Hydroxychloroquine Use Is Not Associated With QTc Length in a Large Cohort of SLE and RA Patients

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Abstract

Background

Hydroxychloroquine (HCQ) is a cornerstone therapy for systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). However, reports of its use and subsequent fatal arrhythmias in patients with Coronavirus disease 19 (COVID-19) have raised concern regarding its cardiovascular (CV) safety. Therefore, we examined the relationship between HCQ use and corrected QT (QTc) length in SLE and RA patients without clinical CV disease (CVD).

Methods

One SLE (n=352) and two RA cohorts (n=178) with electrocardiograms (ECGs) collected as part of study data were analyzed. RA cohort participants were recruited from tertiary referral centers with additional referrals from community rheumatologists, while SLE subjects originated from the Columbia University Lupus Cohort. All patients met American College of Rheumatology (ACR) classification criteria for SLE or RA, and lacked known CVD. The exposure of interest was HCQ use and main outcome measure was QTc length [continuous or categorical (≥ 440 ms and ≥ 500 ms)].

Results

Of the combined SLE and RA cohorts (n=530), 70% were HCQ users and 44% had a QTc≥ 440 ms. The adjusted mean QTc length was comparable between HCQ users vs non-users (438 ms vs 437 ms). In multivariable logistic models, HCQ use was not a significant predictor of a QTc≥440 ms for the entire cohort (OR 0.77; 95% CI 0.48-1.23; p=0.27). Importantly, a QTc≥ 500 ms was inversely associated with HCQ use and not associated with arrhythmias or deaths. A significant interaction was found between HCQ use and use of anti-psychotics. Ultimately, the use of HCQ combined with any QTc prolonging medication as a group was associated with a QTc length (434 ms; 95%CI 430, 439) which was comparable to that of use of HCQ alone (433 ms; 95% CI 429, 437).

Conclusion

In a combined cohort of SLE and RA patients without clinical CVD, adjusted QTc length was comparable between HCQ and non-HCQ users, supporting its CV safety in patients with rheumatic diseases.

Background

Hydroxychloroquine (HCQ) has long been a cornerstone therapy for systemic lupus erythematosus (SLE) and is commonly used as monotherapy or combined with other disease modifying anti-rheumatic drugs (DMARDs) for rheumatoid arthritis (RA). HCQ neutralizes acidic cytoplasmic components within the lysosome, leading to downstream alterations in antigen processing and inhibition of toll-like receptors(1, 2). The observed cutaneous, retinal, and musculoskeletal toxicities are thought to arise from long term exposure of these tissues to HCQ and its metabolites(2).
Acute cardiovascular (CV) toxicities from short term exposure of HCQ (and subsequent blocking of potassium channels within myocytes) manifest as QT interval prolongation and acute arrhythmic events (i.e. torsades de pointes)\(^{(3)}\). With long term exposure, HCQ metabolites may also accumulate in the myocardium and result in a cardiomyopathy with concentric hypertrophy and conduction abnormalities\(^{(1, 3)}\)\(^{(4)}\). In fact, 33 of 42 histologically confirmed cases of HCQ induced cardiomyopathy originated from RA and SLE patients, who on average had been on treatment for 13 years\(^{(1)}\). Moreover, 14 of those 42 cases progressed to third-degree atrioventricular block. However, there are no current guideline-based recommendations for CV screening in the setting of prolonged HCQ use.

Recent reports\(^{(5, 6)}\) of possible associations between concurrent HCQ and azithromycin use and QTc prolongation in those receiving treatment for coronavirus disease 2019 (COVID19) associated pneumonia have raised further concerns for HCQ-associated cardiotoxicity. However, the wide spectrum of cardiotoxic effects of COVID19 itself (arrhythmias, myocarditis, microvascular injury, stress cardiomyopathy)\(^{(7)}\) confound these observations. In observational (mostly retrospective studies) in rheumatic disease patients\(^{(8)}\)\(^{(9-12)}\) there were no differences in QTc prolongation in HCQ users vs non-users, nor was there an association between QTc length and HCQ use. However, these studies did not consistently account for the use of other prolonging QTc medications. We therefore investigated associations between HCQ use and QTc length in an SLE and RA cohort without known CV disease (CVD), accounting for the use of various QTc prolonging medications.

**Methods**

**Study Population**

A total of 530 SLE and RA patients on whom HCQ use information was available were included in the study.

**SLE Patients**: With approval from the Columbia University Institutional Review Board, electronic clinical data from the Columbia University Lupus Cohort registry was retrospectively reviewed. The patients consisted of all inpatients and outpatients seen at Columbia University Irving Medical Center (CUIMC)/New York Presbyterian Hospitals (NYPH) with an SLE or Lupus Nephritis diagnosis attested by the International Classification of Diseases, Ninth and Tenth Revision, Clinical Modification (ICD-9/ICD-10) billing code diagnosis, between January 2015 and December 2019. Inclusion criteria were: 1) \(\geq 2\) SLE ICD-9/ICD-10 billing diagnoses confirmed by manual chart review (fulfilling at least 4 ACR classification criteria\(^{(13)}\)) or \(\geq 1\) SLE diagnosis PLUS \(\geq 1\) lupus nephritis proven on renal pathology report review; 2) at least 2 clinical visits on record; 3) ECG information available and 4) those residing locally in the boroughs of Manhattan and Bronx (to increase the likelihood of having patients with continuous and multidisciplinary care at CUIMC). Exclusion criteria were: 1) major ST-T changes/ bundle branch block on ECG; 2) prior CVD; and 3) missing documentation of medications. These criteria are summarized in Fig. 1.

**RA Cohorts. Two established RA cohorts were studied: 1)** ESCAPE-RA (Evaluation of Subclinical Arthritis) was a prospective study to...
investigate subclinical atherosclerosis in an RA cohort without clinical CV disease (14). Participants were recruited from the Johns Hopkins Arthritis Center and referrals from community rheumatologists between 2004–2008. Inclusion criteria were age > 45 for men and > 50 for women and fulfillment of the 1987 ACR RA classification criteria (15). 2) RHYTHM-RA (RHeumatoid arthritis: studY of The Myocardium) is a cross-sectional study (subsequently extended to 4–6 year follow up) of myocardial phenotypes in RA patients without clinical CVD recruited from CUIMC and local rheumatology clinics between 2011–2020. Inclusion criteria included age ≥ 18 years old and fulfillment of 2010 ACR RA classification criteria (13). In both RA cohorts, ECGs were obtained during the first study visit.

**Outcome Measure:**

**QTc length**

The 12-lead ECGs (25 mm/s paper speed and 10 mm/mV amplitude) obtained at the first/baseline study visits (RA) and regular clinical care (SLE) were interpreted by a board-certified cardiologist (PP) with specialization in electrophysiology blinded to diagnosis. The QT-interval was calculated and adjusted for the heart rate using Bazett’s formula \(QTc = \frac{QT}{\sqrt{RR}}\) (16), and evaluated both as a continuous variable and as a binary variable using cutoffs of ≥ 440 and ≥ 500 ms. These cut-offs have been associated with an increased risk of clinical cardiac events including myocardial infarction, cardiac arrest, and stroke, as well as sudden cardiac death (17–19).

**Clinical Covariates:**

**SLE**

Patient characteristics and medications were collected from chart review. SLE disease duration was calculated as the duration in years from the date of physician diagnosis. Medication data were ascertained via clinician notes from the Electronic Medical Record (EMR). All medication data including HCQ use, were ascertained at the time of the ECG.

**RA Cohorts (ESCAPE-RA/RHYTHM):** Patient characteristics and medications were obtained through study patient questionnaires. RA disease duration was assessed by patient self-report of the date of diagnosis. Medication data was ascertained from medication bottles, and HCQ use was ascertained at the time of the ECG. Information regarding cumulative dosage or length of therapy for HCQ were not available for both SLE and RA cohorts. Hypertension was defined as a systolic blood pressure (BP) of ≥ 140 mm Hg or diastolic BP of ≥ 90 mm Hg or use of antihypertensives at the time of the evaluation. Diabetes was defined as a fasting serum glucose of ≥ 126 mg/dL or glycosylated hemoglobin (HbA1c) greater than 6.4% or antidiabetic medication use. QT-modifying medications were defined as any medication included in the following categories: antidepressants, antipsychotics, antiarrhythmics, muscle relaxants, antimicrobials (antivirals/ macrolides/fluoroquinolones), tacrolimus, anticonvulsants, and antiemetics. Medication data (clearly noted as taking in EMR or study visits) was recorded in 76% of biologics, 92% of steroids, 77% of statin, 79% of aspirin, and 38% of any QTc prolonging medications. If QTc prolonging
medication use (categorical variable) was not reported on the medication list, it was assumed that the patient was not on QTc prolonging medications.

**Laboratory Covariates**

**SLE**

Laboratory measures, including anti-cardiolipin IgG/IgM (acL IgG/IgM), anti-nuclear antigen (ANA), anti-extra nuclear antigen (anti-ENA), double strand DNA antibody, lupus anticoagulant (LAC), anti-Sjogren's syndrome type a/b antibody (SSA/SSB), anti-Smith, U1 small nuclear ribonucleoprotein antibody (U1-RNP), C-reactive protein (CRP), and complement levels (C3, C4) were collected from the EMR.

**RA Cohorts (ESCAPE-RA/RHYTHM)**

Rheumatoid factor (seropositivity ≥ 40 units; IBL America, Minneapolis, MN) and Anti-CCP (anticyclic citrullinated peptide antibody) (seropositivity ≥ 60 units; Inova Diagnostics, Woburn, MA) were measured using Enzyme-Linked Immunosorbent Assay (ELISA). The levels of C-reactive protein (CRP) was measured in the Biomarkers Core Laboratory of the CUIMC Clinical and Translational Research Center.

**Statistical Analysis**

Variables were summarized and compared using Student’s t-tests if normally distributed, Wilcoxon rank-sum tests for non-normally distributed variables, or χ² or Fisher’s exact tests for categorical variables. Linear and logistic regression were used to model the associations of clinical and laboratory covariates with QTc length (continuous), and with QTc ≥ 440 ms and QTc ≥ 500 ms, respectively. Multivariable models were constructed by including any covariate significantly (p < 0.25) associated with the primary outcomes (QTc length, QTc ≥ 440 ms, QTc ≥ 500 ms) in univariate regression models. All analyses were performed using Stata version 15 (StataCorp, College Station, TX).

Multiple chained imputations were used to impute medication use for those with missing data for medications associated with QTc length (continuous) and QTc ≥ 440 and ≥ 500.

**Results**

**Patient Population:** Patient disease characteristics, medications, and CV risk factors of combined SLE and RA cohorts are summarized in Table 1. Of the 530 study patients included in the study, 371 (70%) reported HCQ use at the time of ECG assessment. In the combined SLE/RA cohort, the mean QTc was 437 ± 29ms. The mean QTc measurements for the SLE and RA cohorts were 432 ± 23ms and 444 ± 33ms, respectively. Forty-four % of the combined group had a QTc ≥ 440 ms and 7% had a QTc ≥ 500 ms. On average, the cohort was middle aged (51 ± 14 years), predominantly female (83%) and non-white race (combined Black, Hispanic, and other race: 62%). The median disease duration was 12 years, and 65%
medications. On stratification by HCQ use, HCQ users were significantly younger and used more glucocorticoids and statins \((p < 0.005)\) than non-HCQ users. No arrhythmic episodes or associated deaths were reported during the study periods for the RA or the SLE cohorts (2011–2020 and 2015–2019, respectively).
Table 1  
Baseline Characteristics SLE + RA (N = 530) Stratified by HCQ Use

| Clinical Characteristics | HCQ (N = 371) | NO HCQ (N = 159) | p-value |
|--------------------------|---------------|------------------|---------|
| Demographics             |               |                  |         |
| Female n (%)             | 329 (89)      | 136 (87)         | 0.51    |
| Age (Mean ± SD)          | 46.3(14.1)    | 55.3 (13.1)      | < 0.005 |
| Race                     |               |                  |         |
| White n (%)              | 83 (23)       | 57 (37)          | 0.001   |
| Black n (%)              | 107 (29)      | 33 (21)          | 0.052   |
| Hispanic n (%)           | 166 (46)      | 60 (38)          | 0.13    |
| Other n (%)              | 8 (2)         | 6 (3.8)          | 0.29    |
| Disease Characteristics  |               |                  |         |
| Disease duration years (Mean ± SD) | 12.4 (9.03) | 11.5 (12.3) | 0.43    |
| Immunosuppressant Use    |               |                  |         |
| Current biologics use n/total (%) | 67/238 (28.1) | 59/159 (37.1) | 0.060   |
| Current steroid use n/total (%) | 293/340 (86.2) | 61/159 (38.4) | < 0.005 |
| CVD Risk Factors         |               |                  |         |
| Hypertension n/total (%) | 170/369 (46.1)| 76/155 (49)     | 0.54    |
| Diabetes Mellitus n/total (%) | 25/368(7) | 20/154(13) | 0.02    |
| Current smoking n/total (%) | 23/371 (6.2) | 15/158 (9.5) | 0.18    |
| Current statin use n/total (%) | 79/244 (32.4) | 30/159(18.9) | 0.003   |
| Current aspirin use n/total (%) | 147/257 (57.2) | 31/159(19.5) | < 0.005 |
| Ejection Fraction% (Mean ± SD) | 58.1 ± 9.4 | 62.2 ± 5.1 | < 0.005 |
| Ejection Fraction ≥ 55% n/total (%) | 337/371 (90.8) | 150/159 (93.3) | 0.18    |
| QTc average (Mean ± SD)  | 434 ± 25.7    | 441 ± 30.3       | 0.0079  |
| QTc ≥ 440 n (%)          | 134/371 (36.1)| 86/159 (54.1)   | < 0.005 |
| QTc ≥ 500 n (%)          | 13/371 (3.5)  | 23/159 (14.5)    | < 0.005 |

Abbreviations: CVD, Cardiovascular Disease; HCQ, hydroxychloroquine; QtC, QT Corrected Interval; SD, Standard Deviation
| Clinical Characteristics     | HCQ (N = 371) | NO HCQ (N = 159) | p-value |
|-----------------------------|--------------|-----------------|---------|
| Any QTc meds n/total (%)    | 170/368 (46.2) | 52/148 (35.1)   | 0.022   |
| Antidepressants n/total (%) | 61/173 (35.3)  | 32/44 (72.7)    | < 0.005 |
| Antipsychotics n/total (%)  | 15/150 (10)   | 4/18 (22.2)     | 0.13    |
| Antiarrhythmics n/total (%) | 3/145 (2.07)  | 8/25 (32)       | < 0.01  |
| Muscle relaxants n/total (%)| 11/148 (7.4)  | 5/22 (22.7)     | 0.038   |
| Antimicrobials n/total (%)  | 83/157 (52.9) | 12/20 (60)      | 0.55    |
| Tacrolimus n/total (%)      | 26/155 (16.77)| 1/17 (5.9)      | 0.21    |
| Anticonvulsants n/total (%) | 17/147(11.6)  | 1/18 (5.6)      | 0.39    |
| Antiemetics n/total (%)     | 54/149 (36.2) | 11/20 (55%)     | 0.10    |

Abbreviations: CVD, Cardiovascular Disease; HCQ, hydroxychloroquine; QtC, QT Corrected Interval; SD, Standard Deviation

**Association Between HCQ Use and QTc**

In an adjusted multivariable model, current use of HCQ was not significantly associated with mean QTc length (Table 2), as the mean adjusted QTc was 438 ms vs 437 ms for HCQ vs non-HCQ users, respectively) (Fig. 2). In the SLE only cohort, adjusted QTc was comparable in HCQ vs non-HCQ users (433 ms vs 427 ms, respectively) (Fig. 3). Similarly, in the RA only cohort, adjusted QTc was comparable in HCQ vs non-HCQ users (450 ms vs 443 ms) (Fig. 4). HCQ use was not a significant predictor of a QTc 440 ms for the combined cohort (OR = 0.77; 95% CI 0.48–1.23, p = 0.27) (Table 3) in multivariable logistic models. Current HCQ use was inversely associated with QTc500 ms (OR = 0.39; 95% CI 0.16–0.98; p = 0.044) (Table 4).
| Clinical Covariates                                | Univariable Model QTc (Continuous) | Multivariable Model QTc (Continuous) |
|--------------------------------------------------|------------------------------------|-------------------------------------|
|                                                  | $B$  | $p$    | $a$  | $B$  | $p$    |
| Age                                              | 0.38 | < 0.005 | 0.21 | 0.033 |
| Sex                                               | 0.31 | 0.92   | -----| ----- |
| Race (white vs non-white)                         | 6.2  | < 0.05  | -0.29| 0.92  |
| Disease duration (square root)                    | -0.1 | 0.86   | -----| ----- |
| Current HCQ use                                   | -7.8 | < 0.005 | 0.22 | 0.95  |
| Current prednisone use                            | -9.8 | < 0.005 | -8.27| 0.018 |
| Current biologic use                              | 0.45 | 0.87   | -----| ----- |
| Hypertension                                      | 3.6  | 0.11   | 3.01 | 0.29  |
| Current smoking                                   | 10.6 | < 0.05  | 10.2 | 0.033 |
| Diabetes                                          | 8.9  | < 0.05  | 0.69 | 0.88  |
| Current statin use                                | 2.7  | 0.38   | -----| ----- |
| Current aspirin use                               | -7.1 | < 0.05  | -3.9 | 0.22  |
| Any QTc meds                                      | -1.4 | 0.56   | -----| ----- |
| Antidepressants                                   | 7.1  | < 0.05  | -----| ----- |
| Antipsychotics                                    | -1.6 | 0.80   | -----| ----- |
| Antiarrhythmics                                   | 5.4  | 0.49   | -----| ----- |
| Musclerelaxants                                   | 9.6  | 0.12   | -----| ----- |
| Antimicrobials                                    | -0.2 | 0.96   | -2.4 | 0.46  |
| Antiemetics                                       | 1.8  | 0.63   | -----| ----- |
| Anticonvulsants                                   | 7.9  | 0.21   | -----| ----- |
| Tacrolimus                                        | -0.5 | 0.92   | -----| ----- |
| Ejection fraction %                               | 0.05 | 0.77   | -----| ----- |

**Abbreviations:** HCQ, hydroxychloroquine; QtC, QT Corrected Interval
| Clinical Covariates | Univariable Model QTc (Continuous) | Multivariable Model QTc (Continuous)\(^a\) |
|---------------------|-----------------------------------|------------------------------------------|
|                     | \(Bp\)                           | \(Bp\)                                   |
| Ejection fraction \(\geq 55\%\) | -3.2 0.47                         | --- ---                                 |
| Prob > F            | ---                               | 0.0001                                   |

**Abbreviations:** HCQ, hydroxychloroquine; QtC, QT Corrected Interval

\(^a\)represents final imputed data
Table 3
Associations of Clinical Characteristics with QTc ≥ 440 ms in Combined SLE/RA Cohort

| Clinical Covariates                          | Univariable Model QTc ≥ 440 ms | Multivariable Model QTc ≥ 440 ms<sup>b</sup> |
|---------------------------------------------|--------------------------------|---------------------------------------------|
|                                             | OR 95% CI p                     | OR 95% CI p                                  |
| Age                                         | 1.02 (1.00-1.03)                | 1.00 (0.99-1.02)                             |
| Sex                                         | 1.29 (0.86-1.96)                | ---                                         |
| Race (white vs non-white)                   | 1.48 (1.07-2.03)                | 1.06 (0.68-1.63)                             |
| Disease duration (square root)              | 0.96 (0.86-1.07)                | ---                                         |
| Current HCQ use                             | 0.48 (0.33-0.70)                | 0.77 (0.48-1.23)                             |
| Current prednisone use                      | 0.46 (0.33-0.64)                | 0.56 (0.34-0.92)                             |
| Current biologic use                        | 0.83 (0.58-1.19)                | ---                                         |
| Hypertension                                | 1.18 (0.87-1.61)                | ---                                         |
| Current smoking                             | 1.46 (0.82-2.60)                | ---                                         |
| Diabetes                                    | 1.64 (0.95-2.83)                | 1.38 (0.70-2.72)                             |
| Current statin use                          | 1.08 (0.73-1.60)                | ---                                         |
| Current ASA use                             | 0.51 (0.36-0.73)                | 0.68 (0.43-1.07)                             |
| Any QTc meds                                | 1.07 (0.78-1.47)                | ---                                         |
| Antidepressants                             | 1.79 (1.07-2.99)                | 1.45 (0.90-2.33)                             |
| Antipsychotics                              | 1.62 (0.62-4.22)                | ---                                         |
| Antiarhythmics                              | 1.48 (0.43-5.06)                | ---                                         |
| Musclerelaxants                             | 1.41 (0.57-3.46)                | ---                                         |
| Antimicrobials                              | 0.99 (0.62-1.58)                | ---                                         |
| Antiemetics                                 | 1.15 (0.63-2.08)                | ---                                         |
| Anticonvulsants                             | 2.33 (0.54-1.93)                | ---                                         |
| Tacrolimus                                  | 1.63 (0.72-3.69)                | ---                                         |
| Ejection fraction %                         | 1.00 (0.98-1.03)                | ---                                         |

<sup>b</sup>represents imputed data

Abbreviations: HCQ, hydroxychloroquine; QTcMeds, QTc prolonging medications
| Clinical Covariates | Univariable Model QTc ≥ 440 ms | Multivariable Model QTc ≥ 440 ms<sup>b</sup> |
|---------------------|-------------------------------|---------------------------------------------|
| Ejection fraction ≥ 55% | 0.81 (0.44–1.49) | 0.50 |
|                       | | 0.0001 |

**Abbreviations:** HCQ, hydroxychloroquine; QTcMeds, QTc prolonging medications

<sup>b</sup>represents final imputed data
Table 4
Associations of Clinical Characteristics with QTc ≥ 500 ms in Combined SLE/RA Cohort

| Clinical Covariates                      | Univariable Model QTc ≥ 500 ms | Multivariable Model QTc ≥ 500 ms<sup>c</sup> |
|-----------------------------------------|---------------------------------|-----------------------------------------------|
|                                        | OR 95% CI p                      | OR 95% CI p                                    |
| Age                                     | 0.99 (0.96–1.01)                 | 0.25                                          |
| Sex                                     | 1.12 (0.49–2.57)                 | 0.79                                          |
| Race (white vs non-white)               | 0.92 (0.48–1.76)                 | 0.79                                          |
| Disease duration (square root)          | 0.86 (0.69–1.07)                 | 0.17                                          |
| Current HCQ use                         | 0.21 (0.11–0.44)                 | <0.01                                         |
| Current prednisone use                  | 0.43 (0.23–0.81)                 | 0.010                                         |
| Current biologic use                    | 0.94 (0.48–1.85)                 | 0.86                                          |
| Hypertension                            | 1.37 (0.74–2.55)                 | 0.31                                          |
| Current smoking                         | 2.71 (1.13–6.45)                 | 0.025                                         |
| Diabetes                                | 2.73 (1.20–6.23)                 | 0.017                                         |
| Current statin use                      | 0.56 (0.24–1.29)                 | 0.17                                          |
| Current aspirin use                     | 0.39 (0.18–0.83)                 | 0.015                                         |
| Any QTc meds                            | 1.14 (0.63–2.07)                 | 0.66                                          |
| Antidepressants                         | 2.41 (0.88–6.56)                 | 0.085                                         |
| Antipsychotics                          | 1.14 (0.13–9.83)                 | 0.90                                          |
| Antiarhythmics                          | 2.20 (0.25–19.67)                | 0.48                                          |
| Musclerelaxants                         | 3.36 (0.80–14.10)                | 0.098                                         |
| Antimicrobials                          | 0.55 (0.15–2.01)                 | 0.36                                          |

<sup>c</sup> represents imputed data.

**Abbreviations**: HCQ, hydroxychloroquine, QTcMeds, QTc prolonging medications.
| Clinical Covariates | Univariable Model QTc ≥ 500 ms | Multivariable Model QTc ≥ 500 ms<sup>c</sup> |
|---------------------|-------------------------------|---------------------------------|
|                     | OR 95% CI p                   | OR 95% CI p                     |
| Antiemetics         | 1.0                           | 1.0                             |
| Anticonvulsants     | 1.19 0.14–10.29 0.87          | 1.19 0.14–10.29 0.87           |
| Tacrolimus          | 4.29 0.90–20.33 0.067         | 4.29 0.90–20.33 0.067          |
| Ejection fraction % | 1.07 0.99–1.15 0.060          | 1.07 0.99–1.15 0.060           |
| Ejection fraction ≥ 55% | 1.79 0.42–7.63 0.43     | 1.79 0.42–7.63 0.43           |
| Prob > F            | 0.0066                        | 0.0066                          |

Abbreviations: HCQ, hydroxychloroquine, QTcMeds, QTc prolonging medications

<sup>c</sup>represents final imputed data
| Clinical Characteristics | HCQ (N = 329) | NO HCQ (N = 23) | p-value |
|--------------------------|--------------|----------------|---------|
| **Demographics**         |              |                |         |
| Female n (%)             | 297 (90.3%)  | 22 (96.6%)     | 0.71    |
| Age (Mean ± SD)          | 45.0 ± 13.9  | 63.7 ± 15.3    | < 0.05  |
| **Race**                 |              |                |         |
| White n (%)              | 55 (17.0%)   | 7 (30.4%)      | 0.10    |
| Black n (%)              | 106 (32.8%)  | 6 (26.1%)      | 0.50    |
| Hispanic n (%)           | 156 (48.3%)  | 10 (43.5%)     | 0.63    |
| Other n (%)              | 5 (1.55%)    | 0              |         |
| **Disease Characteristics** |          |                |         |
| Disease duration years (Mean ± SD) | 12.8 ± 9.2 | 17.7 ± 10.5 | 0.021  |
| APS n (%)                | 24 (16.4%)   | 4 (22.2%)      | 0.54    |
| aCL IgM n (%)            | 84 (33.7%)   | 8 (40%)        | 0.57    |
| aCL IgG n (%)            | 83 (32.9%)   | 8 (40%)        | 0.52    |
| LN dx n (%)              | 118 (43.1%)  | 12 (57.1%)     | 0.21    |
| DNA n (%)                | 234 (79.0%)  | 15 (68.2%)     | 0.23    |
| Low c3/c4 n (%)          | 202 (78.3%)  | 8 (40%)        | < 0.005 |
| CRP n (%)                | 219 (78.5%)  | 18 (81.8%)     | 0.71    |
| ANA n (%)                | 299 (97.4%)  | 20 (86.9%)     | 0.007   |
| Anti-ENA n (%)           | 108 (61.0%)  | 11 (55%)       | 0.60    |
| U1RNP n (%)              | 132 (51.9%)  | 6 (31.6%)      | 0.086   |
| Smith n (%)              | 110 (42.5%)  | 4 (21.0%)      | 0.067   |
| DNA n (%)                | 234 (79.0%)  | 15 (68.2%)     | 0.23    |
| LAC n (%)                | 57 (28.2%)   | 5 (25%)        | 0.76    |

**Abbreviations:** aCL IgG, Anti-Cardiolipin IgG; aCL IgM, Anti-Cardiolipin IgM; ANA, Anti-Nuclear Antigen; Anti-ENA, Anti-Extra Nuclear Antigen; APS, Antiphospholipid Syndrome; AZA, Azathioprine; Anti-CCP, Cyclic Citrullinated Peptide Antibody; CRP, C-Reactive Protein; DNA, Double Strand DNA Antibody; DMARDs, Disease-Modifying Anti-rheumatic Drug; HCQ, Hydroxychloroquine; LAC, Lupus Anticoagulant; LN dx, Lupus Nephritis Diagnosis; MMF, Mycophenolate Mofetil; QTcMeds, QTc Prolonging Medications; SSA, Anti-Sjögren's Syndrome Type A Antibody; SSB, Anti-Sjögren's Syndrome Type B Antibody; U1RNP, U1 Small Nuclear Ribonucleoprotein Antibody
| Clinical Characteristics | HCQ (N = 329) | NO HCQ (N = 23) | p-value |
|--------------------------|---------------|-----------------|---------|
| SSA n (%)                | 141 (54.0%)   | 8 (24.1%)       | 0.31    |
| SSB n (%)                | 57 (23.3%)    | 2 (10.5%)       | 0.19    |
| Anti-CCP n (%)           | 14 (9.15%)    | 0               | 0.37    |
| **Immunosuppressants**   |               |                 |         |
| Current biologic use n (%) | 53 (27.0%)  | 3 (13.0%)       | 0.145   |
| Cyclophosphamide n (%)   | 64 (31.4%)    | 4 (17.4%)       | 0.16    |
| MMF n (%)                | 163 (67.4%)   | 8 (34.8%)       | 0.002   |
| AZA n (%)                | 86 (39.3%)    | 4 (17.4%)       | 0.039   |
| Current prednisone use n (%) | 281 (94.3%) | 16 (69.6%)      | <0.005  |
| DMARDs (leflunomide) n (%) | 35 (18.3%)  | 1 (4.3%)        | 0.09    |
| **CVD Risk Factors**     |               |                 |         |
| Hypertension n (%)       | 157 (47.7%)   | 19 (82.6%)      | 0.001   |
| Diabetes Mellitus n (%)  | 23 (7.0%)     | 3 (13.0%)       | 0.29    |
| Smoking n (%)            | 310 (94.2%)   | 1 (4.3%)        | 0.77    |
| Current statin use n (%) | 75 (37.1%)    | 10 (43.5%)      | 0.55    |
| Current ASA use n (%)    | 136 (63.3%)   | 17 (73.9%)      | 0.31    |
| Ejection fraction % (Mean ± SD) | 57.2 ± 6.5 | 57.7 ± 9.6     | 0.42    |
| Ejection fraction ≥ 55%  | 297 (90.3%)   | 19 (82.6%)      | 0.24    |
| QTc average (Mean ± SD)  | 431.7 ± 23.9  | 434.6 ± 23.2    | 0.57    |

**Abbreviations:** aCL IgG, Anti-Cardiolipin IgG; aCL IgM, Anti-Cardiolipin IgM; ANA, Anti-Nuclear Antigen; Anti-ENA, Anti-Extra Nuclear Antigen; APS, Antiphospholipid Syndrome; AZA, Azathioprine; Anti-CCP, Cyclic Citrullinated Peptide Antibody; CRP, C-Reactive Protein; DNA, Double Strand DNA Antibody; DMARDs, Disease-Modifying Anti-rheumatic Drug; HCQ, Hydroxychloroquine; LAC, Lupus Anticoagulant; LN dx, Lupus Nephritis Diagnosis; MMF, Mycophenolate Mofetil; QTcMeds, QTc prolonging medications; SSA, Anti-Sjögren's Syndrome Antibody; SS A, Anti-Sjögren's Syndrome Type A Antibody; SSB, Anti-Sjögren's Syndrome Type B Antibody; U1RNP, U1 Small Nuclear Ribonucleoprotein Antibody

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| Clinical Characteristics     | HCQ (N = 329) | NO HCQ (N = 23) | p-value |
|-----------------------------|--------------|----------------|---------|
| QTc ≥ 440 n (%)             | 109 (33.1%)  | 8 (34.8%)      | 0.87    |
| QTc ≥ 500 n (%)             | 9 (2.7%)     | 0              |         |
| Any QTc meds n(%)           | 158 (48.2%)  | 16 (69.6%)     | 0.047   |
| Antidepressants             | 51 (21.3%)   | 6 (33.3%)      | 0.86    |
| Antipsychotics              | 13 (8.8%)    | 3 (17.6%)      | 0.22    |
| Antiarrhythmics             | 3 (2.1%)     | 0              |         |
| Muscle relaxants            | 8 (5.5%)     | 0              |         |
| Antimicrobials              | 82 (52.6%)   | 9 (52.9%)      | 0.98    |
| Tacrolimus                  | 26 (16.8%)   | 1 (5.9%)       | 0.48    |
| Anticonvulsants             | 17 (11.6%)   | 0              | 0.22    |
| Antiemetics                 | 53 (35.8%)   | 8 (47.1%)      | 0.36    |

**Abbreviations:** aCL IgG, Anti-Cardiolipin IgG; aCL IgM, Anti-Cardiolipin IgM; ANA, Anti-Nuclear Antigen; Anti-ENA, Anti-Extra Nuclear Antigen; APS, Antiphospholipid Syndrome; AZA, Azathioprine; Anti-CCP, Cyclic Citrullinated Peptide Antibody; CRP, C-Reactive Protein; DNA, Double Strand DNA Antibody; DMARDs, Disease-Modifying Anti-rheumatic Drug; HCQ, Hydroxychloroquine; LAC, Lupus Anticoagulant; LN dx, Lupus Nephritis Diagnosis; MMF, Mycophenolate Mofetil; QTcMeds, QTc Prolonging medications; SSA, Anti-Sjögren’s Syndrome Type A Antibody; SSB, Anti-Sjögren’s Syndrome Type B Antibody; Sm, Anti-Smith Antibody; U1RNP, U1 Small Nuclear Ribonucleoprotein Antibody.
Table 6
Baseline Characteristics RA (N = 178) Stratified by HCQ Use

| Clinical Characteristics | HCQ (N = 42) | NO HCQ (N = 136) | p-value |
|--------------------------|--------------|------------------|---------|
| **Demographics**         |              |                  |         |
| Female, n (%)            | 32 (76.2%)   | 114 (85.1%)      | 0.18    |
| Age (Mean ± SD)          | 56.7 ± 9.7   | 53.9 ± 12.3      | 0.18    |
| **Race**                 |              |                  |         |
| White                    | 28 (68.29%)  | 50 (37.59%)      | 0.001   |
| Black                    | 1 (2.44%)    | 27 (20.30%)      | 0.006   |
| Hispanic                 | 9 (21.95%)   | 50 (37.59%)      | 0.064   |
| Other                    | 3 (7.32%)    | 6 (4.51%)        | 0.44    |
| **Disease Characteristics** |          |                  |         |
| Disease duration years (Mean ± SD) | 9.6 ± 7.5 | 10.5 ± 12.3 | 0.39    |
| RF n (%)                 | 11 (64.7%)   | 115 (89.1%)      | 0.006   |
| Anti-CCP n (%)           | 14 (82.3%)   | 122 (94.6%)      | 0.094   |
| CRP (Mean ± SD)          | 3.9 ± 7.3    | 5.6 ± 8.1        | 0.11    |
| **Immunosuppressants**   |              |                  |         |
| Current biologic use n (%)| 14 (33.3%) | 56 (41.2%)      | 0.36    |
| Current prednisone use n (%) |12 (28.6%) | 45 (33.1%) | 0.58    |
| **CVD Risk Factors**     |              |                  |         |
| Hypertension n (%)       | 13(32.5%)    | 57(43.2%)        | 0.23    |
| Diabetes mellitus n (%)  | 2 (5%)       | 17(12.9%)        | 0.25    |
| Smoking n (%)            | 4(9.5%)      | 14(10.4%)        | 0.57    |
| Current statin use n (%) | 4 (9.5%)     | 20 (14.7%)       | 0.45    |
| Current ASA use n (%)    | 11 (26.2%)   | 14 (10.3%)       | 0.01    |
| Ejection fraction% (Mean ± SD) | 62.8 ± 5.1 | 62.7 ± 4.8 | 0.89    |
| Ejection fraction ≥ 55% n(%) | 40 (95.2%) | 131 (96.3%) | 0.75    |
| QTc average (Mean ± SD)  | 450.0 ± 33.3 | 442.9 ± 31.3 | 0.24    |

**Abbreviations**: Anti-CCP, *Cyclic Citrullinated Peptide Antibody*; CRP, *C-Reactive Protein*; CVD, *Cardiovascular Disease*; QtC, *QT Corrected Interval*; RF, *Rheumatoid Factor*. 

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### Clinical Characteristics

|                     | HCQ (N = 42) | NO HCQ (N = 136) | p-value |
|---------------------|-------------|------------------|---------|
| QTc ≥ 440 n (%)     | 25 (59.5%)  | 78 (57.3%)       | 0.80    |
| QTc ≥ 500 n (%)     | 4 (9.5%)    | 23 (16.9%)       | 0.24    |
| Any QTc meds n (%)  | 12 (30%)    | 36 (28.8%)       | 0.88    |
| Antidepressants     | 10 (23.8%)  | 26 (19.1%)       | 0.51    |
| Antipsychotics      | 2 (4.8%)    | 1 (0.74%)        | 0.14    |
| Antiarrhythmics     | 0           | 8 (5.9%)         | 0.20    |
| Muscle relaxants    | 3 (7.1%)    | 5 (3.7%)         | 0.39    |
| Antimicrobials      | 1 (2.4%)    | 3 (2.2%)         | ————   |
| Tacrolimus          | ————       | ————            | ————   |
| Anticonvulsants     | 0           | 1 (0.74%)        | ————   |
| Antiemetics         | 1 (2.4%)    | 3 (2.2%)         | ————   |

**Abbreviations:** Anti-CCP, Cyclic Citrullinated Peptide Antibody; CRP, C-Reactive Protein; CVD, Cardiovascular Disease; QTc, QT Corrected Interval; RF, Rheumatoid Factor

### Significant Associations with QTc Length

In multivariable models, age, current prednisone use, and current smoking were significantly associated with QTc length (Table 2). Current prednisone use and current aspirin use were significantly associated with QTc440 ms (Table 3). The only significant predictor of QTc500 ms was current use of tacrolimus (Table 4).

### Subgroup Analyses

#### SLE only cohort

In the SLE cohort, HCQ use was not a significant predictor of QTc length (Table 7) or a QTc440 ms (Table 8). However, of the 11 SLE patients with QTc500 ms, 9/11 were reported to be on HCQ. Given the small sample size, statistically significant differences could not be ascertained between the HCQ groups with a QTc 500ms, yet no arrhythmias or associated deaths were reported, as per retrospective chart review over 4 years. In multivariable analyses, elevated CRP level (≥ 10.0 mg/L) was significantly associated with QTc length, and diabetes and use of any QTc prolonging medications were significantly associated with QTc440 ms (Table 8). Adjusted QTc was comparable in the HCQ vs non-HCQ users groups (433 ms vs 429 ms, respectively) (Fig. 3).
Table 7
Associations of Clinical Characteristics with QTc Length in SLE Cohort

| Clinical Covariates                  | Univariable Model QTc (Continuous) | Multivariable Model QTc (Continuous) |
|--------------------------------------|------------------------------------|--------------------------------------|
|                                      | $B$ $p$                            | $B$ $p$                               |
| Age                                  | 0.21 0.012                         | 0.077 0.46                           |
| Sex                                  | 3.62 0.387                         | —— ——                               |
| Race (white vs non-white)            | -4.89 0.124                        | —— ——                               |
| Disease duration years (square root) | 1.12 0.229                         | —— ——                               |
| LN dx                                | 0.11 0.968                         | —— ——                               |
| ANA                                  | -16.08 0.020                       | -13.93 0.074                        |
| DNA                                  | -6.17 0.053                        | -4.27 0.22                          |
| Anti-ENA                             | -5.98 0.072                        | —— ——                               |
| U1RNP                                | -5.51 0.040                        | —— ——                               |
| SSA                                  | -4.97 0.068                        | —— ——                               |
| SSB                                  | -7.21 0.029                        | —— ——                               |
| Anti-CCP (binary) ≥ 19 units         | 2.90 0.648                         | —— ——                               |
| CRP (binary) ≥ 10.0 mg/L             | 6.72 0.038                         | 9.04 0.020                          |
| Current HCQ use                      | -2.89 0.575                        | 0.81 0.88                           |
| MMF                                  | -1.57 0.619                        | —— ——                               |
| AZA                                  | 2.11 0.484                         | —— ——                               |
| Current DMARDs use                   | 1.41 0.742                         | —— ——                               |
| Current prednisone use               | -2.25 0.663                        | —— ——                               |

Abbreviations: aCL IgG, Anti-Cardiolipin IgG; aCL IgM, Anti-Cardiolipin IgM; ANA, Anti-Nuclear Antigen; Anti-ENA, Anti-Extra Nuclear Antigen; APS, Antiphospholipid Syndrome; AZA, Azathioprine; Anti-CCP, Cyclic Citrullinated Peptide Antibody; CRP, C-Reactive Protein; DNA, Double Strand DNA Antibody; DMARDs, Disease-Modifying Anti-rheumatic Drug; HCQ, Hydroxychloroquine; LAC, Lupus Anticoagulant; LN dx, Lupus Nephritis Diagnosis; MMF, Mycophenolate Mofetil; QTcMeds, QTc prolonging medications; SSA, Anti-Sjögren's Syndrome Type A Antibody; SSB, Anti-Sjögren's Syndrome Type B Antibody; Sm, Anti-Smith Antibody; U1RNP, U1 Small Nuclear Ribonucleoprotein Antibody
| Clinical Covariates          | Univariable Model QTc (Continuous) | Multivariable Model QTc (Continuous)\(^d\) |
|-----------------------------|------------------------------------|-----------------------------------------|
|                             | \(B\) \(p\)                       | \(B\) \(p\)                              |
| Cyclophosphamamide         | -1.43 0.677                        | --- ---                                  |
| Current biologic use        | -5.06 0.167                        | --- ---                                  |
| Smith                       | -5.16 0.059                        | 4.56 0.14                                |
| LAC                         | 1.42 0.685                         | --- ---                                  |
| APS                         | 1.19 0.806                         | --- ---                                  |
| aCL IgG                     | -1.35 0.663                        | --- ---                                  |
| aCL IgM                     | 0.58 0.850                         | --- ---                                  |
| Low c3/c4                   | -5.23 0.110                        | --- ---                                  |
| Hypertension                | 3.50 0.157                         | --- ---                                  |
| Current smoking             | 9.74 0.072                         | 8.49 0.15                                |
| Diabetes mellitus           | 12.72 0.005                        | 5.82 0.27                                |
| Current statin use          | 9.43 0.007                         | 6.29 0.078                               |
| Current aspirin use         | -0.47 0.89                         | --- ---                                  |
| Any QTc meds                | 3.44 0.16                          | --- ---                                  |
| Antidepressants             | 4.60 0.23                          | --- ---                                  |
| Antipsychotics             | 1.56 0.81                          | --- ---                                  |
| Antiarrhythmics             | 9.31 0.52                          | --- ---                                  |
| Musclerelaxants            | 1.32 0.88                          | --- ---                                  |
| Antimicrobials             | -1.11 0.76                         | --- ---                                  |
| Antiemetics                 | 1.45 0.72                          | --- ---                                  |
| Anticonvulsants            | 7.87 0.21                          | --- ---                                  |

**Abbreviations:** aCL IgG, Anti-Cardiolipin IgG; aCL IgM, Anti-Cardiolipin IgM; ANA, Anti-Nuclear Antigen; Anti-ENA, Anti-Extra Nuclear Antigen; APS, Antiphospholipid Syndrome; AZA, Azathioprine; Anti-CCP, Cyclic Citrullinated Peptide Antibody; CRP, C-Reactive Protein; DNA, Double Strand DNA Antibody; DMARDs, Disease-Modifying Anti-rheumatic Drug; HCQ, Hydroxychloroquine; LAC, Lupus Anticoagulant; LN dx, Lupus Nephritis Diagnosis; MMF, Mycophenolate Mofetil; QTcMeds, QTc prolonging medications; SSA, Anti-Sjögren's Syndrome Type A Antibody; SSB, Anti-Sjögren's Syndrome Type B Antibody; Sm, Anti-Smith Antibody; U1RNP, U1 Small Nuclear Ribonucleoprotein Antibody
| Clinical Covariates | Univariable Model QTc (Continuous) | Multivariable Model QTc (Continuous)\(^d\) |
|---------------------|----------------------------------|------------------------------------------|
| Tacrolimus          | \(-0.54\)                        | \(0.92\)                                 |
| Ejection fraction   | \(-0.25\)                        | \(0.15\)                                 |
| Ejection fraction \(\geq 55\%\) | \(-6.81\)                        | \(0.095\)                                |
| Prob > F            | \(0.0023\)                       | \(0.0023\) \(d\)                        |

Abbreviations: aCL IgG, Anti-Cardiolipin IgG; aCL IgM, Anti-Cardiolipin IgM; ANA, Anti-Nuclear Antigen; Anti-ENA, Anti-Extra Nuclear Antigen; APS, Antiphospholipid Syndrome; AZA, Azathioprine; Anti-CCP, Cyclic Citrullinated Peptide Antibody; CRP, C-Reactive Protein; DNA, Double Strand DNA Antibody; DMARDs, Disease-Modifying Anti-rheumatic Drug; HCQ, Hydroxychloroquine; LAC, Lupus Anticoagulant; LN dx, Lupus Nephritis Diagnosis; MMF, Mycophenolate Mofetil; QTcMeds, QTc prolonging medications; SSA, Anti-Sjögren's Syndrome Type A Antibody; SSB, Anti-Sjögren's Syndrome Type B Antibody; Sm, Anti-Smith Antibody; U1RNP, U1 Small Nuclear Ribonucleoprotein Antibody

\(^d\)represents final imputed data
| Clinical Covariates                        | Univariable Model QTc ≥ 440 ms | Multivariable Model QTc ≥ 440 ms<sup>e</sup> |
|-------------------------------------------|--------------------------------|-----------------------------------------------|
|                                           | OR 95% CI p                     | OR 95% CI p                                    |
| Age                                       | 1.01 (0.99–1.02)                | ---                                           |
| Sex                                       | 1.50 (0.68–3.31)                | ---                                           |
| Race (white vs non-white)                 | 0.67 (0.37–1.22)                | ---                                           |
| Disease duration years (square root)      | 1.04 (0.89–1.23)                | ---                                           |
| LN dx                                      | 0.89 (0.56–1.43)                | ---                                           |
| ANA                                        | 0.24 (0.071–0.82)               | 0.43 (0.11–1.65)                              |
| DNA                                        | 0.65 (0.38–1.12)                | ---                                           |
| Anti-ENA                                   | 0.94 (0.52–1.68)                | ---                                           |
| U1RNP                                      | 0.62 (0.38–1.028)               | 0.74 (0.40–1.37)                              |
| SSA                                        | 0.87 (0.53–1.41)                | ---                                           |
| SSB                                        | 0.63 (0.33–1.17)                | ---                                           |
| Anti-CCP (binary) ≥ 19 units               | 1.40 (0.48–4.07)                | ---                                           |
| CRP (binary)                              | 1.58 (0.86–2.91)                | ---                                           |
| ≥ 10.0 mg/L                                | 0.93 (0.38–2.26)                | 2.15 (0.71–6.58)                              |
| Current HCQ use                           | 0.84 (0.49–1.42)                | ---                                           |
| MMF                                        | 0.94 (0.55–1.62)                | ---                                           |
| Current DMARDs use                        | 1.07 (0.52–2.22)                | ---                                           |
| Current prednisone use                    | 0.49 (0.21–1.13)                | 0.43 (0.16–1.17)                              |

Abbreviations: aCL IgG, Anti-Cardiolipin IgG; aCL IgM, Anti-Cardiolipin IgM; ANA, Anti-Nuclear Antigen; Anti-ENA, Anti-Extra Nuclear Antigen; APS, Antiphospholipid Syndrome; AZA, Azathioprine; Anti-CCP, Cyclic Citrullinated Peptide Antibody; CRP, C-Reactive Protein; DNA, Double Strand DNA Antibody; DMARDs, Disease-Modifying Anti-rheumatic Drug; HCQ, Hydroxychloroquine; LAC, Lupus Anticoagulant; LN dx, Lupus Nephritis Diagnosis; MMF, Mycophenolate Mofetil; QTcMeds, QTc prolonging medications; SSA, Anti-Sjögren's Syndrome Type A Antibody; SSB, Anti-Sjögren's Syndrome Type B Antibody; Sm, Anti-Smith Antibody; U1RNP, U1 Small Nuclear Ribonucleoprotein Antibody

<sup>e</sup>represents imputed data
| Clinical Covariates         | Univariable Model QTc ≥ 440 ms OR 95% CI p | Multivariable Model QTc ≥ 440 ms OR 95% CI p |
|-----------------------------|------------------------------------------|-----------------------------------------------|
|                             | OR                                       | 95% CI                                        | p   |
| Cyclophosphamide            | 0.88                                    | 0.49–1.58                                    | 0.67|     |
| Current biologic use        | 0.65                                    | 0.34–1.24                                    | 0.19|     |
| Smith                       | 0.71                                    | 0.43–1.18                                    | 0.19|     |
| LAC                         | 1.03                                    | 0.56–1.88                                    | 0.93|     |
| APS                         | 0.78                                    | 0.33–1.86                                    | 0.58|     |
| aCL IgG                     | 0.71                                    | 0.43–1.22                                    | 0.21|     |
| aCL IgM                     | 0.99                                    | 0.60–1.67                                    | 0.99|     |
| Low c3/c4                   | 0.62                                    | 0.36–1.07                                    | 0.088| 0.73 | 0.37–1.43 | 0.36 |
| Hypertension                | 1.57                                    | 1.02–2.42                                    | 0.041| 1.06 | 0.58–1.92 | 0.86 |
| Current smoking             | 1.52                                    | 0.62–3.72                                    | 0.35|     |     |
| Diabetes Mellitus           | 2.87                                    | 1.35–6.12                                    | 0.006| 3.26 | 1.10–9.67 | 0.033|
| Current statin use          | 1.77                                    | 1.03–3.05                                    | 0.038| 1.64 | 0.71–3.77 | 0.24 |
| Current aspirin use         | 0.73                                    | 0.42–1.26                                    | 0.26|     |     |
| Any QTc meds                | 1.90                                    | 1.23–2.94                                    | 0.004| 1.98 | 1.09–3.59 | 0.024|
| Antidepressants             | 1.52                                    | 0.82–2.85                                    | 0.19|     |     |
| Antipsychotics              | 1.80                                    | 0.64–5.06                                    | 0.27|     |     |
| Antiarrhythmics             | 3.55                                    | 0.31–40.02                                   | 0.30|     |     |
| Musclerelaxants             | 0.56                                    | 0.11–2.88                                    | 0.49|     |     |
| Antimicrobials              | 0.99                                    | 0.54–1.83                                    | 0.99|     |     |
| Antiemetics                 | 1.04                                    | 0.54–1.99                                    | 0.91|     |     |
| Anticonvulsants             | 2.10                                    | 0.76–5.76                                    | 0.15|     |     |

**Abbreviations:** aCL IgG, Anti-Cardiolipin IgG; aCL IgM, Anti-Cardiolipin IgM; ANA, Anti-Nuclear Antigen; Anti-ENA, Anti-Extra Nuclear Antigen; APS, Antiphospholipid Syndrome; AZA, Azathioprine; Anti-CCP, Cyclic Citrullinated Peptide Antibody; CRP, C-Reactive Protein; DNA, Double Strand DNA Antibody; DMARDs, Disease-Modifying Anti-rheumatic Drug; HCQ, Hydroxychloroquine; LAC, Lupus Anticoagulant; LN dx, Lupus Nephritis Diagnosis; MMF, Mycophenolate Mofetil; QTcMeds, QTc prolonging medications; SSA, Anti-Sjögren's Syndrome Type A Antibody; SSB, Anti-Sjögren's Syndrome Type B Antibody; Sm, Anti-Smith Antibody; U1RNP, U1 Small Nuclear Ribonucleoprotein Antibody
| Clinical Covariates | Univariable Model QTc ≥ 440 ms | Multivariable Model QTc ≥ 440 ms<sup>e</sup> |
|---------------------|-----------------------------|---------------------------------|
| Tacrolimus Use      | 1.63 0.72–3.69 0.24          | ——— ——— ———                  |
| Ejection fraction   | 0.98 0.96–1.01 0.30          | ——— ——— ———                  |
| Ejection fraction ≥ 55% | 0.63 0.31–1.25 0.18  | ——— ——— ———                  |
| Prob > F            | ———                         | 0.025                           |

Abbreviations: aCL IgG, Anti-Cardiolipin IgG; aCL IgM, Anti-Cardiolipin IgM; ANA, Anti-Nuclear Antigen; Anti-ENA, Anti-Extra Nuclear Antigen; APS, Antiphospholipid Syndrome; AZA, Azathioprine; Anti-CCP, Cyclic Citrullinated Peptide Antibody; CRP, C-Reactive Protein; DNA, Double Strand DNA Antibody; DMARDs, Disease-Modifying Anti-rheumatic Drug; HCQ, Hydroxychloroquine; LAC, Lupus Anticoagulant; LN dx, Lupus Nephritis Diagnosis; MMF, Mycophenolate Mofetil; QTcMeds, QTc prolonging medications; SSA, Anti-Sjögren's Syndrome Type A Antibody; SSB, Anti-Sjögren's Syndrome Type B Antibody; Sm, Anti-Smith Antibody; U1RNP, U1 Small Nuclear Ribonucleoprotein Antibody

e<sup>e</sup>represents final imputed data
Table 9
Associations of Clinical Characteristics with QTc ≥ 500 ms in SLE Cohort

| Clinical Covariates | Univariable Model QTc ≥ 500 ms |
|---------------------|--------------------------------|
|                     | OR 95% CI p                     |
| Age                 | 0.97 0.93–1.01 0.19             |
| Sex                 | 1.03 0.13–8.32 0.97             |
| Race (white vs non-white) | ----------- |-----------|
| Disease duration years (square root) | 0.83 0.53–1.31 0.43 |
| LN dx               | 1.59 0.47–5.32 0.45             |
| ANA                 | ----------- |-----------|
| DNA                 | ----------- |-----------|
| Anti-ENA            | ----------- |-----------|
| U1RNP               | 0.56 0.13–2.38 0.43             |
| SSA                 | 0.63 0.14–2.89 0.56             |
| SSB                 | 1.33 0.25–7.05 0.73             |
| Anti-CCP (binary)   | 0.63 0.14–2.89 0.56             |
| ≥ 19 units          | ----------- |-----------|
| CRP (binary)        | 0.63 0.14–2.89 0.56             |
| ≥ 10.0 mg/L         | ----------- |-----------|
| Current HCQ use     | 1.064 0.26–4.35 0.93           |
| MMF                 | 1.064 0.26–4.35 0.93           |
| AZA                 | 0.55 0.11–2.77 0.47             |
| Current DMARDs use  | 1.60 0.31–8.26 0.57             |
| Current prednisone use | 0.60 0.072–5.05 0.64 |
| Cyclophosphamide    | 0.31 0.037–2.55 0.27             |
| Current biologic use | 0.39 0.047–3.27 0.39             |

Abbreviations: aCL IgG, Anti-Cardiolipin IgG; aCL IgM, Anti-Cardiolipin IgM; ANA, Anti-Nuclear Antigen; Anti-ENA, Anti-Extra Nuclear Antigen; APS, Antiphospholipid Syndrome; AZA, Azathioprine; Anti-CCP, Cyclic Citrullinated Peptide Antibody; CRP, C-Reactive Protein; DNA, Double Strand DNA Antibody; DMARDs, Disease-Modifying Anti-rheumatic Drug; HCQ, Hydroxychloroquine; LAC, Lupus Anticoagulant; LN dx, Lupus Nephritis Diagnosis; MMF, Mycophenolate Mofetil; QTcMeds, QTc prolonging medications; SSA, Anti-Sjögren's Syndrome Type A Antibody; SSB, Anti-Sjögren's Syndrome Type B Antibody; U1RNP, U1 small nuclear ribonucleoprotein.
| Clinical Covariates | Univariable Model QTc ≥ 500 ms |
|---------------------|--------------------------------|
|                     | OR 95% CI p                     |
| Smith               | 8.89 1.06–74.87 0.044           |
| LAC                 |                                  |
| APS                 |                                  |
| aCL IgG             | 1.51 0.33–6.88 0.60             |
| aCL IgM             | 0.74 0.14–3.87 0.72             |
| Low c3/c4           | 0.65 0.16–2.67 0.55             |
| Hypertension        | 1.77 0.51–6.15 0.37             |
| Current Smoking     | 1.71 0.21–14.03 0.62             |
| Diabetes Mellitus   |                                  |
| Current statin use  | 1.23 0.32–4.70 0.76             |
| Current aspirin use | 0.67 0.17–2.56 0.56             |
| Any QTc meds        | 1.88 0.54–6.54 0.32             |
| Antidepressants     | 0.66 0.13–3.37 0.62             |
| Antipsychotics      |                                  |
| Antiarrhythmics     |                                  |
| Musclerelaxants     |                                  |
| Antimicrobials      | 0.14 0.017–1.21 0.075           |
| Antiemetics         |                                  |
| Anticonvulsants     |                                  |
| Tacrolimus Use      | 4.29 0.90–20.33 0.067           |
| Ejection fraction   | 1.12 0.91–1.39 0.28             |

**Abbreviations:** aCL IgG, Anti-Cardiolipin IgG; aCL IgM, Anti-Cardiolipin IgM; ANA, Anti-Nuclear Antigen; Anti-ENA, Anti-Extra Nuclear Antigen; APS, Antiphospholipid Syndrome; AZA, Azathioprine; Anti-CCP, Cyclic Citrullinated Peptide Antibody; CRP, C-Reactive Protein; DNA, Double Strand DNA Antibody; DMARDs, Disease-Modifying Anti-rheumatic Drug; HCQ, Hydroxychloroquine; LAC, Lupus Anticoagulant; LN dx, Lupus Nephritis Diagnosis; MMF, Mycophenolate Mofetil; QTcMeds, QTc prolonging medications; SSA, Anti-Sjögren's Syndrome Type A Antibody; SSB, Anti-Sjögren's Syndrome Type B Antibody; Sm, Anti-Smith Antibody; U1RNP, U1 Small Nuclear Ribonucleoprotein Antibody

**RA only cohorts**
In the RA cohorts analyzed separately, HCQ use was not a significant predictor of QTc length (Table 10), nor of a QTc 440 (p = 0.79) or 500 ms (p = 0.75) (Tables 11 and 12). Notably, significant predictors of prolonged QTc500 ms included age, current smoking, and diabetes (Table 12). Adjusted QTc was comparable in HCQ vs non-HCQ users (449 ms vs 443 ms, respectively) (Fig. 4).
| Clinical Covariates                          | Univariable Model QTc (Continuous) | Multivariable Model QTc (Continuous) |
|---------------------------------------------|-----------------------------------|--------------------------------------|
|                                             | $B$ $p$                           | $B$ $p$                              |
| Age                                         | 0.35 $< 0.10^*$                   | 0.047 0.86                           |
| Sex                                         | 5.19 0.23                        | 2.23 0.75                            |
| Race (white vs non-white)                   | 5.24 0.203                       | 4.06 0.47                            |
| Disease duration years (square root)        | -0.010 0.99                      | —— ——                                |
| Current use of HCQ                          | 7.08 0.22                        | 6.25 0.32                            |
| Current use of prednisone                   | -3.53 0.40                       | —— ——                                |
| Current use of biologics                    | 0.11 0.98                        | —— ——                                |
| Hypertension                                | 6.61 0.10                        | 6.40 0.28                            |
| Current smoking                             | 8.14 0.23                        | 12.07 0.18                           |
| Diabetes Mellitus                           | 3.70 0.61                        | —— ——                                |
| Current use of statin                       | 2.10 0.70                        | —— ——                                |
| Current use of aspirin                      | -4.13 0.39                       | —— ——                                |
| Any QTc meds                                | -1.30 0.78                       | —— ——                                |
| Antidepressants                              | -3.48 0.50                       | —— ——                                |
| Antipsychotics                              | -38.27 0.10                      | -34.92 0.13                          |
| Antiarrhythmics                             | -8.27 0.51                       | —— ——                                |
| MuscleRelaxants                             | 3.92 0.68                        | —— ——                                |
| Antimicrobials                              | 10.40 0.53                       | —— ——                                |
| Antiemetics                                 | -6.13 0.65                       | —— ——                                |
| Anticonvulsants                             | —— ——                            | —— ——                                |
| Ejection fraction                           | 0.48 0.42                        | —— ——                                |
| Ejection fraction $>$ 55%                   | -10.74 0.43                      | —— ——                                |
| Prob $>$ F                                  | —— 0.30                          | —— ——                                |
| R-Squared                                   | —— 0.056                         | —— ——                                |

Abbreviations: HCQ, Hydroxychloroquine; QTc meds, QTc prolonging medications.
| Clinical Covariates | Univariable Model QTc (Continuous) | Multivariable Model QTc (Continuous) |
|--------------------|-----------------------------------|-------------------------------------|
|                    | $B \ p$                           | $B \ p$                             |
| Adjusted R-Squared | _____                             | 0.0095                              |

**Abbreviations:** HCQ, Hydroxychloroquine; QTc meds, QTc prolonging medications
### Table 11

Associations of Clinical Characteristics with QTc ≥ 440 ms in RA Cohort

| Clinical Covariates                          | Univariable Model QTc ≥ 440 ms | Multivariable Model QTc ≥ 440 ms |
|----------------------------------------------|--------------------------------|----------------------------------|
|                                              | OR 95% CI p                     | OR 95% CI p                      |
| Age                                          | 1.00 0.98–1.023 0.90            | —— 0.53–2.29 0.79               |
| Sex                                          | 1.99 1.18–3.35 0.010            | 1.76 0.79–3.92 0.17             |
| Race (white vs non-white)                    | 1.27 0.79–2.05 0.32             | —— —— ——                       |
| Disease duration years (square root)         | 0.99 0.85–1.15 0.87             | —— —— ——                       |
| Current use of HCQ                           | 1.09 0.54–2.21 0.80             | 1.10 0.53–2.29 0.79            |
| Current use of prednisone                    | 0.79 0.49–1.29 0.35             | —— —— ——                       |
| Current use of biologics                     | 0.72 0.45–1.15 0.17             | 0.77 0.42–1.44 0.42            |
| Hypertension                                 | 1.05 0.65–1.69 0.84             | —— —— ——                       |
| Current smoking                              | 1.14 0.52–2.47 0.75             | —— —— ——                       |
| Diabetes Mellitus                            | 0.83 0.38–1.85 0.66             | —— —— ——                       |
| Current use of statin                        | 1.029 0.54–1.94 0.93            | —— —— ——                       |
| Current use of aspirin                       | 0.68 0.39–1.20 0.18             | 0.92 0.38–2.22 0.85            |
| Any QTc meds                                  | 0.87 0.51–1.49 0.62             | —— —— ——                       |
| Antidepressants                               | 0.77 0.44–1.37 0.38             | —— —— ——                       |
| Antipsychotics                                | 0.37 0.034–4.19 0.43            | —— —— ——                       |
| Antiarrhythmics                               | 0.44 0.10–1.90 0.27             | —— —— ——                       |
| MuscleRelaxants                               | 1.01 0.34–2.99 0.98             | —— —— ——                       |
| Antimicrobials                                | 4.68 0.56–39.34 0.16            | —— —— ——                       |
| Antiemetics                                   | 0.37 0.067–2.063 0.26           | —— —— ——                       |
| Anticonvulsants                               | —— —— ——                       | —— —— ——                       |
| Ejection fraction                             | 0.99 0.93–1.06 0.88             | —— —— ——                       |
| Ejection fraction > 55%                       | 0.43 0.086–2.17 0.31            | —— —— ——                       |
| Prob > Chi2                                   | —— 0.58                        | —— —— ——                       |

*Abbreviations: HCQ, Hydroxychloroquine; QTc meds, QTc prolonging medications*
### Clinical Covariates

|                      | Univariable Model QTc ≥ 440 ms | Multivariable Model QTc ≥ 440 ms |
|----------------------|-------------------------------|----------------------------------|
|                      | OR 95% CI p                   | OR 95% CI p                      |
| Pseudo R-Squared     | ---                           | 0.012                            |

**Abbreviations:** HCQ, Hydroxychloroquine; QTc meds, QTc prolonging medications
## Table 12
Associations of Clinical Characteristics with QTc ≥ 500 ms in RA Cohort

| Clinical Covariates                      | Univariable Model QTc ≥ 500 ms | Multivariable Model QTc ≥ 500 ms |
|------------------------------------------|---------------------------------|----------------------------------|
|                                          | OR 95% CI p                      | OR 95% CI p                      |
| Age                                      | 0.95 (0.92–0.98)                 | 0.94 (0.90–0.98)                 |
| Sex                                      | 1.73 (0.68–4.36)                 | 0.59 (0.17–2.11)                 |
| Race (white vs non-white)                | 0.59 (0.27–1.25)                 | 1.01 (0.38–2.70)                 |
| Disease duration years (square root)     | 0.95 (0.74–1.22)                 |                                  |
| Current use of HCQ                       | 0.54 (0.18–1.68)                 | 0.82 (0.24–2.78)                 |
| Current use of prednisone                | 0.91 (0.41–2.03)                 |                                  |
| Current use of biologics                 | 0.91 (0.43–1.93)                 |                                  |
| Hypertension                             | 1.41 (0.67–2.98)                 |                                  |
| Current smoking                          | 2.62 (0.97–7.06)                 | 3.60 (1.06–12.25)                |
| Diabetes Mellitus                        | 4.57 (1.80–11.64)                | 4.57 (1.12–17.23)                |
| Current use of statin                    | 0.55 (0.16–1.89)                 |                                  |
| Current use of aspirin                   | 0.55 (0.18–1.64)                 |                                  |
| Any QTc meds                             | 1.51 (0.71–3.19)                 |                                  |
| Antidepressants                          | 1.57 (0.72–3.44)                 |                                  |
| Antipsychotics                           | 3.49 (0.31–39.38)                |                                  |
| Antiarrhythmics                          | 0.98 (0.12–8.16)                 |                                  |
| Muscle Relaxants                         | 1.15 (0.25–5.34)                 |                                  |
| Antimicrobials                           | 5.48 (1.18–25.48)                | 1.26 (0.077–20.50)               |
| Antiemetics                              |                                  |                                  |
| Anticonvulsants                          |                                  |                                  |
| Ejection fraction                        | 0.99 (0.90–1.08)                 |                                  |
| Ejection fraction > 55%                  | 0.42 (0.083–2.18)                |                                  |
| Prob > Chi2                              |                                  | 0.045                            |
| Pseudo R-Squared                         |                                  | 0.11                             |

**Abbreviations:** HCQ, Hydroxychloroquine; QTc meds, QTc prolonging medications.
Interaction with other QTc prolonging medications

In the combined RA + SLE cohort, a significant interaction was found between HCQ use and use of antipsychotics (Table 13a), with QTc length being longer in those on both vs only HCQ (439 ms vs 432 ms; Fig. 5). Overall, QTc length was comparable in those on HCQ + any QTc prolonging medications vs only HCQ (434 ms vs 433 ms; Fig. 6). When stratified by RA vs SLE cohort, no significant interactions were found between HCQ use and use of any QTc medications (Table 13b-13c).

**Table 13**
a. Interactions in Combined SLE/RA Cohort

| QTc                                | B  | p   |
|------------------------------------|----|-----|
| Current HCQ Use#AnyQTcMeds         | 3.70 | 0.52 |
| Current HCQ Use#Antidepressants    | 4.35 | 0.65 |
| Current HCQ Use#Antipsychotics     | 40.1 | 0.01 |
| Current HCQ Use#Antiarrhythmics    | 7.46 | 0.68 |
| Current HCQ Use#Musclerelaxants   | -2.95 | 0.89 |
| Current HCQ Use#Antimicrobials    | -1.47 | 0.90 |
| Current HCQ Use#Antiemetics       | 2.97 | 0.80 |
| Current HCQ Use#Tacrolimus         | 22.23 | 0.39 |

**Table 13**
b. Interactions in RA Cohort

| QTc                                | B  | p   |
|------------------------------------|----|-----|
| Current HCQ Use#AnyQTcMeds         | -5.53 | 0.68 |
| Current HCQ Use#Antidepressants    | -15.9 | 0.26 |
| Current HCQ Use#Antipsychotics     | -36.3 | 0.26 |
| Current HCQ Use#Musclerelaxants   | 1.10 | 0.97 |
| Current HCQ Use#Antimicrobials    | 6.17 | 0.88 |
| Current HCQ Use#Antiemetics       | -53.4 | 0.15 |
Table 13  
b. Interactions in RA Cohort

| Interactions                          | B   | p   |
|---------------------------------------|-----|-----|
| Current HCQ Use#AnyQTcMeds            | -5.53 | 0.68 |
| Current HCQ Use#Antidepressants       | -15.9  | 0.26 |
| Current HCQ Use#Antipsychotics        | -36.3  | 0.26 |
| Current HCQ Use#Musclerelaxants       | 1.10  | 0.97 |
| Current HCQ Use#Antimicrobials        | 6.17  | 0.88 |
| Current HCQ Use#Antiemetics           | -53.4  | 0.15 |

**Discussion**

In this large cohort of RA and SLE patients, HCQ use was not associated with QTc length when adjusted for potential confounders such as age and other medications affecting QTc length. The adjusted QTc length was comparable between HCQ users and non-users (438 ms vs 437 ms). Although up to 44% of the combined cohort had a QTc $\geq$ 440 ms, HCQ use was not a predictor of prolonged QTc.

QTc length as an outcome remains of paramount interest, since in the general population and in selected subpopulations (i.e. the elderly, patients with coronary artery disease, and the critically ill), prolonged QTc length (defined in those studies as $>450$ ms in men and $>470$ ms in women) independently predicts sudden cardiac death([17](#), [18](#)). In fact, even moderate QTc prolongation between 420–440 ms has been associated with all-cause mortality([19](#)). In a retrospective cohort study of RA patients, idiopathic QTc prolongation([20](#)) was associated with an almost 30% increase in all-cause mortality (HR: 1.28; 95% CI: 0.91–1.81, $p = 0.16$). Furthermore, in a prospective cohort of RA patients, a 50-ms increase in QTc interval was independently associated with a two-fold risk of mortality (HR = 2.18, 95% CI 1.09, 4.35), but this association was lost when CRP was added to the final model (HR = 1.73; 95% CI 0.83, 3.62; $p = 0.143$)(8).

In our study, prednisone use was associated with a lower QTc length in the combined RA + SLE cohort, in addition to being a negative predictor of QTc $\geq$ 440 ms, further signaling a possible interplay between inflammation and arrhythmogenic potential.

HCQ-associated QTc prolongation and subsequent arrhythmia development received considerable attention during its widespread use in COVID-19 patients. In an uncontrolled study of COVID-19 patients receiving HCQ alone or HCQ and azithromycin for associated pneumonia(6), baseline to treatment change in QTc was higher in the HCQ + azithromycin group vs HCQ alone. It is also worthwhile noting that in the prior study, up to 19% of those receiving HCQ alone had a QTc $> 500$ ms (and 21% in combination group) and 8% had a clinically significant increase $> 60$ ms, with one episode of torsades de pointes reported. However, independent effects of COVID-19 infection on the cardiac conduction system([7](#)) and indication bias (severe COVID-19 patients more likely to receive HCQ) must be considered in interpretation.

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to treatment in the HCQ and azithromycin group vs HCQ alone (17 ± 39 ms vs 0.5 ± 40 ms; p = 0.07). More concerning, up to 12% of total patients in this study (receiving HCQ alone, azithromycin alone, or both), had critical QTc prolongation (defined as maximum QTc ≥ 500 ms if QRS < 120 ms or QTc ≥ 550 ms if QRS ≥ 120 ms) and QTc increase of ≥ 60 ms), however no torsades de pointes was documented. The results of a more recent randomized controlled trial (22) were more reassuring in that, in 1,561 COVID patients randomized to the HCQ arm and loaded with high doses of HCQ (800 mg x 2 doses followed by 400 mg every 12 hours for 9 days or until discharge), there were no significant differences in terms of frequency of arrhythmias compared to the usual care group.

As for rheumatologic patients, SLE patients treated with high cumulative doses (700g-1300g) of antimalarials from several months to decades, demonstrated bundle branch block and third degree AV block (with some leading to Torsades de Pointes)(23–26). However, interpretation from these case reports is limited due to absence of controls. It is also important to note that current trends in HCQ dosing have become more conservative due to heightened awareness of retinal toxicity. More recently, Lane et al(27) reported no increased risk of cardiac arrhythmias (calibrated HR 0.90; 95% CI 0.78–1.03; p < 0.01) in HCQ users (400 mg/day for 30 days) vs sulfasalazine users in a retrospective review of 14 multinational databases of RA patients. Liu et al(28) reported a lower risk of CV disease including sudden cardiac arrest/death in HCQ/chloroquine (CQ) users vs non-users (RR 0.72; 95% CI 0.56–0.94; p = 0.013) in a meta-analysis of various rheumatologic patients. Various cardioprotective (thromboprotective and cholesterol reducing) effects of HCQ/CQ(29, 30) may partially explain this finding but the absence of clinical trial data and CV/metabolic parameters limit interpretation. In another prospective study(31) of RA patients, incidence of long QT syndrome or arrhythmia related hospitalizations were comparable between HCQ use vs non-HCQ disease modifying anti-rheumatic drug (DMARD) use.

Specifically, the lack of association of HCQ use with overall QTc length in our results is consistent with prior publications in RA and SLE patients(8–11, 20). The main strength of our study is its sample size as it represents one of the largest multiethnic studies inclusive of both SLE and RA patients. Importantly, we accounted for the concurrent use of a wide variety of QTc prolonging or arrhythmogenic medications, which was not consistently done in previous literature. Although SLE data were obtained retrospectively via ICD 9/10 codes on EMR review, we restricted analyses to SLE patients who demonstrated consistent care at our institution (≥ 2 visits). For both the SLE and RA cohorts, QTc length was calculated by standardized Bazett’s formula and confirmed by a blinded, trained cardiac electrophysiologist (PP). The main limitations of our study include the lack of data on HCQ adherence (i.e. via patient report, and/or metabolite levels), as well as cumulative dosage or length of therapy. In addition, we did not obtain or analyze pre-HCQ ECGs (determined only at the time of HCQ use for both SLE and RA cohorts) and therefore, cannot make conclusions about pre and post exposure change in QTc length. Finally, although we excluded patients with clinical CVD and our findings may not directly apply to those patients, our patients likely had underlying, subclinical CVD given the prevalence of associated risk factors (hypertension, diabetes).
In a combined large multiethnic cohort of RA and SLE patients, QTc length did not significantly differ in HCQ users compared with non-HCQ users, nor was it associated with a QTc $\geq 440$ ms, even while adjusting for potential confounders. There was a notable statistical interaction between the use of HCQ and use of antipsychotics in the combined RA and SLE cohort. Our data suggests that HCQ does not increase the arrhythmogenic risk for patients with rheumatologic conditions.

**Abbreviations**

Acl IgG/IgM  
Anti-cardiolipin IgG/IgM  
ACR  
American College of Rheumatology  
ANA  
Anti-nuclear antigen  
Anti-CCP  
Anticyclic citrullinated peptide antibody  
Anti-ENA  
Anti-extra nuclear antigen  
BP  
Blood pressure  
COVID19  
Coronavirus disease 19  
CQ  
Chloroquine  
CRP  
C-reactive protein  
CUIMC  
Columbia University Irving Medical Center  
CV/D  
Cardiovascular Disease  
DMARD  
Disease modifying anti-rheumatic drug  
ECG  
Electrocardiograms  
ELISA  
Enzyme-Linked Immunosorbent Assay  
EMR  
Electronic Medical Record  
ESCAPE-RA  
Evaluation of Subclinical Cardiovascular Disease and Predictors of Events in Rheumatoid Arthritis
Declarations

Ethics approval and consent to participate: ESCAPE-RA, RHYTHM, and use of data from the Columbia University Lupus Cohort Registry, were all approved by the CUIMC/New York Presbyterian Hospital Institutional Review Board.

Consent for publication: Not applicable

Availability of data and materials: The datasets used and analysed during the current study are included in this published article (and its supplementary information files) or otherwise available from the corresponding author on request.

Competing interests:

EP JTG TPR PP CD YG ADA JB LGP: Nothing to disclose

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Author's Contributions:

JTG, TPR, PP, CD, YG, ADA, JB, and LGP: recruitment and data collection. EP and LGP: constructed analysis plan and first draft of manuscript. EP, JTG, ADA, JB, and LGP: substantial modification of manuscript and final approval. All authors read and approved final manuscript.

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Figures
Figure 1

Columbia University Lupus Cohort
Figure 2

Adjusted QTc length and 95% CI in HCQ vs. NO HCQ in combined SLE/RA cohorts
Figure 3

Adjusted QTc length and 95% CI in HCQ vs. NO HCQ in SLE Cohort
Figure 4

Adjusted QTc length and 95% CI in HCQ vs. NO HCQ in RA Cohort
Figure 5

Mean QTc length and 95% CI in HCQ vs. HCQ + Antipsychotic in SLE/RA Cohort
Figure 6

Mean QTc length and 95% CI in HCQ vs. HCQ+QTcMeds in Combined SLE/RA Cohort