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Discontinuation of Dofetilide From QT Prolongation and Ventricular Tachycardia in the Real World

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ABSTRACT

OBJECTIVES The purpose of this study was to determine the incidence and correlates of QT prolongation or ventricular tachycardia (VT) resulting in discontinuation of dofetilide in a real-world setting.

BACKGROUND Dofetilide is a class III antiarrhythmic agent approved for achieving and maintaining sinus rhythm in patients with symptomatic atrial fibrillation. Because of a risk of QT prolongation and VT, patients starting dofetilide need to be hospitalized for 3 days to closely monitor telemetry and electrocardiography. In large clinical trials, <3% of patients had to discontinue dofetilide because of QT prolongation, but data from real-world experience are lacking.

METHODS We examined 114 consecutive patients with atrial fibrillation who were hospitalized for starting dofetilide at the Minneapolis Veterans Affairs Health Care System from 2011 to 2014.

RESULTS The mean age of the patients was 64 ± 8 years. Dofetilide was discontinued in 22 (19%) patients because of QT prolongation (17%) or VT (2%). A total of 32 (28%) patients were taking other QT-prolonging drugs. Of these, 10 (31%) had to discontinue dofetilide versus 12 (15%) of the 82 patients who were not taking any other QT-prolonging drugs ($p = 0.04$). Patients who were taking concomitant QT-prolonging drugs were 1.9 times more likely to discontinue dofetilide (95% confidence interval: 1.1 to 3.4; $p = 0.04$) compared with those who were not taking any other QT-prolonging drugs.

CONCLUSIONS The incidence of QT prolongation or VT that lead to discontinuation of dofetilide is remarkably higher in the real-world setting than in clinical trials. Concomitant use of other QT-prolonging drugs was associated with discontinuation of dofetilide. (J Am Coll Cardiol EP 2016;2:777–81) © 2016 by the American College of Cardiology Foundation.

Atrial fibrillation (AF) is the most common arrhythmia, affecting nearly 1% of the general population (1,2). By the year 2050, the prevalence of AF in the United States is estimated to rise from 5 to ~16 million (3). In large-scale population studies, AF has been associated with adverse cardiovascular events, including thromboembolism, heart failure, sudden cardiac death, and cardiovascular mortality (4–6).

In symptomatic patients with AF, antiarrhythmic therapy can be useful to achieve and maintain normal sinus rhythm to alleviate symptoms and optimize heart failure management (7–12). Dofetilide, a class III antiarrhythmic drug, is frequently used for rhythm control in patients with AF. In randomized trials, dofetilide had ~40% efficacy in achieving (13–16) and up to 65% efficacy in maintaining (13,17) sinus rhythm at 1 year. Further, dofetilide is the only antiarrhythmic drug, besides amiodarone, that is approved for use in patients with severe left ventricular systolic dysfunction (15,16). However, because of the risk of QT prolongation and ventricular tachycardia (VT), which occurred in <3% of the patients in clinical trials (13,15,16), dofetilide has to be initiated in the hospital, under continuous telemetry and electrocardiography (ECG) monitoring (13,16,18,19).

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

ECG = electrocardiography

GFR = glomerular filtration rate

QTc = corrected QT interval

VT = ventricular tachycardia

Little is known about the incidence and risk factors for discontinuation of dofetilide in the real world, where patients are usually sicker than those enrolled in clinical trials (18–20) and might be taking other QT-prolonging medications (21). The aim of this study was to evaluate the incidence and predictors of QT prolongation or VT leading to discontinuation of dofetilide in a real-world clinical setting.

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METHODS

STUDY PATIENTS. We conducted a retrospective cohort study of 115 consecutive patients hospitalized for starting dofetilide to treat AF at the Minneapolis Veterans Affairs Health Care System from 2011 to 2014. One patient in whom dofetilide was discontinued for reasons other than QT prolongation or VT was excluded from the analysis. Clinical, demographic, laboratory, and medication data were obtained from electronic medical records. This study was approved by the institutional review board and the Research and Development Committee at our institution.

TABLE 1 Baseline Characteristics of Patients in Whom Dofetilide Was Discontinued and Those Discharged on Dofetilide

	Entire Cohort (n = 114)	Dofetilide Discontinued (n = 22)	Discharged on Dofetilide (n = 92)	p Value
Age, yrs	64.3 ± 7.7	63.5 ± 9.0	64.5 ± 7.0	0.59
BMI, kg/m^2	33 ± 6.7	35 ± 8	33 ± 6	0.25
Race (white)	108 (95)	21 (95)	87 (95)	0.40
EF	48 ± 12	48 ± 13	48 ± 12	0.86
CAD	47 (41)	8 (36)	39 (42)	0.60
Hypertension	73 (64)	15 (68)	58 (63)	0.65
HF	55 (48)	12 (54)	43 (47)	0.51
Diabetes mellitus	37 (32)	10 (45)	27 (29)	0.15
Paroxysmal atrial fibrillation	27 (24)	3 (14)	24 (26)	0.22
Creatinine, mg/dl	1.0 ± 0.2	1.1 ± 0.2	1.0 ± 0.2	0.11
LVEDd, cm	5.6 ± 1.0	5.5 ± 1.2	5.6 ± 1.0	0.67
LVESd, cm	4.0 ± 1.0	4.0 ± 1.3	4.0 ± 1.0	0.99
Left atrial size, cm	5.0 ± 0.8	5.0 ± 0.7	5.0 ± 0.8	0.86
Potassium, mEq/dl	4.0 ± 0.4	4.0 ± 0.4	4.0 ± 0.3	0.56
Magnesium, mg/dl	2.1 ± 0.6	1.9 ± 0.2	2.1 ± 0.7	0.24
Albumin, mg/dl	3.9 ± 0.5	3.6 ± 0.5	3.9 ± 0.4	0.04
Right BBB	9 (8)	1 (4)	8 (9)	0.53
Left BBB	5 (4)	2 (9)	3 (3)	0.22
Interventricular conduction delay	13 (11)	4 (18)	9 (10)	0.25
Ventricular rate	85 ± 23	89 ± 27	88 ± 22	0.38
QT (ms)	386 ± 50.2	379 ± 67	387 ± 46	0.65
QTc (ms)	446 ± 38	451 ± 54	445 ± 34	0.12
Concurrent QT-prolonging drugs	32 (28)	10 (44)	22 (24)	0.04

Values are mean ± SD or n (%).

BBB = bundle branch block; BMI = body mass index; CAD = coronary artery disease; EF = ejection fraction; HF = heart failure; LVESd = left ventricular end-systolic dimension; LVEDd = left ventricular end-diastolic dimension; QTc = corrected QT interval.

DOFETILIDE INITIATION PROTOCOL. Dofetilide was started during a 72-h inpatient hospitalization per standard protocol (22). All patients were adequately anticoagulated prior to initiating dofetilide and were placed on continuous cardiac telemetry. Dofetilide dosing was based on glomerular filtration rate (GFR): 500 μg twice daily if GFR was >60 ml/min; 250 μg twice daily if GFR was 40 to 60 ml/min; and 125 μg twice daily if GFR was 20 to 40 ml/min. ECG was obtained before the initiation of therapy and 2 h after each dose and was monitored for QT interval prolongation. Corrected QT (QTc) interval was calculated using Bazett's formula ($QTc = QT/RR^{1/2}$). Dofetilide dose was reduced if QTc was prolonged by >15% from the baseline or exceeded 500 ms (550 ms if bundle branch block). Dofetilide was discontinued if QTc persisted for >500 ms after dose reduction or if the patient developed VT. Serum electrolytes, including potassium and magnesium, were monitored daily during the hospital stay and corrected as needed. Patients who did not revert to sinus rhythm after 5 doses of dofetilide underwent electrical cardioversion before discharge.

STATISTICAL ANALYSIS. The primary outcome variable was the discontinuation of dofetilide because of QTc prolongation or VT. Patients were categorized into 2 groups according to whether or not dofetilide was discontinued during the index hospitalization. Categorical variables are presented as percentage and continuous variables as mean ± SD. The 2 patient groups were compared using the chi-square test for categorical variables and the Student *t* test for continuous variables. Logistic regression analysis was used to determine the odds ratio of discontinuing dofetilide. Survival analysis was performed using the Kaplan-Meier method in patients who were discharged on dofetilide versus those in whom dofetilide was discontinued, and the groups were compared using log-rank test. A p value <0.05 was considered significant. Analysis was performed using SPSS statistics software version 19, SPSS Inc., Chicago, Illinois.

RESULTS

PATIENT CHARACTERISTICS. The mean age of 114 patients was 64 ± 8 years and all patients were men (Table 1). Nearly 95% of the patients were white. AF was persistent or long-standing persistent in 76% of

patients. Nearly 41% of patients had coronary heart disease and 48% had heart failure. The mean left ventricular ejection fraction was 48 ± 12%. The mean QTc was 446 ± 38 ms at baseline. Concomitant QT-prolonging drugs were used in 32 (28%) patients (Figure 1). Most common among these were venlafaxine, trazodone, and paroxetine (Figure 2).

The initial dofetilide dose was 500 mg twice a day, 250 mg twice a day, and 125 mg twice a day in 88 (77%), 23 (20%), and 3 (3%) patients, respectively. The dosage was subsequently reduced because of QT prolongation in 27 (24%) patients. None of the patients had worsening of renal function during the index hospitalization.

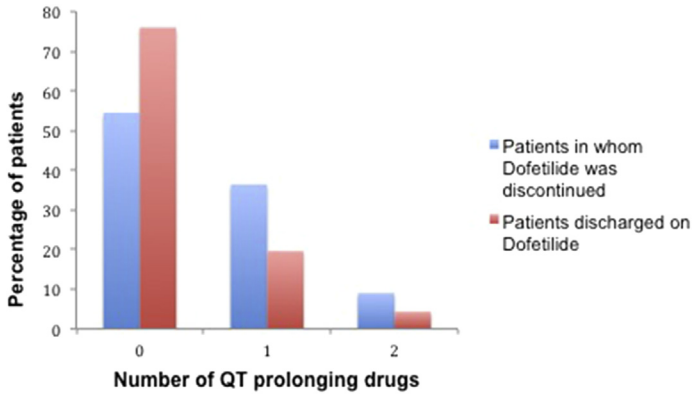
DISCONTINUATION OF DOFETILIDE. Dofetilide was discontinued during the index hospitalization in 22 (19%) patients because of QT prolongation (n = 20; 17%) or VT (n = 2; 2%). The mean number of doses before discontinuation was 3 ± 1. The longest QTc was 527 ± 53 ms in patients in whom dofetilide was discontinued versus 461 ± 33 ms in patients discharged on dofetilide ($p < 0.0001$) (Table 1). Two patients with a normal baseline QTc developed VT after the second dose. One of these had developed QT prolongation (QTc >500 ms) before VT.

A significantly greater proportion of patients who had to discontinue dofetilide were taking other QT-prolonging drugs (45% vs. 24%; p = 0.04) (Figures 1 and 2). Incidence of dofetilide discontinuation was 31% in those taking other QT-prolonging drugs versus 15% in patients who were not taking any other QT-prolonging drugs (p = 0.04). In comparison to patients who were taking no other QT-prolonging medications, the odds of dofetilide discontinuation was 1.9 times higher (odds ratio: 1.9; 95% confidence interval: 1.1 to 3.4; p = 0.04) in patients taking 1 or more additional QT-prolonging drugs. There were no other differences between patients who discontinued versus those who were discharged on dofetilide.

During a mean follow-up of 3.7 ± 1.7 years, 15 deaths occurred: 10 [11%] in the group that was discharged on dofetilide and 5 [23%] in whom dofetilide was discontinued [p = 0.15]). Although there appeared to be trend toward higher mortality in patients in whom dofetilide was discontinued, this difference did not reach statistical significance (Figure 3).

SUBGROUP ANALYSIS. At baseline, 51 patients had QTc >440 ms (>500 ms if bundle branch block) and 8 were taking hydrochlorothiazide. In 6 of the 8 patients, hydrochlorothiazide was discontinued during the hospital admission for dofetilide. Of these 8 patients, 1 (12.5%) had to stop dofetilide after the first dose because QTc prolongation. Among patients with QTc <440 ms (<500 ms for bundle branch block) and no concomitant use of hydrochlorothiazide (n = 63), the rate of dofetilide discontinuation was 12.7%.

FIGURE 1 Bar Graph Showing the Number of Other QT-Prolonging Drugs Among Patients Started on Dofetilide



DISCUSSION

This study showed that almost 20% of the patients with AF that were hospitalized for starting dofetilide had to discontinue this medication before discharge because of QT prolongation or VT. Concomitant usage of other QT-prolonging drugs increased the risk of these adverse events by almost 2-fold. These results suggest that the incidence of discontinuation of dofetilide because of adverse events is much higher in a real-world setting than has been reported in clinical trials.

FIGURE 2 Pie Chart Showing the Types of Concomitant QT-Prolonging Drugs in Patients in Whom Dofetilide Was Discontinued

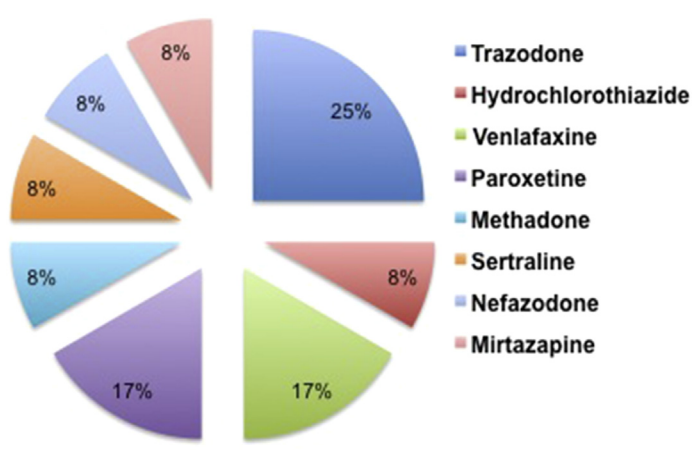
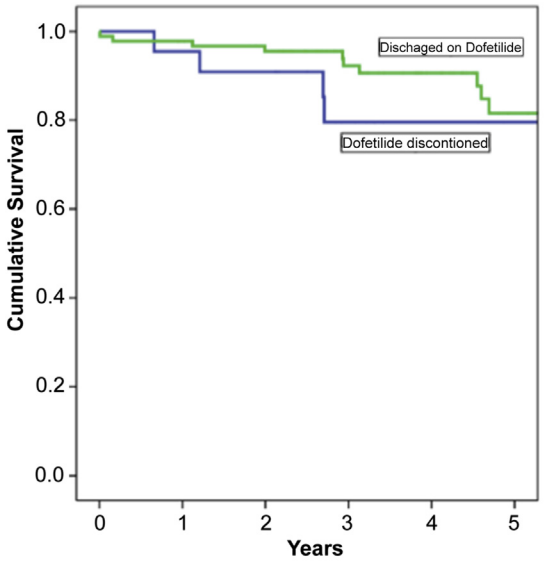


FIGURE 3 Kaplan-Meier Survival Curves in Patients Who Were Discharged on Dofetilide Versus Those in Whom Dofetilide Was Discontinued



Years	0	1	2	3	4	5
Dofetilide Discontinued	22	21	20	12	7	5
Discharged on dofetilide	92	88	80	57	41	23

Log-rank test, 0.15.

The QT interval on ECG represents depolarization and repolarization of the ventricular myocardium. Prolongation of the QT interval is associated with ventricular arrhythmias, including torsades de pointes, and is a risk factor for sudden cardiac death (23). QT interval prolongation occurs because of congenital and acquired abnormalities, with acquired causes being much more prevalent. Indeed, the most common cause of acquired QT prolongation is exposure to QT-prolonging drugs, which act by blocking hERG-encoded potassium channels (24–26). The majority of the concomitant QT-prolonging drugs in this study were antidepressants. Although it is ideal to stop or replace these medications with alternatives when starting dofetilide, it is not always possible. Indeed, Rector et al. (27) recently showed that psychiatric hospitalizations were increased when clinicians reduced the dosage of citalopram to <40 mg in response to a stipulation by the U.S. Food and Drug Administration because of concerns about QT prolongation and sudden death. In these patients, it may be necessary to consider ablation or alternate medical therapies early in the management of AF.

The reported incidence of QT prolongation that led to discontinuation of dofetilide was <3% in the large clinical trials such as EMERALD (Enhanced Myocardial Efficacy and Removal by Aspiration of Liberated Debris) (17) and SAFIRE-D (Symptomatic Atrial Fibrillation Investigative Research on Dofetilide) (13). However, the discontinuation rate of dofetilide is higher in cohort studies such as ours. Agusala et al. (28) reported a 32% (33 of 102) incidence of discontinuation of dofetilide during the inpatient initiation phase. They also reported concomitant use of thiazide diuretics in 10% of their patients. In their study, a higher baseline QTc was the only risk factor associated with dofetilide discontinuation. Abraham et al. (29) reported a discontinuation rate of 7.5% in 1,400 patients undergoing inpatient dofetilide loading at Cleveland Clinic. Neither study reported information on the concomitant use of QTc-prolonging drugs.

Also, some additional information can be gleaned from retrospective observational studies published for other reasons. Brumberg et al. (18) found higher rates of pathologic QT prolongation in patients who chemically cardioverted with dofetilide compared with those who required electrical cardioversion. Prystowsky et al. (19) reported that dofetilide had 63% efficacy in converting AF to sinus rhythm with one-third of the patients maintaining sinus rhythm for up to 2 years. The incidence of QTc prolongation was up to 9% in these studies (18,19). However, neither study examined the factors associated with the discontinuation of dofetilide (19).

The higher rate of dofetilide discontinuation in our cohort compared with other observational studies is likely from inclusion of patients who were taking other QT-prolonging drugs, which reflects the real-world experience (19). The incidence of VT in this study was similar to what was noted in the DIAMOND (Danish Investigators of Arrhythmia and Mortality on Dofetilide) trials (15,16) (3.3% in DIAMOND-Congestive Heart Failure and 0.9% in DIAMOND-Myocardial Infarction) in which, just as with our patients, there was a high prevalence of coronary artery disease, hypertension, and heart failure.

To our knowledge, this is the one of the few studies study assessing the incidence and predictors of discontinuation of dofetilide in a real-world, inpatient setting. As such, this study fills an important gap in our knowledge.

STUDY LIMITATIONS. Limitations of this study include the following: 1) study design was retrospective; 2) the experience was from a single center; 3) all study patients were men; and 4) because of the small sample size, many of the nonsignificant results could be due to lack of power (type 2 error).

CONCLUSIONS

These data indicate that the incidence of dofetilide discontinuation because of QT prolongation or VT in a real-world setting is remarkably higher than that reported in clinical trials. The rate of dofetilide discontinuation remained high in the subgroup of patients who had normal QTc at baseline and were not taking concomitant hydrochlorothiazide. Concomitant use of other QT-prolonging drugs was the only significant predictor of discontinuation of dofetilide.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In patients undergoing inpatient dofetilide initiation, use of other QT-prolonging drugs doubles the risk of discontinuation of dofetilide resulting from QT prolongation or VT.

TRANSLATIONAL OUTLOOK: Additional multicenter studies are needed to confirm the findings in this study in larger patient populations.

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