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## Population-Based Study of QT Interval Prolongation in Patients with Rheumatoid Arthritis

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### Abstract

**Background**—Patients with rheumatoid arthritis (RA) are at increased risk of cardiovascular morbidity and mortality. Heart rate corrected QT interval (QTc) (which is obtained from a 12-lead electrocardiogram (ECG) and reflects ventricular repolarization duration) is a strong predictor of cardiovascular mortality. Our primary purpose is to determine the impact of QTc prolongation on mortality in RA patients.

**Methods**—A population-based inception cohort of patients with RA fulfilling 1987 ACR criteria in 1988–2007 was identified, with an age- and sex-matched comparison cohort and followed until death, migration or 12-31-2008. Data were collected on ECG variables, medications known to prolong QT interval, electrolytes, cardiovascular risk factors and disease status and RA disease characteristics. Cox proportional hazards models were used to examine QTc prolongation as predictor of mortality.

**Results**—QTc prolongation prior to RA incidence/index date was similar in RA (15%) and non-RA (18%) subjects. During follow-up, the cumulative incidence of QTc prolongation was higher among RA (48% at 20 years after RA incidence) than non-RA (38% at 20 years after index date;  $p=0.004$ ). Idiopathic QTc prolongation (excluding prolongations explained by ECG changes, medications, etc.) was marginally associated with all-cause mortality (HR: 1.28; 95% CI: 0.91–1.81,  $p=0.16$ ), but was not associated with cardiovascular mortality (HR: 1.10; 95% CI: 0.43–2.86,  $p=0.83$ ) in RA.

**Conclusion**—RA patients have a significantly elevated risk of developing QTc prolongation. However, idiopathic prolonged QTc was only marginally associated with all-cause mortality in RA patients. The clinical implications of these findings in RA require further study.

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## Keywords

rheumatoid arthritis; QT prolongation; cardiovascular disease

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## Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by progressive joint destruction, excess morbidity and mortality. Patients with RA have a 50% increase in cardiovascular disease events and cardiovascular mortality as compared to the general population (1, 2). More specifically, patients with RA are twice as likely to experience sudden cardiac death (SCD) compared with non-RA subjects (3) and suffer increased case fatality rates following acute cardiovascular events (4).

The QT interval is a measure of cardiac repolarization duration of the ventricles and is readily obtainable from a 12-lead electrocardiogram (ECG). QT prolongation is a vital predictor of cardiovascular mortality, coronary artery disease mortality, SCD, and total mortality in general population (5–9). Ventricular arrhythmias and conduction defects have been observed in patients with RA (10–12), these arrhythmias are associated with QT prolongation.

Patients with RA appear to have cardiovascular autonomic dysfunction (13), similar to patients with diabetes mellitus (14). In patients with diabetes mellitus, a prolonged QT interval has high sensitivity, specificity and positive predictive value to detect cardiac autonomic dysfunction (14). Furthermore, in patients with chronic inflammatory arthritis, heart rate variability depression independently predicts QT prolongation, demonstrating a link between systemic inflammation and autonomic dysfunction (15). Therefore, a prolonged QT interval may identify autonomic dysfunction in patients with RA, and could be a useful indicator of excess risk for cardiovascular mortality. Hence, the primary objective of our study was to determine the frequency of QT prolongation in patients with RA as compared to non-RA subjects, and to examine the influence of QT prolongation in patients with RA.

## Methods

This retrospective, population-based cohort study was conducted using the Rochester Epidemiology Project (REP). The REP is a medical record linkage system, which provides access to the complete (inpatient and outpatient) medical records from all community providers. An incident cohort of residents of Olmsted County, Minnesota, age ≥ 18 years who satisfied the 1987 American College of Rheumatology (ACR) classification criteria for RA (16) from January 1, 1988 to December 31, 2007 was identified. This cohort was followed until death, migration or December 31, 2008. The earliest date for fulfillment of 4 ACR criteria for RA was considered the RA incident date. An Olmsted County resident of the same age ( $\pm 1$  year) and sex, without diagnosis of RA was selected for each RA patient; the RA incidence date was used as the index date for each of these non-RA subjects. This study was approved by Institutional Review Boards of the Mayo Clinic and the Olmsted Medical Center.

All ECGs performed as part of each patient's clinical visit were obtained and retrospectively examined. These ECG analyses were performed using the 12SL ECG analysis program from GE Marquette Medical System, ESAOTE organizer. All electronically generated ECG were reviewed by an ECG technician, and corrections were made, if necessary. For each ECG, data on following parameters was recorded: Heart rate, QRS interval, QT interval, heart rate corrected QTc as calculated using the Bazett's formula, atrial fibrillation, atrial flutter. Questionable abnormal ECGs were reviewed by a cardiologist. The QT interval was also manually calculated by using a mean of 3 consecutive beats derived from either lead II or V5. The end of the T wave was determined by the tangent method, and the U waves were not incorporated if separate from the T wave (17). ECG were also assessed manually for the presence of changes which could affect the QT interval: bundle branch block, ventricular pacing, atrial fibrillation, atrial flutter, other supraventricular tachycardia, ST-T wave changed of ischemic origin and left ventricular hypertrophy by voltage criteria.

All lab data for measures of serum potassium, magnesium, calcium and creatinine were obtained from the medical records. For serum potassium, magnesium, calcium, data were collected 48 hours prior or 48 hours after each ECG was done, if there was no data within 48 hours prior or after ECG measurement, then the value closest to ECG measurement was chosen. Hypokalemia was defined as  $< 3.6$  mmol/L, hypomagnesemia  $< 1.7$  mg/dl and hypocalcemia  $< 4.65$  mg/dl. Creatinine values were collected up to two weeks prior to ECG measurement and the value closest to the time of ECG was chosen. If no creatinine value was available prior to ECG measurement, values until 2 days after were chosen.

Medication data for all subjects with a "prolonged QTc" was collected from the electronic medical records. All the medications taken two weeks prior to the ECG measurement were reviewed and all QT prolonging medications were noted. QT prolonging medications were defined as medications present on the Arizona CERT QT drug list. [[www.crediblemeds.org](http://www.crediblemeds.org)]

ECGs were evaluated on the basis of heart rate; those with a resting heart rate  $> 100$  bpm or  $< 50$  bpm were not assessed. The American Heart Association/American College of Cardiology (AHA/ACC) guidelines based definition of a "prolonged QTc": 450 ms in males and 460 ms in females were used (17). The designation of "marked QT prolongation" was assigned for ECGs with either i) a QTc  $\geq 500$  msec if the QRS duration is  $< 120$  msec or ii) a QTc  $\geq 550$  msec if the QRS duration  $> 120$  msec. Besides these qualitative QTc thresholds, the QTc was also analyzed as a continuous variable. QTc prolongation which occurred in the absence of ECG changes, electrolyte disturbances and QTc prolonging medications was defined as Idiopathic QTc prolongation.

Cardiovascular risk factors at RA incidence were determined by review of the medical records. These include smoking status (never, current, former), systolic and diastolic blood pressure measurements, use of antihypertensive medications, body mass index, diabetes mellitus (defined as  $> 2$  measurements of fasting blood glucose  $\geq 126$  mg/dl or 2 hour plasma glucose level  $\geq 200$  mg/dl, physician diagnosis, documented use of insulin or oral hypoglycemic medications) and results of fasting serum lipid measurement including total cholesterol, high density lipoprotein, low density lipoprotein and triglycerides. Dyslipidemia was defined according to the National Cholesterol Education Program Expert Panel on

Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) guidelines (18).

CVD (including myocardial infarction, cardiovascular death, sudden death, angina, stroke, intermittent claudication and heart failure) was also determined through review of medical records. Myocardial infarction was identified as per the standardized criteria, cardiovascular death was ascertained from the death certificates (International Classification of Diseases, Ninth Revision, codes 350.0 to 459.9, and International Classification of Diseases, 10th Revision, codes I00 to I99). Angina was defined by physician diagnosis. Stroke and intermittent claudication were identified by physician diagnosis and also confirmed by imaging, cerebrospinal fluid analysis or autopsy (19). Heart failure was determined using the Framingham criteria (20). Sudden death was defined as out-of-hospital deaths which occurred in emergency departments (including patients dead on arrival), private homes, public places, and nursing homes, and which were recorded as International Classification of Diseases, Ninth Revision, Clinical Modification codes 410–414 as the underlying cause of death on the death certificates. These criteria are validated and published (21).

RA disease characteristics collected from the medical records include rheumatoid factor status, erythrocyte sedimentation rate at RA incidence and repeatedly high ESR (>3 ESR measures of 60 mm/hr with minimum interval of 30 days between the measurements), large joint swelling, joint erosions/ destructive changes on radiographs, joint surgeries (arthroplasty and synovectomy) and extraarticular manifestation of RA as defined by Turesson et-al (22). We defined severe extra-articular manifestations using Malmo criteria (23) which include: pericarditis, pleuritis, Felty's syndrome, glomerulonephritis, vasculitis, peripheral neuropathy, scleritis and episcleritis. We also collected data for the use of systemic corticosteroids (oral/parental/intraarticular forms of prednisone, prednisolone, methylprednisolone, hydrocortisone, dexamethasone), disease modifying anti-rheumatic drugs (DMARDs): methotrexate, hydroxychloroquine, other DMARD, biologic agents (anti-tumor necrosis inhibitors, anakinra, abatacept, rituximab) and non-steroidal anti-inflammatory agents (NSAIDs).

## Statistical Methods

Descriptive statistics (means, percentages, etc.) were used to summarize the data. The cumulative incidence of QT prolongation adjusted for the competing risk of death was estimated (24). Patients whose first occurrence of QT prolongation was prior to the diagnosis of RA, or prior to the index date for subjects in the non-RA comparison cohort, were excluded from the analysis of cumulative incidence. Cumulative incidence rates for the two cohorts (RA and non-RA) were compared using methods by Gray (25).

Cox proportional hazards models were used to assess the association of risk factors with the development of QT prolongation among patients with RA. Risk factors of interest include those described above. Time-dependent covariates were used to model risk factors that developed over time. These time-dependent covariates allowed patients to be modeled as unexposed to the risk factor during the follow-up time prior to development of the risk factor, then change to exposed following development of the risk factor.

Cox models were also used to examine the association between QT prolongation and both all-cause and cardiovascular mortality in patients with RA. All factors known to be associated with mortality in RA based on previous work were included in multivariate models for adjustment (26). These factors include the following: smoking status, rheumatoid factor positivity, history of alcoholism, obesity, cardiovascular disease (including hospitalized or silent myocardial infarction, heart failure, revascularization, angina, or a physician diagnosis of coronary artery disease), renal disease, liver disease, cancer, metastases, dementia, and severe extra-articular RA manifestations (i.e., pleuritis, pericarditis, Felty's syndrome, RA vasculitis, scleritis, neuropathy, or glomerulonephritis). Statistical analyses were performed using the SAS software package version 9.3 (SAS Institute, Cary, NC) and R software version 3.0.2 ([www.r-project.org](http://www.r-project.org)).

## Results

A total of 650 RA and 650 non-RA subjects were identified from 1988–2007. Of these, 518 RA and 499 non-RA subjects had at least 1 ECG performed after RA incidence/index date (Table 1). Mean age at RA incidence/index date was 59 years and 69% of subjects were females. Mean length of follow up was 12 years for RA and 13 years for non-RA subjects.

A total of 417 RA and 422 non-RA patients had at least 1 ECG prior to RA incidence/index date, the prevalence of “prolonged QTc” (per AHA/ACC guidelines) was similar in the two groups (30% RA and 31% non RA,  $p=0.80$ ), the results were similar for idiopathic QTc prolongation as defined in the methods. (RA: 15%, non RA: 18%,  $p=0.30$ ; Table 2). Similarly, marked QT prolongation (i.e. QTc  $> 500$  ms) did not differ among the two groups both before and after excluding QT prolongations occurring in the presence of the above variables.

Cumulative incidence of QT prolongation during follow up was significantly higher among the RA (48% at 20 years after RA incidence) as compared to the non-RA (38% at 20 years after index date,  $p= 0.004$ ; Table 3). The cumulative incidence of idiopathic QT prolongation was also higher among the RA than the non-RA (22% in RA vs. 17% in non-RA at 20 years follow-up,  $p=0.025$ ). RA patients had significantly higher risk of QT prolongation (HR: 1.58, 95% CI: 1.22–2.04) as well as idiopathic QT prolongation (HR: 1.60, 95% CI: (1.11–2.30). During follow-up, RA patients also had higher incidence of some factors associated with prolonged QT, including tachycardia (Heart rate  $> 100$ ) (RA: 32% vs. non-RA: 29% at 20 years follow-up,  $p=0.016$ ), ST-T wave changes (RA: 33% vs. non-RA: 21% at 20 years follow-up,  $p<0.001$ ) and low potassium levels (RA: 40% vs. non-RA: 34% at 20 years follow-up,  $p=0.019$ ).

Among RA patients: sedimentation rate at the time of diagnosis (HR: 1.14 per 10mm/hr increase, 95% CI: 1.03–1.27) and current smoking (HR: 2.07, 95% CI 1.21–3.54) were significantly associated with risk of idiopathic QT prolongation. None of the other RA disease characteristics, anti-rheumatic medications or cardiovascular risk factors were significantly associated with developing idiopathic QT prolongation. Results were similar for risk of any QT prolongation (data not shown).

During follow-up, a total of 149 patients with RA died and 20 of these deaths were attributed to cardiovascular causes. Idiopathic QT prolongation was marginally, but not significantly, associated with all-cause mortality (HR: 1.28, 95% CI: 0.91–1.81, adjusted for age, sex, calendar year of RA diagnosis), the results remained similar after further adjusting for factors known to be associated with mortality in patients with RA and for RA medications. QT prolongation was not associated with coronary heart disease mortality (HR: 1.12; 95% CI: 0.43–2.92), after adjusting for age, gender, calendar year of RA diagnosis, smoking status, hypertension, diabetes mellitus and dyslipidemia. However, any QT prolongation was significantly associated with all-cause mortality (HR: 2.99, 95% CI: 1.93–4.65) following full adjustment and was marginally associated with coronary heart disease mortality (HR: 2.68; 95% CI: 0.84–5.6;  $p=0.09$  after adjusting for age, gender, calendar year of RA diagnosis, smoking status, hypertension, diabetes mellitus and dyslipidemia).

## Discussion

In our population-based study of QT interval prolongation, we found that incident RA patients had a higher frequency of QT prolongation and were at higher risk of developing QT prolongation.

QT interval is affected by sympathetic and parasympathetic arms of the autonomic nervous system (27–29). Alteration of sympathetic system by isoproterenol, a beta adrenergic agonist, causes an initial prolongation and then shortening of QTc (28). Stimulation of beta adrenergic receptor, modulates ionic currents, L-type  $\text{Ca}^{2+}$  currents, the slow potassium current, and the  $\text{Na}^+/\text{Ca}^{2+}$  exchange current. The sum of these ionic currents, controls repolarization and the QT interval (30). Rapid activation of L-type calcium current initially prolongs repolarization, later on activation of delayed potassium current, accelerates repolarization, hence QTc interval is transiently prolonged and shortened by  $\beta$ -adrenergic stimulation (31). Inhomogeneity of repolarization through the ventricular myocardium, results in spatial or transmural dispersion of repolarization, offering substrate for reentry resulting in ventricular arrhythmia (31).

In animal models, electrical stimulation of the vagus nerve; the parasympathetic component of the autonomic nervous system results in decreased serum and myocardial level of Tumor Necrosis Factor (TNF) (32). The molecular association between the cholinergic nervous system and the immune system is nicotinic, alpha bungarotoxin-sensitive macrophage acetylcholine receptor. Exposure of tissue macrophage acetylcholine receptor results in suppression of TNF-1, IL-1 and other cytokines, termed as cholinergic anti-inflammatory pathway (33).

Autonomic dysfunction occurs as a complication of RA (34, 35). Sympathetic tone is increased in patients with RA (36), and the presence of parasympathetic dysfunction in RA has been shown by Edmund and Toussirot (34). Abnormalities of autonomic dysfunction explain the increased risk of QT interval prolongation as observed in our study.

In our study however, idiopathic QT prolongation was marginally, but not significantly, associated with all-cause mortality, These findings differ from the recently published article



by Panoulas et al. (37). However, we believe the fundamental reason for this difference is the way data was analyzed by Panoulas et al and our study. In our analysis, we utilized the published guideline-based definition of a “prolonged QTc” (450 ms for males and 460 ms for females). In Panoulas’ study, only 24 subjects (9 males and 15 females) developed QT prolongation, so Panoulas define a 50 millisecond increase in QT interval and associated it with mortality. More importantly, in our analyses, we excluded QT prolongation occurring in the presence of ECG changes, electrolytes imbalance and use of medications known to prolong QT interval, so that we could define whether idiopathic prolongation of the QT interval in patients with RA predicts mortality.

Furthermore, regarding the association of RA disease characteristics and cardiovascular risk factors with QT prolongation, we used Cox analysis defining association over the study period whereas Panoulas et al used linear regression analysis measuring association at one time point. Here also we exclude events which are known to alter the QT prolongation, so as to predict variables which explain idiopathic QT prolongation in patients with RA.

Among patients with RA, ESR at the time of diagnosis was significantly associated with risk of QTc prolongation. This finding supports mounting data in the literature demonstrating the key role of systemic inflammation in increasing the arrhythmic risk in RA patients, either indirectly, by accelerating the development of structural cardiovascular disease, or directly by affecting cardiac electrophysiology (including direct prolonging effects of pro-inflammatory cytokines on action potential duration (38–40). The association here reported between ESR and QTc prolongation represents a further confirmation of this view.

Our study has potential limitations. In particular, being an retrospective, observational study, no causal relationship can be established between QTc prolongation and overall mortality or cardiovascular mortality in RA patients. Since the population of Olmsted County, Minnesota is predominantly Caucasian, the results may not be generalizable to other population groups.

The strengths of our study include its population-based longitudinal study design with large number of RA patients and comparison subjects. The comprehensive medical record linkage system provides almost complete medical information for study subjects. The review of medical records ensures there is no recall bias.

Our study shows patients with RA are at increased risk of developing a QTc that exceeds the guideline-based thresholds for a prolonged QTc. Further studies are needed to understand the clinical implications of this prolongation in QT interval, such as whether it can explain some part of the increased all-cause and cardiovascular mortality in RA patients.

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**Table 1**

Characteristics of patients with electrocardiogram (ECG) measures in rheumatoid arthritis (RA) and non-RA cohorts.

<b>Characteristic*</b>	<b>Non-RA (N=499)</b>	<b>RA (N=518)</b>	<b>p value</b>
Age at incidence/index date, yrs	58.7 (14.7)	58.5 (15.1)	0.86
Sex, female	346 (69%)	354 (68%)	0.73
Length of follow-up, years	12.6 (5.7)	12.0 (5.7)	--
Number of ECGs before index date	6.1 (6.6)	6.1 (6.8)	0.74
Number of ECGs after index date	7.6 (9.6)	7.9 (10.2)	--
Rate of ECGs per 1 person-year	0.7 (1.1)	1.2 (4.1)	0.038
QTc interval at incidence/index date, msec**	428.4 (26.7)	428.5 (27.8)	1.0
Hypertension	189 (38%)	221 (43%)	0.12
Diabetes Mellitus	51 (10%)	55 (11%)	0.84
Dyslipidemia	293 (59%)	316 (61%)	0.46

\* Values in the tables are mean (SD) or n (%)

\*\* Available within  $\pm$  1 year of incidence/index date for 282 Non-RA and 319 RA patients

**Table 2**

Characteristics of patients with electrocardiogram measures **prior to incidence/index** data in rheumatoid arthritis (RA) and non-RA cohorts.

	<b>Non-RA (N=422)</b>	<b>RA (N=417)</b>	<b>p value</b>
QT prolongation	131 (31%)	126 (30%)	0.80
Idiopathic QT prolongation	75 (18%)	63 (11%)	0.30
Marked QT prolongation	32 (8%)	35 (8%)	0.66
Idiopathic Marked QT prolongation	12 (3%)	9 (2%)	0.52
Heart Rate < 50 beats/min	37 (9%)	52 (12%)	0.08
Heart Rate > 100 beats/min	61 (14%)	65 (16%)	0.65
Bundle Branch Block	57 (14%)	50 (12%)	0.51
Paced rhythm	4 (1%)	8 (2%)	0.24
Atrial Flutter	23 (6%)	19 (5%)	0.55
Atrial fibrillation	5 (1%)	5 (1%)	0.98
Left Ventricular Hypertrophy	33 (8%)	48 (12%)	0.07
SVT	56 (13%)	61 (15%)	0.57
ST-T	74 (18%)	76 (18%)	0.79
Low calcium	0	0	
Low magnesium	12 (3%)	18 (4%)	0.25
Low potassium	109 (26%)	103 (25%)	0.71

**Table 3**

Cumulative incidence of QT prolongation and factors associated with QT prolongation in patients with rheumatoid arthritis (RA) compared to subjects without RA.

	Number of events Non-RA / RA	Cumulative incidence* (%) for non-RA (± SE)	Cumulative incidence* (%) for RA (± SE)	p-value
QT prolongation	99 / 144	38.2 ± 3.6	47.5 ± 3.6	0.004
Idiopathic QT prolongation	48 / 75	16.9 ± 2.6	21.9 ± 2.6	0.025
Marked QT prolongation	36 / 39	9.5 ± 1.7	11.5 ± 2.2	0.82
Idiopathic Marked QT prolongation	4 / 6	0.9 ± 0.5	2.0 ± 1.0	0.57
Heart Rate <50 beats/min	41 / 46	11.4 ± 1.8	13.2 ± 2.0	0.64
Heart Rate >100 beats/min	91 / 122	28.7 ± 3.0	32.4 ± 2.8	0.016
Bundle Branch Block	70 / 80	21.1 ± 2.6	24.4 ± 2.8	0.60
Paced rhythm	14 / 14	3.4 ± 0.9	3.4 ± 1.2	0.93
Atrial flutter	45 / 59	13.9 ± 2.2	15.6 ± 2.1	0.22
Atrial Fibrillation	57 / 57	17.0 ± 2.3	15.2 ± 2.1	0.89
Left Ventricular Hypertrophy	40 / 54	11.0 ± 1.7	14.9 ± 2.2	0.15
SVT	90 / 109	27.6 ± 2.9	28.5 ± 2.7	0.13
ST-T	73 / 120	20.6 ± 2.4	32.9 ± 2.8	<0.001
Low calcium	0 / 0			
Low magnesium	52 / 71	16.5 ± 2.5	21.3 ± 2.6	0.079
Low potassium	92 / 125	34.0 ± 3.5	40.0 ± 3.5	0.019

\* Cumulative incidence rate 20 years after RA incidence/index date