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Safety of dofetilide in stable patients and investigating traits of susceptibility to torsade de pointes

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ABSTRACT

Background: Atrial fibrillation is the most prevalent cardiac arrhythmia, presenting symptomatic patients with diminished quality of life and worsening of heart failure. Dofetilide, a class 3 antiarrhythmic agent, is a proven and safe rhythm control medication. Initial risk of QT prolongation leading to torsade de pointes (TdP) necessitates a standard protocol mandating hospitalization for three days for initiation.

Objectives: To assess safety when adhering to initiation protocol and identify traits for susceptibility to TdP in elective dofetilide admissions.

Methods: We conducted a retrospective study involving patients admitted to Mayo Clinic sites across four states for elective inpatient initiation of dofetilide between 2003 and 2022. Patients' charts underwent review, focusing on dofetilide-related TdP occurrences, baseline characteristics including QT intervals, laboratory values, comorbidities, and concomitant medications. Patients who experienced TdP were subjected to further evaluation to identify potential risk factors.

Results: Of 2036 patients identified, mean age 66.4 ± 11.4 years, and 67.2 % male, 16 experienced dofetilide-related TdP (incidence rate 0.79%). Notably, 81% (13/16) of TdP cases occurred in patients who deviated from the FDA/manufacturer algorithm protocol. The concomitant use of active intravenous diuretic therapy, digoxin, and QT-prolonging drugs emerged as identifiable risk factors. Additionally, females exhibited a higher incidence of TdP (1.5%) than males (0.44%) {odd ratio [OR] 3.46; P = 0.017}.

Conclusion: Overall incidence of TdP related to dofetilide initiation was low (0.79%). Adherence to protocol during elective hospital admissions appears extraordinarily safe. Patients who did not require concurrent use of intravenous diuretics, digoxin, or QT prolonging drugs exhibited lower risk of TdP.

1. Introduction

Atrial fibrillation is the most commonly treated cardiac arrhythmia, typically managed through medications aimed at controlling heart rate or restoring normal rhythm. Older clinical trials have shown no significant difference in mortality between rhythm control and rate control strategies, although newer trials are challenging this [1,2,3]. Nonetheless, symptomatic patients often endure diminished quality of life and face elevated risks of strokes, systemic thromboembolism, and heart failure symptoms. Antiarrhythmic drugs are frequently utilized as an alternative or adjunctive therapy to ablation in efforts to maintain normal sinus rhythm for symptom control.

Among these drugs, amiodarone emerges as the most potent antiarrhythmic agent; however, its long-term usage is associated with notable extracardiac side effects. In cases where maintaining sinus rhythm is paramount, dofetilide, classified as a class III antiarrhythmic

Abbreviations: AF/AFL, Atrial fibrillation/atrial flutter; CrCl, Creatinine Clearance; ECG, Electrocardiogram; eGFR, Estimated glomerular filtration rate; FDA, US Food and Drug Administration; ICD, Implantable cardioverter-defibrillator; IQR, Interquartile range; IV, Intravenous; msec, Milliseconds; OR, Odd ratio; SD, Standard deviation; TdP, Torsade de Pointes.

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agent, is often administered to patients with atrial fibrillation, particularly those with underlying structural heart disease such as cardiomyopathy and congestive heart failure. Dofetilide is approved for used in atrial fibrillation in the United States with mandatory loading in the hospital, however, it is not approved in Europe or Australia. Dofetilide is considered safe and effective, with a low incidence of non-arrhythmic adverse effects.

Previous clinical trials have highlighted dofetilide's proarrhythmic effects and the risk it poses for QT prolongation and torsade de pointes (TdP) during initiation [4,5,6]. Consequently, the US Food and Drug Administration (FDA) and the drug's manufacturer have mandated inpatient initiation of dofetilide for three days. During this time, continuous electrocardiogram (ECG) monitoring is conducted under the supervision of personnel trained in managing ventricular arrhythmias.

The dofetilide initiation protocol is meticulously designed based on factors such as QT/QTc interval and creatinine clearance. These parameters are critical for minimizing the risk of adverse events. Additionally, strict measures are taken to ensure potassium and magnesium levels remain within normal limits before dofetilide administration.

However, despite its efficacy in maintaining sinus rhythm and its favorable side-effect profile, the stringent dofetilide initiation requirements may deter prescribers and patients. This poses a significant challenge in balancing the benefits of dofetilide therapy with the logistical and safety considerations associated with its initiation.

There is limited published data regarding adherence to algorithm protocol for dofetilide initiation and its associated outcomes [7,8]. Hence, we conducted a retrospective, observational study involving patients who were electively admitted to all Mayo Clinic sites for the initiation of dofetilide therapy targeting atrial fibrillation (AF) or atrial flutter (AFL). Our primary objective was to assess the safety of dofetilide initiation in stable patients, examine the incidence, and identify traits associated with susceptibility to TdP. This study aims to provide valuable insights into the real-world implementation of dofetilide initiation protocol and their impact on patient outcomes, shedding light on potential areas for improvement in clinical practice.

2. Methods

2.1. Study population and baseline characteristics

Institutional Review Board approval was received prior to conducting this study. We conducted a retrospective chart review of all patients who were electively admitted for the initiation of dofetilide therapy targeting AF or AFL across all Mayo Clinic sites (Arizona, Florida, Minnesota, and Wisconsin) from January 2003 to December 2022. Patients who were hospitalized for reasons other than the initiation of dofetilide therapy for AF/AFL were excluded from the study. However, we included patients who were electively admitted for cardiac ablation, electrical cardioversion followed by dofetilide initiation, as well as those admitted solely for the initiation of drug therapy. This comprehensive approach aimed to capture a representative sample of patients undergoing dofetilide initiation in various clinical contexts, enabling a thorough examination of safety and outcomes associated with the initiation protocol.

The chart review process involved collecting comprehensive data on baseline characteristics, including concomitant medications, comorbidities, and the location sites where dofetilide initiation took place. Baseline parameters such as QT/QTc interval, serum potassium, magnesium levels, and estimated glomerular filtration rate (eGFR) were meticulously recorded before the administration of dofetilide. Moreover, details regarding the starting dose, discharge dose, and reasons for discontinuation of dofetilide were reviewed and documented for each patient.

In the case of the 16 patients who experienced TdP, their charts underwent additional scrutiny to identify any deviations from the FDA/manufacturer algorithm protocol for dofetilide initiation. Additionally, we examined these patients' circumstances and susceptible traits that could have contributed to the TdP event.

Furthermore, all-cause mortality data were extracted for one month and one-year post-initiation of dofetilide to assess the impact of the medication on patient outcomes. This thorough analysis aimed to provide insights into the safety, adherence to protocol, and clinical outcomes associated with dofetilide initiation in patients with AF/AFL.

2.2. Measurement of QT/QTc interval and creatinine clearance

QTc interval measurements were obtained from patients' electronic medical records that had been formally interpreted by board-certified cardiologists to ensure consistency. QT interval measurement was used if heart rate was below 60 beats per minute on ECG. For some patients whose QRS duration $>$ 130 ms, corrected JT interval (JTc) was measured. JTc interval is defined as QTc-QRS duration. For the 16 patients who experienced TdP, QT/QTc intervals were manually reviewed by the senior author (KS) to ensure accuracy. The Bazett formula was used to measure QTc, and for patients in AF/AFL was assessed over 5 beats. Additionally, creatinine clearance (CrCl) for these 16 patients was calculated using the Cockcroft-Gault equation [9]. This meticulous approach aimed to maintain the quality and reliability of the data collected, particularly regarding key parameters relevant to dofetilide initiation and the occurrence of TdP events.

2.3. Statistical analysis

Continuous variables were summarized using the mean and standard deviation (SD) or the median and interquartile range (IQR), and categorical variables were summarized using frequencies and percentages. Logistic regression was used to assess association between gender and TdP incidence. Results of logistic regression are presented as odds ratio with 95 % confidence interval. A p-value of $<$ 0.05 was considered significant.

For the statistical analysis, R Statistical Software version 4.1.2 was utilized.

3. Results

- A total of 2036 patients were identified across four Mayo Clinic hospital sites, with Minnesota accounting for the majority of patients (52 %), followed by Wisconsin (20 %), Florida (16.3 %), and Arizona (11.2 %).
- The mean age of the patients was 66.4 $\pm$ 11.4 years, with 67.2 % being male.
- Baseline mean serum potassium was 4.4 $\pm$ 0.4, magnesium was 2.0 $\pm$ 0.2, and 97.5 % had an eGFR $>$ 60.
- Over half of the patients (57 %) were in AF/AFL before the initiation of dofetilide.

The mean baseline QT/QTc intervals were 396.3 $\pm$ 52.8/449.3 $\pm$ 39.5 ms (msec), and mean QT/QTc intervals at discharge were 453.8 $\pm$ 45.2/469.4 $\pm$ 36.2 msec

Incidence of TdP

Summary of the characteristics of the 16 patients who developed TdP after dofetilide initiation:

- Mean age: 69.0 $\pm$ 10.1 years
- Gender distribution: 62.5 % females
- Left ventricular ejection fraction (LVEF %): 45.0 $\pm$ 15.3
- Baseline heart rate: 82.8 $\pm$ 22.6 beats per minute
- Baseline mean serum potassium: 4.45 $\pm$ 0.4
- Baseline mean serum magnesium: 1.99 $\pm$ 0.2
- 93.75 % had an eGFR $>$ 60, with creatinine clearance (CrCl) of 81.8 $\pm$ 23.9

- The majority of patients were in AF/AFL before dofetilide initiation (62.5 %)
- Mean baseline QT/QTc interval: 394.1 ± 46.4/452.0 ± 34.6 msec

The distribution of TdP incidence across the four Mayo Clinic sites was as follows: Minnesota (11 cases), Florida (4 cases), Wisconsin (1 case), and Arizona (0 cases) (Table 1).

- The most common reasons for discontinuation of dofetilide during hospital stay were significant QT/QTc prolongation in 105 patients (5.2 %), failure to maintain sinus rhythm in 58 patients (2.8 %), and ventricular arrhythmias other than TdP in 27 patients (1.3 %).
- Among the cohort of 2036 patients, 16 developed TdP (0.79 %), with no incidence of cardiac arrhythmia-related death in the hospital.
- All-cause mortality at 30 days and one-year post-initiation of dofetilide were 0.2 % and 0.9 %, respectively (Table 2).

Additional details regarding the 16 patients who developed TdP after dofetilide initiation: (Table3).

- Three patients were electively admitted for cardiac ablation for AF/AFL, followed by initiation of dofetilide.
- Two patients underwent elective direct current cardioversion first, followed by dofetilide initiation.
- The remaining patients were electively admitted exclusively for dofetilide initiation.
- All patients except one (who received a starting dose of 250 mcg) were started on a 500 mcg dose of dofetilide.
- Six patients who developed TdP received active intravenous (IV) diuresis during hospitalization. IV diuresis can result in hypokalemia, hypomagnesemia, and fluctuations of creatinine clearance that can increase risk for TdP.
- Four patients received digoxin within 36 hours of dofetilide loading. Although digoxin is not a contraindication with dofetilide, concomitant use of both these drugs are associated with higher incidence of TdP. This association raises potential drug-drug interactions between dofetilide and digoxin.
- Three patients received concomitant QT-prolonging drugs (fluoxetine, sertraline, ondansetron, and promethazine) during their hospital stay for dofetilide initiation. One of the patients received ondansetron and promethazine after atrial fibrillation ablation and admitted to the hospital for dofetilide initiation. Her baseline QTc was 450msec and was started on 500 mcg of dofetilide.
- Two patients were found to have hypokalemia following the TdP event. One of the patients was getting active IV diuresis during dofetilide initiation. She was started on 250 mcg of dofetilide with creatinine clearance on 31 mL/min (Dofetilide 125 mcg should be starting dose based on FDA/drug manufacturer initiation recommendation). Her potassium level was 3.1 following TdP event.
- Two of the 16 TdP patients had underlying congenital heart disease (pulmonary atresia and tetralogy of fallot).
- An interesting and important finding from this study is that females had a higher incidence of TdP (1.5 %) than their male counterpart (0.44 %) {OR 3.46; P = 0.017}. This observation underscores the potential influence of gender on susceptibility to TdP in patients undergoing dofetilide initiation.

Table 1
Clinical Characteristics of Study Population and TdP Group.

Variable	Total n = 2036 (%)	TdP group n = 16
Age, mean ± SD	66.4 ± 11.4	69.0 ± 10.1
Female	667 (32.8 %)	10 (62.5 %)
Clinical characteristics		
Hypertension	1576 (77.4 %)	11 (68.8 %)
CHF	929 (45.6 %)	8 (50 %)
Prior MI	300 (14.7 %)	1 (6 %)
Diabetes	299 (14.7 %)	3 (18.8 %)
Chronic Kidney Disease	299 (14.7 %)	2 (12.5 %)
Implantable cardiac device history	277 (13.6 %)	3 (18.8 %)
AF/AFL rhythm prior to initiation	1153 (57 %)	10 (62.5 %)
Baseline potassium	4.4 ± 0.4	4.45 ± 0.4
Baseline magnesium	2.0 ± 0.2	1.99 ± 0.2
Baseline QT interval, msec	396.3 ± 52.8	394.1 ± 46.4
Baseline QTc interval, msec	449.3 ± 39.5	452.0 ± 34.6
Baseline QRS duration	100.9 ± 24.6	101.6 ± 29.2
Sites		
Arizona	228 (11.2 %)	0 (0 %)
Florida	332 (16.3 %)	4 (25 %)
Minnesota	1069 (52.5 %)	11 (68.8 %)
Wisconsin	407 (20 %)	1 (6.2 %)
Susceptible traits of dofetilide-associated TdP		
Female		10 (62.5 %)
Intravenous active diuresis		6 (37.5 %)
Concomitant use of digoxin		4 (25 %)
Concomitant use of QT prolonging drugs (Fluoxetine, sertraline, ondansetron, promethazine)		3 (18.75 %
Electrolyte abnormality (hypokalemia)		2 (12.5 %)
Deviation from algorithm protocol		n = 13 (81 %)
Baseline QT/QTc exceeding > 440 msec (500 msec with ventricular conduction abnormalities		9 (69 %)
Continued use of dofetilide despite QTc interval > 500 msec any time after second dose		4 (31 %)
No dose reduction of dofetilide despite QT/QTc interval > 500 msec after the first dose		3 (19 %)
Started on higher dose of dofetilide despite decreased CrCl		2 (15 %)

Table 2
Dofetilide treatment characteristics. Total N = 2036 (%).

Dofetilide dose	Starting dose	Discharge dose
500 mcg	1255 (61.6 %)	901 (49.4 %)
375 mcg	5 (0.2 %)	21 (1.2 %)
250 mcg	696 34.2 %)	751 (41.2 %)
125 mcg	80 (3.9 %)	150 (8.2 %)
Reason for dofetilide discontinuation in the hospital		
Prolonged QT/QTc	105 (5.2 %)	
Failure to maintain sinus rhythm	58 (2.8 %)	
Ventricular arrythmia other than TdP	27 (1.3 %)	
Incidence of TdP during dofetilide initiation	16 (0.79 %)	
Arrhythmia related death in the hospital	0 (0 %)	
30-day mortality	4 (0.2 %)	
1 year mortality	18 (0.9 %)	

Deviation from FDA/Drug Manufacturer Algorithm Protocol

Any departure from FDA/drug manufacturer algorithm for initiation of dofetilide was considered a deviation from the protocol (Fig. 1). The key findings regarding deviations from the FDA/drug manufacturer algorithm protocol observed in the group of patients who developed TdP after dofetilide initiation:

- Eighty-one percent of patients (13 out of 16) in the TdP group deviated from the algorithm protocol.
- The most common deviations were as follows: a) Baseline QT/QTc interval exceeding > 440 msec (500 msec with ventricular conduction abnormalities), accounting for 69 % (9 out of 13) of deviations. b) Continued use of dofetilide despite QTc interval > 500 msec at any time after the second dose, observed in 31 % (4 out of 13) of deviations. c) No dose reduction of dofetilide despite QT/QTc interval > 500 msec after the first dose, seen in 19 % (3 out of 16) of patients.
- Additionally, 15 % (2 out of 13) of patients were started on a higher dose of dofetilide despite decreased baseline CrCl.
- It was noted that several patients deviated from the algorithm more than once, indicating potential areas for improvement in adherence to protocol guidelines.

Table 3
Detailed clinical characteristics of the 16 patients who developed dofetilide-induced TdP.

TdP patient cases	Gender	Dofetilide dose at time of TdP event	Rhythm at time of TdP: Sinus rhythm (SR), Atrial fibrillation (AF), junctional rhythm (JR)	QTc (QT if HR < 60, JTc for QRS > 130 msec) after TdP event on ECG	Maximum QTc (QT if HR < 60, JTc for QRS > 130 msec) during dofetilide initiation on ECG	Serum potassium after TdP event	Serum magnesium after TdP event
1	male	500 mcg	SR	469 msec	500 msec	4.2	2.4
	Baseline HR 53 bpm, QT 468 msec, dofetilide not recommended based on FDA/drug manufacturer protocol.						
2	male	500 mcg	SR	504 msec	568 msec (QT)	4.0	2.0
	Baseline QTc 441 msec, dofetilide not recommended based on FDA/drug manufacturer protocol. Developed bradycardia, HR 50 s after first dose, metoprolol was stopped, continue on dofetilide 500 mcg, QT after second dose > 500 msec, developed TdP shortly after second dofetilide dose.						
3	female	500 mcg	SR, HR 40 s	554 msec (QT)	554 msec (QT)	4.0	2.4
	Baseline HR 48 bpm, QT 470 msec, dofetilide not recommended based on FDA/drug manufacturer protocol. Pt was on digoxin 250 mcg daily prior to initiation but was stopped. Pt also received active IV diuresis shortly after AF ablation and QT prolonging drug (Fluoxetine) during dofetilide initiation.						
4	female	500 mcg	SR, HR 40 s	532 msec (QT)	780 msec	4.7	2.1
	Pharmacologic conversion after third dose of dofetilide, had 10-sec pause, then developed bradycardia with HR 40 s-50 s prior to TdP. Concomitant medication: digoxin						
5	female	500 mcg	SR, HR 52	504 msec (JT)	504 msec (JTc)	4.6	1.8
	Pharmacologic conversion after 4th dofetilide dose, developed bradycardia, HR 50 s, JT prolonged after conversion. Received active IV diuresis during dofetilide loading						
6	male	500 mcg	AF	487 msec	497 msec	4.5	1.9
	Baseline QTc 477 msec, dofetilide not recommended based on FDA/drug manufacturer protocol. Developed 3.5 secs polymorphic VT, dofetilide reduced to 250 mcg, continued to have ventricular ectopies, decision was made to discontinue dofetilide.						
7	Female	500 mcg	SR, HR 49	506 msec (QT)	506 msec	4.2	2.0
	Pharmacologic conversion after 1 dose with dofetilide, developed 5.87 conversion pause with bradycardia, prolong QTc, 2nd dose held overnight, restarted the following day with same dose of 500 mcg (QT back to baseline), still bradycardic, developed TdP after second dose. Concomitant medication: digoxin						
8	female	500 mcg	JR	544 msec	544 msec	3.9	1.7
	Patient received multiple doses of active IV diuresis after AF ablation. Concomitant medication: sertraline						
9	female	500 mcg	SR	423 msec (JTc)	423 msec (JTc)	4.6	2.0
	After 3rd dose to dofetilide and following electrical cardioversion, became bradycardic, HR < 60, JT was prolonged, continued 500 mcg of dofetilide						
10	male	500 mcg	SR, HR = 39	630 msec (QT)	630 msec (QT)	4.5	1.9
	Baseline QTc 472 msec, dofetilide not recommended based on FDA/drug manufacturer protocol. Pharmacologically converted after first dose, was bradycardic, HR in the 40 s, metoprolol held, QTc 550 after 1st dose, HR 43, continued on dofetilide, went into TdP, Following TdP event, QT was 630 msec, HR 39						
11	female	500 mcg	SR	442 msec	442 msec	4.1	2.0
	Cr Cl < 60 (45), recommended starting dose of dofetilide is 250 mcg per drug protocol. Pharmacologically converted after 2 doses of dofetilide. Continued higher dose of dofetilide 500 mcg BID						
12	male	500 mcg	SR, HR = 51	544 msec (QT)	544 msec (QT)	4.4	2.0
	Baseline QTC 440 msec, started on dofetilide 500 mcg. Hydrochlorothiazide was discontinued one day prior to dofetilide initiation. QT after second dose of dofetilide 544 msec, HR 51. Went into TdP after second dose. Prior history of ventricular tachycardia ablation.						
13	female	250 mcg	JR	540 msec	579 msec	3.6	1.7
	Baseline QTc 467 msec, dofetilide not recommended based on FDA/drug manufacturer protocol. Patient was started on dofetilide 500 mcg BID, developed TdP after 5th dose. Concomitant medications: received ondansetron and promethazine following AF ablation.						
14	female	125 mcg	SR	486 msec (JTc)	486 msec (JTc)	3.1	2.0
	Baseline creatinine clearance 31, based on drug protocol, recommended starting dose is 125 mcg BID. Patient received dofetilide 250 mcg BID. Baseline JTc prolonged. Concomitant medications: active IV diuresis during dofetilide loading. Potassium level following TdP event was 3.1						
15	male	500 mcg	SR	626 msec	626 msec	4.1	2.2
	Baseline QTc 447, dofetilide not recommended based on FDA/drug manufacturer protocol. Concomitant medication: active IV diuresis during dofetilide initiation						
16	female	500 mcg	SR	694 msec	694 msec	4.0	1.7
	Baseline QTc 462, dofetilide not recommended based on FDA/drug manufacturer protocol. Patient was in acute decompensated HF requiring IV diuresis during initiation of dofetilide. Pharmacologic conversion after 4th dose, developed TdP after 5th dose. QTc 694 msec following TdP event.						

4. Discussion

Significant deviations and non-adherence from the FDA/manufacturer algorithm protocol emerged as major contributors to dofetilide-induced TdP. Strict adherence to the initiation protocol could substantially mitigate the risk of TdP related to dofetilide therapy. Notably, a substantial portion (69 %) of the TdP cohort exhibited baseline QT/QTc intervals exceeding 440 ms, which contraindicates the initiation of dofetilide therapy. Moreover, failure to adjust dosage and discontinue drug therapy in patients exceeding QT/QTc interval and creatinine clearance recommendations likely played a role in the incidence of TdP.

Dofetilide is an efficacious and relatively safe antiarrhythmic drug for maintaining sinus rhythm in stable patients with AF/AFL when adhering to the FDA/manufacturer algorithm drug initiation protocol. Our study, encompassing 2036 patients across four Mayo Clinic hospital sites, revealed a low overall incidence of dofetilide-induced TdP at 0.79 %, aligning closely with earlier findings such as those from The Symptomatic Atrial Fibrillation Investigative Research on Dofetilide (SAFIRE-D) study (0.8 %).

Susceptible traits and modifiable risk factors identified in the TdP cohort include concomitant use of active intravenous diuretic therapy, digoxin, and QT-prolonging drugs. Patients undergoing cardiac ablation for AF/AFL followed by dofetilide initiation often received aggressive intravenous diuresis for volume overload post-procedure. Rapid changes in electrolytes and fluctuations in renal clearance alongside IV diuresis may have contributed to QTc prolongation leading to TdP. Additionally, one patient received multiple doses of QT-prolonging anti-nausea medications (ondansetron/promethazine) before dofetilide initiation.

These modifiable risk factors mirror findings from earlier studies and underscore the importance of their avoidance, if possible, to mitigate the risk of dofetilide-induced TdP [10]. Notably, our study revealed a greater than threefold incidence of TdP (1.5 %) in females compared to males (0.44 %). This observation aligns with previous study by Torp-Pedersen et al indicating that TdP occurs more frequently in women than in men (Odds ratio −3.2). As women tend to have longer baseline QTc intervals, it is postulated that differences in the distribution of ion channels contribute to this disparity. Women account for two thirds of drug induced TdP, consequently, this gender disparity significantly impact women's health outcomes [11,12,13]. The female gender emerges as a non-modifiable risk factor for drug induced TdP due to longer baseline QTc durations. Perhaps the time has come to revisit and address revision to the dofetilide drug initiation protocol to accommodate this gender disparity, such as reducing the baseline QTc duration requirement or adjusting the starting dose for women.

Indeed, if strict adherence to the manufacturer's guidelines for dofetilide initiation were ensured, the incidence of TdP could potentially

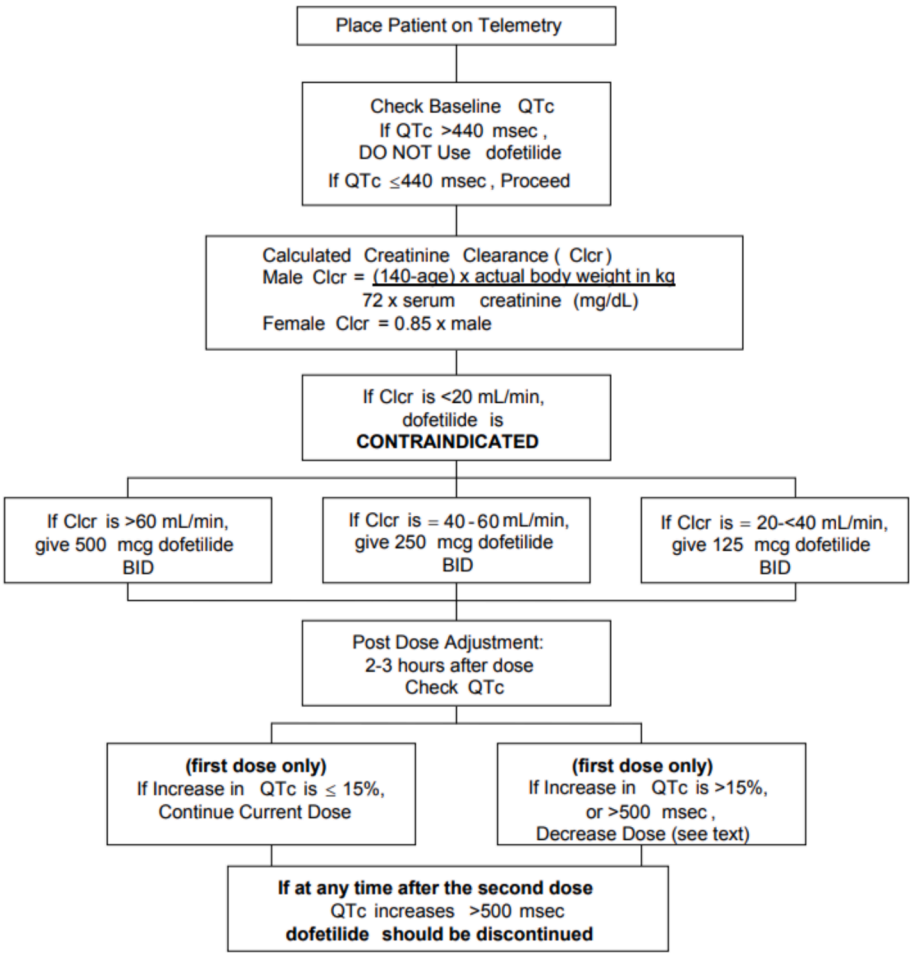

Fig. 1. FDA/Dofetilide manufacturer algorithm protocol for initiation of dofetilide (package insert).

be reduced to a negligible level, such as amiodarone. In one study by Dar et al, the impact of drug protocol deviations caused significant adverse events in the group that deviated compared to the group that fully adhered to the drug protocol. This underscores the critical importance of meticulously following established protocols and guidelines to minimize the risk of adverse events.

The concept of close follow-up in a virtual hospital setting or even outpatient initiation, particularly in patients with an implanted implantable cardioverter-defibrillator (ICD), presents an intriguing possibility. Leveraging telemedicine and remote monitoring technologies could facilitate frequent monitoring of key parameters such as QT/QTc intervals and electrolyte levels, allowing for timely intervention and adjustment of therapy as needed.

In patients with implanted ICDs, continuous remote monitoring of cardiac rhythm and device diagnostics could provide valuable, timely data on arrhythmia occurrence and device function. This proactive approach to monitoring could enable early detection of potential arrhythmic events, facilitating prompt intervention and management. A small study at the Veterans Administration System evaluated the efficacy and safety of outpatient dofetilide initiation with AF during the COVID-19 pandemic. Their study showed effective and safe outpatient initiation of dofetilide was possible in patient with AF who had cardiac implantable electronic devices [14].

However, it is essential to consider the feasibility and safety implications of outpatient initiation, particularly in patients with known risk factors for TdP or those requiring close monitoring. Careful risk stratification and individualized management plans would be crucial to ensure patient safety and optimize treatment outcomes, and this would need to be prospectively explored.

The notion of close follow-up in a virtual hospital setting or outpatient initiation, particularly in select patient populations, holds promise as a potential strategy to enhance the safety and convenience of dofetilide initiation while minimizing the risk of adverse events like TdP. Further research and evaluation of these approaches are warranted to determine their efficacy and feasibility in clinical practice. Our study has limitations including the small event rate of TdP, which limits statistical significance for a comparative analysis of observed risk factors compared to those who did not develop TdP, as well as the inherent bias present in any type of retrospective cohort study. While rate of protocol deviation was high in patients who developed TdP, data for rate of protocol deviation in the remainder of the cohort is not available. Multicenter studies involving larger patient cohorts are warranted to validate further and strengthen our findings. These studies would provide a broader perspective and more robust evidence regarding the safety and efficacy of dofetilide initiation, particularly in diverse patient populations, including women. Given the observed gender disparity in the incidence of TdP, a revision of the algorithm protocol specifically tailored to women may be considered. This revision could involve adjusting the baseline QTc duration requirement or modifying the starting dose to account for gender-specific differences in susceptibility to TdP.

Overall, our study contributes valuable insights into the safety profile of dofetilide initiation and highlights the importance of protocol adherence and consideration of patient-specific factors in optimizing treatment outcomes. Further research and collaborative efforts are essential to validate our findings and inform potential revisions to

dofetilide initiation protocols, ultimately improving the safety and efficacy of dofetilide therapy for patients with AF/AFL.

5. Conclusion

As observed in our study, the overall incidence of TdP related to dofetilide initiation was indeed low at 0.79 %. Our findings suggest that dofetilide initiation appears to be safe in elective hospital admissions when the protocol is strictly followed, and concurrent use of intravenous diuretics, digoxin, or QT-prolonging drugs is avoided. These observations underscore the importance of adherence to established guidelines and protocols to minimize the risk of adverse events associated with dofetilide therapy.

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CRediT authorship contribution statement

Maria Cecilia Tagle-Cornell: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Chadi Ayoub:** Writing – review & editing, Validation, Supervision, Methodology, Investigation, Formal analysis. **Christen Bird:** Visualization, Methodology, Investigation, Data curation, Conceptualization. **Milagros Pereyra:** Validation, Methodology, Investigation, Formal analysis, Data curation. **Courtney Kenyon:** Resources, Investigation, Data curation. **Moaz Kamel:** Resources, Investigation, Data curation. **Shruti Iyengar:** Resources, Investigation, Data curation. **Hema Vemulapalli:** Resources, Investigation, Data curation. **Francesca Galasso:** Resources, Investigation, Data curation. **Marlene Girardo:** Validation, Methodology, Formal analysis. **Klanderman Molly:** Validation, Methodology, Formal analysis. **Komandoor Srivathsan:** Writing – review & editing, Visualization, Supervision, Methodology, Investigation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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