Catheter ablation of atrial fibrillation results in significant QTc prolongation in the postoperative period

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BACKGROUND The corrected QT interval (QTc) is a measure of ventricular repolarization time, and a prolonged QTc increases risk for malignant ventricular arrhythmias. Pulmonary vein isolation (PVI) may increase QTc but its effects have not been well studied.

OBJECTIVE Determine the incidence, risk factors, and outcomes of patients presenting for PVI in sinus and atrial fibrillation with postoperative QTc prolongation in a large cohort.

METHODS We performed a single-center retrospective study of consecutive atrial fibrillation ablations. QTc durations using Bazett correction were obtained from electrocardiograms at different postoperative intervals and compared to preoperative QTc. We studied clinical outcomes including clinically significant ventricular arrhythmia and death. A multivariable model was used to identify factors associated with clinically significant QTc prolongation, defined as ΔQTc ≥60 ms or new QTc duration ≥500 ms.

RESULTS A total of 352 PVIs were included in this study. We observed a statistically significant increase in mean QTc compared to baseline (446.3 ± 37.8 ms) on postoperative day (POD) 0 (471.7 ± 38.2 ms, $P < .001$) and at POD1 (456.5 ± 35.0 ms, $P < .001$). There was no significant difference at 1 month (452.4 ± 33.5 ms, $P = .39$) and 3 months (447.3 ± 40.0 ms, $P = .78$). Sixty-six patients (19.2%) developed ΔQTc ≥60 ms or QTc ≥500 ms on POD0, with 4.1% persisting past 90 days. Female sex (odds ratio [OR] = 1.82, 95% confidence interval [CI] =1.01–3.29, $P = .047$) and history of coronary artery disease (OR = 2.16, 95% CI = 1.03–4.55, $P = .042$) were independently predictive of QTc prolongation ≥500 ms or ΔQTc ≥60 ms. There were no episodes of clinically significant ventricular arrhythmia or death attributable to arrhythmia.

CONCLUSION QTc duration increased significantly immediately post-PVI and returned to baseline by 1 month. PVI did not provoke significant ventricular arrhythmias in our cohort.

KEYWORDS Atrial fibrillation; Catheter ablation; Pulmonary vein isolation; Prolonged QT; QTc

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Introduction

Catheter-based pulmonary vein isolation (PVI) is a rhythm control strategy for the management of atrial fibrillation (AF). Over the past 2 decades, catheter ablation technologies have evolved rapidly, leading to a significant improvement in the efficacy and safety of this procedure. Despite this increasing familiarity, AF ablation is associated with important risks and major complications, with 1 worldwide study of risks showing a 4.5% incidence of major complications, including but not limited to pericardial tamponade, pulmonary vein stenosis, transient ischemic attack/stroke, and death.[1]

While the structural complications resulting from PVI have been delineated, the electrophysiological complications are not well known. Small case series and a retrospective study by Chikata and colleagues have suggested that the corrected QT interval (QTc) may be prolonged post-PVI[2,3] and that female sex may increase risk.[3] QTc is a measure of ventricular repolarization, and a prolonged QTc interval increases the risk for malignant ventricular arrhythmias. A QTc greater than 500 ms increases the risk of torsades de pointes (TdP) by 2- to 3-fold, and each 10 ms increase above 500 ms additionally increases risk by 5%–7%.[4–6] The mechanism of QTc prolongation after PVI is not well understood but may be related to unintentional denervation of surface autonomic ganglionic plexi, as ganglionic plexus ablation has been demonstrated to increase relative refractory period and ventricular arrhythmias in canine models.[7]

At present, the impact of QTc prolongation after PVI on risk of malignant ventricular arrhythmia and sudden cardiac death in adult patients is limited to case reports.[8,9] One

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KEY FINDINGS

- The incidence of clinically significant corrected QT interval (QTc) prolongation, defined as new QTc ≥500 ms or ΔQTc ≥60 ms, is common immediately after pulmonary vein isolation, but appears to return to baseline after 1 month.
- Despite the high incidence of clinically significant QTc prolongation, there were no episodes of ventricular tachycardia, ventricular fibrillation, or torsades de pointes.
- Female sex and patients with a history of coronary artery disease were independently predictive of clinically significant QTc changes. These patient populations may benefit from cautious prescribing of antiarrhythmic drugs and increased electrocardiographic (ECG) monitoring/ambulatory ECG monitoring for ventricular arrhythmias.

nationwide study of PVIs in Germany demonstrated a cardiac arrest risk of 0.2%, but there was no ascertainment as to whether the arrest was precipitated by ventricular arrhythmia.[10] The purpose of this study is to determine the incidence of worrisome QTc prolongation after PVI and subsequent risk of clinically significant ventricular arrhythmia in the immediate postoperative setting.

Methods

Study population

We identified patients undergoing catheter-based PVI performed for the treatment of AF at the University of Washington Medical Center, a large urban tertiary care center. All patients older than 18 years who underwent PVI between January 2016 and June 2018 were identified and included in the study. First-time and repeat ablations were included. As the study data were deidentified, patient consent was waived. This study was approved by the University of Washington Institutional Review Board and all study protocols conducted in accordance with the Declaration of Helsinki.

Data collection

Patient data including demographics, comorbidities, electrocardiograms (ECGs), and procedural details were abstracted from the medical record. Information obtained by abstraction was confirmed by review of provider progress notes and dictated operative reports. We collected ECG data of these patients at different time points, including immediately preablation (baseline), immediately postoperatively within 12 hours (postoperative day [POD]0), and on POD1, POD30, and POD90. These ECGs were collected as available through routine clinical care of these patients. If 1 individual underwent multiple PVIs over the study period, each ablation was treated as an independent data point.

Outcome variables

Electrocardiographic variables studied include heart rate (HR), QRS, and QTc duration at POD0, POD1, POD30, and POD90 compared to baseline. We also studied the following QTc outcomes: QTc ≥500 ms, increase in QTc ≥60 ms, and a composite variable of newly prolonged QTc ≥500 ms or increase in QTc ≥60 ms at the postoperative intervals. These safety cutoffs were chosen in concordance with the US Food and Drug Administration International Conference on Harmonization E14 guidance document for assessing arrhythmic risk of noncardiac pharmaceuticals.[11,12] Clinical outcomes studied included 90-day mortality attributable to ventricular arrhythmia or sustained TdP, ventricular tachycardia, or ventricular fibrillation requiring medical intervention. Patients with a cardiac implantable electronic device and ventricularly paced baseline rhythm were removed from the QTc analysis to account for difficulties measuring QTc in paced rhythm but included in the clinical outcomes analysis.

QTc measurement

Electrocardiographic data were obtained manually by retrospective review of patient electrocardiograms available in the chart at the above-specified intervals and adjudicated by 2 separate investigators (DDN and JH). When multiple ECGs were available during the set time frame, the first ECG was chosen. The ECGs obtained were 12-lead ECGs recorded at 25 mm/s and 10 mV/cm calibration. The QTc duration was manually measured from the beginning of the QRS complex to the end of the T wave, defined as where the tangent of the downslope intersects the baseline, in either lead II, V_5, or V_6, with the largest result recorded. The Bazett correction ($QTc = QT / \sqrt{[RR]}$) was used to calculate QTc in milliseconds. If the patient was in atrial fibrillation, the average R-R interval over the duration of the ECG (10 seconds) was used.

Ablation technique and anesthesia considerations

All patients underwent induction of anesthesia with propofol, etomidate, or both, and general anesthesia was maintained with 2% sevoflurane. During PVI and routine clinical care, electrolytes were regularly assessed and replaced per institutional standard of care for magnesium ≤2.0 mg/dL and potassium ≤4.0 mEq/L. Antiarrhythmic drugs were continued or discontinued prior to ablation depending on treating physician preference.

All patients underwent PVI using either radiofrequency (RF) ablation or cryoballoon ablation, with some patients ablated using both modalities in a single procedure. Procedural management was largely uniform between the various operators. Described briefly, the left atrium was accessed using transseptal puncture and geometry and position of pulmonary veins mapped using a spiral mapping catheter (LASSO™ Catheter; Biosense Webster, Irvine, CA) using the CARTO mapping system. If cryoablation was performed (Arctic Front™ cryoballoon; Medtronic, Minneapolis, MN), each

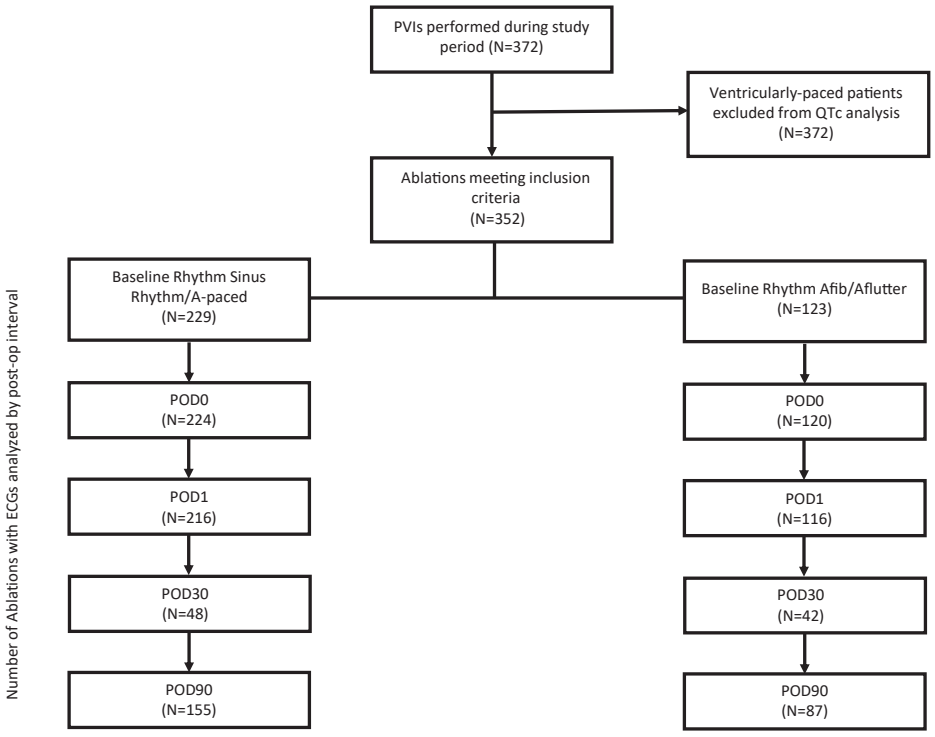

Figure 1 Study design, number of electrocardiograms analyzed according to baseline rhythm and operative interval. Afib = atrial fibrillation; Aflutter = atrial flutter; POD = postoperative day; PVI = pulmonary vein isolation; QTc = corrected QT interval.

pulmonary vein was occluded and ablated sequentially to achieve a temperature of -40°C to -50°C for 180 seconds per ablation until entrance and exit block was confirmed. If RF ablation was performed (ThermoCool™; Biosense Webster, Irvine, CA), wide-area, point-by-point circumferential ablation was performed until entrance and exit block was confirmed, using a power of no more than 40 W for no longer than 30 seconds per ablation.

If the patient was still in atrial fibrillation after bidirectional pulmonary vein block was confirmed, biphasic direct current cardioversion was performed using 200–360 J. After sinus rhythm was restored, bidirectional block was confirmed with pacing maneuvers. Additional typical/atypical flutter ablation or substrate modification using linear ablation, posterior wall isolation, or complex fractionated atrial electrogram ablation was performed based on the discretion and judgment of the treating physician. Patients were monitored overnight and discharged the following day pending clinical stability.

Statistical analysis

All statistical analyses were performed in SAS (University Edition; SAS, Cary, NC). Graphs were created using GraphPad Prism (Version 8; GraphPad, San Diego, CA). Descriptive statistics were reported as means and standard deviations for continuous variables and percentages for categorical variables. Paired *t* testing was used to compare ECG variables at POD0, POD1, POD30, and POD90 to baseline. All other continuous variables were compared using 2-tailed *t* test. Categorical variables were compared with χ^2 analysis for unpaired variables and McNemar test for paired variables. A multivariable logistic regression model was created to determine factors predictive of the composite QTc outcome. Variables were included in the multivariable analysis if the univariate logistic *P* value was $\leq$.10. Because the greatest proportion of patients experienced the composite outcome immediately postoperatively, logistic regression was performed using this postoperative time point. Lastly, multiple sensitivity analyses were performed for the QTc comparisons under varying conditions: Hodges ($QTc = QT + 1.75 \times [HR - 60]$), Fridericia ($QTc = QT / RR^{1/3}$), and Framingham ($QTc = QT + 0.156 \times [1 - RR]$) correction for QTc; baseline rhythm (atrial fibrillation/flutter vs sinus/atrial paced); patients with new QTc $\geq$500 ms post-PVI; and a subset of patients with complete ECG data set at baseline, POD0, POD1, POD30, and POD90 (n = 61). All probability values were 2-sided, and a *P* value cutoff of $\leq$.05 was used to determine statistical significance.

Results

A total of 372 atrial fibrillation ablations were performed over the studied period. Twenty patients were ventricularly paced from a cardiac implantable electronic device and were removed from the QTc analysis. Of the patients studied, ECGs were available for 352 (100%), 344 (97.7%), 332 (94.3%), 90 (25.6%), and 242 (68.8%) patients at baseline, POD0, POD1, POD30, and POD90, respectively. The number of ECGs analyzed by baseline rhythm and operative interval is shown in Figure 1.

Table 1 Baseline patient characteristics stratified by baseline rhythm

Clinical variable	Sinus/a-paced (n = 229, 65.1%)	Afib/flutter (n = 123, 34.9%)	*P* value
Demographics			
Age (years)	60.6 ± 11.6	62.8 ± 10.8	.083
Female sex, n (%)	60 (26.2%)	32 (26.0%)	.97
Comorbidities			
Hypertension	122 (53.3%)	68 (55.3%)	.72
Coronary artery disease	31 (13.6%)	16 (13.0%)	.88
Diabetes	27 (11.8%)	14 (11.4%)	.91
Congestive heart failure	58 (25.3%)	43 (35.0%)	.057
Ejection fraction			.16
EF >50%	179 (86.1%)	94 (79.7%)	
EF 40%–49%	15 (7.2%)	7 (5.9%)	
EF 30%–39%	6 (2.9%)	7 (5.9%)	
EF <30%	8 (3.9%)	10 (8.5%)	
Afib type			<.001*
Paroxysmal	141 (61.8%)	22 (17.9%)	
Persistent	87 (38.2%)	101 (82.1%)	
Patients on AAD	126 (55.0%)	50 (40.7%)	.010*
Amiodarone	52 (22.7%)	21 (17.1%)	.21
Non-amiodarone class 3	31 (13.5%)	16 (13.0%)	.89
Non-amiodarone class 1	43 (18.8%)	13 (10.6%)	.045*
Patients on rate control	185 (80.8%)	97 (78.0%)	.67
Beta blocker	147 (64.2%)	73 (59.4%)	.37
Calcium channel blocker	48 (21.0%)	30 (24.4%)	.46
Digoxin	8 (3.5%)	9 (7.3%)	.11
Baseline ECG parameters			
HR (beats/min)	61.6 ± 13.8	90.8 ± 21.1	<.001*
QRS (ms)	100.6 ± 19.8	99.0 ± 19.3	.45
QTc (ms)	440.8 ± 34.3	456.5 ± 41.9	<.001*
Operative factors			
Cryoballoon	126 (55.0%)	55 (44.7%)	.065
Radiofrequency	113 (49.3%)	78 (63.4%)	.011*
Concurrent atrial flutter ablation	46 (20.8%)	34 (27.0%)	.256
Additional substrate ablation	40 (17.5%)	31 (25.2%)	.085
Intraoperative DCCV	26 (11.8%)	72 (57.1%)	<.001*
First-time ablation	170 (74.2%)	97 (78.9%)	.33
Second-time ablation	42 (18.3%)	23 (18.7%)	.93
>Second-time ablation	16 (7.0%)	3 (2.4%)	.072

AAD = antiarrhythmic drug; Afib = atrial fibrillation; DCCV = direct current cardioversion; ECG = electrocardiogram; EF = ejection fraction; HR = heart rate.

Baseline patient clinical characteristics are shown in Table 1 stratified by atrial rhythm. A total of 229 (65.1%) patients were in sinus or an atrial paced direct current cardioversion; ECG rhythm prior to the procedure, and 123 (34.9%) patients were in atrial fibrillation or flutter. Demographics and comorbidities were not significantly different between the 2 groups. Patients presenting in atrial fibrillation or flutter were more likely to have persistent atrial fibrillation (82.1% vs 38.2%, $P < .001$), undergo RF ablation (63.4% vs 49.3%, $P = .011$), and require intraoperative direct current cardioversion (57.1% vs 11.8%, $P < .001$), and less likely to be on antiarrhythmic drug (AAD) therapy (40.7% vs 55.0%, $P = .010$), compared to patients presenting in sinus or an atrial paced rhythm. Patients presenting with atrial fibrillation or flutter also had a higher mean HR (90.8 ± 21.1 beats per minute [bpm] vs 61.6 ± 13.8 bpm, $P < .001$) and a longer mean baseline QTc (456.5 ± 41.9 ms vs 440.8 ± 34.3 ms, $P < .001$) compared to those in sinus or atrial paced rhythms.

Electrocardiographic outcomes

Mean QRS duration, HR, QTc, and QTc outcomes at the predetermined postoperative intervals are shown in Table 2 and stratified by atrial rhythm in Tables 3 and 4. The mean baseline QTc was 446.3 ± 37.8 ms for the entire cohort, 442.6 ± 36.0 ms for men, and 456.8 ± 40.9 ms for women. We observed a statistically significant increase in QTc compared to baseline on POD0 (+25.4 ms, $P < .001$) and POD1 (+10.2 ms, $P < .001$) compared to baseline using the Bazett correction, with similar results using different QTc correction methods (Figure 2). This difference was not statistically significant at day 30 or day 90 postablation.

The change in POD0 QTc remained significant in a sensitivity analysis of only sinus/a-paced patients, only afib/flutter patients, patients with newly prolonged QTc ≥500 ms, and a subset of patients with complete ECG data throughout their clinical course (Supplemental Appendix). Patients in sinus/a-paced rhythm had a mean increase in HR immediately postoperatively, while patients in afib/flutter had a mean decrease (+10.5 bpm vs -19.0 bpm, $P < .001$); despite this, the QTc on POD0 was significantly different compared to baseline in both subsets of patients.

There was a significant increase in the number of patients with QTc ≥500 ms with Bazett correction immediately postoperatively compared to baseline (15.1% vs 6.8%, $P < .001$) (Figure 3). A total of 10.5% of patients had a newly prolonged QTc ≥500 ms, 10.2% of patients had a ΔQTc ≥60 ms, and 19.2% of patients had either QTc ≥500 ms or ΔQTc ≥60 ms immediately post-PVI (Figure 4). A smaller percentage of patients experienced these outcomes with the Hodges, Fridericia, and Framingham correction, but the trend was similar (Figures 3 and 4). The percentage of patients with these QTc changes generally decreased on POD1, though a small percentage maintained these changes at POD90.

There was a significant increase in QRS compared to baseline at the various intervals for the entire cohort. The change at POD0, POD1, POD30, and POD90 was +0.2 ms ($P = .25$), +4.1 ms ($P = .006$), +1.0 ms ($P = .037$), and +1.9 ms ($P = .035$), respectively. In patients who had ΔQTc ≥60 ms, new QTc ≥500 ms, and new QTc ≥500 ms, or ΔQTc ≥60 ms on POD0, the change was +2.4 ms ($P = .07$), +3.4 ms ($P = .08$), and +3.4 ms ($P = .015$), respectively, compared to baseline.

Table 2 Electrocardiogram parameters in entire cohort with *P* values compared to corresponding baseline value

ECG parameter	Baseline (n = 352)	POD0 (n = 344, 97.7%)	POD1 (n = 332, 94.3%)	POD30 (n = 90, 25.6%)	POD90 (n = 242, 68.8%)
Rhythm					
Sinus/a-paced, n (%)	229 (65.1%)	338 (98.5%)	320 (86.4%)	66 (72.5%)	216 (89.3%)
Afib/Aflutter, n (%)	123 (34.9%)	5 (1.5%)	12 (3.6%)	25 (27.5%)	26 (10.7%)
HR (beats/min)	71.8 ± 21.7	72.0 ± 12.0 [$P = .82$]	71.3 ± 12.7 [$P = .62$]	76.0 ± 19.6 [$P = .49$]	69.4 ± 17.3 [$P = .11$]
QRS duration (ms)	100.0 ± 19.6	100.3 ± 19.2 [$P = .25$]	104.0 ± 30.9 [$P = .006$]	101.0 ± 19.5 [$P = .037$]	101.9 ± 20.8 [$P = .035$]
QTc duration (ms)	446.3 ± 37.8	471.7 ± 38.2 [$P < .001$]	456.5±35.0 [$P < .001$]	452.4 ± 33.5 [$P = .39$]	447.3 ± 40.0 [$P = .78$]
QTc ≥500 ms, n (%)	24 (6.8%)	*52 (15.1%)* [$P < .001$]	25 (7.8%) [$P = .24$]	8 (8.9%) [$P = .65$]	21 (8.7%) [$P = .47$]
New QTc ≥500 ms, n (%)	–	*36 (10.5%)*	16 (4.8%)	3 (3.3%)	10 (4.1%)
ΔQTc ≥60 ms, n (%)	–	*35 (10.2%)*	15 (4.5%)	6 (6.6%)	0 (0%)
New QTc ≥500 ms or ΔQTc ≥60 ms, n (%)	–	*66 (19.2%)*	24 (7.2%)	7 (7.8%)	10 (4.1%)

Afib = atrial fibrillation; Aflutter = atrial flutter; ECG = electrocardiogram; HR = heart rate; POD = postoperative day.

On univariate analysis, only sex was significantly associated with the composite outcome (Table 5). Multivariable logistic regression results for the composite outcome are shown in Figure 5. Sex, history of coronary artery disease, use of any antiarrhythmic agent, use of amiodarone, additional substrate modification, and second-time ablation met inclusion criteria for the multivariate analysis, but only female sex (odds ratio [OR] = 1.82, 95% confidence interval [CI] = 1.01–3.29, $P = .047$) and history of coronary artery disease (OR = 2.16, 95% CI = 1.03–4.55, $P = .042$) independently predicted risk of QTc prolongation ≥500 ms or ΔQTc ≥60 ms. The model showed moderate predictive value with a c-statistic of 0.68.

Clinical outcomes

There were no episodes of TdP, sustained ventricular tachycardia requiring medical intervention, or ventricular fibrillation in any patient undergoing PVI. Two of the 372 patients (0.54%) died in the 90-day follow-up period. The first patient died unexpectedly at home without a clear cause of death on autopsy. This patient had a baseline QTc of 413 ms that increased to 479 ms on POD0. He was discharged the day of his ablation and died 1 week later, so there were no data available for POD1, POD30, or POD90. The second patient's death was noncardiac, as the patient died from hypoxemic respiratory failure in the setting of interstitial lung disease.

Discussion

Our study systematically evaluated ventricular repolarization changes after catheter ablation for atrial fibrillation. We show that there is a significant increase in QTc in the postoperative setting. The QTc interval is maximally elevated immediately postoperatively and appears to return to baseline within 30 days. A significant percentage of patients developed a new QTc duration ≥500 ms immediately

Table 3 Electrocardiogram parameters in patients with baseline sinus/atrial paced rhythm with *P* values compared to corresponding baseline value

ECG parameter	Baseline (n = 229)	POD0 (n = 224, 97.8%)	POD1 (n = 216, 94.3%)	POD30 (n = 48, 20.9%)	POD90 (n = 155, 67.7%)
HR (beats/min)	61.6 ± 13.8	72.1 ± 12.4 [$P < .001$]	69.8 ± 12.2 [$P < .001$]	74.1 ± 19.3 [$P < .001$]	68.3 ± 15.2 [$P < .001$]
QRS duration (ms)	100.6 ± 19.8	100.6 ± 20.6 [$P = .94$]	104.8 ± 36.0 [$P = .050$]	100.0 ± 21.1 [$P = .31$]	101.8 ± 20.9 [$P = .79$]
QTc duration (ms)	440.8 ± 34.3	472.4 ± 38.6 [$P < .001$]	454.1 ± 33.8 [$P < .001$]	448.8 ± 28.8 [$P = .67$]	444.8 ± 34.5 [$P = .25$]
QTc ≥500, n (%)	11 (4.8%)	*35 (15.6%)* [$P < .001$]	15 (6.9%) [$P = .55$]	3 (6.3%) [$P = 1.0$]	10 (6.5%) [$P = .53$]
New QTc ≥500 ms, n (%)	–	*25 (11.6%)*	11 (5.1%)	0 (0.0%)	6 (3.9%)
ΔQTc ≥60 ms, n (%)	–	*25 (11.2%)*	6 (2.8%)	3 (6.3%)	0 (0.0%)
New QTc ≥500 ms or ΔQTc ≥60 ms, n (%)	–	*46 (20.5%)*	13 (6.0%)	3 (6.3%)	6 (3.9%)

Afib = atrial fibrillation; Aflutter = atrial flutter; ECG = electrocardiogram; HR = heart rate; POD = postoperative day.

Table 4 Electrocardiogram parameters in patients with atrial fibrillation / atrial flutter with *P* values compared to corresponding baseline value

ECG parameter	Baseline (n = 123)	POD0 (n = 120, 97.6%)	POD1 (n = 116, 94.3%)	POD30 (n = 42, 34.1%)	POD90 (n = 87, 70.1%)
HR (beats/min)	90.8 ± 21.1	71.8 ± 11.2 [$P < .001$]	74.1 ± 13.0 [$P < .001$]	78.3 ± 19.9 [$P = .013$]	71.3 ± 20.6 [$P < .001$]
QRS duration (ms)	98.9 ± 19.3	99.6 ± 16.4 [$P = .032$]	102.6 ± 17.9 [$P < .001$]	102.1 ± 17.7 [p=0.056]	102.1 ± 20.6 [p<0.001]
QTc duration (ms)	456.4 ± 41.9	470.3 ± 37.7 [$P < .001$]	461.0 ± 36.7 [$P = .076$]	456.6 ± 38.0 [$P = .64$]	451.5 ± 48.2 [$P = .17$]
QTc ≥500 ms, n (%)	13 (10.6%)	*17 (14.2%)* [$P = .22$]	11 (9.5%) [$P = 1.0$]	5 (11.9%) [$P = .65$]	11 (12.6%) [$P = .71$]
New QTc ≥500 ms, n (%)	–	*11 (9.2%)*	5 (4.3%)	3 (7.1%)	4 (4.6%)
ΔQTc ≥60 ms, n (%)	–	*10 (8.3%)*	9 (7.8%)	3 (7.1%)	0 (0.0%)
New QTc ≥500 ms or ΔQTc ≥60 ms, n (%)	–	*20 (16.7%)*	11 (9.5%)	4 (9.5%)	4 (4.6%)

Afib = atrial fibrillation; Aflutter = atrial flutter; ECG = electrocardiogram; HR = heart rate; POD = postoperative day.

after the procedure, and a similar percentage developed an increased QTc of ≥60 ms. While most return to baseline, a small but significant proportion of patients continued to have clinically significant QTc changes up to 90 days post-ablation. Female sex and history of coronary artery disease were independent predictors of significant QTc changes, increasing the risk of ΔQTc ≥60 ms or QTc duration ≥500 ms by approximately 2-fold. Notably, baseline QTc, adjunct ablation, perioperative use of QT-prolonging medications such as antiemetics and proton pump inhibitors, and postablation AAD use were not associated with the composite outcome. Our results are similar to a smaller study by Chikata and colleagues[3] that demonstrated that QTc may be prolonged up to 3 months after PVI and in increased risk in women in a retrospective study of 117 patients with paroxysmal atrial fibrillation presenting in sinus

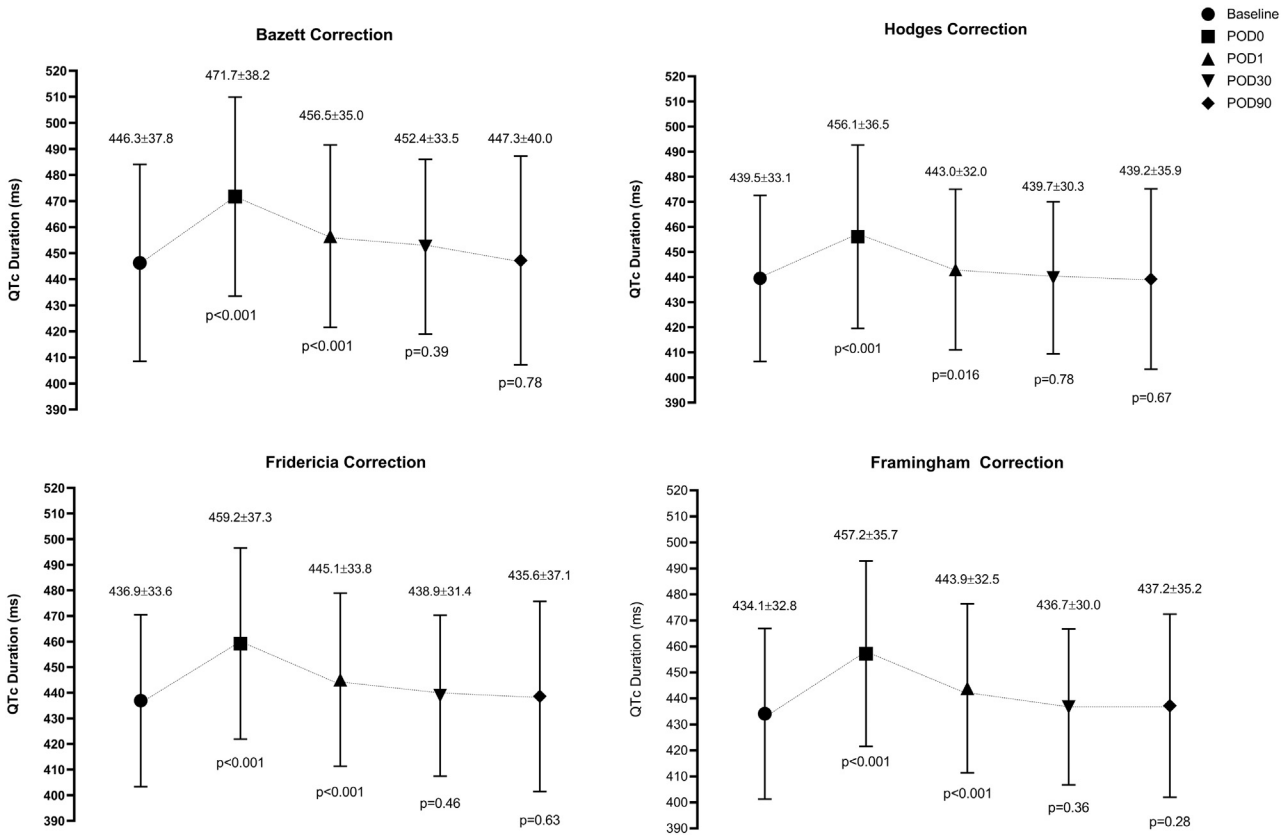

Figure 2 Mean corrected QT interval (QTc) at baseline and postoperative intervals of entire cohort. QTc duration remains significantly elevated compared to baseline at postoperative day (POD)0 and POD1 and returns to baseline by POD30.

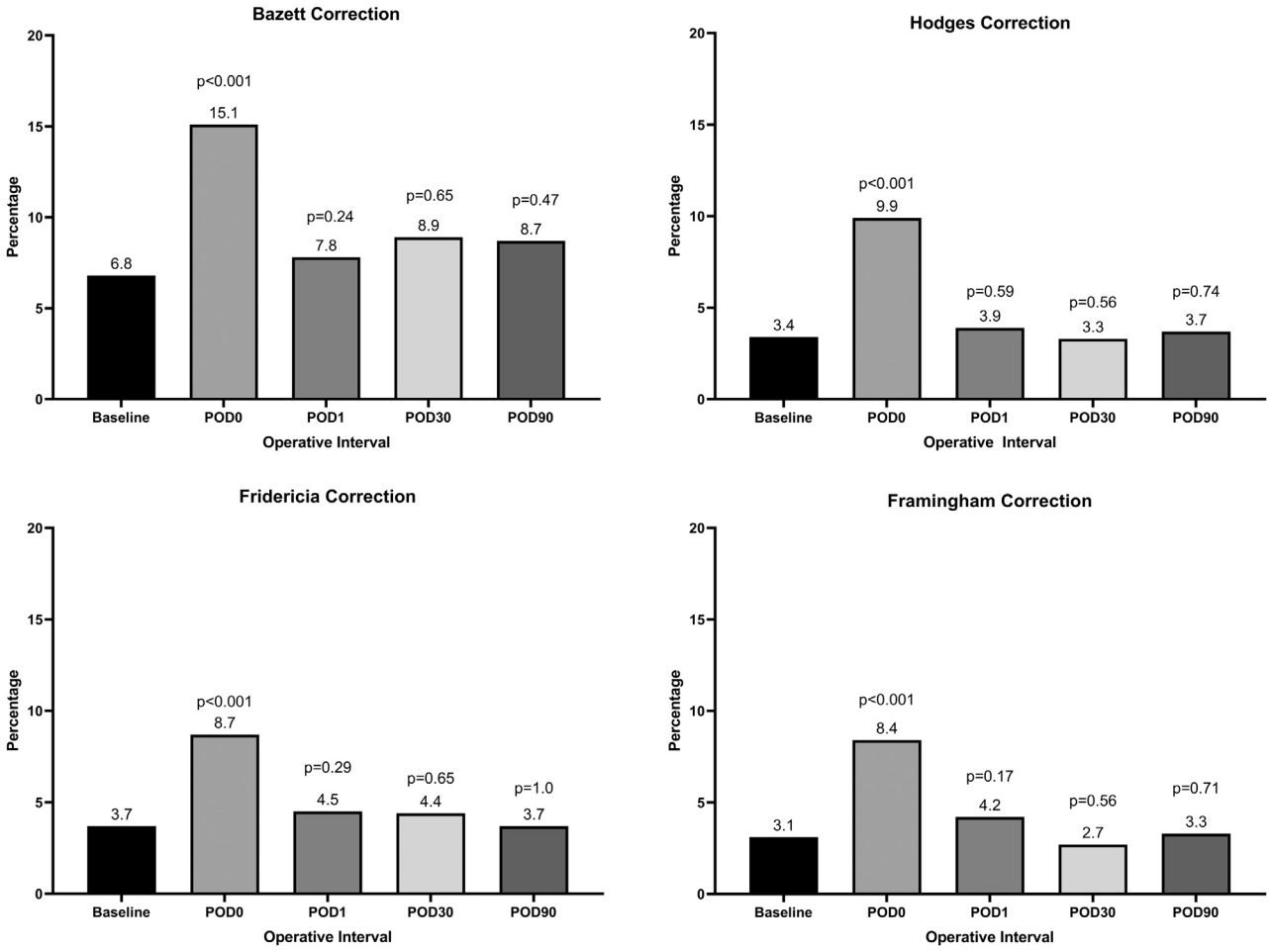

Figure 3 Percentage of patients with QTc $\geq$ 500 at postoperative intervals. With all correction methods, the number of patients with postoperative QTc $\geq$500 was greatest at POD0. POD = postoperative day.

rhythm. Our study adds to theirs by showing that patients with atrial fibrillation/flutter also have significant QTc changes postablation and that coronary artery disease may also increase this risk.

Catheter ablation is now accepted as standard of care for atrial fibrillation patients with AAD-resistant, symptomatic atrial fibrillation. However, the risk of significant ventricular arrhythmias in association with post-PVI QTc prolongation has not been well studied. Despite the observed percentage of patients with QTc $\geq$500 ms immediately postablation in our study, we did not observe any instances of cardiac arrest or clinically significant ventricular arrhythmias. One patient died suddenly during the 90-day follow-up period, but an arrhythmic cause of death was not firmly established in this patient. This patient showed a significant 60 ms increase in baseline QTc immediately post-PVI and may have benefited from additional monitoring. Though our sample size was 352 patients, our study may have been underpowered to detect clinically significant ventricular arrhythmias. Our cohort also had high rates of beta-blocker use, which may have been protective against ventricular arrhythmias. The rate of ventricular arrhythmias after PVI remains unknown, and future large-scale studies are required to determine the incidence, which may require the use of ambulatory ECG monitoring.

Overall, the results of our study suggest that the proarrhythmic ECG changes seen postablation in our cohort are likely well tolerated, possibly owing to their transient nature. However, to minimize the risk of postprocedural cardiac arrest, we suggest that patients with marked QTc prolongation or others who are on QT-prolonging agents be monitored postoperatively with serial ECGs until the QTc interval demonstrates a downward or stable trend. High-risk populations may include women, those with coronary artery disease, patients with significant hypokalemia and hypomagnesemia, and patients being initiated de novo on AAD therapy. Based on our results, clinicians can expect the QTc duration to return to baseline within 1 month of PVI. Whether AAD continuation or initiation in high-risk patients remains uncertain, as our study was not designed to answer this question, but we did not find a significant association on multivariable regression with new AAD use and significant QTc change. This may be due to our study being underpowered to detect differences in new AAD use between groups.

The Bazett formula was used as the primary QTc correction method and in our multivariate model using the average

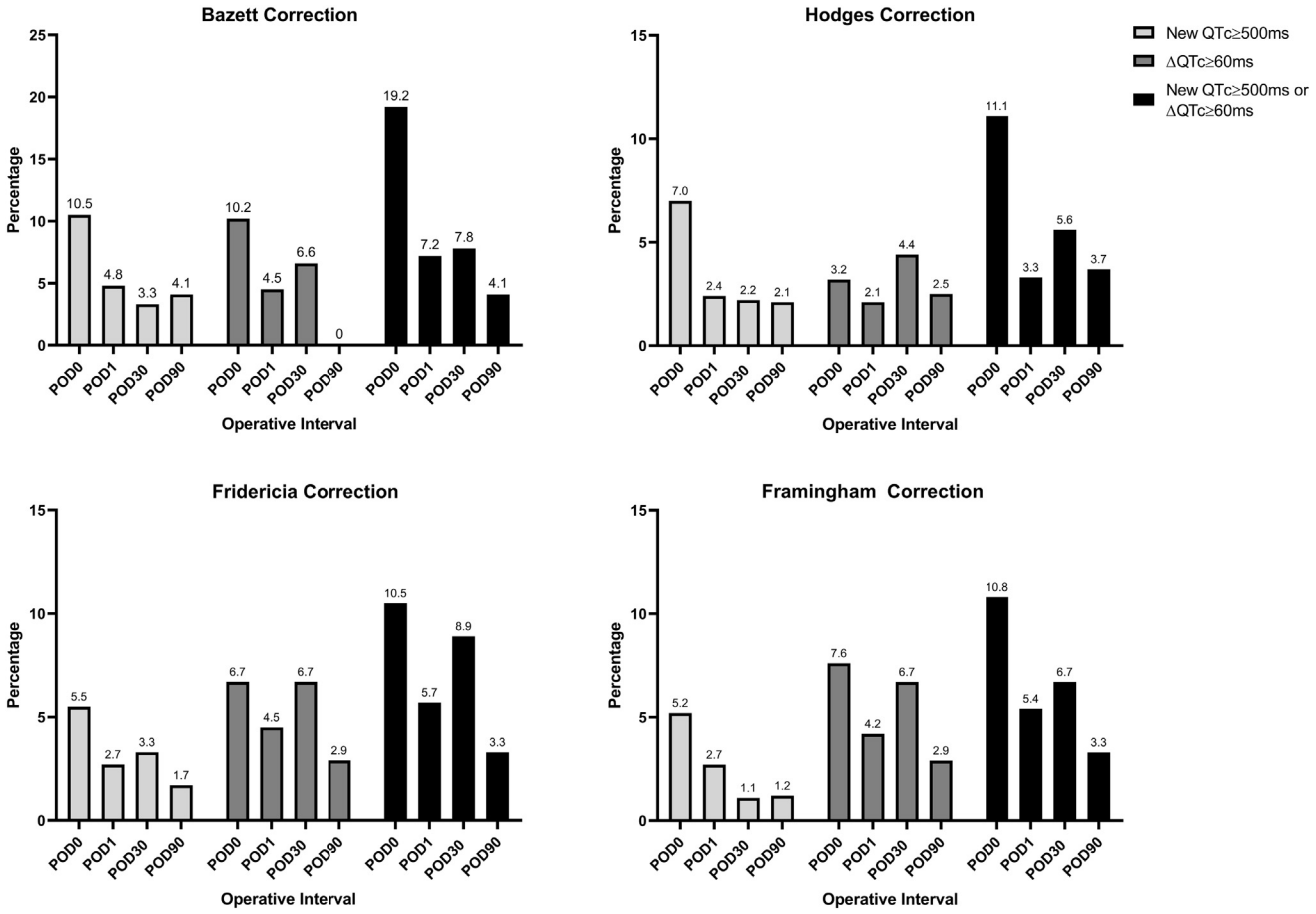

Figure 4 Percentage of patients experiencing new, clinically significant QTc changes at postoperative intervals. POD = postoperative day.

R-R interval for patients in atrial fibrillation owing to its widespread use in our hospital system. The optimal method to correct for QTc remains unknown. Recently, the Fridericia and Framingham formulas have been shown to be superior to the Bazett formula in predicting all-cause mortality in healthy patients, with the Bazett correction overestimating the QTc at high heart rates.[12] Despite these differences, we found a similar increase in QTc at POD0 with the Hodges, Fridericia, and Framingham corrections and sensitivity analysis stratified by baseline rhythm. Thus, the QTc changes likely occurred independently of HR and heart rhythm changes postoperatively. While the POD1 QTc was not significant in patients with atrial fibrillation/flutter and in the subset of patients with complete data, the small sample of these subgroups may have limited our ability to detect a difference.

There are several possible mechanisms for QTc prolongation after PVI. One possible mechanism includes temporary stimulation of or damage to atrial ganglionic plexi that reside on the epicardial fat pads. It is becoming increasingly clear that autonomic nervous system changes are responsible for atrial fibrillation propagation, and ganglionic plexus ablation has been a target for managing patients with persistent atrial fibrillation.[13,14] Studies in which ganglionic plexi were ablated in canines demonstrated ventricular depolarization and repolarization abnormalities with prolonging of both the effective refractory period and action potential duration.[7] Another possible contributor to QTc prolongation is general anesthesia. Our cohort underwent general anesthesia with sevoflurane, and volatile anesthetic agents are known to cause QTc prolongation intraoperatively. However, it is unlikely that volatile medications, which are rapidly eliminated from the body, would prolong QTc beyond the intraoperative course.[15–17] In addition, patients undergoing PVI without general anesthesia also had a similar increase in QTc in the study by Chikata and colleagues.[3] Increase in sympathetic tone[18,19] or decreased parasympathetic tone[20] after surgery could also influence the QTc. However, and the autonomic changes in PVI patients in the periablation period are complex and may include a combination of competing sympathetic and parasympathetic factors such as sedation, pain, ablation-related inflammation, and direct damage to autonomic ganglia.

Our study has certain limitations. First, the risk factors associated with QTc prolongation must be interpreted in the context of this study's retrospective nature and inability to completely account for confounding factors, including management of postoperative QTc prolongation. Second, while all patients uniformly received PVI, variations in

Table 5 Clinical and procedural factors associated with QTc ≥500 ms or ΔQTc ≥60 ms on postoperative day 0 on univariate analysis

Variable	No QTc ≥500 ms or ΔQTc ≥60 ms (n = 278)	QTc ≥500 ms or ΔQTc ≥60 ms (n = 66)	*P* value
Demographics			
Age (years)	61.0 ± 11.2	63.3 ± 11.6	.13
Female sex	66 (23.7%)	24 (36.4%)	.036*
Comorbidities			
Hypertension	145 (52.2%)	40 (60.6%)	.22
Coronary artery disease	31 (11.2%)	13 (19.7%)	.063
Diabetes	34 (12.2%)	6 (9.1%)	.47
Congestive heart failure	81 (29.1%)	17 (25.8%)	.58
Ejection fraction			.62
EF >50%	212 (82.8%)	55 (87.3%)	
EF 40%–49%	18 (7.0%)	3 (4.8%)	
EF 30%–39%	12 (4.7%)	1 (1.6%)	
EF <30%	14 (5.5%)	4 (6.4%)	
Afib type			.22
Paroxysmal	126 (45.3%)	35 (53.9%)	
Persistent	152 (54.7%)	30 (46.2%)	
Baseline ECG parameters			
Rhythm			.39
Sinus/a-paced	178 (64.0%)	46 (69.7%)	
Afib/flutter	100 (36.0%)	20 (30.3%)	
Baseline HR (ms)	72.5 ± 20.9	68.2 ± 25.3	.15
Baseline QRS (ms)	99.4 ± 18.4	101.1 ± 95.6	.53
Baseline QTc (ms)	445.5 ± 33.5	448.7 ± 51.5	.54
Patients on AAD	135 (48.6%)	36 (54.6%)	.081
Amiodarone	53 (19.1%)	19 (28.8%)	.10
Non-amiodarone class 3	37 (13.3%)	8 (12.1%)	.80
Non-amiodarone class 1	45 (16.2%)	9 (13.6%)	.61
AAD after ablation	149 (53.6%)	35 (53.0%)	.93
New AAD	33 (11.9%)	4 (6.1%)	.17
AAD continued	116 (41.7%)	31 (47.0%)	.44
Patient on rate control	221 (80.0%)	56 (84.9%)	.33
Beta blocker	173 (62.2%)	43 (65.2%)	.66
Calcium channel blocker	60 (21.6%)	17 (25.8%)	.47
Digoxin	14 (5.0%)	3 (4.6%)	.87
Operative factors			
Perioperative antiemetic	247 (89.2%)	55 (84.6%)	.30
Perioperative PPI	207 (76.7%)	49 (77.8%)	.85
Cryoballoon	141 (50.7%)	37 (56.1%)	.44
Radiofrequency	153 (55.0%)	32 (48.5%)	.34
Concurrent atrial flutter ablation	65 (23.4%)	16 (24.2%)	.88
Additional substrate ablation	61 (21.9%)	8 (12.1%)	.073
Intraoperative DCCV	81 (29.1%)	14 (21.2%)	.20
First-time ablation	207 (74.5%)	55 (83.3%)	.13
Second-time ablation	55 (19.8%)	7 (10.6%)	.081
>Second-time ablation	16 (5.8%)	3 (4.6%)	.70

AAD = antiarrhythmic drug; Afib = atrial fibrillation; DCCV = direct current cardioversion; ECG = electrocardiogram; EF = ejection fraction; HR = heart rate; PPI = proton pump inhibitor.

Additional factors included in the multivariate model—based on entry criteria of univariate *P* value ≤.05—were history of diabetes and coronary artery disease, amiodarone use, any AAD use, additional substrate ablation, and repeat ablation.

ablation technique and duration of ablation time were not tracked in our study. Third, our study did not assess electrolyte shifts during postoperative care on QTc, though electrolyte levels were regularly measured and replenished during routine operative care, and a similar study by Chikata and colleagues[3] did not find an independent association between electrolyte changes and QTc prolongation. Similarly, we did not study postoperative opiate use, but this was not independently associated with QTc prolongation in the study by Chikata and colleagues. Fourth, this is a single-center experience in a tertiary hospital with relatively homogenous care through the operative course, including general anesthesia for all patients and postoperative monitoring in the hospital, limiting generalizability. Future studies could compare patients undergoing ablations of different arrhythmias under general anesthesia and conscious sedation when studying QTc changes. This would inform us on whether these findings are unique to AF ablation and/or unique to a certain

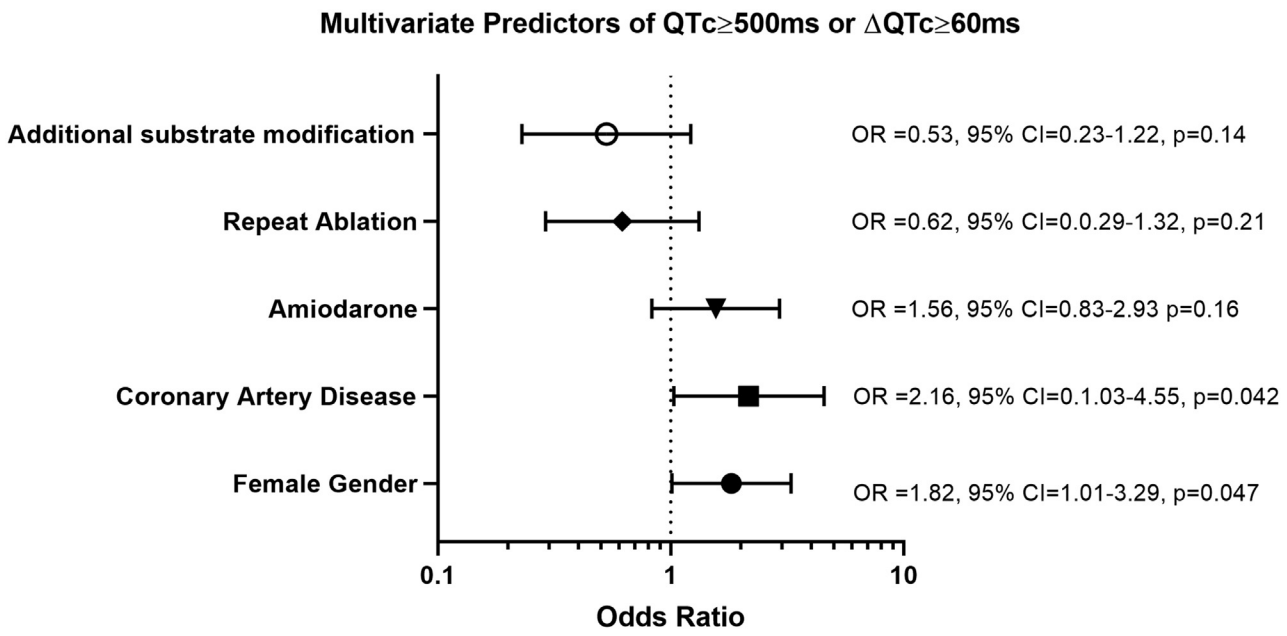

Figure 5 Multivariate predictors for developing new QTc prolongation ≥500 ms or ΔQTc ≥60 ms. Female sex and history of coronary artery disease were independently associated with new, clinically significant QTc changes.

mode of anesthesia, and thus provide insights into the mechanistic cause of QTc prolongation. Lastly, availability of ECG data was incomplete across the cohort at POD30 and POD90, which may limit our ability to detect significant differences at these time points.

Conclusion

A statistically significant increase in QTc is noted transiently post-PVI. This increase in QTc appears to be maximum in the immediate postoperative period and returns to baseline at 1 month. Despite the large percentage of patients with clinically significant QTc changes, PVI does not appear to provoke clinically significant ventricular arrhythmias. Nonetheless, clinicians should proceed with watchful caution when prescribing AADs during the immediate postablation period.

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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Disclosures

The authors have no conflicts to disclose.

Authorship

All authors attest they meet the current ICMJE criteria for authorship.

Patient Consent

As the study data were deidentified, patient consent was waived.

Ethics Statement

This study was approved by the University of Washington Institutional Review Board and all study protocols conducted in accordance with the Declaration of Helsinki.

Disclaimer

Given his role as Associate Editor of *Heart Rhythm O*^{2}, Nazem Akoum had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Dennis H. Lau.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hroo.2021.08.004.

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