Assessment of the Impact of Risk Factors on the QTc Interval and ECG Monitoring in Patients on Dronedarone

by Veronica Maher, PharmD, Tonja Larson, PharmD, and Sara Griesbach, PharmD

Abstract

Objective: Approximately 450,000 reported cases of sudden cardiac death occur annually in the United States. Torsade de Pointes (TdP) is responsible for 2% of these cases. The primary objective of this study was to determine the frequency of QTc >500 ms during dronedarone therapy and to assess the impact of risk factors for QTc prolongation and drug-drug interactions on the QTc interval in a clinic practice setting.

Methods: A retrospective electronic data abstraction was undertaken between July 2009 and April 2014 (n=662) including QTc interval during dronedarone therapy and risk factors for QTc prolongation. Electrocardiogram (ECG) measurements during dronedarone therapy were assessed to evaluate impact of risk factors on the QTc interval.

Results: A significantly higher incidence of QTc prolongation was observed in patients with: 1–2 ECG measurements and age ≥65 years, history of QTc ≥500 ms, hypokalemia, or renal dysfunction ($p<0.05$); 3–4 ECG measurements and female gender, history of QTc ≥500 ms, or renal dysfunction ($p<0.05$); 5–15 ECG measurements and history of QTc ≥500 ms ($p<0.05$); and 3–4 ECG measurements and experiencing a drug-drug interaction with a known TdP risk drug ($p<0.05$). Patients with 1–5 and 5–15 ECG measurements and drug-drug interactions did not have a significantly higher incidence of QTc prolongation rate.

Conclusion: This study identified age ≥65, hypokalemia, renal dysfunction, structural heart disease, female gender, or history of QTc ≥500 ms, and exposure to a known TdP risk-associated drug increased the risk for QTc prolongation. Increased frequency of ECG monitoring increased the likelihood of identifying QTc prolongation, which may potentially highlight the importance of frequent monitoring in patients with risk factors for QTc prolongation.

The incidence of reported sudden cardiac death ranges from 180,000 to 450,000 cases annually in the United States.[1] Torsade de Pointes (TdP), a potentially fatal polymorphic ventricular tachyarrhythmia caused by a prolonged QTc interval, is responsible for 2% of cases.[1] TdP can occur in the context of acquired and congenital long QT syndrome. A QTc interval prolongation is defined as a QTc interval greater than 450 ms in men and greater than 470 ms in women.[1] However, most arrhythmias are often associated with values of 500 ms or more.[2] Acquired long QT syndrome is most commonly drug induced, with anti-arrhythmics being the most common class of drugs implicated.[1] Although TdP is rare, an incidence up to 2-3% has been reported with some medications.[3]

Many patients prescribed anti-arrhythmics also have additional risk factors for QTc prolongation such as concomitant use of non-cardiac medications that can prolong the QTc interval (e.g., citalopram) and concomitant use of a medication with a pharmacokinetic drug-drug interaction (e.g., ketoconazole).[4] Patients may have inherent underlying risk factors for QTc prolongation, such as female gender.[1] Presence of multiple risk factors may amplify the risk of developing a potentially fatal arrhythmia.

Dronedarone is a class III antiarrhythmic, approved by the Food and Drug Administration in July 2009, to reduce the risk of hospitalization for atrial fibrillation in patients in sinus rhythm with a history of paroxysmal or persistent atrial fibrillation.[5] Dronedarone is associated with antiarrhythmic properties in all four Vaughan-Williams classes and induces a moderate QTc prolongation (average QTc interval increase of about 10 milliseconds [ms] from baseline). In clinical trials comparing dronedarone to placebo, 28% of patients treated with dronedarone had a QTc prolongation, compared to 19% of patients treated with placebo.[5] Prescribing information recommends obtaining an electrocardiogram (ECG) once every 3 months to assess safety of dronedarone use including monitoring for QTc prolongation during dronedarone therapy. Dronedarone has a black box warning for use in patients with symptomatic heart failure with recent decompensation requiring hospitalization or patients with NYHA Class IV heart failure and patients with permanent atrial fibrillation who will not or cannot be converted to normal sinus rhythm, as the risk of death doubles in these patients.[5]

Concomitant use of drugs that prolong the QTc interval increases the risk of TdP (see Table 1). A QTc interval of 500 ms or more both prior to the initiation of dronedarone or at any time during dronedarone therapy is considered a contraindication for use of dronedarone. Examples of drugs that have a pharmacodynamic drug-drug interaction with dronedarone include, but are not limited to, phenothiazine anti-psychotics (e.g., chlorpromazine), tricyclic antidepressants (e.g. amitriptyline), certain macrolide antibiotics (e.g., erythromycin), and Class I and III anti-arrhythmics (Table 1).[1] Co-administration of such medications with dronedarone is contraindicated.[1]

The Arizona Center for Education and Research on Therapeutics maintains lists of medications that cause QT prolongation and TdP. Medications on these lists should also be avoided concomitantly with dronedarone:

www.crediblemeds.org

Since dronedarone is metabolized by CYP3A4, the enzymatic pathway that accomplishes metabolism of >50% of pharmaceuticals,[6] there is high potential for clinically relevant drug-drug interactions (e.g., ketoconazole).[7] Ketoconazole is a strong CYP3A4 inhibitor, and concomitant use of ketoconazole with dronedarone results in a 9-fold increase in the maximum concentration (Cmax) and a 17- to 25-fold increase in area-under-the plasma concentration-time curve of dronedarone.[8] This potentially increases the risk of QTc prolongation and risk of TdP. Diltiazem and verapamil are both moderate CYP3A4 inhibitors and increase dronedarone exposure by approximately 1.4-to 1.7-fold.[1] It is expected that other CYP3A4 inhibitors would have similar effects. Treatment with such drugs should be discontinued before initiation of dronedarone, or alternatives to dronedarone should be considered.

Underlying risk factors for QTc prolongation increase the risk of TdP in patients taking dronedarone. Risk factors include age ≥65 years, bradycardia, electrolyte abnormalities, female gender, structural heart disease, history of documented QTc prolongation, and organ dysfunction. Dronedarone exposure on average is 30% higher among females than in males and 23% higher in patients ≥65 years.[1]

Since dronedarone has only been on the market since 2009, there is limited long-term safety data and experience in the general population. Patients with diagnosed long QT syndrome or those receiving Class Ia or III antiarrhythmics are at the greatest risk for TdP.[9] The purpose of this study was to determine the frequency of a QTc ≥500 ms during dronedarone therapy and to assess the impact of risk factors for QTc

TABLE 1. Medications with Potential Drug Interactions with Dronedarone Assessed During Study Period

CYP3A4 Inhibitors[9]		
Amiodarone	Erythromycin	Posaconazole
Aprepitant	Fluconazole	Ritonavir
Atazanavir	Fluvoxamine	Saquinavir
Clarithromycin	Indinavir	Telithromycin
Cyclosporine	Itraconazole	Verapamil
Darunavir	Ketoconazole	Voriconazole
Delavirdine	Nefazodone	
Diltiazem	Nelfinavir	
Drugs with Known TdP Risk[2]		
Amiodarone	Dofetilide	Ondansetron
Anagrelide	Erythromycin	Pentamidine
Azithromycin	Escitalopram	Pimozide
Chloroquine	Flecainide	Quinidine
Chlorpromazine	Haloperidol	Sotalol
Citalopram	Ibutilide	Thioridazine
Clarithromycin	Methadone	Vandetanib
Disopyramide	Moxifloxacin	
Drugs with Possible TdP Risk[2]		
Alfuzosin	Levofloxacin	Rilpivirine
Apomorphine	Lithium	Risperidone
Atazanavir	Mifepristone	Saquinavir
Bortezomib	Mirabegron	Sorafenib
Bosutinib	Mirtazapine	Sunitinib
Clozapine	Moexipril/HCTZ	Tacrolimus
Crizotinib	Nicardipine	Tamoxifen
Dabrafenib	Nilotinib	Telavancin
Dasatinib	Norfloxacin	Telithromycin
Dolasetron	Ofloxacin	Tetrabenazine
Famotidine	Olanzapine	Tizanidine
Felbamate	Oxytocin	Tolterodine
Fingolimod	Paliperidone	Toremifene
Foscarnet	Pasireotide	Vardenafil
Gemifloxacin	Pazopanib	Vemurafenib
Granisetron	Perflutren lipid microspheres	Venlafaxine
Iloperidone	Promethazine	Voriconazole
Isradipine	Quetiapine	Vorinostat
Lapatinib	Ranolazine	Ziprasidone
Other Drug Interactions		
Digoxin	Mexiletine	Propafenone
HCTZ - hydrochlorothiazide		

Adapted from: [2] Yap YG, Camm AJ. Drug induced QT prolongation and torsade de pointes. Heart. 2003;89(11):1363–1372.
[9] Owens RC Jr, Nolin TD. Antimicrobial-associated QT interval prolongation: pointes of interest. Clin Infect Dis. 2006;43(12):1603–1611.

TABLE 2. Baseline Demographics of Patients on Dronedarone (n=662)

Characteristic	n (%)	Mean	SD	Median	Range
All ages	662 (100%)	69	11.6	70	27-97
Age ≥ 65	432 (65%)				
Female gender	298 (45%)				
Duration of therapy (days)	662 (100%)	541	494	370	0-1633

prolongation and drug-drug interactions on the QTc interval in an ambulatory clinic setting. The goal of this study was to assess prescribing patterns, characterize treatment response for the patient population receiving dronedarone, and further define the clinical significance of drug-induced long QT syndrome within our practice setting.

Methods

Study Design and Population

This was a retrospective cohort study and the target population included patients aged ≥18 years with documented prescriptions of dronedarone and with at least one documented ECG measurement during dronedarone therapy in the timeframe from July 1, 2009 to April 30, 2014. This study took place in an outpatient setting. The study was approved by the Institutional Review Board with waiver of informed consent. Patients were excluded if dronedarone was not prescribed by a provider within our system.

Data were extracted electronically from the electronic health record. The defined risk factors for QTc prolongation assessed during dronedarone therapy are as follows: gender, age ≥65 years, bradycardia (<60 bpm), hypocalcemia (<8.5 mg/dL), hypokalemia (<3.4 mmol/L), hypomagnesemia (<1.7 mg/dL), history of QTc prolongation (history of QTc ≥500 ms), hepatic dysfunction (ALT/AST >3x the upper limit of normal), renal dysfunction (eGFR <60 mL/min), and presence of structural heart disease (all classes of heart failure, coronary artery disease, myocardial infarction, valvular disease, rheumatic heart disease, endocarditis, mitral/aortic/tricuspid/pulmonic valve stenosis/regurgitation/insufficiency, mitral valve prolapse, and cardiomyopathy). The assessment of drug-drug interactions with dronedarone including CYP3A4 inhibitors, drugs with known TdP risk, drugs with possible TdP risk, and other drugs (summarized in Table 1) was performed on the date of the documented ECG measurement or within 3 days of the documented ECG measurement. Drugs defined as having a known TdP risk and a possible TdP risk, were based on the Credible Meds website (https://www.crediblemeds.org/). A drug with a known TdP risk was defined as a drug that causes QTc prolongation and cases of TdP have been documented (e.g., citalopram), whereas a drug with possible TdP risk was defined as a drug that causes QTc prolongation but no cases of TdP have been documented to date (e.g., quetiapine). "Other drugs" are defined as medications that are not CYP3A4 inhibitors or drugs with a known or possible TdP risk but are associated with a potential risk for a drug-drug interaction with dronedarone (e.g., digoxin). Most risk factors for QTc prolongation were assessed on the date of the documented ECG measurement or on the date closest to the documented ECG measurement. Structural heart disease and history of QTc prolongation were assessed by documentation of any type of structural heart disease and any documented history of QTc ≥500 ms in the electronic health record. A 10% manual validation was performed to validate electronically abstracted data for the following: structural heart disease diagnosis, documented torsade de pointes and/or sudden cardiac arrest, and drug-drug interactions. A manual chart review was also performed on all deceased patients with dronedarone exposure during the observational window to determine if the patient was on dronedarone at the time of death.

TABLE 3. Risk Factors for QTc Prolongation in Patients with 1–2 Documented ECG Measurements

Risk Factors		QTc < 500 ms	QTc ≥500 ms	p value
Age ≥65 years	No	150 (94%)	10 (6%)	0.0103
	Yes	134 (85%)	24 (15%)	
Bradycardia	No	77 (88%)	11 (12%)	0.5415
	Yes	212 (90%)	23 (10%)	
Female Gender	No	178 (91%)	17 (9%)	0.1996
	Yes	111 (87%)	17 (13%)	
Hx of QTc Prolongation	No	289 (95%)	14 (5%)	<0.0001
	Yes	0 (0%)	20 (100%)	
Hypocalcemia	No	160 (90%)	17 (10%)	0.5880
	Yes	129 (88%)	17 (12%)	
Hypokalemia	No	220 (93%)	17 (7%)	0.0020
	Yes	69 (80%)	17 (20%)	
Hypomagnesemia	No	226 (90%)	25 (10%)	0.5187
	Yes	63 (88%)	9 (12%)	
Hepatic Dysfunction	No	34 (97%)	1 (3%)	0.1493
	Yes	255 (89%)	33 (11%)	
Renal Dysfunction	No	45 (90%)	5 (10%)	0.0255
	Yes	98 (75%)	33 (25%)	
Structural Heart Disease	No	26 (84%)	5 (16%)	0.6291
	Yes	117 (78%)	33 (22%)	

ECG: electrocardiogram
p-values derived from Fisher's exact test

Statistical Analysis

A total of 662 study subjects treated with dronedarone between July 2009 and April 2014 were included in the statistical analysis. In the univariate analysis, the descriptive statistics were reported at baseline or during the study time period for each of the participant's attributes (e.g., gender, age at study entry, duration of dronedarone therapy). Categorical measurements included frequency count and percentage. Descriptive statistics for continuous measurements included mean, standard deviation (SD), median, and range. Furthermore, subjects were separated into 3 groups based on the number of documented ECG measurements during dronedarone therapy: 1–2, 3–4, and 5–15 documented ECG measurements. The associations between defined risk factors and QTc prolongation outcome (≥500 ms, yes vs. no) were assessed using the Fisher's Exact Test, stratified by number of documented ECG measurements. P-values were derived from statistical analyses and a p-value of < 0.05 was used to indicate a statistical significant association between a specific risk factor and QTc prolongation outcome. Statistical analyses were also performed to evaluate associations between defined drug-drug interactions and QTc prolongation outcome. All data analyses were carried out using commercially available statistical software package SAS, version 9.3.

Results

There were 662 patients who met the inclusion criteria for this study. The baseline characteristics of the patient population are displayed in Table 2. The mean age was 69 years with a range of 27 to 97. Of note, 45% (298 patients) of the patient population was female, and 65% (432 patients) were 65 years of age or older.

Of the patients included in the study, 20% (n=133/662) had a QTc ≥500 ms during dronedarone therapy. The median number of risk factors for QTc prolongation in patients with a QTc ≥500 ms during dronedarone therapy was 7, ranging from 1 to 10. There were no documented cases of TdP or sudden cardiac death. The mean duration of dronedarone therapy was 541 days (1.5 years) ranging from 0 to 1633 days (4.5 years). Of the 193 patients who had expired during the observational window of this study, 36% (70/193 patients) were on dronedarone at the time of death.

Patients were stratified by the number of documented ECGs during dronedarone therapy into one of three groups: those with 1–2 (n=323) (Group 1), 3–4 (n=181) (Group 2) or 5–15 (n=158) (Group 3) documented ECGs during dronedarone therapy. Of note, 11% of patients in Group 1 (n=34/323), 21% in group 2 (n=38/181), and 39% in Group 3 (n=61/158) experienced a QTc ≥500 ms during dronedarone therapy.

Results for risk factors for QTc prolongation in patients with 1–2 documented ECGs during dronedarone therapy are reported in Table 3. Patients with the risk factors of age ≥65 years, history of QTc prolongation, hypokalemia, and renal dysfunction had a significantly higher rate of QTc prolongation compared to patients who did not have these risk factors (p<0.05). Patients with the risk factors of bradycardia, female gender, hypocalcemia, hypomagnesemia, structural heart disease and hepatic dysfunction did not have a significantly higher rate of QTc prolongation compared to patients without these risk factors (p>0.05).

Results for risk factors for QTc prolongation in patients with 3–4 documented ECG measurements during dronedarone therapy are reported in Table 4. Patients with the risk factors of female gender, history of QTc prolongation, and renal dysfunction had a significantly higher rate of QTc prolongation compared to patients who did not have these risk factors (p<0.05). Patients with the risk factors of age ≥65 years, bradycardia, hypocalcemia, hypokalemia, hypomagnesemia, hepatic dysfunction, and structural heart disease did not have a significant difference in QTc prolongation compared to patients without these risk factors (p>0.05).

Results for risk factors for QTc prolongation in patients with 5–15 documented ECG measurements during dronedarone therapy are reported in Table

TABLE 4. Risk Factors for QTc Prolongation in Patients with 3–4 Documented ECG Measurements

Risk Factors		*QTc < 500 ms*	*QTc ≥500 ms*	*p value*
Age ≥65 years	No	50 (86%)	8 (14%)	0.1199
	Yes	93 (76%)	30 (24%)	
Bradycardia	No	32 (89%)	4 (11%)	0.1155
	Yes	111 (77%)	34 (23%)	
Female Gender	No	86 (87%)	13 (13%)	0.0057
	Yes	57 (70%)	25 (30%)	
Hx of QTc Prolongation	No	143 (91%)	14 (9%)	<0.0001
	Yes	0 (0%)	24 (100%)	
Hypocalcemia	No	88 (83%)	18 (17%)	0.1391
	Yes	55 (73%)	20 (27%)	
Hypokalemia	No	107 (80%)	27 (20%)	0.6788
	Yes	36 (77%)	11 (23%)	
Hypomagnesemia	No	114 (83%)	24 (17%)	0.0518
	Yes	29 (67%)	14 (33%)	
Hepatic Dysfunction	No	13 (81%)	3 (19%)	1.000
	Yes	130 (79%)	35 (21%)	
Renal Dysfunction	No	45 (90%)	5 (10%)	0.0255
	Yes	98 (75%)	33 (25%)	
Structural Heart Disease	No	26 (84%)	5 (16%)	0.6291
	Yes	117 (78%)	33 (22%)	

ECG: electrocardiogram
p-values derived from Fisher's exact test

TABLE 5. Risk Factors for QTc Prolongation in Patients with 5–15 Documented ECG Measurements

Risk Factors		QTc < 500 ms	QTc ≥500 ms	p value
Age ≥65 years	No	34 (68%)	16 (32%)	0.2933
	Yes	65 (58%)	45 (42%)	
Bradycardia	No	10 (50%)	10 (50%)	0.3270
	Yes	87 (63%)	51 (37%)	
Female Gender	No	64 (62%)	40 (38%)	1.000
	Yes	33 (61%)	21 (39%)	
Hx of QTc Prolongation	No	97 (79%)	26 (21%)	<0.0001
	Yes	0 (0%)	35 (100%)	
Hypocalcemia	No	43 (69%)	19 (31%)	0.1313
	Yes	54 (56%)	42 (44%)	
Hypokalemia	No	72 (66%)	37 (34%)	0.0799
	Yes	25 (51%)	24 (49%)	
Hypomagnesemia	No	73 (63%)	43 (37%)	0.5800
	Yes	24 (57%)	18 (43%)	
Hepatic Dysfunction	No	10 (91%)	1 (3%)	0.0517
	Yes	87 (59%)	60 (41%)	
Renal Dysfunction	No	34 (69%)	15 (31%)	0.2163
	Yes	63 (58%)	46 (42%)	
Structural Heart Disease	No	16 (80%)	4 (20%)	0.0862
	Yes	81 (59%)	57 (41%)	

ECG: electrocardiogram; TdP, Torsade de Pointes
p-values derived from Fisher's exact test

5. Patients with the risk factor of history of QTc prolongation had a significantly higher rate of QTc prolongation compared to patients with no history of QTc prolongation (p<0.0001). Patients with the risk factors including age ≥65 years, bradycardia, female gender, hypocalcemia, hypokalemia, hypomagnesemia, hepatic dysfunction, renal dysfunction, and structural heart disease did not achieve a significantly higher rate of QTc prolongation compared to patients without these risk factors (p>0.05).

Tables 6, 7, and 8 display the impact of drug-drug interactions on the QTc interval in patients on dronedarone. Patients with 1–2 documented ECGs measurements during dronedarone therapy and concomitant use of a CYP3A4 inhibitor, a drug with known TdP risk, possible TdP risk, or other drug with dronedarone, did not have a significantly higher rate of QTc prolongation compared to patients with no concomitant use of these agents with dronedarone (p>0.05). Patients with 3–4 documented ECG measurements and concomitant use of 1 or 2 drugs with known TdP risk had a significantly higher rate of QTc prolongation compared to patients not on a drug with known TdP risk (p<0.0007). However, patients who were taking a CYP3A4 inhibitor, a drug with possible TdP risk, or other drug concomitantly with dronedarone did not have a significantly higher rate of QTc prolongation compared to patients who were not taking these drugs in this QTc measurement group (>0.05). Patients with 5–15 documented ECGs during dronedarone therapy and concomitant use of CYP3A4 inhibitors, a drug with known TdP risk, possible TdP risk, or other drug did not have a significantly higher rate of QTc prolongation compared to patients not taking these drugs concomitantly (p>0.05). The following CYP3A4 inhibitors were identified during dronedarone therapy: amiodarone, digoxin, diltiazem, and erythromycin.

Discussion

This study evaluated patients on dronedarone therapy and risk factors for QTc prolongation and the drug-drug interactions that potentially increased the risk of TdP and/or sudden cardiac arrest. Combined data from the EURIDIS and ADONIS studies report when compared to placebo, dronedarone prolonged the QTc interval by 9 ms, which was found to be statistically significant.[10] Although the manufacturer defines QT prolongation as >450 ms in men and >470 ms in women, this study assessed patients with a QTc ≥500 ms. Within the study period, 20% of patients had a documented report of QTc ≥500 ms at any time during dronedarone therapy since its approval in July 2009.

TABLE 6. Drug-Drug Interactions in Patients with 1–2 Documented ECGs

Risk Factors	Number of Interacting Meds	QTc < 500 ms	QTc ≥500 ms	p value
CYP3A4 Inhibitors	0	195 (89%)	25 (11%)	0.8893
	1	81 (91%)	8 (9%)	
	2	13 (93%)	1 (7%)	
Known TdP Risk	0	256 (90%)	27 (10%)	0.2753
	1	30 (81%)	7 (19%)	
	2	2 (100%)	0 (0%)	
	3	1 (100%)	0 (0%)	
Possible TdP Risk	0	262 (90%)	28 (10%)	0.2946
	1	25 (81%)	6 (19%)	
	2	2 (100%)	0 (0%)	
Other	0	247 (89%)	29 (11%)	1.000
	1	42 (89%)	5 (11%)	

ECG: electrocardiogram; TdP, Torsade de Pointes
p-values derived from Fisher's exact test

TABLE 7. Drug-Drug Interactions in Patients with 3-4 Documented ECGs

Risk Factors	Number of Interacting Meds	QTc < 500 ms	QTc ≥500 ms	p value
CYP3A4 Inhibitors	0	83 (78%)	23 (22%)	1.000
	1	48 (79%)	13 (21%)	
	2	10 (83%)	2 (17%)	
Known TdP Risk	0	2 (100%)	0 (0%)	0.0007
	1	130 (84%)	25 (16%)	
	2	11 (52%)	10 (48%)	
	3	2 (40%)	3 (60%)	
Possible TdP Risk	0	127 (79%)	34 (21%)	1.000
	1	14 (78%)	4 (22%)	
	2	2 (100%)	0 (0%)	
Other	0	109 (76%)	34 (24%)	0.1987
	1	32 (89%)	4 (11%)	
	2	2 (100%)	0 (0%)	

ECG: electrocardiogram; TdP, Torsade de Pointes
p-values derived from Fisher's exact test

This frequency is similar to the findings in dronedarone clinical trials, where 28% of patients had a prolonged QTc interval compared to 19% of placebo-treated patients.

In the ATHENA trial, one patient developed TdP while receiving dronedarone.[11] Although there were no documented cases of TdP or sudden cardiac arrest in this study, of the 193 patients who expired during the enrollment period, 36% of these patients were on dronedarone at time of death.

Of the patients who experienced a QTc ≥500 ms during dronedarone therapy, patients with the risk factors of age ≥65 years, history of a documented QTc ≥500 ms, hypokalemia, renal dysfunction, and/or female gender had a significantly higher incidence of QTc prolongation compared to patients who did not have these risk factors. Notably, patients with a history of QTc prolongation in each QTc measurement group had a significantly higher rate of QTc prolongation compared to patients without a history of QTc prolongation. Therefore, our study suggested a need for increased frequency in monitoring, and likelihood of detecting QTc prolongation. The findings of this study are generally consistent with other studies assessing risk factors for QTc prolongation.[1,5,9] The risk factors of advanced age, hypokalemia, renal dysfunction and female gender reported in other studies were confirmed in this study.[5,9] However, association of other risk factors with QTc prolongation reported in other studies including hypomagnesemia and bradycardia did not achieve statistical significance in this study.[5,9] Notably, as the number of documented ECGs during dronedarone therapy increased, the number of risk factors achieving statistical significance for QTc prolongation rate decreased. A possible explanation for this finding is that some of the risks identified over time were amenable to reduction through clinical interventional strategies (e.g., hypokalemia.) Thus, systematic monitoring of the ECG at regularly scheduled intervals can minimize the number of modifiable risk factors thus marginalizing their impact.

The assessment of drug-drug interactions, specifically, CYP3A4 inhibitors and drugs with known or possible TdP risk when used concomitantly with dronedarone provided valuable insight. The only statistically significant observation was found in patients with 3–4 documented ECGs concomitantly exposed to dronedarone and 1–2 drugs with a known TdP risk. A potential reason why the concomitant use of drugs with possible TdP risk, CYP3A4 inhibitors, and other drugs did not achieve statistical significance in all of the study groups may be due to the small number of patients identified with concomitant use of these medications. This observation could be attributable to awareness by prescribers of these medications of the potential drug-drug interactions with dronedarone. Alternatively, drug-drug interactions may play a smaller role in the risk of QTc prolongation and ultimately TdP and/or sudden cardiac arrest compared to patient-specific risk factors for QTc prolongation. Despite this data, the combined use of

TABLE 8. Drug-Drug Interactions in Patients with 5–15 Documented ECGs

Risk Factors	Number of Interacting Meds	QTc < 500 ms	QTc ≥500 ms	p value
CYP3A4 Inhibitors	0	47 (55%)	38(45%)	0.2625
	1	36 (71%)	15 (29%)	
	2	13 (62%)	8 (38%)	
	3	1 (100%)	0 (0%)	
Known TdP Risk	0	71 (65%)	39 (35%)	1.000
	1	24 (56%)	19 (44%)	
	2	2 (50%)	2 (50%)	
	3	0 (0%)	1 (100%)	
Possible TdP Risk	0	79 (63%)	46 (37%)	0.6494
	1	14 (54%)	12 (46%)	
	2	4 (57%)	3 (43%)	
Other	0	74 (61%)	47 (39%)	0.4067
	1	23 (62%)	14 (38%)	

ECG: electrocardiogram; TdP, Torsade de Pointes
p-values derived from Fisher's exact test

TABLE 9. Drug-Drug Interactions in Study Patients

Drugs with known TdP risk identified during dronedarone therapy	• Amiodarone • Azithromycin • Chlorpromazine • Citalopram • Dofetilide • Erythromycin • Escitalopram • Flecainide • Hydroxychloroquine • Ondansetron • Sotalol • Verapamil
Drugs with a possible TdP risk identified during dronedarone therapy	• Alfuzosin • Ciprofloxacin • Dasatinib • Famotidine • Levofloxacin • Mirtazapine • Promethazine • Quetiapine
Other drug-drug interactions identified during dronedarone therapy	• Digoxin • Propafenone

these medications should be exercised cautiously.

Limitations of this study include its retrospective design, lack of assessment of adherence to dronedarone therapy or duration of individual exposure to dronedarone, and capacity to verify that the medications recorded in the electronic health record was comprehensive and accurate. Likewise, it is unknown if patients were actually taking the medications documented in the electronic health record or if patients were taking additional medications not documented in the electronic health record. We also did not assess whether patients had a ventricular pacemaker. This limitation could potentially affect the results of this study.

In summary, this study identified that patients aged ≥65 years with additional risk factors including hypokalemia, renal dysfunction, female gender, or a history of a prolonged QTc interval and exposure to any drug with known TdP risk, are at potentially greatest risk for TdP and/or sudden cardiac arrest. Therefore, greater caution is needed when initiating antiarrhythmic therapy in these patients. Furthermore, frequent monitoring of patients with multiple risk factors for prolonged QTc interval in general can be established to identify patients at risk for TdP and/or sudden cardiac death. The current prescribing recommendations for dronedarone includes ECG monitoring every 3 months. Monitoring ECG earlier in therapy may be helpful in identifying patients who are candidates for more frequent monitoring. A potential solution would be the development of protocols with standard monitoring parameters for all patients started on dronedarone therapy. This study further demonstrated more frequent monitoring of the ECG was associated with a higher likelihood of identifying QTc prolongation. Due to the small number of patients who had abnormal QTc, we did not conduct a multivariate analysis in this current study; however, a multivariate analysis may be helpful in future studies in determining which risk factors have the greatest association with QTc prolongation. ●

At the time this research was conducted, Veronica Maher was a PGY-1 pharmacy resident at Marshfield Clinic, Marshfield, WI. Tonja Larson and Sara Griesbach are Pharmacists in the Clinical Pharmacy Services Department at Marshfield Clinic, Marshfield, WI.

PR *This article has been peer-reviewed. The contribution in reviewing is greatly appreciated!*

Conflict of Interest/Disclosures: The authors declare no real or potential conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts and honoraria.

Acknowledgments: The authors wish to thank the following for expert assistance: Connie Folz, PharmD, BCPS, Marshfield Clinic Investigational Drug Program; Debra Kempf, BSN, Marshfield Clinic Resident Research Facilitator; Ramya Kolli, Research Programmer Analyst; Aaron Miller, PhD, biomedical informatics ; Po-Huang Chyou, PhD, Biostatistician (director of biostatistics); Marie Fleisner, editorial specialist.

Funding Sources: This research project was funded by the Marshfield Clinic Resident Research Advisory Committee.

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