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ABSTRACT

Background Hydroxychloroquine (HCQ) has been promoted as a potential treatment for COVID-19 but there are safety concerns.

Objectives To determine the effect of HCQ treatment on QT interval

Methods We retrospectively studied the electrocardiograms of 819 patients treated with HCQ for rheumatologic diseases from 2000 to 2020. The primary outcome was corrected QT (QTc) interval, by Bazett formula, during HCQ therapy.

Results The patients were 64.0 (±10.9) years in age and 734 (90%) were men. The median dosage and duration of HCQ were 400mg daily and 1006 (471-2075) days, respectively. The mean on-treatment QTc was 430.9 (±31.8) msec. In total, 55 (7%) patients had QTc 470-500 msec and 12 (1.5%) had QTc >500msec. Chronic kidney disease (CKD), history of atrial fibrillation (AF) and heart failure were independent risk factors for prolonged QTc. In a subset of 591 patients who also had a pre-treatment ECG, the mean QTc increased from 424.4 (±29.7) msec. to 432.0 (±32.3) msec ($p<0.0001$) during HCQ treatment. Of these, 23 (3.9%) patients had either prolongation of QTc >15% or an on-treatment QTc >500 msec. Over 5.97 (3.33-10.11) years of follow-up, 269 (33%) patients died. QTc >470 msec during HCQ treatment was associated with a greater mortality risk of (hazard ratio 1.78, 95% confidence interval 1.16-2.71; $p=0.008$) in univariable but not in multivariable analysis.

Conclusion Hydroxychloroquine is associated with QT prolongation in a significant fraction of patients. The risk of QT prolongation is higher among patients with CKD, AF and heart failure, who may benefit from greater scrutiny.

Keywords: long QT syndrome; drugs; drug-induced arrhythmia; mortality; electrocardiogram

INTRODUCTION

Since December 2019, the novel single-stranded RNA virus known as the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) has caused millions of cases of coronavirus disease (COVID-19) in a global pandemic, leading to substantial morbidity and mortality[1]. Clinical trajectories of COVID-19 vary widely, with worse outcomes observed in older individuals and those with concomitant medical conditions[2]. A significant proportion of hospitalized patients with COVID-19 have cardiovascular disease. Moreover, COVID-19 has been purported to cause several types of cardiac adverse events, including myocardial injury, acute myocardial infarction, acute heart failure, myocarditis, and arrhythmias[3–5].There is no approved treatment for COVID-19, although several strategies are under investigation, such as antivirals, antiretrovirals, immune modulators and hydroxychloroquine (HCQ).

Originally used to treat malaria, HCQ was approved for the treatment of systemic lupus erythematosus (SLE) by the FDA in 1955[6]. It is currently the most commonly prescribed medication for SLE and is frequently used for a variety of other rheumatologic conditions. Cardiac toxicity is rare but there are reports of conduction abnormalities including bundle-branch block, atrioventricular block, QT prolongation, torsade de pointes, and sudden cardiac death[7–10]. There is in vitro evidence that chloroquine and HCQ possess antiviral properties[11]. These data have been extrapolated to hypothesize that HCQ may prevent SARS-CoV-2 infection and attenuate the course and severity of the COVID-19 disease[12]. Indeed, on March 28, 2020 the FDA issued in emergency use authorization for the use of HCQ sulfate (and chloroquine phosphate) in certain hospitalized patients being treated for COVID-19[13]. However, recent studies showing no benefit of HCQ in COVID-19 have since led the FDA to remove that emergency authorization[14–17]. Nonetheless, Case reports and case series of COVID-19 patients treated with HCQ describe significant QT prolongation and torsade de pointes which has expanded clinical concern regarding the arrhythmogenic risk of HCQ[18–21]. The purpose of this

study is to provide information about the effects of HCQ on cardiac conduction abnormalities that appear on a 12-lead electrocardiogram (ECG).

METHODS

This study was approved by the Minneapolis VA Medical Center Institutional Review Board. Informed consent requirement was waived.

Patient Selection

We identified 2665 patients who received at least one prescription for HCQ dispensed at the Minneapolis Veterans Affairs (VA) Health Care System from the year 2000 to 2020. Each prescription represented the first dispense of HCQ until a break in prescriptions for at least 150 days[22,23]. We excluded patients without an ECG performed while they were receiving HCQ treatment (n=1722). After also excluding the 124 duplicate entries, we included 819 unique patients who received treatment in this analysis.

Electrocardiogram

All ECGs were performed with the General Electric MAC 5000 and stored in the Marquette Universal System for Electrocardiography database[24,25]. We selected the first ECG, performed at least 5 days after starting the HCQ treatment for analysis. When present, we also analyzed the last ECG performed before starting the HCQ treatment. We recorded the ventricular rate, QRS duration, QT interval and the corrected QT interval (QTc) calculated via the Bazett, Framingham and Friderica formulas. For patients with a QRS >120 msec we used the Bogossian formula[26] to calculate a modified QT interval (QTm), QTm= QT(measured) – 48.5%*QRS(measured). The QTm was used to calculate the QTc. We manually measured the QT interval, starting from the beginning of the Q wave to the end of the T wave on ECG, using

electronic calipers in 70 (8.5%) randomly selected patients in the cohort[27]. The correlation coefficient was 0.8.

Outcomes

The primary outcome variable was the QTc interval during HCQ therapy. We used the Bazett formula for QT correction because it is the most commonly used method to calculate QTc. QTc > 470 msec represents the 99th percentile of QTc distribution in the general population and is a predictor of symptoms in patients with long-QT syndrome[28,29]. QTc > 500 msec is associated with a higher risk of life-threatening arrhythmias[29]. In a subgroup of patients who had ECGs before and during HCQ treatment, we also assessed the change in QTc[30]. Secondary outcome variable was time to death or last follow-up from the starting date of the HCQ treatment, as recorded in the VA vital status files[24,25,31].

Predictor variables and definitions

We extracted patient demographics, comorbidities, and laboratory data from the VA corporate data warehouse using Structured Query Language. The VA corporate data warehouse contains extracts from VA clinical and administrative system that includes complete clinical data since October 1999[32]. Prescribing reports on HCQ dosing, start and stoppage dates and other medications were also extracted from the VHA CDW[22]. The ECG data were obtained from the Marquette Universal System for Electrocardiography database[24,25]. Chronic kidney disease (CKD) was defined as estimated glomerular filtration rate (eGFR) < 60 ml/min. The eGFR was calculated with the Cockcroft-Gault Equation ([140-age] × weight in kg)/(serum creatinine × 72; multiplied by 0.85 in women).

Statistical Analysis

Data are presented as mean (standard deviation) or median (interquartile range) for continuous variables, and number (n) and percentage (%) for categorical variables. Comparisons of

characteristics among patients with vs. without QTc prolongation were made with chi-square test or Fisher's exact test for categorical variables and unpaired t test for continuous variables. The ECG characteristics before vs. during HCQ therapy were compared using paired t-test. Independent predictors of prolonged QTc were identified by multivariable logistic regression analysis. Survival curves were constructed using the Kaplan–Meier method and the differences of survival among patients with vs. without prolonged QTc was examined by the log-rank test. Cox proportional hazards analysis was used to assess the association between QTc prolongation and mortality, and to calculate the hazard ratio (HR) and 95% confidence interval (CI). Statistical analyses were performed with IBM SPSS (version 25; IBM Corp, Armonk, NY, USA).

RESULTS

Patient characteristics

The baseline characteristics of the 819 study patients are shown in Table 1. The mean age was 64.0 (±10.9) years and 734 (90%) of the patients were male. Cardiovascular comorbidities included hypertension (n=532, 65%), coronary artery disease (n=234, 29%), diabetes (n=202, 25%) and heart failure (n=65, 8%). A total of 99 (12%) patients had chronic kidney disease (Table 1).

Hydroxychloroquine was prescribed to treat systemic lupus erhythematosus in 786 (96%) of the patients at a median starting dosage of 400 mg daily. The median (25^{th}-75^{th} percentile) duration of HCQ therapy was 1006 (471-2075) days.

ECG characteristics during HCQ treatment

A 12-lead ECG was performed 234 (92-586) days after starting HCQ therapy in all study patients. The characteristics of the ECG during HCQ therapy are listed in Table 2. Ventricular rate was 74.8 (±17.3)beats/min. The mean on-treatment QTc, based on Bazett formula, was

430.9 (±31.8) msec. A total of 55 (7%) patients had on-treatment QTc 470-500 msec. and 12 (1.5%) had QTc > 500 msec (Table 2). Compared to those with QTc ≤ 470 msec., patients with prolonged QTc were older and more likely to have CKD, history of atrial fibrillation and history of heart failure (Table 3). In multivariable regression, CKD (odds ratio [OR] 2.30; 95% CI 1.24-4.26; p=0.008), and atrial fibrillation (OR 2.64; 95% CI 1.42-4.90; p=0.002) were independent predictors of QTc >470 msec. Notably, the odds of QTc prolongation was >5 times higher (OR 5.1; 95% CI 1.23-21.1; p=0.025) when eGFR was < 30 ml/min. There was a negative correlation between eGFR and QTc (Figure 1).

Paired ECG before and during HCQ treatment

A total of 591 (72%) patients had ECGs performed *before* (median 345 [98-833] days) *and after* (median 204 [84-489] days) starting the HCQ treatment. On these paired ECGs, there was a modest prolongation of QTc from 424.4 (±29.7) msec. to 432.0 (±32.3) msec. (p<0.0001) during HCQ treatment (Table 4). A total of 23 (3.9%) patients had either a >15% increase in QTc or a QTc > 500 msec with HCQ treatment. These patients were more likely to have chronic kidney disease (44% vs. 14%; p=0.0001) than the rest of the cohort with paired ECGs.

Survival in relation to QTc

Of the 819 patients in the whole study cohort, 269 (33%) died over a median 5.97 (3.33-10.11) years of follow up. In comparison to those who survived, the patients who died were older, more likely to be men and more likely to have coronary disease, heart failure and CKD. In univariable Cox regression analysis, QTc > 470 msec. during HCQ therapy was associated with greater mortality (hazard ratio , 1.78, 95% CI 1.16-2.71, p=0.008) (Figure 2). However, after adjustment for age, sex, and comorbidities QTc > 470 msec. during HCQ treatment was no longer associated with long-term mortality. In patients with paired ECG, delta QTc was *not* associated with mortality (HR 1.001, 95% CI 0.998-1.005; p=0.51).

DISCUSSION

This investigation showed that a significant fraction (8.3%) of the patients prescribed HCQ for the treatment of SLE had QTc > 470 msec on ECG, including 1.5% who had QTc > 500 msec. Chronic kidney disease, atrial fibrillation and heart failure were associated with QTc prolongation. Among patients with ECGs performed both before and during treatment, HCQ had a modest effect on QTc (mean increase 8 msec) except in 3.4% of the patients who had > 15% increase in QTc. The QTc interval during HCQ treatment was associated with long-term survival in univariable analysis, while the change in QTc was not.

Hydroxychloroquine blocks the KCNH2-encoded hERG/Kv11.1 potassium channel and can contribute to prolongation of the QTc interval[12]. Mutations involving these potassium channels cause the long QT syndrome and their blockage by certain drugs can be associated with QT prolongation, torsade de pointes, and sudden death. While QT prolongation and ventricular arrhythmias related to HCQ are uncommon, there are published case reports and postings on the FDA Adverse Events Reporting System[7,8,10]. A retrospective study of 112 patients with SLE treated with HCQ reported that cardiac conduction abnormalities were present in 18% of the subjects. These included incomplete bundle branch blocks and second and third degree atrioventricular blocks. The presence of conduction abnormalities were not associated with mortality during the first 10 years of follow-up but thereafter, subjects with cardiac conduction abnormalities had a higher risk of death[33]. In a larger series of 453 consecutive SLE patients, 84% of whom were taking HCQ, 16% had cardiac conduction abnormalities[34]. Since some conduction abnormalities can be related to myocardial involvement of SLE, the authors were not able to attribute them directly to the use of HCQ. In fact, higher cumulative doses of HCQ were associated with fewer conduction abnormalities. QTc prolongation was rare and only noted in 0.7% of patients. In 2007, a retrospective review of 85 patients on HCQ showed that

the incidence of conduction delays and QT prolongation was similar to what is expected in the general public[35].

There are currently more than 7.15 million confirmed cased of COVID-19 world-wide. Initially, HCQ has emerged as a potential therapy for COVID-19 given in vitro evidence of antiviral properties[11,36]. Guidelines quickly emerged cautioning the use of the medication in patients with prolonged QTc. The Heart Rhythm Society published guidelines suggesting that the arrhythmic toxicity risk of HCQ is likely low given the relatively short duration of treatment for COVID-19[37]. They recommend using caution in patients with known congenital long QT syndrome, renal insufficiency, on QT prolonging medications (e.g. certain antiarrhythmics, antipsychotics, antifungals, and macrolide antibiotics such as azithromycin), or with electrolyte derangements[37–39]. Mayo clinic proceedings recently published guidelines recommending caution when using HCQ +/- azithromycin in any patient with a prolonged QTc > 470msec in males and >480 msec in females[12]. Most recently, a small randomized controlled trial and several observational studies of COVID-19 patients treated with HCQ showed no evidence of benefit and some concerning trends for harm[14–17,40]. At this moment, the FDA has removed the emergency authorization of HCQ as a therapy for COVID-19. the COVID-19 treatment guidelines put forth by the National Institutes of Health, recommend against use of HCQ in combination with azithromycin, except in the context of a clinical trial[41]. However, despite the negative trials the medication has received significant media attention and it remains possible that a significant portion of the population is exposed to the medication. The association of impaired kidney function with QTc prolongation is especially concerning since reports from China indicate that patients with COVID-19 are more likely to experience renal dysfunction[42]. Given the higher co-morbidity burden and acuity of patients hospitalized with COVID-19, it is possible that a higher percentage would exhibit QTc prolongation with HCQ treatment.

The current report provides contemporary information on the effect of HCQ on QTc to support the above recommendations. While the additional prolongation of QTc with HCQ was in

general modest, substantial prolongation occurred in 3.2% of the patients. Guidelines for performing screening ECGs and recommendations for monitoring patients started on HCQ have been proposed[18,43]. Therefore, it is prudent to check a baseline ECG prior to initiating therapy, avoid hypokalemia and monitor patients with impaired kidney function and those taking other QT prolonging medications closely[38,39]. Although this study did not include genetic data, extra precautions are also recommended in patients with congenital long QT syndrome.

This study showed that 1.5% of patients taking HCQ had QTc >500 msec. Class III antiarrhythmic medications dofetilide and sotalol, used for the treatment atrial fibrillation, can also cause QT prolongation. In the DIAMOND-CHF study, dofetilide was discontinued in 2% of the patients for QT prolongation[44]. However, more recent data from general practice showed that dofetilide was discontinued in up to 17% of patients due to QT prolongation[38]. Sotalol, on the other hand, was discontinued in 4.3% of patients due to prolonged QT interval[45]. The results of the current study should be evaluated within this context.

Limitations

We acknowledge the limitations of this study. There may be a selection bias for patients who had ECGs while on therapy. Patients with SLE are different from ill patients with COVID-19 who are likely to have a higher burden of cardiovascular comorbidities and impaired kidney function making them more vulnerable to the adverse effects of HCQ. Further, HCQ has a long half-life. Steady state is achieved after 3-4 months of therapy[46]. The average time on HCQ at the time the ECG was performed in this study was 237 (92-575) days suggesting that steady state had been achieved. However, patients treated for COVID-19 are likely to receive shorter courses of therapy and this study cannot address expected ECG changes in this timeframe. Finally, this study was retrospective, lacked genetic diagnostics and largely consisted of men.

Conclusions

Hydroxychloroquine therapy is associated with QT prolongation in a significant fraction of patients who were on chronic therapy with this medication for SLE. While recent trials have not supported the expansion of HCQ use for COVID-19, it has raised significant concerns with QT prolongation and arrhythmogenic risk. Avoiding hypokalemia and carefully monitoring of QTc are warranted; particularly in those with impaired kidney function and those receiving other QT prolonging drugs.

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FIGURE LEGENDS

Figure 1. Association of estimated glomerular filtration rate with QTc prolongation

Figure 2. Survival in relation to QTc during HCQ treatment. QTc > 470 msec. during HCQ therapy was associated with greater mortality in univariable analysis but not after adjustment for age, sex and comorbidities.

Table 1. Characteristics of the 819 patients treated with hydroxychloroquine

	All patients (n=819)
Age, years	64.0 (±10.9)
Male, n (%)	734 (90%)
Hypertension, n (%)	532 (65%)
Coronary artery disease, n (%)	234 (29%)
Heart failure, n (%)	65 (8%)
Diabetes, n (%)	202 (25%)
Atrial fibrillation, n (%)	90 (11%)
Chronic kidney disease, n (%)	99 (12%)
End-stage renal failure, n (%)	10 (1%)
SLE, n (%)	786 (96%)
Magnesium, mg/dl	2.0 (±0.3)
Potassium, mmol/L	4.1 (±0.4)
Creatinine, mg/dl	1.0 (±0.5)
eGFR, ml/min/1.73 m^2	78.6 (±24.7)
eGFR, ml/min	100.5 (±37.9)

Continuous variables were represented as mean (±standard deviation)
Abbreviations: eGFR=estimated glomerular filtration rate; HCQ= hydroxychloroquine; SLE= systemic lupus erythematosus

Table 2. ECG characteristics of the study patients during hydroxychloroquine treatment

	All patients (n=819)	QTc ≤ 470 (n=752)	QTc 471-500 (n=55)	QTc > 500 (n=12)	P value*
Ventricular rate, bpm	74.8 (±17.3)	74.1 (±17.0)	80.9 (±16.5)	85.4 (±25.7)	0.001
QRS duration, msec	100.9 (±22.8)	101.0 (±23.2)	98.3 (±16.3)	104.0 (±24.2)	0.47
QT interval, msec	392.8 (±44.5)	389.6 (±42.6)	421.3 (±40.0)	462.6 (±73.6)	<0.0001
QTc-Bazett, msec	430.9 (±31.8)	425.5 (±26.2)	481.6 (±7.9)	535.3 (±39.0)	<0.0001
QTc-Framingham, msec	417.8 (±30.3)	413.3 (±27.3)	457.3 (±15.9)	491.5 (±45.7)	<0.0001
QTc-Friderica, msec	418.1 (±30.5)	413.4 (±27.2)	460.2 (±13.3)	494.2 (±49.4)	<0.0001

Continuous variables were represented as mean (±standard deviation)
*Comparison of QTc ≤ 470 msec vs. QTc > 470 msec

Table 3. Clinical characteristics of the patients based on QTc during hydroxychloroquine treatment

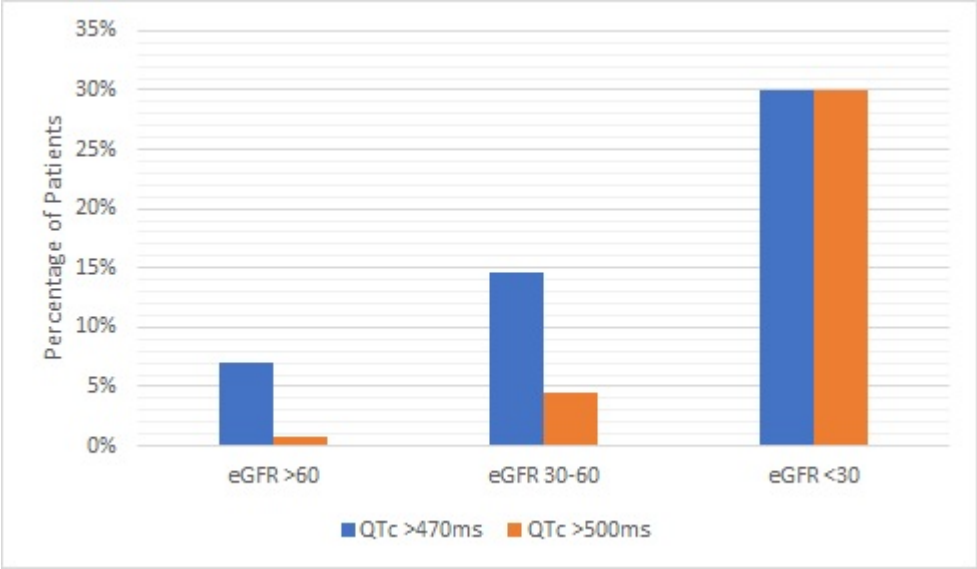
	QTc ≤ 470 (n=752)	QTc 471-500 (n=55)	QTc > 500 (n=12)	P value*
Age, years	63.7 (±10.8)	68.3 (±9.3)	66.4 (±16.9)	0.002
Male, n (%)	675 (90%)	48 (87%)	11 (92%)	0.66
Hypertension, n (%)	487 (65%)	37 (67%)	8 (67%)	0.41
Coronary artery disease, n (%)	213 (28%)	18 (33%)	3 (25%)	0.60
Heart failure, n (%)	55 (7%)	7 (13%)	3 (25%)	0.03
Diabetes, n (%)	179 (24%)	20 (36%)	3 (25%)	0.06
Atrial fibrillation, n (%)	74 (10%)	13 (24%)	3 (25%)	<0.0001
Chronic kidney disease, n (%)	83 (11%)	9 (16%)	7 (58%)	0.002
Magnesium, mg/dl	2.03 (±0.27)	1.96 (±0.27)	1.97 (±0.37)	0.054
Potassium, mmol/L	4.15 (±0.42)	4.04 (±0.37)	4.25 (±0.49)	0.21
Creatinine, mg/dl	1.02 (±0.30)	1.06 (±0.39)	2.62 (±2.99)	0.07
eGFR, ml/min/1.73 m^2	79.2 (±24.2)	75.3 (±25.9)	53.7 (±41.7)	0.08
eGFR, ml/min	101.2 (±37.2)	96.5 (±40.4)	72.4 (±63.4)	0.12

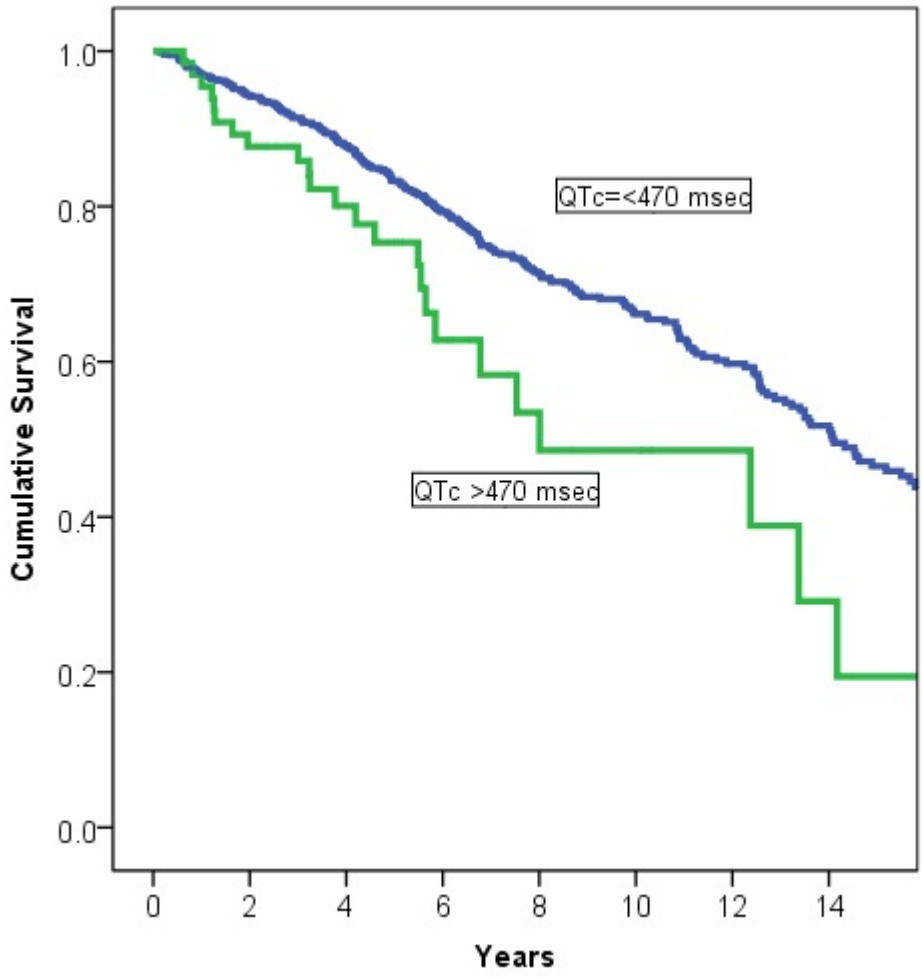
Continuous variables were represented as mean (±standard deviation)
Abbreviations: eGFR=estimated glomerular filtration rate; HCQ= hydroxychloroquine; SLE= systemic lupus erythematosus
*Comparison of QTc ≤ 470 msec vs. QTc > 470 msec

Table 4. Characteristics of the 591 paired ECGs before and during hydroxychloroquine treatment

	Pre-treatment	On treatment	P value
Ventricular rate, bpm	72.3 (±14.9)	74.9 (±17.7)	0.001
QRS duration, msec	98.1 (±20.2)	101.7 (±23.3)	<0.0001
QT interval, msec	392.6 (±42.8)	393.9 (±45.2)	0.49
QTc-Bazett, msec	424.4 (±29.7)	432.0 (±32.3)	<0.0001
QTc-Framingham, msec	412.7 (±28.3)	416.8 (±29.9)	0.006
QTc-Friderica, msec	412.9 (±28.3)	417.4 (±30.4)	0.003

Continuous variables were represented as mean (±standard deviation)




1.0
0.8
0.6
0.4
0.2
0.0
Cumulative Survival
QTc=<470 msec
QTc >470 msec
0
2
4
6
8
10
12
14
Years