# RHEUMATOLOGY

## Original article

# Prolonged QTc interval predicts all-cause mortality in patients with rheumatoid arthritis: an association driven by high inflammatory burden

**Vasileios F. Panoulas[1,2], Tracey E. Toms[2], Karen M. J. Douglas[2], Aamer Sandoo[2], George S. Metsios[2], Antonios Stavropoulos-Kalinoglou[2] and George D. Kitas[2,3]**

## Abstract

**Objective.** RA associates with an increased rate of sudden cardiac death (SCD). A prolonged QTc interval has been associated with arrhythmogenic and SCD in patients with long QT syndrome. Despite the previously reported contemporary association of CRP with SCD, thus far no studies have examined the association of QTc with mortality in RA, a condition characterized by high inflammatory burden. The aim of this study was to examine the role of electrocardiography (QT corrected interval) in predicting all-cause mortality in patients with RA who have an increased rate of SCD and a high inflammatory burden.

**Methods.** Three hundred and fifty-seven RA patients with detailed baseline clinical characterization and 12-lead ECGs were followed up for a mean of 73.0 (S.D. 18.3) months. Linear and Cox regression analyses were used to identify variables that associate with QTc and examine its association with all-cause mortality.

**Results.** The patients' mean age was 60.6 (S.D. 12.0) years, 267 (74.8%) were females and 54 (15.1%) died during the follow-up period. Age ($\beta = 0.231$, $P < 0.001$), gender ($\beta = 0.137$, $P = 0.008$) and CRP ($\beta = 0.144$, $P = 0.006$) associated independently with QTc in RA patients. The crude hazard ratio (HR) for total mortality per 50-ms increase in QTc was 2.17 (95% CI 1.21, 3.90). This association remained significant [HR = 2.18 (95% CI 1.09, 4.35)] after adjustment for identified confounders (cardiovascular and RA specific), but was lost [HR = 1.73 (95% CI 0.83, 3.62)] when CRP was included in the model.

**Conclusion.** A 50-ms increase in QTc interval associates with a doubling of the hazard for all-cause mortality in patients with RA. The observed contemporary association of QTc with CRP levels indicates a potentially hazardous interplay between inflammation and arrhythmogenesis. Future studies are needed to confirm the above findings and explore underlying mechanisms.

**Key words:** QTc, prolongation, rheumatoid arthritis, death, sudden cardiac, mortality.

## Introduction

RA is the most common inflammatory arthritis, affecting ∼0.8% of the adult population [1]. Mounting evidence associates RA with increased morbidity and mortality from atherosclerotic cardiovascular disease (CVD) [2], which appears to be of equal frequency and severity in RA as in diabetes mellitus of similar duration [3, 4]. RA patients are less likely to report angina symptoms and are more prone to unrecognized myocardial infarctions (MIs) and sudden cardiac death (SCD) [5].

The ECG is a widely available, inexpensive but informative screening tool for underlying heart disease. The QT interval represents the time from onset of ventricular depolarization (beginning of the Q wave) to completion of repolarization (end of the T wave). Given the variability

[1]Department of Cardiology, Hammersmith Hospital, Imperial College Healthcare NHS Trust, London, [2]Department of Rheumatology, Dudley Group NHS Foundation Trust, Russells Hall Hospital, Dudley, West Midlands and [3]Arthritis Research UK Epidemiology Unit, Manchester University, Manchester, UK.

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Correspondence to: Vasileios F. Panoulas, Hammersmith Hospital, Imperial College Healthcare NHS Trust, Du Cane Road, London W12 0HS, UK. E-mail: v.panoulas@imperial.ac.uk

CLINICAL SCIENCE

of the QT interval in relation to the heart rate, several formulas (most commonly the Bazett's) are used to yield a corrected measure. In patients with congenital prolonged QTc, SCD is one of the initial presentations, accounting for up to 13% of deaths in this population [6]. In patients with type 2 diabetes mellitus, who are equally severely affected by CVD as RA patients [3], QTc is a good predictor of mortality [7]. In the general population, however, the evidence of an association between prolonged QTc and SCD remains controversial [6]. Interestingly, some data have shown a link between CRP and QTc [8], and inflammatory markers and SCD [9], but no study has so far examined the effects of CRP or other inflammatory markers on QTc and their association with mortality in RA. Despite the increased prevalence of SCD in RA, the role of QTc as a predictor of mortality in this population remains unknown. Given the increased inflammatory burden among RA patients, studying the interplay of inflammation with QTc and its association with mortality is of particular interest.

## Methods

The study was approved by the local research ethics committee (Black Country Research Ethics Committee) and research and development directorate and all participants gave written informed consent. Four hundred consecutive patients fulfilling 1987 ACR criteria for RA [10] were recruited from routine rheumatology outpatient clinics of the Dudley Group NHS Foundation Trust, UK, from July 2004 to October 2006. Patients with atrial flutter, atrial fibrillation, bundle branch block or missing ECG data were excluded from this study ($n = 43$).

All RA patients underwent a thorough clinical and contemporary laboratory evaluation that has been described in previous papers [11, 12]. CVD at baseline was defined as the presence of coronary heart disease (CHD), cerebrovascular accident (CVA) or transient ischaemic attack, or peripheral arterial disease (PAD). CHD was defined as having any of the following: angina diagnosed by a physician or elicited by the use of the Rose questionnaire [13], MI, angioplasty, coronary artery bypass grafting or/and ischaemic heart failure.

In our analyses we accounted for medications that associate with risk for torsades de pointes (http://www.qtdrugs.org/) and are present in our study population, such as HCQ, thiazide diuretics (indapamide), amitriptyline, anti-TNF, glucocorticosteroids and other antidepressants [including selective serotonin reuptake inhibitors (SSRIs)].

Resting 12-lead ECGs (25 mm/s paper speed and 10 mm/mV amplitude) were recorded using a three-channel direct writing machine (Marquette MAC PC; GE Healthcare, UK). Electronic calipers (Cardiocaliper v3.3) capable of measuring to within 0.1 mm precision after standard calibration were used to determine the cycle length, QRS duration and QT interval. All intervals were measured by two trained personnel (A.S., G.M.) who were blinded to the clinical and survival data. The QT interval was measured from the beginning of the earliest

onset of the QRS complex to the end of the T wave. The end of the T wave was defined as the return of the descending limb to the TP baseline when not followed by a U wave or if distinct from the following U wave. If a second low-amplitude repolarization wave interrupted the terminal portion of the T wave, the T wave offset was measured as the nadir between the T and U waves. After measurements in all precordial and limb leads, the longest QT interval was recorded. The QT interval was corrected with the Bazett formula. The presence of ST depression or T wave inversions were coded using the Minnesota Code Classification System [14].

The Office for National Statistics (ONS; General Register Office, Southport, UK) provided details of the patients' deaths, including the cause and date of death. Notification of patient deaths was obtained from the ONS within 6 months of death. Cardiovascular death was defined as the presence of International Classification of Diseases, 10th revision (ICD-10) codes I00–I99 on Ia section (primary cause of death) of the participant's death certificate. Data regarding inpatient episodes for MI, CVA and PAD were obtained from the hospital's information department.

Each patient was followed up from the time of enrolment until death or 1 January 2013 (censored), whichever was sooner. Cardiovascular outcomes were defined as cardiovascular death, incident MI, stroke or PAD. Follow-up (until 1 January 2013) consecutive CRP and ESR measurements were available for 201 RA patients who were still alive.

### Statistical analysis

Statistical analysis was performed using SPSS software, version 17 (SPSS Inc., Chicago, IL, USA). Variables were tested for normality by the Kolmogorov–Smirnov test. The interrater variability in QTc measurements was established using the intraclass correlation coefficient (ICC), a marker of reproducibility of measurements of the same quantity, performed by different operators. Linear regression analysis was used to identify the crude and multivariable associations of various variables with QTc interval.

Cox regression analysis was used to determine the crude predictors of all-cause and cardiovascular mortality and cardiovascular outcomes. Cox regression analysis was also used to assess the independence of the association between QTc and all-cause mortality (i) crudely and (ii) after adjustment for confounders. In a similar fashion we analysed the association of QTc with cardiovascular outcomes. Furthermore, we split the QTc interval into two percentiles using the median value (QTc = 424 ms). Cox regression analysis and Kaplan–Meyer curves were used to assess the association of upper *vs* lower QTc interval percentile with all-cause mortality.

## Results

Of the 400 RA patients, 43 patients did not fulfil the inclusion criteria. Six had complete left bundle branch block, 12 had complete right bundle branch block, 4 had atrial fibrillation, 1 had atrial flutter and in 20 patients baseline

**TABLE 1** Demographics of the study population ($n = 357$)

| General demographics | |
|---|---|
| Age, mean (S.D.), years | 60.6 (12.0) |
| Female, $n$ (%) | 267 (74.8) |
| Baseline CVD and CVD risk factors | |
| Baseline CVD, $n$ (%) | 71 (19.9) |
| HTN, $n$ (%) | 251 (70.3) |
| Dyslipidaemia, $n$ (%) | 242 (68.6) |
| IR, $n$ (%) | 128 (35.9) |
| BMI, mean (S.D.), kg/m$^2$ | 27.8 (5.1) |
| Smoking status, $n$ (%) | |
| Current smokers | 56 (15.7) |
| Ex-smokers | 132 (37) |
| Never smoked | 162 (45.4) |
| Pack-years of smoking, median (IQR) | 10 (4–18) |
| RA-specific parameters | |
| RF positive, $n$ (%) | 267 (74.8) |
| ACPA positive, $n$ (%) | 234 (65.5) |
| CRP, median (IQR) | 8 (5–17) |
| ESR, median (IQR) | 20 (9–36) |
| DAS, mean (S.D.) | 4.21 (1.37) |
| HAQ score, mean (S.D.) | 1.39 (0.91) |
| Years of RA, median (IQR) | 10 (4–18) |
| Prednisolone, $n$ (%) | 116 (32.5) |
| Anti-TNF, $n$ (%) | 42 (11.8) |
| ECG-related parameters | |
| QTc, mean (S.D.), ms | 424.9 (22.5) |
| LVH SL. $n$ (%) | 14 (3.9) |
| QRS, mean (S.D.), ms | 88.0 (10.8) |
| Medication posing a definite or possible risk for torsades de pointes | |
| Amitriptyline, $n$ (%) | 26 (7.3) |
| Thiazide diuretic, $n$ (%) | 69 (19.3) |
| HCQ, $n$ (%) | 70 (19.6) |
| SSRIs, $n$ (%) | 24 (6.7) |

IQR: interquartile range; SL: Sokolov–Lyon criteria.

**TABLE 2** List of primary causes of death as they appear on death certificates ($n = 50$)

| Category | Primary cause of death | Frequency, $n$ (%) |
|---|---|---|
| Cardiovascular causes | MI | 5 (10) |
| | Ischaemic heart disease | 1 (2) |
| | CHD | 1 (2) |
| | PAD | 1 (2) |
| | Infective endocarditis | 1 (2) |
| | Total cardiovascular causes | 9 (18) |
| Cancer related | Carcinomatosis | 3 (6) |
| | Metastatic cancer | 3 (6) |
| | Metastatic squamous cell lung cancer | 2 (4) |
| | Intra-abdominal carcinoma | 2 (4) |
| | Carcinoma of the tongue | 1 (2) |
| | Metastatic ovarian cancer | 1 (2) |
| | Carcinoma of the bladder | 1 (2) |
| | Total cancer-related causes | 13 (26) |
| Sepsis related | Pneumonia | 12 (24) |
| | Septicaemia | 3 (6) |
| | Septic shock | 3 (6) |
| | Infective exacerbation of COPD | 3 (6) |
| | Chest infection | 1 (2) |
| | Faecal peritonitis | 1 (2) |
| | Urinary tract infection | 1 (2) |
| | Total sepsis-related causes | 24 (48) |
| Other | Pulmonary fibrosis | 2 (4) |
| | Old age | 1 (2) |
| | Renal failure | 1 (2) |
| | Total other causes | 4 (8) |

COPD: chronic obstructive pulmonary disease.

ECG data were missing (poor quality traces or patient refused). The mean age of the study population ($n = 357$) was 60.6 (S.D. 12.0) years, 267 (74.8%) were females and the mean QTc was 424.9 (S.D. 22.5) ms. Baseline demographics are shown in Table 1. The ICC for QTc measurements was 0.983 (95% CI 0.979, 0.986), indicating excellent agreement between different operators. When using established cut-offs for abnormally prolonged QTc [15] ($\geqslant 450$ ms for men and $\geqslant 460$ ms in women), we identified 9 (10%) males and 15 (5.6%) females with prolonged QTc.

Of the 357 patients, a total of 54 (15.1%) died during the follow-up period [73 (S.D. 18) months]. Of those, death certificates were available for 50 (93%). Table 2 shows the primary cause of death breakdown. The vast majority of deaths were caused by sepsis (48%), followed by malignancies (26%) and cardiovascular causes (18%). During follow-up, 3 (0.8%) patients were hospitalized for MI, 3 (0.8%) for CVA and 7 (2%) for PAD. A total of 21 (5.9%) cardiovascular outcomes were recorded. In a sample of 201 patients who were alive and reviewed at the end of 2012, baseline CRP was strongly correlated with mean follow-up CRP ($\rho = 0.514$, $P < 0.001$) and mean follow-up ESR ($\rho = 0.333$, $P < 0.001$). At baseline, 70 patients (19.6%) were on HCQ, 69 (19.3%) on thiazide diuretics (which include indapamide), 26 (7.3%) on amitriptyline and 24 (6.7%) on SSRIs. There were no patients on amiodarone, sotalol, flecanaide, macrolides, ketoconazole or haloperidol.

### Crude and multivariable associations with QTc prolongation

Crude linear regression analysis revealed advanced age and female gender were associated with prolonged QTc interval (Table 3). Regarding cardiovascular risk factors, there was only a trend for an association between hypertension (HTN), insulin resistance (IR) and increased BMI with QTc prolongation (Table 3). No association was identified between smoking status, pack-years or dyslipidaemia and QTc. RA-specific parameters that significantly correlated to QTc included CRP and ACPA positivity,

Table 3 Crude and multivariable linear regression analyses with dependent variable QTc interval

| Crude | | | Linear regression | | |
|---|---|---|---|---|---|
| **Variable** | **β** | **P-value** | **Variable** | **β** | **P-value** |
| General demographics | | | | | |
| Age | 0.235 | <0.001 | Age | 0.231 | <0.001 |
| Female gender | 0.151 | 0.004 | Female gender | 0.137 | 0.008 |
| | | | CRP | 0.144 | 0.006 |
| Cardiovascular risk factors | | | ACPA positive | 0.091 | 0.085 |
| HTN | 0.094 | 0.078 | | | |
| IR | 0.093 | 0.086 | | | |
| BMI | 0.093 | 0.084 | | | |
| RA-specific parameters | | | | | |
| CRP | 0.150 | 0.005 | | | |
| ACPA | 0.144 | 0.008 | | | |
| ESR | 0.121 | 0.023 | | | |
| RF positivity | 0.093 | 0.083 | | | |
| Medication posing a definite or possible risk for TdP | | | | | |
| Thiazide diuretic | 0.102 | 0.055 | | | |
| Amitriptyline | 0.101 | 0.056 | | | |
| HCQ | 0.091 | 0.085 | | | |
| ECG-related parameters | | | | | |
| LVH SL | −0.094 | 0.076 | | | |

All variables with $P < 0.1$ in the crude analysis are presented in the present table. SL: Sokolov–Lyon criteria.

whereas there was a trend towards ESR and RF positivity (Table 3). There was no association between RA duration, DAS, HAQ score, prednisolone use, SSRIs or anti-TNF use and QTc. In our cohort, the only medications showing a non-significant trend for an association with QTc prolongation were thiazide diuretics, amitriptyline and HCQ (Table 3). Common cardiovascular medications frequently used in patients with RA, such as aspirin, β-blockers, angiotensin-converting enzyme (ACE) inhibitors and statins did not associate with QTc interval. Regarding ECG parameters, left ventricular hypertrophy (LVH) assessed by the Sokolov–Lyon criteria showed a trend for an inverse association with QTc, whereas no association was seen between QRS and QTc. No association was observed between ST depression ($β = 0.046$, $P = 0.391$) or T wave inversion ($β = 0.039$, $P = 0.467$) and QTc interval. There was no association between the presence of CVD at baseline and QTc ($β = 0.082$, $P = 0.122$). In linear regression analysis, variables independently associated with QTc prolongation included advanced age, female gender and CRP (Table 3).

### Predictors of all-cause mortality

*Univariable analysis (crude) for all-cause mortality*
A 50 ms increase in QTc interval was crudely associated with a 2.17 increase in the odds for all-cause mortality in patients with RA. Other factors associated in the univariable analysis with increased all-cause mortality included advanced age, male gender, presence of CVD at baseline, HTN, IR, number of pack-years smoked, DAS, HAQ score, prednisolone use, CRP and ESR (Table 4). There was an inverse association observed between QRS duration and

mortality. There was a trend towards increased odds for all-cause mortality for patients on amitriptyline and SSRIs (Table 4). When splitting the QTc variable into two groups using the median (QTc = 424 ms), patients in the highest percentile exhibited increased mortality compared with those in the lowest [hazard ratio (HR) 1.91, 95% CI 1.01, 3.32, $P = 0.022$] (Fig. 1).

*Association of QTc with all-cause mortality after adjustments for confounders*
Table 5 shows a significantly increased HR (HR = 2.18) per 50 ms increase in QTc interval despite adjustments for cardiovascular (history of CVD, HTN, IR, pack-years of smoking) and RA-specific (HAQ score, DAS, prednisolone use) parameters. However, the significance of the association was lost after adjustment for CRP levels (Table 5).

*Association of QTc with cardiovascular mortality and outcomes*
QTc duration (per 50 ms increase) was not significantly associated with cardiovascular mortality (HR 2.12, 95% CI 0.51, 8.83, $P = 0.488$) or cardiovascular outcomes (HR 1.52, 95% CI 0.59, 3.90, $P = 0.387$).

## Discussion

This is the first prospective study in RA patients showing a contemporary association between CRP and QTc interval. A 50 ms increase of the latter was associated with a doubling of risk for all-cause mortality. However, the significance of this association was lost when CRP was included in the regression model, suggesting that inflammation may prolong the QTc interval and create an

TABLE 4 Crude odds ratios for all-cause mortality

| Variable | OR | 95% CI | P-value |
|---|---|---|---|
| General demographics | | | |
| Age | 1.09 | 1.05, 1.12 | <0.001 |
| Female gender | 0.44 | 0.26, 0.75 | 0.003 |
| Baseline CVD and CVD risk factors | | | |
| Baseline CVD | 3.67 | 2.15, 6.28 | <0.001 |
| HTN | 3.49 | 1.50, 8.16 | 0.004 |
| Dyslipidaemia | 1.24 | 0.70, 2.18 | 0.459 |
| IR | 2.68 | 1.54, 4.64 | <0.001 |
| BMI | 0.96 | 0.91, 1.02 | 0.202 |
| Pack-years of smoking[a] | 1.20 | 1.07, 1.35 | 0.002 |
| RA specific parameters | | | |
| RF positive | 0.79 | 0.44, 1.44 | 0.447 |
| ACPA positive | 1.17 | 0.63, 2.18 | 0.620 |
| CRP[b] | 1.15 | 1.07, 1.24 | <0.001 |
| ESR[b] | 1.17 | 1.08, 1.27 | <0.001 |
| DAS | 1.37 | 1.12, 1.68 | 0.002 |
| HAQ score | 1.34 | 1.03, 1.90 | 0.034 |
| Years of RA | 1.01 | 0.99, 1.03 | 0.437 |
| Prednisolone | 2.49 | 1.46, 4.26 | 0.001 |
| Anti-TNF | 0.44 | 0.137, 1.4 | 0.165 |
| ECG-related parameters | | | |
| QTc | 2.17 | 1.21, 3.90 | 0.009 |
| LVH SL | 0.98 | 0.94, 1.02 | 0.247 |
| Medication associated with QTc prolongation | | | |
| Amitriptyline | 2.23 | 0.94, 5.28 | 0.068 |
| SSRIs | 2.01 | 0.93, 4.55 | 0.076 |
| Thiazide diuretics | 1.54 | 0.84, 2.84 | 0.163 |

[a]Per 10-unit increase. [b]Per 50-unit increase. SL: Sokolov–Lyon criteria.

FIG. 1 Increased mortality among RA patients with a QTc interval >424 ms (median QTc).
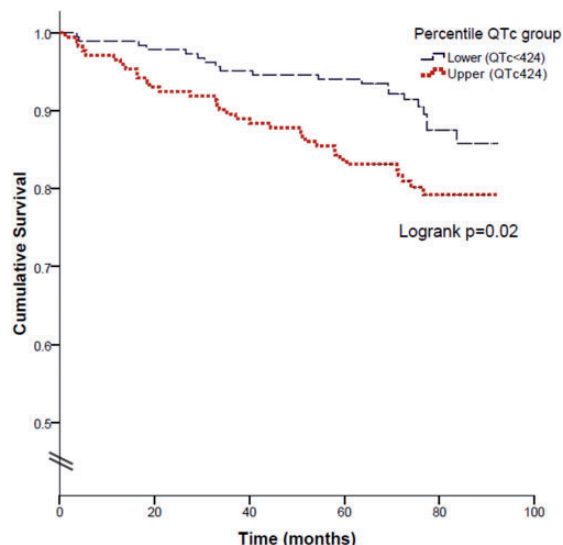


arrhythmogenic substrate that is linked to higher future mortality rates.

An association between QTc and all-cause mortality was reported in a cohort of 697 patients with type 1 diabetes mellitus [16] and 324 Caucasian patients with type 2 diabetes mellitus [17]. RA and diabetic patients seem to not only share unfavourable cardiovascular profiles with early subclinical atherosclerosis [3, 4], but also a similar substrate for arrhythmogenic death. On the contrary, evidence of an association of prolonged QTc with all-cause mortality in the general population was controversial until recently. A qualitative review of seven prospective cohort studies [6] (including 36 031 individuals) revealed inconsistent evidence for an association of prolonged QTc and all-cause mortality, with the exception of patients with prior CVD (relative risks ranging from 1.1 to 3.8). However, a recent meta-analysis of 23 observational studies found consistent, albeit weak, associations between prolonged QT interval and increased risk of total and cardiovascular mortality, with a 50 ms increase in QT interval being associated with a relative risk of 1.2 (95% CI 1.15, 1.26) for all-cause mortality [18]. The association of QTc with SCD, however, did not reach statistical significance. One has to interpret the above results with caution given the suboptimal patient characterization, the large heterogeneity (particularly when it comes to QTc category cut-offs) and the large variability in the presence of CVD and its risk factors at baseline across studies. Of note, in the present study the relative risk for total mortality per 50 ms increase in QTc interval is almost double that reported in the above meta-analysis [HR 2.17 (95% CI

TABLE 5 Cox regression analysis showing the HR for all-cause mortality per 50 ms increase in QTc interval, crudely and after adjustment for several confounders

| Model (adjustments) | HR | 95% CI | P-value |
|---|---|---|---|
| Crude[a] | 1.97 | 1.11, 3.52 | 0.021 |
| Baseline CVD, HTN, IR, pack-years[a] | 1.96 | 1.06, 3.64 | 0.033 |
| Baseline CVD, HTN, IR, pack-years, HAQ, DAS28[a] | 2.05 | 1.05, 3.99 | 0.035 |
| Baseline CVD, HTN, IR, pack-years, HAQ, DAS28, prednisolone[a] | 2.18 | 1.09, 4.35 | 0.028 |
| Baseline CVD, HTN, IR, pack-years, HAQ, DAS28, prednisolone, CRP[a] | 1.73 | 0.83, 3.62 | 0.143 |

[a]All models are adjusted for age and gender.

1.21, 3.90)], suggesting a substantially increased risk of death among RA patients with arrhythmogenic substrate when compared with the general population.

Several mechanisms have been proposed to explain the increased mortality associated with prolonged QTc. In animal models, prolonged QTc associates with depolarization during phases 2 and 3 of the action potential prior to completion of repolarization [19]. These premature action potentials can generate fatal ventricular arrhythmias such as torsade de pointes, which can progress to ventricular fibrillation and SCD [20, 21]. Even though a link between low-grade inflammation (as evidenced by raised CRP levels) and QTc interval prolongation has been shown in a cross-sectional study of 179 male college students [8], the mechanisms underlying this association are yet to be elucidated. Our study confirms and highlights the importance of the link between QTc and CRP in a population burdened by increased inflammation.

One of the limitations of the present study is that none of the 54 deaths was sudden, thus rendering it impossible for us to study an immediate link between SCD and prolonged QTc. However, we should highlight that the use of infection or cancer as the primary cause of death on death certificates does not rule out a fatal arrhythmia being the terminal event. Other RA cohorts [5] have reported an increased prevalence of SCD, which could be attributed to their increased CRP levels (either baseline or during flares) causing prolongation of QTc, a substrate for fatal arrhythmias. Second, the present study does not examine temporal associations between CRP and QTc interval. However, the contemporary, independent association between CRP and the QTc interval suggests that a within-patient temporal relationship between CRP and the QTc interval is possible and may partially explain the large burden of deaths from sepsis. In a subset population (201 patients) we showed a strong correlation between baseline and follow-up mean CRP and ESR, suggesting that single, baseline CRP measurements can predict future inflammatory burden. Future studies are needed to explore the impact of long-term increased inflammatory burden on QTc interval duration and the temporal association of CRP and the QTc interval in individual patients. Another limitation is the absence of imaging data in the current cohort, which would have been of interest since a recent study in mice expressing human CRP has shown a relationship between raised CRP and increased cardiac fibrosis [22]. Our findings highlight for the first time a contemporary link between inflammatory burden (CRP) and arrhythmogenic substrate (prolonged QTc), which subsequently impacts on all-cause mortality. Future studies are needed to (i) investigate the temporal relationship between CRP and QTc interval length, (ii) explore their association with cardiac structural changes (such as myocardial fibrosis) and (iii) examine the benefit of anti-inflammatory agents on the prevention of SCD and arrhythmogenic death in RA.

### Rheumatology key messages

- QTc prolongation associates with CRP levels in patients with RA.
- QTc prolongation predicts all-cause mortality in RA patients.

*Disclosure statement*: The authors have declared no conflicts of interest.

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