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QT Interval Prolongation and Torsade De Pointes in Patients with COVID-19 treated with Hydroxychloroquine/Azithromycin

Ehud Chorin MD PhD[1*], Lalit Wadhwani MD[1], Silvia Magnani MD[2], Matthew Dai MD[1], Eric Shulman MD[1], Charles Nadeau-Routhier MD[1], Robert Knotts MD[1], Roi Bar-Cohen MD[1], Edward Kogan MD[1], Chirag Barbhaiya MD[1], Anthony Aizer MD[1], Douglas Holmes MD[1], Scott Bernstein MD[1], Michael Spinelli MD[1], David S. Park MD PhD[1], Carugo Stefano MD PhD[2], Larry A. Chinitz MD[1], Lior Jankelson MD PhD[1*]

From the [1]Leon H. Charney Division of Cardiology, Cardiac Electrophysiology, NYU Langone Health, New York University Grossman School of Medicine, NY, USA, and

[2]Division of Cardiology, Department of Health Science, San Paolo Hospital, University of Milan, Milan, Italy.

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***Corresponding authors**:

Lior Jankelson MD PhD
NYU Langone Health, New York University School of Medicine
560 1st Avenue
New York, NY 10016
Lior.jankelson@nyumc.org

Ehud Chorin MD PhD
NYU Langone Health, New York University School of Medicine
560 1st Avenue
New York, NY 10016
Ehud.chorin@nyumc.org

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Abstract

Background: There is no known effective therapy for patients with COVID-19. Initial reports suggesting the potential benefit of Hydroxychloroquine/Azithromycin (HY/AZ) have resulted in massive adoption of this combination worldwide. However, while the true efficacy of this regimen is unknown, initial reports have raised concerns regarding the potential risk of QT prolongation and induction of torsade de pointes (TdP).

Objective: to assess the change in QTc interval and arrhythmic events in patients with COVID-19 treated with HY/AZ

Methods: This is a retrospective study of 251 patients from two centers, diagnosed with COVID-19 and treated with HY/AZ. We reviewed ECG tracings from baseline and until 3 days after completion of therapy to determine the progression of QTc and incidence of arrhythmia and mortality.

Results: QTc prolonged in parallel with increasing drug exposure and incompletely shortened after its completion. Extreme new QTc prolongation to > 500 ms, a known marker of high risk for TdP had developed in 23% of patients. One patient developed polymorphic ventricular tachycardia (VT) suspected as TdP, requiring emergent cardioversion. Seven patients required premature termination of therapy. The baseline QTc of patients exhibiting extreme QTc prolongation was normal.

Conclusion: The combination of HY/AZ significantly prolongs the QTc in patients with COVID-19. This prolongation may be responsible for life threating arrhythmia in the

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form of TdP. This risk mandates careful consideration of HY/AZ therapy in lights of its unproven efficacy. Strict QTc monitoring should be performed if the regimen is given.

Introduction

The evidence supporting effective drug therapy for COVID-19 is limited. In vitro studies have suggested that Hydroxychloroquine alone and in combination with Azithromycin could be a viable therapy [1, 2]. A small, controversial study enrolling 26 treated patients and 16 non-randomized controls showed that HY/AZ shortened the viral shedding of SARS-CoV-2 [3]. Based on this, clinicians in many countries have begun using these medications, and multiple randomized trials are ongoing [4]. However, HY and AZ have each been independently shown to increase the risk for QT interval prolongation, drug-induced torsade de pointes (TdP), and sudden cardiac death (SCD) [5-8]. We recently reported QT prolongation in a preliminary series of 84 patients with COVID-19 treated with HY/AZ [9]. Here we report a study from two centers evaluating the effects of HY/AZ on the QT interval and the arrhythmic risk in patients with COVID-19.

Methods

This is a retrospective study including 251 consecutive adult patients hospitalized at NYU Langone Health (211 patients) and at San Paolo University Hospital (40 patients) with COVID-19 disease, treated with the combination of HY/AZ. Patients with a baseline ECG and at least one ECG performed after medication administration were

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included. Of 325 patient screened, we excluded 40 (12.3%) patients without baseline ECG and 34 (10.4%) patients without follow up ECG.

Of the 211 patients from the NYU site, 84 were reported in our recent publication [9]. Hydroxychloroquine was given orally at 400 mg BID for one day (loading dose) followed by 200 mg BID for 4 days. Azithromycin was given orally at a dose of 500 mg daily for 5 days. For QTc measurement, five cardiologists trained and experienced in QT measurement performed all electrocardiographic measurements. The QT interval was measured using the "Tangent" method [10]. Briefly, a tangent is drawn to the steepest last limb of the presumed T-wave to define the end of the T-wave as the intersection of this tangent with the baseline. QTc was calculated from the QT and RR intervals using the Bazetts' formula. The QRS interval was measured from the onset of the Q wave, or R wave if no Q wave was visible, to the J point. JTc interval was calculated by subtracting the QRS duration from the QTc interval (QTc – QRS).

For quality assurance, QT measurements were validated by a senior electrophysiologist experienced in QT measurements who repeated the measurement at arbitrary times, corroborating ~10% (100/978) of all QT measurements. This validation showed very high agreement between measurements, with a correlation coefficient of R=0.95 ($p<0.01$). The closing date of follow-up was April 15th 2020. The primary endpoint was extreme QTc prolongation. This included absolute QTc >500ms (or JTc >410ms to adjust for patients with QRS>120 ms), known marker of high risk for malignant arrhythmia and sudden

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cardiac death [11-13], or QTc prolongation of >60 ms, another high risk marker regardless of baseline QRS[14, 15].

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 26, and figures were constructed using GraphPad Prism 8. Continuous variables are expressed as mean ± standard deviation, and categorical variables are expressed as percentages (95% confidence interval). Normality of data samples was assessed using Shapiro-Wilk test. Two sample hypothesis testing for continuous variables was performed using Student's t-test if samples had normal distributions, Mann-Whitney U test if samples did not have normal distributions, or paired samples t-test for paired samples. Two sample hypothesis testing for categorical variables was performed using Fisher's exact test. For Figure 2A, a mixed-effects analysis with Geisser-Greenhouse correction was performed, followed by Dunnett's multiple comparisons test to compare each day's QTc to the baseline QTc. For Figure 2B, one sample t-test (if samples were normally distributed) or one sample Wilcoxon signed rank test (if samples were not normally distributed) was performed to compare each sample against a delta QTc of 0 ms (i.e. no change from baseline), and p values were adjusted using the Holm-Bonferroni method to $\alpha < 0.05$. Univariate and multivariate logistic regression were performed to identify predictors of prolonged JTc, delta QTc, and QTc. The univariate predictors with $p < 0.05$ and greatest clinical utility were selected for subsequent multivariate analysis, as allowed by our sample size.

The study was performed according to the NYU Institutional Review Board and Quality Improvement initiative and the University Hospital of Milan Institutional

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Review Board guidance in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Results

We included 251 patients in our cohort with a maximal follow up of 8 days and mean ECG follow up time of 5.2 ± 2 days (Table 1). The median age was 64±13 years and 75% were male. Forty four (17.5%) patients died of respiratory or multi-organ failure. One patient with extreme QTc prolongation developed TdP and required emergent cardioversion (Figure 1), representing an arrhythmic risk of 0.4%. QTc interval prolonged from a baseline of 439 ± 29 ms to a maximal value of 473 ± 36 ms ($p<0.001$) which occurred on day 4.1 ± 2 of therapy) in the general cohort (Figure 2). JTc prolonged from a baseline of 342±25 ms to a maximal value of 375±35 ms which occurred on day 4.1±1.9. For patients with QRS < 120 ms, QTc prolonged from a baseline of 434 ± 25 to a maximum of 469 ± 34 ms, which occurred on day 4 ± 1.9. The individual change between baseline and maximal QTc is presented in figure 3. Figure 4 represents the distribution of QTc ranges at each day. Of note, In 58 of 251 (23%) patients, at least one measure of extreme QTc prolongation was observed. Specifically, QTc>500 msec was seen in 28 of 222 (13%) patients with QRS<120. JTc>410 was seen in 4 of 29 (14%) patients with QRS >120, and ΔQTc>60 was seen in 51 of 251 (20%) patients with any QRS. These numbers include 25 patients who had more than one of these endpoints. Thirty five (60%) of the 58 patients who met the composite endpoint were not on any other QTc prolonging medication. In this high risk group, QTc increased from a baseline of 431 ± 32 to 513 ± 38 ms and JTc increased from 335±28 to 417± ms ($p<0.01$ for both). In 8 patients, extreme QTc

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prolongation triggered discontinuation of therapy prematurely, including the patient who developed TdP where therapy was halted on day 4. In 29 (11.5%) patients, baseline QRS was more than 120 ms. The baseline JTc and the maximal ΔJTc were similar between patients with and without QRS≥120 (Table 2). On multivariate analysis, baseline QTc and co-administration of Amiodarone were significant predictors of QTc > 500 ms, while baseline Creatinine and co-administration of Amiodarone were predictors of ΔQTc > 60 ms (Tables 3 and 4). The predictors of extreme JTc prolongation > 410 ms included baseline JTc and Creatinine (Supplementary Table 1). Patients with extreme QTc prolongation had lower body weight, greater frequency of kidney disease, and greater Amiodarone exposure (Supplementary Table 2).

Discussion

Drug-induced QT prolongation is an important substrate for TdP, a potentially lethal polymorphic VT. In our study of 251 patients with COVID-19, we found high incidence of QTc prolongation, with at least one documented polymorphic VT (suspected TdP) for a rate of 0.4%. To put the incidence of TdP in perspective, the risk of TdP induction by Sotalol is estimated at 0.1% [16]. Due to this risk, Sotalol is introduced under ECG monitoring in the hospital for at least 3 days. In our study, we observed QTc prolongation in parallel with increasing HY/AZ exposure, which partially shortened after medication cessation. For example, the proportion of patients with QTc > 500 ms was 20% at day 4 after completion of HY/AZ therapy and declined to 10% one day later. Baseline QTc/JTc, Creatinine level and co-

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administration of Amiodarone were significant predictors of extreme QTc/JTc prolongation and ΔQTc > 60 ms. We show that the effect on the QTc was driven entirely by prolonging the repolarization and regardless of QRS, as evident by the corresponding JTc prolongation. In this regard, it is worth mentioning that there is limited data regarding high arrhythmic risk markers in patients with QRS >120 ms and QTC prolongation. We utilized QTc change by > 60 ms as a marker, a cutoff that was initially proposed in an algorithm designed to automatically detect QTc prolongation taking into account the normal variation in QTc [17]. In addition we utilized a cutoff of JTc>410 ms as the correlate of QTc>500 ms for patients with wide QRS, based on the deduction of the mean QRS value we found in our patients with normal QRS, which was 90 ms. Previous information on the potential proarrhythmic effect of the combination Chloroquine/Hydroxychloroquine and Azithromycin is limited. In a randomized, placebo-controlled parallel trial in 116 young healthy controls receiving Chloroquine alone or in combination with Azithromycin, co-administration increased the QTc interval (Fridericia) by up to 14 ms [18, 19]. However, the risk for drug induced TdP is substantially higher in hospitalized patients. This, is due to greater prevalence of other risk factors for TdP, including older age, presence of underlying heart disease, genetic factors [20], electrolyte disturbances and co-treatment with other QT prolonging medications [21-24]. Indeed, in a recent study assessing Chloroquine therapy in COVID-19 patients, extreme QT prolongation and excess cardiac mortality in the higher dose arm led to premature interruption of the regimen [25]. Concordantly, recently published studies confirmed a QT prolonging effect of HY/AZ ranging between 23 to 41 ms (Supplementary Table 3). In the current study, we found a significant proportion of patients with extreme QTc prolongation,

23%, with at least one polymorphic VT requiring cardioversion. Another 7 patients who developed extreme QTc prolongation by day 3 had the treatment stopped, possibly preventing additional arrhythmic events. Interestingly, the coupling interval of the arrhythmia initiating beat observed in our study was ~380 ms, which is shorter than expected for TdP [26]. In this regard, Azithromycin has been shown to induce short-coupled polymorphic VT regardless of QT prolongation [27]. It is thus impossible to be certain about the nature of the arrhythmia. Since this polymorphic VT took place at the time of significant QT prolongation, it is reasonable to assume that HY/AZ played an important pro-arrhythmic role. However, in view of its relatively short coupling interval, it is not clear if this is true TdP or a polymorphic VT triggered by Azithromycin via increased sodium current. The alarming proportion of COVID-19 patients developing extreme QT prolongation with HY/AZ therapy in our study can be explained by the specific characteristics of this population, which includes older age, greater prevalence of underlying and acute renal failure and co-administration of additional QT prolonging medications, particularly Amiodarone.

Recently published guidance statements addressing QTc surveillance and arrhythmic risk in COVID-19 patients are based on LQTS risk stratification principals and include pretreatment assessment of the QTc, considering stopping other QTc prolonging medications, and providing special attention to those with highest risk features [15, 28, 29]. Yet, our findings suggest that risk stratification of patients with COVID19 may be more complex. For example, we found that the baseline QTc in patients with extreme QTc prolongation was only 431 ± 32 ms, within the “normal” QTc range. Moreover, 42 (72%) of the 58 patients in the high risk group had a baseline QTc <450

and JTc < 350 ms. Additionally, it is important to consider that even careful monitoring of the QT interval may only partially mitigate the risk for TdP. This is because arrhythmia often occurs in the setting of sudden, intermittent changes in the R-R interval, such as when PVCs, APCs or pauses occur. In these cases, TdP can present even if the QTc in only mildly prolonged at baseline [30]. We therefore suggest that individual risk/benefit assessment should be applied before treating with HY/AZ. We recommend daily ECG monitoring, with reassessment of the therapy if high risk markers appear (QTc >500 ms or ΔQTc > 60 ms). For this, triggered alerting systems may be applied [31]. Finally, we observed only partial resolution of the QTc at 3 days after completion of therapy. This may be attributed to the prolonged half-life of Hydroxychloroquine, which is approximately 20 days. This finding requires special attention when considering discharging patients receiving HY/AZ or if outpatient treatment with HY/AZ is planned.

Conclusions

Treatment of COVID-19 with HY/AZ prolongs the QTc to an extreme degree in a significant proportion of patients, increasing the risk for TdP. Risk/benefit considerations should be carefully and individually evaluated and preventive measures should be applied when using this regimen.

Limitations

Our study has several limitations. This is an observational, retrospective study. We did not include patients treated with each medication separately and each patient served as a self-control. Patients without baseline or follow up ECG were excluded

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from analysis, which can represent a bias. This is partially mitigated by the consecutive inclusion of patients meeting study criteria. The population in our study was primarily Caucasian, thus applicability to other populations warrants further study. Relatively short follow-up time after HY/AZ regimen completion was available. We did not assess serum drug concentrations.

Figure legends:

Figure 1: QTc prolongation and Torsdaes de point. This 68-year-old male patient, without any past medical history was found to be positive for SARS-COV 2 and HY/AZ was initiated. The patient did not receive any other QT prolonging medications. Baseline ECG is presented in panel A. ECG before the initiation of HY/AZ. QTc = 447 ms. QTc prolonged gradually to 477 ms on day 1, 480 ms on day 2 and 505 ms on day 3. In panel B, ECG at day 4 of HY/AZ revealed QTc prolongation to 546 ms. C. The same night, multiple short runs of TdP were noted on telemetry. HY/AZ was stopped, the patient developed TdP requiring cardioversion which was given in <10s due to incidental presence of a physician by the patient. Laboratory from day 4 revealed Creatinine 1.1 (mg/dL), K – 3.5 (mEq/L) and mildly elevated liver function tests.

Figure 2: A. Daily absolute QTc in patients treated with HY/AZ and B. change in QTc by day. Number of patients, mean QTc +/- SD are presented at each day. * represents $p<0.01$ for the comparison with baseline QTc. Blue lines indicate end of HY/AZ therapy.

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Figure 3: Individual QTc changes from baseline to the individual maximal QTc. In A, patient with maximal QTc>500 ms are marked in red. In B, patients with ΔQTc>60 ms are marked in red.

Figure 4: Distribution of QTc ranges by day of therapy. Note that therapy was given on days 1-5 (dashed line).

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Tables:

Table 1. Baseline Characteristics. N=251

Age (yrs)	64 ± 13
Gender (% male)	75% (70% - 81%)
Weight (kg)	86.0 ± 17.9
Coronary artery disease	12% (8% - 16%)
Hypertension	54% (48% - 60%)
Chronic kidney disease	11% (7% - 15%)
Diabetes mellitus	27% (21% - 32%)
Chronic obstructive pulmonary disease	7% (4% - 10%)
Congestive heart failure	3% (1% - 5%)
Creatinine at initiation (mg/dL)	1.2 ± 0.9
Creatinine at max QTc (mg/dL)	1.6 ± 1.5
CrCl at initiation (mL/min)	84 ± 43
CrCl at max QTc (mL/min)	80 ± 52
Abnormal LFTs at initiation	21% (16% - 27%)
Abnormal LFTs at max QTc	38% (27% - 48%)
Potassium at baseline (mEq/L)	4.1 ± 0.6
Potassium at max QTc (mEq/L)	4.2 ± 0.5
QTc-prolonging medications	
Psychiatric medications	12% (8% - 16%)
Anti-microbials	10% (7% - 14%)
Amiodarone	9% (6% - 13%)
# QTc-prolonging medications	0.3 ± 0.5
0 medications	71% (65% - 77%)
1 medication	27% (22% - 33%)
2 medications	2% (0% - 4%)
Baseline QTc (ms)	439 ± 29
Maximum QTc (ms)	473 ± 36
Maximum delta QTc (ms)	34 ± 35
Day of maximum QTc	4.1 ± 2.0

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Baseline JTc (ms)	342 ± 25
Maximum JTc (ms)	375 ± 35
Maximum delta JTc (ms)	33 ± 36
Day of maximum JTc	4.1 ± 1.9
Mortality	20% (14% - 25%)

Table 2. Characteristics by Baseline QRS. N=251

	Baseline QRS <120ms (n = 222)	Baseline QRS ≥120ms (n = 29)	*p*
Age (yrs)	63 ± 13	73 ± 9	<0.01
Gender (% male)	75% (70% - 81%)	76% (59% - 92%)	1
Weight (kg)	85.8 ± 17.5	87.7 ± 21.1	0.54
Coronary artery disease	10% (6% - 14%)	21% (5% - 36%)	0.12
Hypertension	53% (47% - 60%)	59% (40% - 78%)	0.69
Chronic kidney disease	9% (6% - 13%)	21% (5% - 36%)	0.10
Diabetes mellitus	24% (18% - 30%)	48% (29% - 68%)	0.01
Chronic obstructive pulmonary disease	8% (4% - 11%)	3% (-4% - 11%)	0.70
Congestive heart failure	1% (0% - 3%)	14% (0% - 27%)	<0.01
Creatinine at initiation (mg/dL)	1.2 ± 0.9	1.6 ± 1.4	0.01
Creatinine at max QTc (mg/dL)	1.6 ± 1.5	1.7 ± 0.9	0.02
CrCl at initiation (mL/min)	87 ± 43	65 ± 35	0.01
CrCl at max QTc (mL/min)	82 ± 53	59 ± 36	0.03
Abnormal LFTs at initiation	22% (17% - 28%)	15% (0% - 29%)	0.46
Abnormal LFTs at max QTc	40% (28% - 52%)	19% (3% - 34%)	0.23
Potassium at baseline (mEq/L)	4.1 ± 0.6	4.2 ± 0.4	0.65
Potassium at max QTc (mEq/L)	4.2 ± 0.5	4.0 ± 0.4	0.16
QTc-prolonging medications			
Psychiatric medications	11% (7% - 15%)	17% (3% - 32%)	0.35
Anti-microbials	11% (7% - 15%)	7% (-3% - 17%)	0.75
Amiodarone	8% (4% - 11%)	21% (5% - 36%)	0.04
# QTc-prolonging medications	0.3 ± 0.5	0.4 ± 0.6	0.12
0 medications	73% (67% - 78%)	59% (40% - 78%)	0.13
1 medication	26% (20% - 31%)	38% (19% - 57%)	0.18

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2 medications	2% (0% - 4%)	3% (-4% - 11%)	0.46
Baseline QTc (ms)	434 ± 25	475 ± 33	<0.01
Maximum QTc (ms)	469 ± 34	503 ± 39	<0.01
Maximum delta QTc (ms)	35 ± 35	29 ± 40	0.43
Day of maximum QTc	4.0 ± 1.9	4.8 ± 2.2	0.05
Baseline JTc (ms)	344 ± 24	333 ± 26	0.06
Maximum JTc (ms)	377 ± 35	363 ± 33	0.01
Maximum delta JTc (ms)	33 ± 36	30 ± 39	0.52
Day of maximum JTc	4.0 ± 1.9	4.7 ± 2.3	0.13
Number of follow-up ECGs	2.9 ± 1.3	3.2 ± 1.5	0.33
Follow-up time (days)	5.2 ± 2.0	5.8 ± 1.9	0.09

Table 3. Predictors of Maximum QTc ≥500ms. N=40/251 (16%)

Univariate Logistic Regressions			
Variable	*p* value	OR	95% CI
Age (years)	0.62	1.01	.98 - 1.03
Gender (% male)	0.25	1.66	.7 - 3.97
Weight (kg)	0.25	0.99	.97 - 1.01
Coronary artery disease	0.21	1.82	.72 - 4.61
Hypertension	0.87	1.06	.54 - 2.09
Chronic kidney disease	0.05	2.53	1.02 - 6.26
Diabetes mellitus	0.20	1.61	.78 - 3.3
Chronic obstructive pulmonary disease	0.93	1.06	.29 - 3.84
Congestive heart failure	0.01	7.70	1.66 - 35.87
Creatinine at initiation (mg/dL)	0.01	1.79	1.2 - 2.69
Creatinine at max QTc (mg/dL)	<0.01	1.35	1.12 - 1.63
CrCl at initiation (mL/min)	0.04	0.91	.84 - 1.
CrCl at max QTc (mL/min)	<0.01	0.88	.8 - .95
Abnormal LFTs at initiation	0.72	1.16	.51 - 2.64
Abnormal LFTs at max QTc	0.42	0.74	.35 - 1.55
Potassium at baseline (mEq/L)	0.61	0.84	.42 - 1.65
Potassium at max QTc (mEq/L)	0.86	0.94	.44 - 1.99
Psychiatric medications	0.21	1.82	.72 - 4.61
Anti-microbials	0.94	0.96	.31 - 2.94
Amiodarone	<0.01	5.08	2.05 - 12.61
# QTc-prolonging medications	0.01	2.40	1.31 - 4.38
Baseline QTc (ms)	<0.01	1.32	1.16 - 1.51
Number of follow-up ECGs	<0.01	2.05	1.54 - 2.73
Follow-up time (days)	0.01	1.28	1.06 - 1.55

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Multivariate Logistic Regression			
Variable	*p* value	OR	95% CI
Congestive heart failure	0.53	1.79	.3 - 10.65
Creatinine at initiation (mg/dL)	0.06	1.54	.99 - 2.4
Amiodarone	0.02	3.27	1.18 - 9.11
Baseline QTc (ms)	<0.01	1.26	1.09 - 1.45

Table 4. Predictors of Maximum Delta QTc ≥60ms. N=51/251 (20%)

Univariate Logistic Regressions			
Variable	*p* value	OR	95% CI
Age (yrs)	0.18	1.02	.99 - 1.04
Gender (% male)	0.56	1.25	.59 - 2.61
Weight (kg)	0.03	0.98	.96 - 1.
Coronary artery disease	0.05	2.32	1.01 - 5.37
Hypertension	0.15	1.59	.84 - 2.98
Chronic kidney disease	0.08	2.17	.91 - 5.16
Diabetes mellitus	0.23	1.50	.77 - 2.92
Chronic obstructive pulmonary disease	0.69	0.77	.21 - 2.77
Congestive heart failure	0.59	1.59	.3 - 8.45
Creatinine at initiation (mg/dL)	0.04	1.38	1.02 - 1.87
Creatinine at max QTc (mg/dL)	0.01	1.27	1.05 - 1.52
CrCl at initiation (mL/min)	0.07	0.93	.86 - 1.01
CrCl at max QTc (mL/min)	<0.01	0.90	.83 - .96
Abnormal LFTs at initiation	0.26	0.62	.27 - 1.42
Abnormal LFTs at max QTc	0.39	0.76	.4 - 1.43
Potassium at baseline (mEq/L)	0.22	1.49	.79 - 2.82
Potassium at max QTc (mEq/L)	0.24	1.52	.76 - 3.04
Psychiatric medications	0.59	1.29	.52 - 3.21
Anti-microbials	0.71	1.20	.46 - 3.16
Amiodarone	0.01	3.51	1.44 - 8.55
# QTc-prolonging medications	0.03	1.88	1.07 - 3.31
Baseline QTc (ms)	<0.01	0.78	.69 - .89
Number of follow-up ECGs	<0.01	1.82	1.41 - 2.34

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Follow-up time (days)	<0.01	1.44	1.2 - 1.74
Multivariate Logistic Regression			
Variable	*p* value	OR	95% CI
Weight (kg)	0.11	0.98	.96 - 1.
Creatinine at initiation (mg/dL)	0.02	1.73	1.1 - 2.7
Amiodarone	<0.01	5.47	1.87 - 16.02

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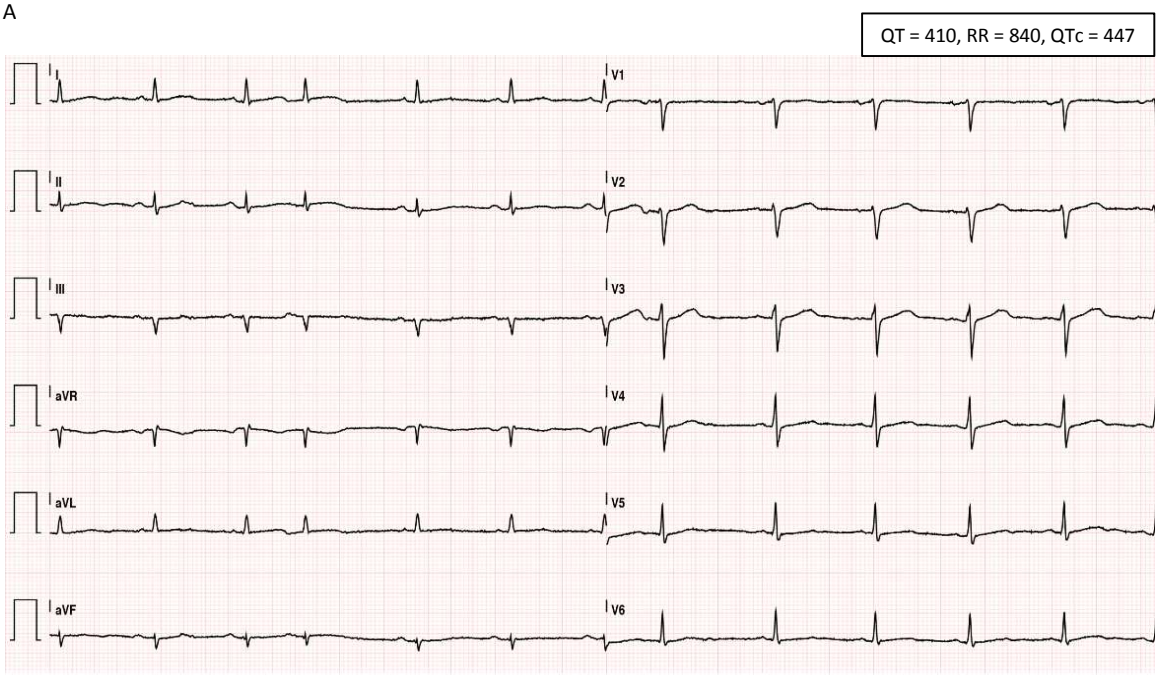
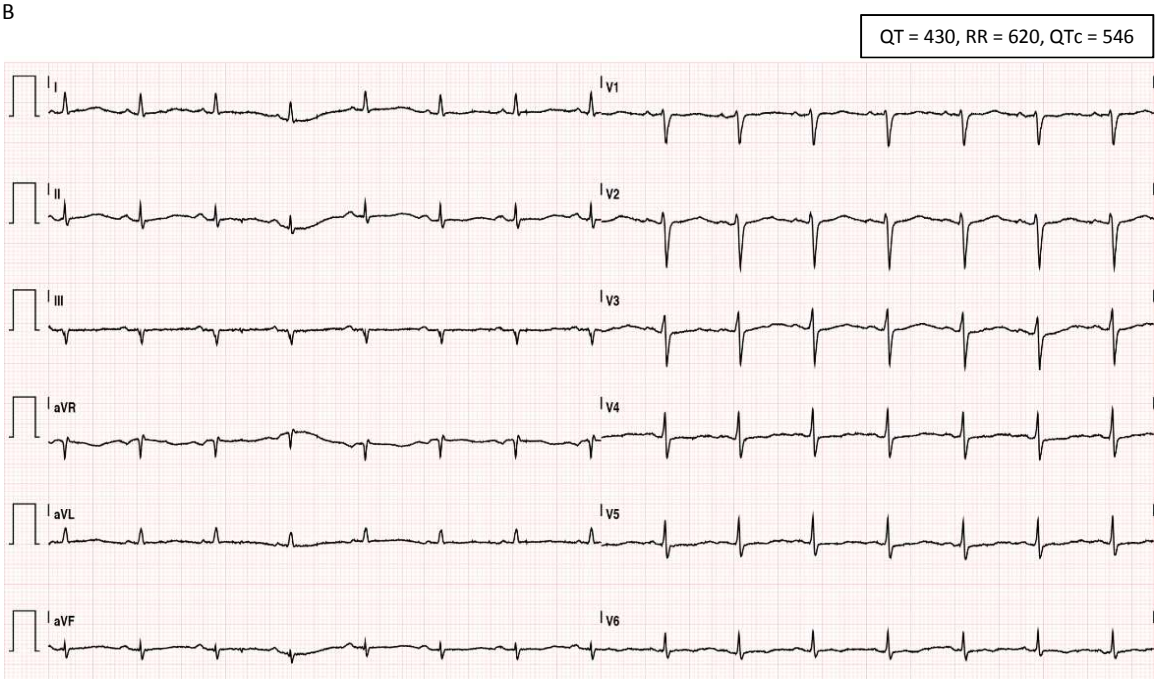
Figure 1

A


QT = 410, RR = 840, QTc = 447
I
II
III
aVR
aVL
aVF
V1
V2
V3
V4
V5
V6

B


QT = 430, RR = 620, QTc = 546
I
II
III
aVR
aVL
aVF
V1
V2
V3
V4
V5
V6

C

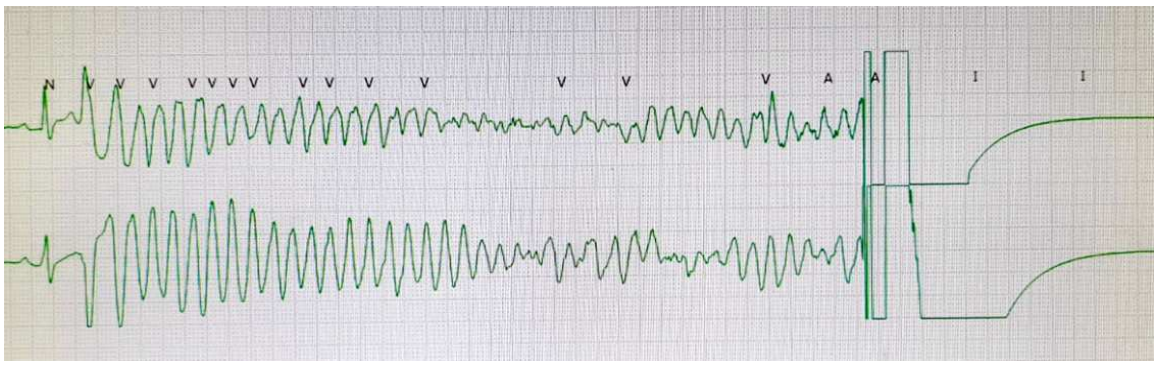
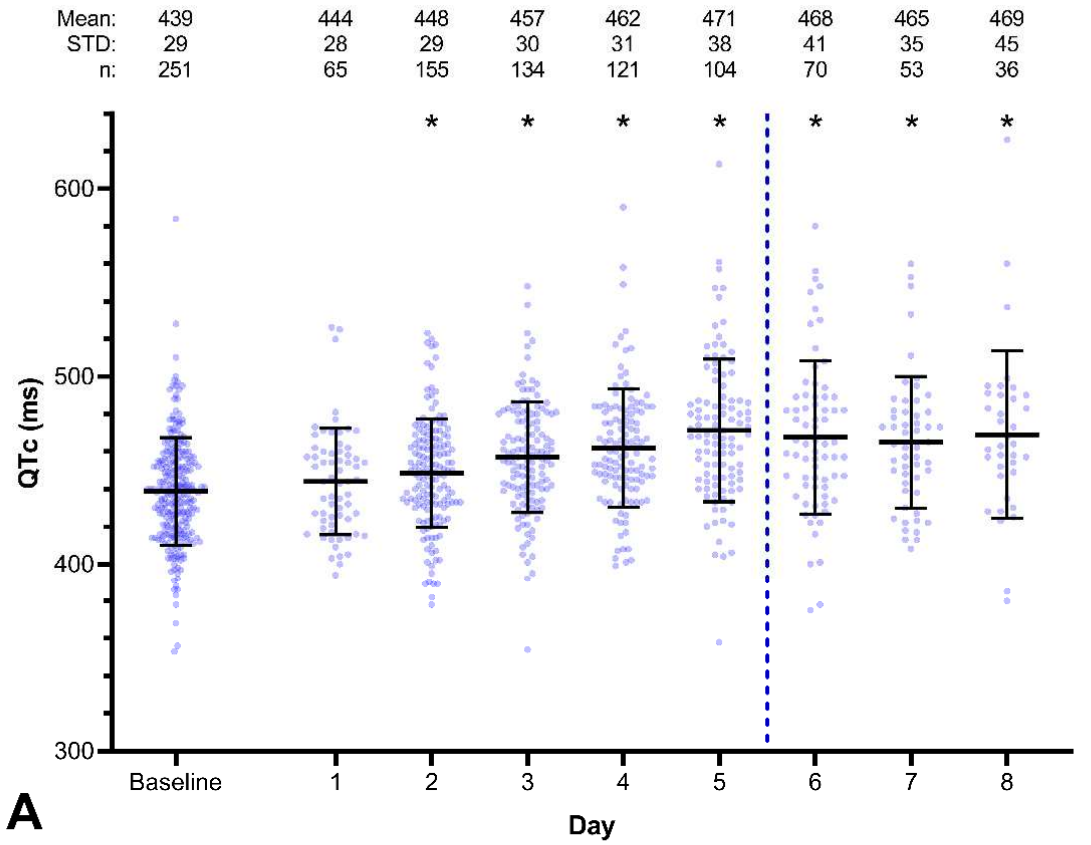

N
V
V
V
V
V
V
V
V
V
V
V
V
V
V
A
A
I
I

Figure 2


Mean: 439 444 448 457 462 471 468 465 469
STD: 29 28 29 30 31 38 41 35 45
n: 251 65 155 134 121 104 70 53 36
QTc (ms)
600
500
400
300
Baseline
1
2
3
4
5
6
7
8
Day
A

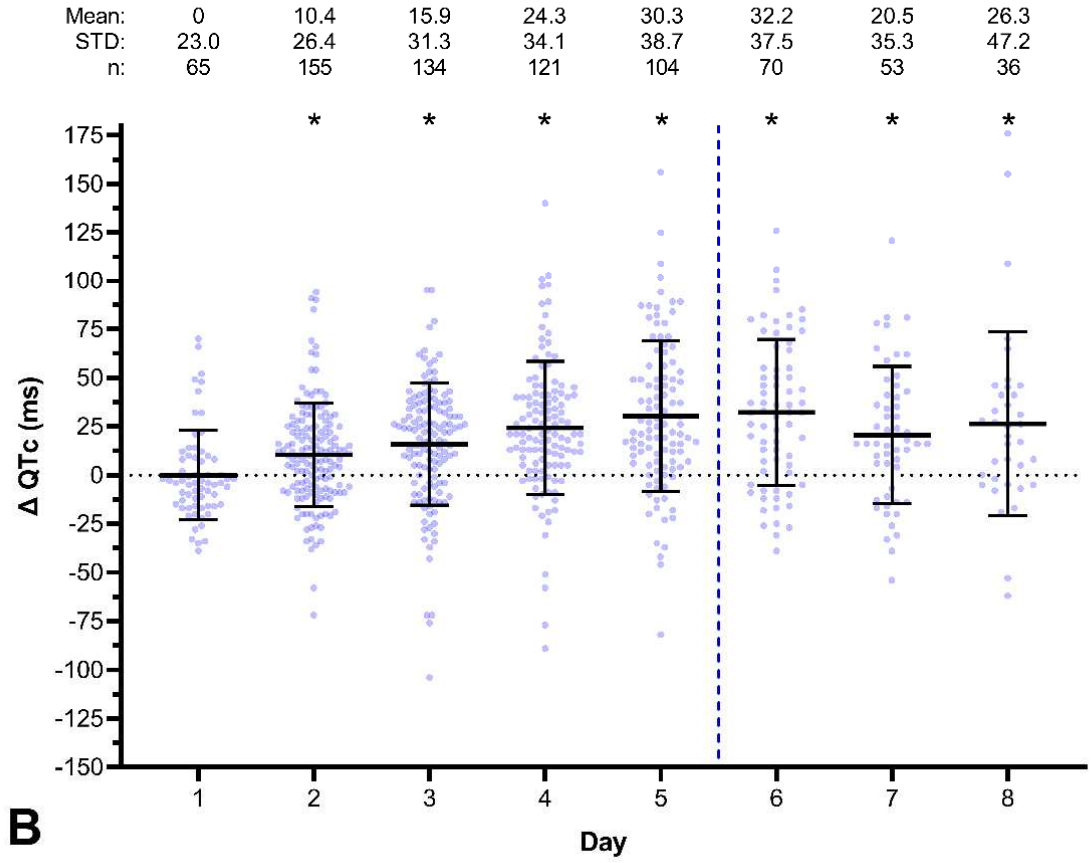
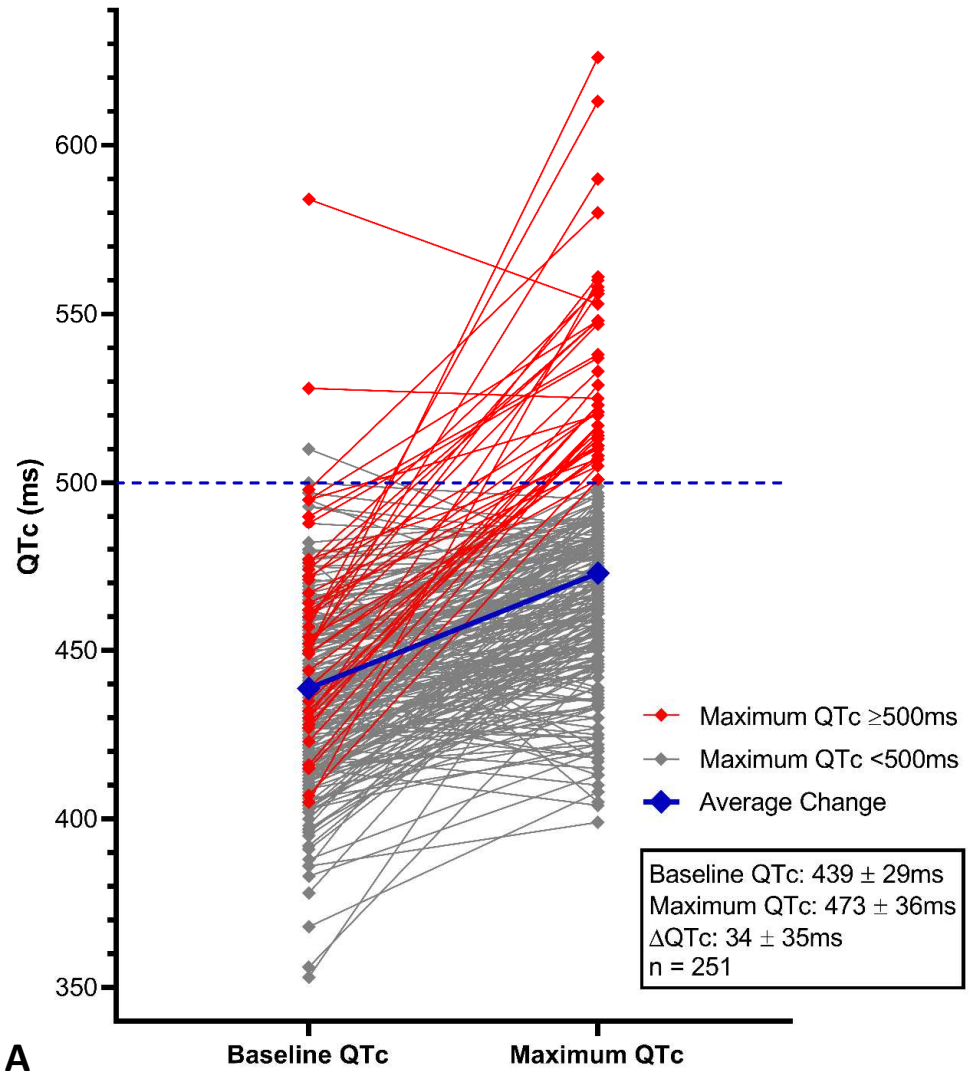

Mean: 0 10.4 15.9 24.3 30.3 32.2 20.5 26.3
STD: 23.0 26.4 31.3 34.1 38.7 37.5 35.3 47.2
n: 65 155 134 121 104 70 53 36
Δ QTc (ms)
175
150
125
100
75
50
25
0
-25
-50
-75
-100
-125
-150
1
2
3
4
5
6
7
8
Day
B

Figure 3


600
550
500
450
400
350
QTc (ms)
Maximum QTc ≥500ms
Maximum QTc <500ms
Average Change
Baseline QTc: 439 ± 29ms
Maximum QTc: 473 ± 36ms
ΔQTc: 34 ± 35ms
n = 251
Baseline QTc
Maximum QTc
A

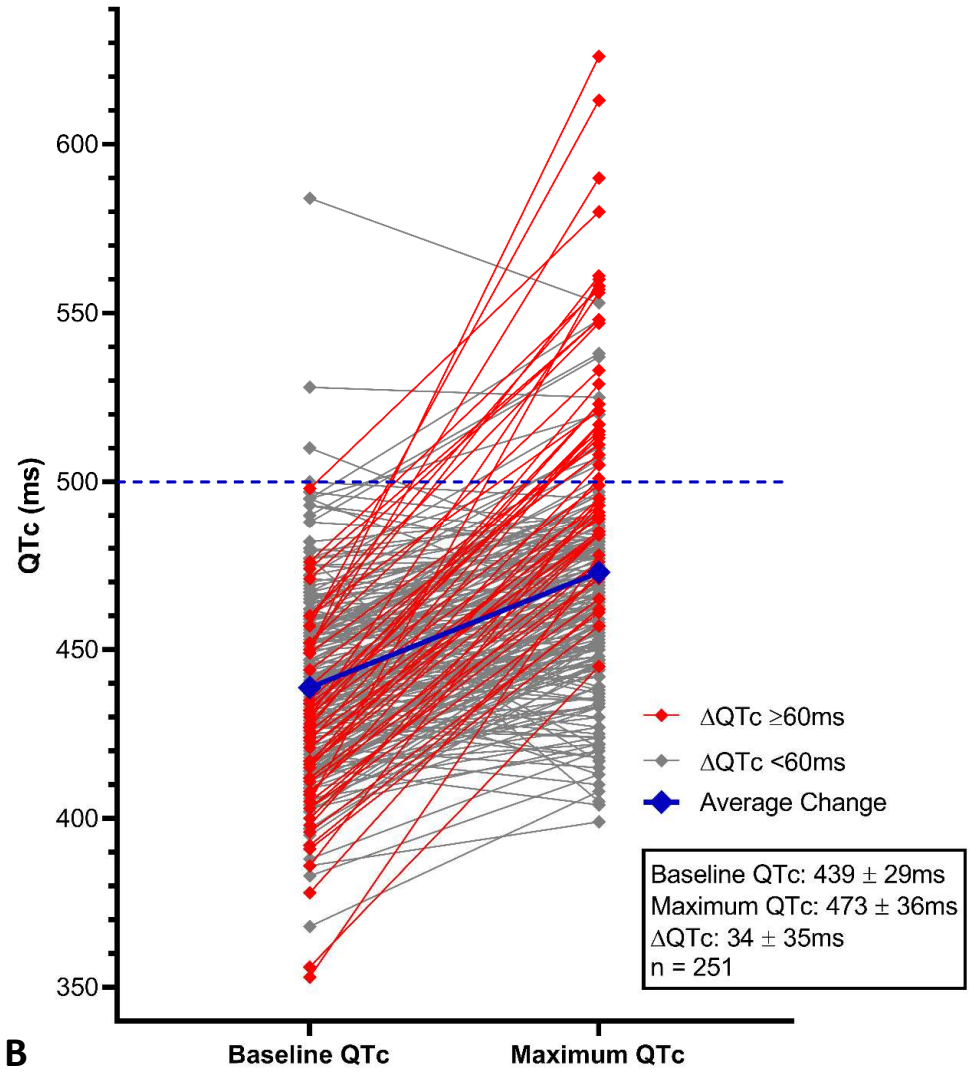
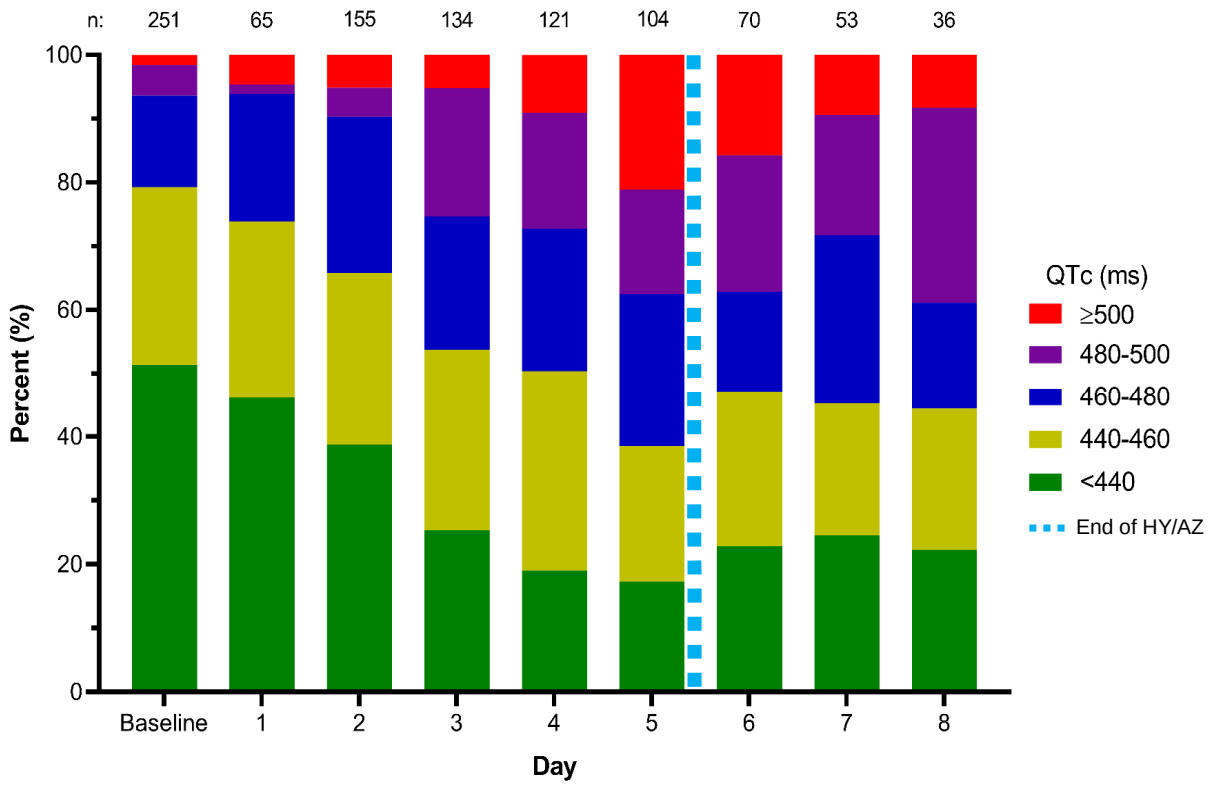

600
550
500
450
400
350
QTc (ms)
ΔQTc ≥60ms
ΔQTc <60ms
Average Change
Baseline QTc: 439 ± 29ms
Maximum QTc: 473 ± 36ms
ΔQTc: 34 ± 35ms
n = 251
Baseline QTc
Maximum QTc
B

Figure 4


n:
251
65
155
134
121
104
70
53
36
100
80
60
40
20
0
Percent (%)
Baseline
1
2
3
4
5
6
7
8
Day
QTc (ms)
≥500
480-500
460-480
440-460
<440
End of HY/AZ