men was not seen in this study, which may have been due to selection bias, as patients were not eligible for dofetilide initiation if their QTc interval was prolonged. Early afterdepolarizations can cause polymorphic ventricular tachycardia, so the findings of longer QTc intervals in women could contribute to the association between female sex and torsades de pointes with class III antiarrhythmic medications. Our analysis did not identify any cases of in-hospital torsades de pointes. Sinus bradycardia was the second most common reason for discontinuations or dose reductions. It is difficult to determine from the chart review what portion of these events were related to better identification of bradycardia due to continuous telemetry monitoring vs bradycardia associated with the dofetilide itself. Dofetilide has previously been shown to decrease heart rate and prolong sinus node recovery time.

Despite the potential sex differences in QTc interval, female sex was underrepresented in the landmark dofetilide clinical trials, as women comprised 28% of all enrolled patients in both the DIAMOND CHF and DIAMOND MI trials as well.

Table 3  Adjusted association between female sex vs male sex and outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Adjusted odds ratio</th>
<th>95% confidence interval</th>
<th>P</th>
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<tbody>
<tr>
<td>Dofetilide discontinuations</td>
<td>2.92</td>
<td>1.13–7.54</td>
<td>.03</td>
</tr>
<tr>
<td>Dofetilide dose reductions</td>
<td>1.93</td>
<td>1.00–3.74</td>
<td>.05</td>
</tr>
<tr>
<td>Dofetilide discontinuations or dose reductions</td>
<td>3.01</td>
<td>1.58–5.71</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>
as 16% of patients in the Symptomatic Atrial Fibrillation Investigative Research on Dofetilide trial. Fewer than 25% of DIAMOND patients with AF at baseline were women. Several of the pharmacokinetic and pharmacodynamic analyses of dofetilide were done only in men. Pharmacokinetic and pharmacodynamic data show that women have clearance rates of dofetilide that are 12%–18% lower than those in men, resulting in plasma concentrations of dofetilide that are 14%–22% higher in women than in men.

Two small studies, consisting of 107 patients with AF (41% women) and 22 healthy patients (50% women), evaluated potential differences in QTc prolongation between the sexes in response to dofetilide, and neither study found a statistical difference in QTc prolongation. However, the 22-patient study involved giving single doses of dofetilide to healthy control patients. The larger study that included 44 women did not restrict the patient population to the 500 μg twice daily dose, and the patient population did not include matching or adjustment. A third study of 114 male patients identified a 19% rate of dofetilide discontinuations during hospitalization for initiation of dofetilide, and 88 of the 114 patients were on the 500 μg twice daily dose. We had nearly twice as many patients as the largest of these 3 previous studies, and our analysis was the only study limited to patients initiating on 500 μg twice daily dofetilide. Our study also included matched women and men. These factors likely contributed to our ability to demonstrate higher unadjusted rates of dofetilide discontinuations (P = 0.024), dose reductions (P = 0.042), and discontinuations or dose reductions (P < .001) in women in the present analysis. Similarly, even after adjustment for baseline characteristics, female sex was associated with higher rates of dofetilide discontinuations (OR 2.92), dose reductions (OR 1.93), and discontinuations or dose reductions (OR 3.01). Reasons for these findings are likely multifactorial and related to disproportionate effects of actual body weight vs ideal body weight on eCrCl by sex and gender-specific differences, with women being more prone to QTc prolongation. The concept that women are more prone to QTc prolongation is supported by the 1:1 matching for age and eCrCl in this analysis, as well as the fact that twice as many men (n = 29 [26%]) as women (n = 14 [13%]) had baseline QTc interval >440 ms with a narrow QRS complex or QTc interval >500 ms with QRSD duration ≥120 ms, but women still had greater QTc prolongation.

Study limitations

Even though women and men were well matched and appropriate statistical adjustment was performed, residual measured and unmeasured confounders could have affected the analysis. This was a single-center experience with limited racial diversity, as only 7% of the population was black, so our data may not generalize to racial minorities. The Bazett formula was used for QTc interval calculation, and there are limitations on the accuracy of this formula, especially in the setting of tachycardia; however, the same methodology was used for patients of both sexes. Although there were no episodes of torsades de pointes, this study focused on safety during the in-hospital initiation period of dofetilide in a study population that was smaller than that of the dofetilide clinical trials. Follow-up data are needed to determine the long-term safety of the 500 μg twice daily dose in women who tolerate the initiation and are discharged on the 500 μg twice daily dose. There was no standardized approach to monitor for AF recurrence. The 1-year follow-up data are not sufficient to prove effectiveness of the 250 μg twice daily dose for women, and additional effectiveness data of the maintenance of rhythm control after dose reduction are needed. This study was limited to dofetilide initiation through late 2012, because around that time many providers at our institution began to systematically avoid the 500 μg twice daily dose in women even in patients with eCrCl >60 mL/min. This analysis focused on the 500 μg twice daily dose, and no comments can be made about differences in the tolerability of loading women and men meeting the dosing recommendations for the 250 or 125 μg twice daily doses.

Conclusion

More than half of women with normal renal function who initiated on dofetilide 500 μg twice daily required dofetilide discontinuations or dose reductions during the in-hospital initiation period as compared with about one-third of age- and CrCl-matched men. Female sex was associated with 3-fold higher odds of dofetilide discontinuations or dose reductions relative to male sex. Further studies are needed to better understand the optimal dofetilide dose for women, including evaluating short-term tolerance of the medication load as well as long-term persistence and clinical outcomes.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2018.01.027.

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