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MULTIMEDIA REPORT

Potentially modifiable factors of dofetilide-associated risk of torsades de pointes among hospitalized patients with atrial fibrillation

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Abstract

Purpose There is a significant variation in the clinical approach of initiation and dose adjustment of dofetilide in atrial fibrillation (AF). Excessive QT prolongation could predispose patients to torsades de pointes (TdP), which can be fatal.

Methods We performed a retrospective case-control study at Mayo Clinic Rochester (January 1, 2003 to December 31, 2016). "TdP risk" cases were defined as patients on dofetilide therapy for AF with subsequent TdP *or* excessive QTc prolongation requiring dose reduction or discontinuation ($N = 31$). A control group was matched 1:1 with cases by age, gender, year of admission, and dofetilide dose ($N = 31$).

Results Using multivariate regression analysis, independent predictors of TdP risk included baseline QTc exceeding recommendations (adjusted odd ratio [AOR] 4.57; $P = 0.023$); underlying AF with rapid ventricular rate (AOR 16.95; $P = 0.004$); and diuretic therapy for acute heart failure (AOR 8.42; $P = 0.007$). Poor inter-observer agreement was identified among QT interval measurement in patients with AF and rapid ventricular rate compared to those in rate controlled AF or sinus rhythm. TdP risk cases receiving diuretics for acute heart failure had a significant decline in creatinine clearance than controls, although serum electrolytes and replacement did not differ among the two groups.

Conclusions Excessive QTc prolongation and AF with rapid ventricular rate at time of dofetilide initiation (likely due to difficulty in measuring QT intervals), and diuretic therapy for acute heart failure were independent factors for dofetilide-related TdP risk. Based on these data, possible preventive strategies could be adapted for safety protocols among hospitalized patients.

Keywords Acquired long QT syndrome · Dofetilide · Torsades de pointes, risks, prevention

Abbreviations

AF	Atrial fibrillation
AOR	Adjusted odds ratio
CHF	Congestive heart failure
CI	Confidence interval
CrCl	Creatinine clearance
DIAMOND trial	The Danish Investigations of Arrhythmia and Mortality on Dofetilide
FDA	The US Food and Drug Administration
TdP	Torsades de Pointes

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1 Introduction

Dofetilide has become one of the most commonly used antiarrhythmic drugs for the management of symptomatic atrial fibrillation (AF), particularly in patients with structural heart disease [1]. However, the risk of potentially fatal or symptomatic torsades de pointes (TdP) is an important concern. Recent studies from real-world settings estimated nearly 20% of drug-induced QT prolongation necessitates dofetilide discontinuation [2, 3]; however, there is a wide variation in the clinical approach to drug initiation and dose adjustment [4, 5]. This

notable variation could result in excess TdP risk, some of which may be modifiable or preventable. In this case-control study, we aimed to review risk factors for TdP or QTc prolongation due to dofetilide among patients with AF in order to identify intervention points for optimizing patient care.

2 Methods

2.1 Study population and baseline characteristics

Approved by the Institutional Review Board, this retrospective case-control study used data from the patient database that was validated with sensitivity and specificity > 90% [6]. The initial screening step selected consecutive inpatients (age > 18 years) who received dofetilide for treatment of AF during hospitalization at Mayo Clinic in Rochester, Minnesota, from January 1, 2003 to December 31, 2016 [7]. Patients were excluded if they did not provide research authorization or were prescribed dofetilide for management of ventricular arrhythmias. At this step, 1755 patients met inclusion criteria. The TdP risk group was comprised of 15 patients with TdP and 16 patients with prolonged QTc interval after dofetilide initiation and needing dose reduction or drug discontinuation. Control subjects were recruited from the same hospital database and were matched one to one by age, gender, year of admission, and dofetilide dose.

Chart review was conducted to obtain baseline characteristics and the events around the time of TdP and the rationale of dose adjustment. At our institution, the initial and subsequent dofetilide doses were chosen, and adjusted, based on the baseline creatinine clearance (CrCl) which was calculated with the Cockcroft-Gault equation. Baseline CrCl was measured at time of admission prior to the first dose of diuretics and dofetilide administration. In the TdP group, subsequent CrCl was measured at the closest time to the event or the closet time when dofetilide was discontinued due to QTc prolongation. In the control group, subsequent CrCl was calculated from the highest Cr level during admission.

Mean serum potassium and magnesium levels were obtained. The 12-lead electrocardiograms selected for analysis were those recorded at admission closest to the first dose of dofetilide (in patients starting dofetilide), and the first available at time of admission (in patients who were on dofetilide long-term).

2.2 Measurement of the QT and calculating QTc interval

Manual measurements included R-R interval, QRS width, and QT interval (reviewed by AS and DK blinded to the outcomes). The QT interval was measured from the onset of the Q wave to the intersection of the line of the maximal slope of the T wave and the T-P baseline. For those in AF, the authors assigned to measure the QT intervals were instructed to measure the 10 longest QT. Then, the intervals were averaged and used for analysis. The difference within 20 ms was defined as acceptable and this value was used as calculated QTc in this analysis. If there was a difference > 20 ms, QTc interval was defined by group consensus. To calculate the corrected QT (QTc), the Bazett and Fridericia formulas were used when the heart rate was < 100 and ≥ 100 beats per minute (bpm), respectively [8].

2.3 Risk factors

Pre-determined risk factors of interest included (1) QTc interval exceeding recommendations (baseline QTc > 440 ms or > 500 ms if QRS > 120 ms [9] or subsequent QTc > 500 ms or > 550 ms if QRS > 120 ms) [10]; (2) underlying AF with rapid ventricular rate response at time of drug initiation which could potentially obscure accurate QT measurement; (3) bradycardia with ventricular response < 50 bpm [9]; (4) potential drug-drug interactions; (5) concomitant QT-prolonging drugs; (6) electrolyte abnormalities; and (7) active diuretic therapy for treatment of acute congestive heart failure (CHF).

2.4 Statistical analysis

Patients were analyzed in two groups: (1) TdP risk cases ($N = 31$) which included patients who developed TdP *or* whose dofetilide dose had to be adjusted due to QTc prolongation and (2) controls ($N = 31$) which included age, gender, year of admission, and dofetilide dose-matched cases without events of interest. Continuous variables are presented as mean (SD) and compared using *t* test. Categorical variables are reported as count (percentage) and compared using Chi-square or Fisher's exact test as appropriate. To test agreement on measuring QT, we defined that the difference between two observers less than 20 ms as acceptable.

A multivariate logistic regression analysis adjusted for risk factors that were significantly different between the two groups was performed and reported as the adjusted odds ratio (AOR) with a 95% confidence interval (CI). Subgroup analysis including patients admitted only for dofetilide initiation was also performed. A P value < 0.05 was considered significant. Analysis was performed using JMP statistical software version 9.0 (SAS, Cary, NC) and MedCalc version 12.5 (Ostend, Belgium).

3 Results

Of the overall cohort, mean age was 68 ± 7 years and 82.6% were women. Among AF patients admitted to the hospital

from 2003 to 2016, the overall prevalence of dofetilide use increased considerably (Supplemental Fig. 1).

3.1 TdP risk cases

Age, gender, baseline CrCl, dofetilide dose, as well as baseline characteristics were well matched among the cases and the controls (Table 1). In the TdP risk group, a total of 15 patients had dofetilide-induced TdP, accounting for an annual incidence of 5.9% and an overall prevalence of 0.9% per user. One in-hospital death (0.07%) was directly related to dofetilide-induced TdP. There were 4 chronic dofetilide users admitted for other non-arrhythmic conditions who developed TdP (Supplemental Table 1).

3.2 Baseline QTc interval in patients starting dofetilide and first available QTc in patients on long-term dofetilide

Overall, the TdP risk group had longer baseline QTc (472 ± 41 ms vs. 441 ± 32 ms; $P = 0.002$) (Table 2), with 14 cases (46.7%) with baseline or subsequent QTc exceeding the recommendations, as compared to 5 patients (17.2%) in the control group ($P = 0.03$).

3.3 Underlying AF and heart rate at time of dofetilide initiation

AF was more prevalent in the TdP risk group starting dofetilide (72.7% vs 25.0%; $P = 0.001$) compared to controls. Accordingly, AF with rapid ventricular rate (RVR) was found in 50.0% vs. 7.1%, respectively ($P = 0.001$). Baseline heart rate < 50 bpm was observed equally in both groups.

In patients with AF with RVR, agreement in measuring QT was poor (35.7%; difference in QT measurement, median 36 IQR (12–120) ms) as compared to patients with rate controlled AF or sinus rhythm (61.7%; difference in QT measurement, median 12 IQR (4–32) ms), $P = 0.02$. Figure 1 presents an example of a TdP case with non-discernible QT intervals because of AF with RVR.

3.4 Active diuretic therapy and electrolyte abnormalities

Prevalence of active diuretic therapy for treatment of acute heart failure was higher in the TdP risk cases (32.3% vs. 9.7% in the controls; $P = 0.059$). The total furosemide doses in the TdP risk group were 254 ± 57 mg as compared to 107 ± 105 mg in the controls. The TdP risk group receiving active diuretic therapy had subsequent lower CrCl (54 ± 18 mL/min) as compared to the controls (67 ± 18 mL/min; $P = 0.03$), despite their comparable baseline CrCl. Mean serum magnesium and potassium, as well as supplemental therapy were not different among the two groups (Table 2).

3.5 Potential drug interactions

Potential drug interactions identified in this entire cohort were digoxin, diltiazem, and amiodarone. Overall digoxin or amiodarone was used more often in the study group (25.8% vs. 3.2%; $P = 0.026$), while prevalence of diltiazem use was equal in both groups. Among patients with concomitant digoxin and dofetilide, serum digoxin levels were available in 2 patients in the TdP risk group (1.7 and 1.9 ng/mL) and 1 in the control group (1.0 ng/mL, reference range reference range 0.5–2.0 ng/mL).

3.6 Concomitant QT prolonging drugs

Drugs with potential QT prolonging effect were found in 21.0% of the entire cohort. The prevalence was not different between the TdP risk group and the controls. The most common drugs were antidepressants (12.9%, including fluoxetine, escitalopram, and citalopram), followed by amiodarone (4.8%, serum level not available), ondansetron (3.3%), levofloxacin (1.6%), and sotalol (1.6%).

Table 1 Baseline characteristics of the study patients and the control group

	All ($N = 62$)	TdP cases ($N = 31$)	Controls (N = 31)	*P* value
Age, years	68.4 ± 7.4	69.0 ± 7.0	69.5 ± 7.9	0.49
Female, %	46 (74.2%)	23 (74.2%)	23 (74.2%)	1.00
Creatinine clearance, mL/min	71 ± 21	69 ± 23	74 ± 20	0.34
Left ventricular ejection fraction < 35%, %	4 (6.5%)	4 (12.9%)	0 (0%)	0.11
Congestive heart failure, %	12 (18.8%)	10 (32.3%)	5 (16.1%)	0.24
Long-term dofetilide users, %	12 (19.4%)	9 (29.0%)	4 (12.9%)	0.30
Dofetilide dose, %				1.00
125 or 250 μg bid	50 (80.6%)	25 (80.6%)	25 (80.6%)	
500 μg bid	12 (19.4)	6 (19.4%)	6 (19.4%)	

Table 2 Comparison of potential risk factors of prolonged QTc interval and dofetilide-induced TdP in the study patients and the control group

	All ($N = 62$)	Study ($N = 31$)	Controls ($N = 31$)	P value
ECG				
Baseline QTc, ms	457 ± 39	472 ± 41	441 ± 32	0.002
Baseline QRS, ms	106 ± 31	113 ± 35	99 ± 25	0.068
Excessive QTc interval[*], %	19/59[†] (32.2%)	14/30 (46.7%)	5/29 (17.2%)	0.03
AF at time of dofetilide initiation in de novo dofetilide patients, %	23/50[‡] (46.0%)	16/22 (72.7%)	7/28 (25.0%)	0.0008
AF with ventricular rate > 100 bpm	13/50[‡] (26.0%)	11/22 (50.0%)	2/28 (7.1%)	0.0009
AF with ventricular rate < 100 bpm	10/50[‡] (20.0%)	5/22 (20.0%)	5/28 (17.9%)	0.73
Baseline heart rate at time of dofetilide initiation in de novo dofetilide patients, bpm	80 ± 28	89 ± 32	70 ± 18	0.008
Heart rate < 50 bpm, %	16 (25.8%)	11 (35.5%)	5 (16.1%)	0.15
Diuretics and electrolytes				
Active diuretic for treatment of heart failure, %	13 (21.0%)	10 (32.3%)	3 (9.7%)	0.059
Furosemide[x], mg ($N = 13$)	220 ± 184	254 ± 57	107 ± 105	0.242
Serum magnesium, mg/dL	2.1 ± 0.2	2.1 ± 0.2	2.1 ± 0.2	0.67
Serum potassium, mmol/L	4.3 ± 0.3	4.3 ± 0.4	4.4 ± 0.3	0.31
Magnesium supplement[§], %	19 (30.7%)	10 (32.3%)	9 (29.0%)	0.78
Magnesium supplement[§], total mg per person	0 (0–0.6)	0 (0–2)	0 (0–0.4)	0.41
Potassium supplement[§], %	24 (38.7%)	14 (45.2%)	10 (32.3%)	0.30
Potassium supplement[§], total MEQ per person	0 (0–33)	0 (0–60)	0 (0–20)	0.61
Medications				
Potential drug-drug interaction, %	19 (30.6%)	13 (41.9%)	6 (19.4%)	0.097
Diltiazem, %	12 (19.4%)	6 (19.4%)	6 (19.4%)	1.00
Digoxin, %	8 (25.0%)	7 (22.6%)	1 (3.2%)	0.053
Amiodarone, %	3 (4.8%)	3 (9.7%)	0 (0%)	0.24
Digoxin or amiodarone, %	9 (14.5%)	8 (25.8)	1 (3.2%)	0.026
QTc prolonging drugs, %	13 (21.0%)	7 (22.6%)	6 (19.4%)	0.76
Ondansetron, %	2 (3.3%)	2 (6.7%)	0 (0%)	0.24
Sotalol, %	1 (1.6%)	1 (3.2%)	0 (0%)	0.50
Amiodarone, %	3 (4.8%)	3 (9.7%)	0 (0%)	0.24
Levofloxacin, %	1 (1.6%)	1 (3.2%)	0 (0%)	0.50
Antidepressants[II], %	8 (12.9%)	2 (6.5%)	6 (19.4%)	0.26

[*] Baseline QTc > 440 (or 500 ms in QRS > 120 ms) or subsequent QTc > 500 or (or 550 ms in QRS > 120 ms)

[†] Patients on chronic dofetilide did not have an electrocardiogram during their hospitalization

[‡] Patients admitted for initiating dofetilide

[x] Doses of diuretics reported as equivalent to intravenous furosemide Intravenous furosemide 20 mg is equal to oral furosemide 40 mg, oral and intravenous torsemide 20 mg, oral and intravenous bumetanide 1 mg, and oral and intravenous ethacrynic acid 50 mg

[§] Electrolyte replacement prior to the TdP event

[II] Fluoxetine, escitalopram and citalopram

In 2 patients who developed TdP secondary to potential drug interaction between dofetilide and amiodarone, one had a brief run of TdP after the initiation of dofetilide. Amiodarone was subsequently initiated as an alternate drug, but owing to an inadequate time interval between the two events, there was excessive QT prolongation and sustained TdP. In another patient who also developed TdP, amiodarone was discontinued less than 30 days before initiation of dofetilide, thus we presume that the serum levels of amiodarone may not have decreased sufficiently prior to the initiation of dofetilide leading to a similar interaction between the drugs.

3.7 Multivariate logistic regression analysis

In the entire cohort, baseline QTc intervals > 440 ms (> 500 with significant ventricular delay) or subsequent QTc intervals > 500 ms (or > 550 with QRS > 120 ms) (AOR

4.57; $P = 0.016$), active diuretic therapy for acute heart failure (AOR 8.42; $P = 0.007$) and an increase in creatinine clearance (AOR 1.38; $P = 0.016$) were independent risk factors for the primary outcome (Fig. 2 and Table 3). In subgroup analysis, including only patients who were admitted for dofetilide initiation ($N = 49$), QTc intervals that exceeded the recommendations (AOR 5.57; $P = 0.02$) and underlying AF with rapid ventricular rate during initiation of dofetilide (AOR 16.95; $P = 0.004$) were independently associated with TdP or QTc prolongation needing dose adjustment. Concomitant use of digoxin did not reach statistical significance to influence outcomes in either the entire cohort or the subgroup analysis.

4 Discussion

We report potentially modifiable risk factors in a series of AF patients with TdP secondary to dofetilide therapy (both initiation and long-term use) and those needing dose reduction or discontinuation due to prolongation of QTc. The identified risk factors included baseline or subsequent QTc exceeding the recommendations [10], underlying AF with rapid ventricular rate at time of dofetilide initiation, and active diuretic therapy for acute heart failure. These data provide insight into possible preventive strategies that could be adapted for safety protocols among hospitalized patients.

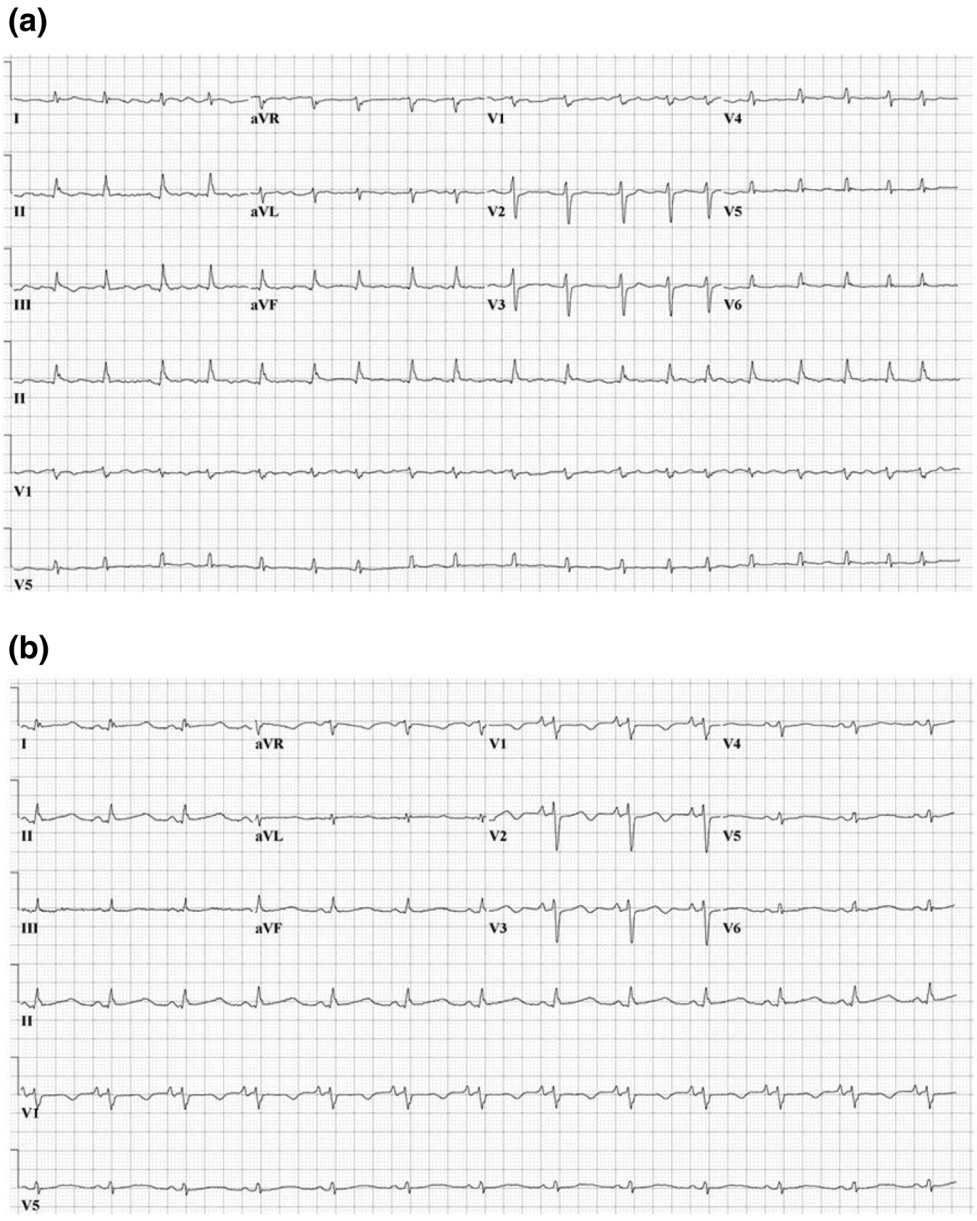

Fig. 1 **a** Electrocardiogram from the study group showing atrial fibrillation and rapid ventricular rate. Note that QT interval was almost indiscernible. **b** After initiating dofetilide (at dose 250 μg bid) and cardioversion, immediate electrocardiogram reveals markedly prolonged QTc interval of 530 ms

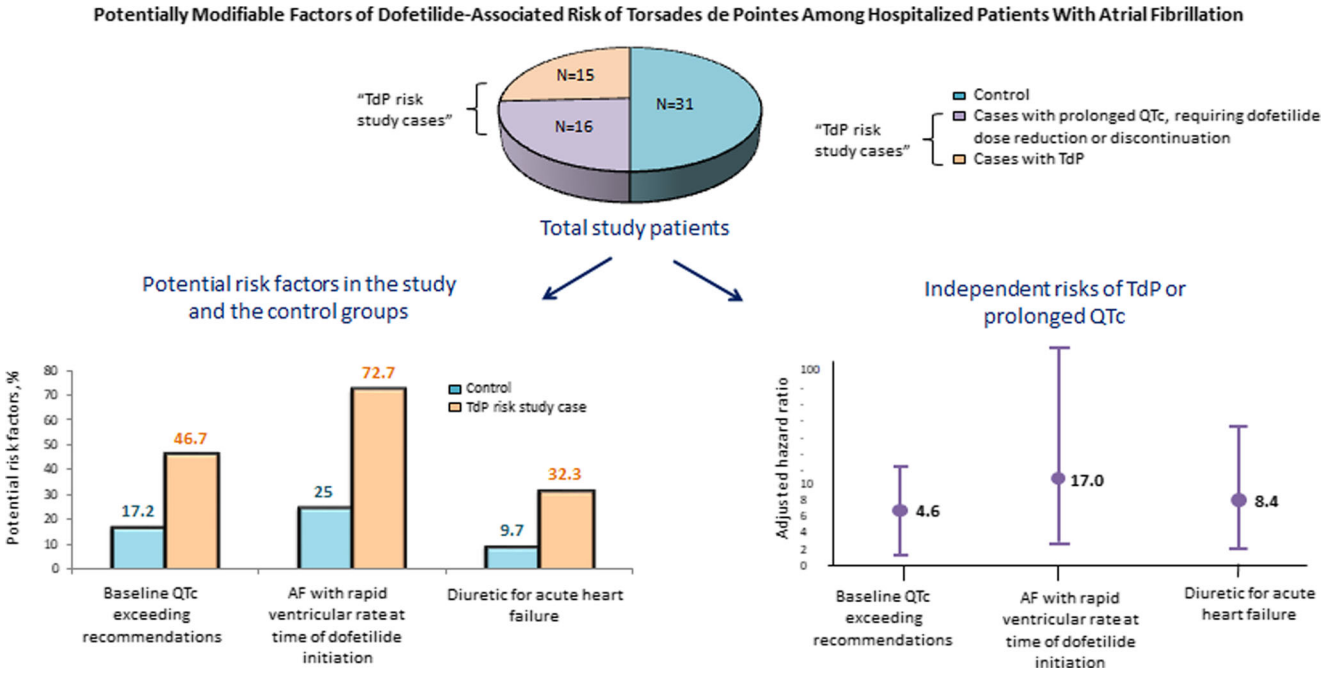

Fig. 2 Independent factors of dofetilide-associated risk of TdP among hospitalized patients with atrial fibrillation

The overall incidence of dofetilide-induced TdP in our series is comparable to previous clinical trial and real-world data, which estimate the risk at 0.8 to 3.3% per user [2, 3, 9, 11, 12]. However, the prevalence of TdP among patients taking dofetilide long-term remains poorly defined. While it is possible that the risk may be less with long-term use of dofetilide, our observation that 4 of 15 (26.7%) patients who developed TdP were chronic users who developed other medical illnesses underscores that these patients are not free of risk. In line with our observation, a recent study observed that dose adjustment was commonly required during reloading dofetilide [4]. Susceptibility to dofetilide-induced TdP is an ongoing risk and changes in the patients' clinical condition may change their susceptibility to TdP.

Previous studies have identified risk factors of acquired QT prolongation and TdP. Specifically for dofetilide, woman, older age, CHF (and active diuretic therapy), and prolonged baseline QTc are among the strongest predictors [13]. Essentially, these are not modifiable with few exceptions. First, one should avoid use of dofetilide in the setting of excessive QT prolongation. The Danish Investigations of Arrhythmia and Mortality on Dofetilide (DIAMOND) trial excluded patients with a baseline QTc > 440 ms or > 500 ms with significant interventricular conduction delay [10]. Additionally, the US Food and Drug Administration (FDA) suggests dofetilide should be discontinued if the QTc is greater than QTc > 500 ms (or > 550 ms in patients with ventricular conduction abnormalities) at any time during follow-up.

Table 3 Independent predictors of TdP risk by multivariate logistic regression analysis

	Adjusted odd ratio	95% confidence interval	*P* value
Total cohort ($N = 62$)*			
Baseline or subsequent QTc exceeding recommendations	4.57	1.16–18.10	0.023
Increase in creatinine clearance (per 10 mL/min)	1.38	1.03–1.86	0.016
Active diuretics	8.42	1.52–46.65	0.007
Patients admitted for dofetilide initiation ($N = 49$)†			
Baseline or subsequent QTc exceeding recommendations	5.57	1.21–25.61	0.02
Increase in creatinine clearance (per 10 mL/min)	1.31	0.95–1.81	0.081
Underlying AF with RVR at time of dofetilide initiation	16.95	2.46–116.88	0.004

* The initial multivariate logistic regression model also included concomitant digoxin and amiodarone, which was not statistically significant

† The initial multivariate logistic regression model included concomitant digoxin and amiodarone, and active diuretics, which were not statistically significant

Our clinical practice found unexpectedly significant numbers of patients who had QTc intervals that exceeded the recommendations and few TdP patients without appropriate dose reduction despite subsequent QTc prolongation > 20% after dofetilide initiation [10]. Recent studies observed that this practice, as well as variation in dofetilide dose adjustment, is not uncommon [4, 5, 14]. Whether this variation (at the high end) is due to clinicians' deliberate up-titration in cases where AF is refractory and no other options exist or whether it is due to difficultly in measuring the QTc interval is difficult to know from the available data. Nonetheless, this practice is associated with an almost sevenfold increase in risk of TdP or QTc prolongation, which can lead to a fatal event.

The TdP cases in this cohort were predominantly female. Female gender is one of established risks of a longer baselined QTc interval and drug-induced TdP. A recent study observed more than 50% of woman required dofetilide dose adjustment or discontinuation (compared to 32% in men) [14]. The study also found that 43% of women and 45% of men whose baseline QTc intervals above the suggestions required drug discontinuation. Our data therefore provide important factors that clinicians should monitor prior to dofetilide initiation or continuation in both genders.

Accurate QT monitoring is critical. However, uniform QT measurements and QTc calculation during AF can be challenging. Formulas available for calculating the QTc have known limitations. Although the Bazett formula is one of the most commonly used, it has a tendency to overcorrect the QT interval when the heart rate is < 60 or > 100 bpm [15]. The Fridericia formula may be appropriate in tachycardia [16]. However, when the RR interval is highly variable, accurate assessment remains challenging. In patients with ventricular conduction delay (which could be transient during AF), the JT and corrected JT can be used, but this is not well standardized [4]. With aforementioned limitations, it is possible that initiating dofetilide during AF, especially with rapid ventricular heart rate, could result in inaccurate estimation of QT interval proved by poor inter-observer agreement in this current study. Thus, in an uncertain situation, providers may consider lower dofetilide dose [9] or cardioversion to restore sinus rhythm prior to dofetilide initiation.

The association of diuretic use with in-hospital TdP has been proposed [13, 17]. Patients receiving active diuretic therapy for treatment of acute CHF may undergo rapid changes in electrolyte levels and renal clearance. Despite that the mean serum magnesium and potassium levels were equal in both study and control groups, subtle changes or under detection cannot be excluded. While the DIAMOND trial found safety of dofetilide used among symptomatic heart failure patients, detail of concurrent diuretic therapy was not reported. Indeed, the incidence of TdP and prolonged QTc interval in the trial were remarkably high (3.3% and 2% of the study patients, respectively) [9] and post hoc analysis of the DIAMOND-HF trial identified CHF as one of an independent risk of TdP [13]. Giving concern of multiple risk factors of TdP among hospitalized patients [17], it may be prudent to hold dofetilide during active diuretic therapy in patients with acute CHF, especially in patients with high-risk profiles.

4.1 Limitations

This study was a single-center, retrospective review and was subject to inherent biases. Despite the relatively large database available, attempt to match more than 1:1 ratio was not possible due to strict criteria of age, gender, sex, year of admission, and dofetilide dose. However, using multivariate regression analysis enabled risk factor identification which is likely useful in clinical practice.

Patients were not tested for a predisposing genetic susceptibility which has been proposed [18]. While bradycardia did not reach statistical significance as a predictor of TdP, bradycardia can prolong repolarization and precipitate pause-dependent TdP. It becomes particularly important during post-cardioversion, a known vulnerable phase for initiation of TdP, justifying the recommendation to monitor post-cardioversion patients for ≥ 12 h [9, 10].

5 Conclusions

This case-control study describes a series of AF patients, predominantly female, who have developed TdP or QTc prolongation requiring dose reduction or discontinuation during dofetilide initiation or long-term use. Independent risk factors included baseline QTc > 440 ms if QRS < 120 ms (or > 500 ms if QRS > 120 ms) or subsequent QTc intervals > 500 ms (or > 550 ms if QRS > 120 ms), underlying AF with rapid ventricular rate during dofetilide initiation and active diuretic therapy in acute heart failure.

We believe that these risk factors are potentially modifiable. Implementing a prevention protocol especially for patients with high-risk profiles may be prudent. This may include (1) following the guideline recommendations regarding baseline and subsequent QTc interval as an indicator to discontinue dofetilide; (2) considering cardioversion to restore sinus rhythm when accurate measurement of QT interval is not possible; and (3) holding dofetilide during active diuretic therapy when changes in electrolytes or creatinine clearance is anticipated.

Author contributions Niyada Naksuk: Concept/design, data collection, data analysis/interpretation, drafting article, and approval of article.

Alan M. Sugrue: Data collection, data analysis/interpretation, drafting article, and approval of article.

Deepak Padmanabhan: Data collection, data analysis/interpretation, drafting article, approval of article.

Danesh Kella: Data collection, data analysis/interpretation, drafting article, and approval of article.

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Critical revision of article

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Critical revision of article.

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Critical revision of article.

Compliance with ethical standards

Conflicts of interest MJA is a consultant for Audentes Therapeutics; Boston Scientific Corp; Gilead Sciences, Inc.; Invitae Corp; Medtronic; MyoKardia, Inc.; and St Jude Medical (Abbott). PAN and MJA and Mayo Clinic are in an equity relationship with Alive Cor, Inc. However, none of these entities were involved with this study. The other authors report no conflicts of interest.

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