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**Sudden cardiac death in patients with rheumatoid arthritis**

Masoud S *et al.* Sudden cardiac death and rheumatoid arthritis

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**Abstract**

An increased cardiovascular morbidity and mortality, including the risk of sudden cardiac death (SCD), has been shown in patients with rheumatoid arthritis (RA). Abnormalities in autonomic markers such as heart rate variability and ventricular repolarization parameters, such as QTc interval and QT dispersion, have been associated with sudden death in patients with RA. The interplay between these parameters and inflammation that is known to exist with RA is of growing interest. In this article, we review the prevalence and predictors of SCD in patients with RA and describe the potential underlying mechanisms, which may contribute to this. We also review the impact of biologic agents on arrhythmic risk as well as cardiovascular morbidity and mortality.

**Key words:** Sudden death; Rheumatoid arthritis; Cardiovascular; Arrhythmia; QT; Autonomic nervous system

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**Core tip:** Patients with rheumatoid arthritis are twice as likely to experience sudden cardiac death (SCD). This excess risk can only partially be explained by the higher rates of heart failure and ischaemic heart disease. Abnormalities of the autonomic nervous system, such as decreased heart rate variability, and abnormalities of ventricular repolarization parameters, such as QTc interval and QT dispersion, have also been implicated. In this article we review the interplay between these parameters and inflammation, exploring whether Biologic agents and disease modifying anti-rheumatic drugs may have a role in reducing the burden of SCD.

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**INTRODUCTION**

Rheumatoid arthritis (RA) is a chronic inflammatory condition which affects 0.8% of the adult population[1]. It causes significant morbidity as a result of synovial inflammation, joint destruction, and associated disability. In addition to articular manifestations, there is substantial data demonstrating excess cardiovascular morbidity and mortality in RA[2,3]. Studies as early as the 1950s have shown that RA is associated with premature death[4], with 50% of excess deaths being attributed to cardiovascular disease[2,5]. Sudden cardiac death (SCD) is estimated to account for 50% of cardiovascular deaths in the general population[6,7]. Patients with RA are twice as likely to experience SCD[8], a figure comparable to patients with diabetes mellitus[9]. This review will seek to explore the risk factors that make SCD more prevalent in RA, including coronary artery disease (CAD), structural heart disease, electrophysiological abnormalities including myocardial repolarization (QTc interval, QT dispersion) and autonomic dysfunction [heart rate variability (HRV) analysis], and the interplay of inflammation on all these factors[10]. We will also review the effect that the new biologic agents may have on the incidence of cardiovascular events and SCD.

**DEFINING SCD AND PREVALENCE IN RA**

Sudden death is defined as “non-traumatic, unexpected fatal event occurring within 1 h of the onset of symptoms in an apparently healthy subject. If death is not witnessed, the definition applies when the victim was in good health 24 h before the event”[11]. The term SCD is used when a congenital, or acquired, potentially fatal cardiac condition was known to be present during life, or an autopsy has identified a cardiac or vascular anomaly as the probable cause of the event, or no obvious extra-cardiac causes have been identified by post-mortem examination, and therefore an arrhythmic event is a likely cause of death[11]. SCD is largely thought to result from fatal arrhythmias, in particular, ventricular tachycardia degenerating to ventricular fibrillation[12,13]. Bradyarrhythmia or electromechanical dissociation can also be associated with SCD but these tend to occur in patients with advanced cardiac disease[12,14].

In the general population sudden death accounts for 60% of cardiovascular deaths in those with known CAD[15], and is the first presentation of CAD in 15% of cases[16]. Over 70% of fatal arrhythmias are thought to be secondary to CAD[12]. These arrhythmias can occur acutely secondary to direct repolarisation changes occurring during ischaemia, or remotely, typically due to initiation of re-entry circuits within areas of electrically unexcitable scar tissue or diseased myocardium in patients with established myocardial infarction (MI)[17]. Dilated and hypertrophic cardiomyopathies account for the second largest number of sudden deaths followed by valvular, congenital, infiltrative, ion- channel disorders which only account for the small remainder[12,13].

Within the RA population, there is a wealth of data regarding the rates of cardiovascular death, however few studies have looked specifically at the epidemiology of SCD. In an inception cohort of 1010 RA patients, Goodson *et al*[18] found an excess of cardiovascular mortality without a corresponding increase in cardiovascular admission rates as compared to controls, suggesting that cardiovascular disease has a higher case fatality in the RA population, or that it often goes unrecognized before the fatal event. Indeed, Solomon *et al*[19] found that the rate ratio for cardiovascular death was highest in young RA adults and those with no known prior cardiovascular events. Whilst Van Doornum *et al*[20] demonstrated that RA patients have a higher 30-d case fatality following MI as compared to controls, 17.6% *vs* 10.8%. In a large population cohort study of 603 RA patients followed up for 15 years, Maradit-Kremers *et al*[5] demonstrated that RA patients were twice as likely to experience SCD (hazard ratio 1.94, 95%CI: 1.06-3.55)[8], a figure similar to the risk of SCD amongst patients with diabetes mellitus[21]. The authors also noted a higher risk of unrecognized MIs and a lower likelihood of angina symptoms, suggesting that CAD manifests differently in RA and is more likely to manifest as cardiovascular death[8]. Similarly Mantel *et al*[22] demonstrated that RA is associated with higher risk acute coronary syndromes, higher cumulative incidence of SCD ( 0.2% *vs* 0.13% over 3 years), and higher short term case fatality rate at 7 and 30 d. Indeed, certain RA genetic polymorphisms have been linked to premature cardiovascular disease and mortality[23-26], although none with a strong clinical implication[27,28].

**RISK FACTORS FOR SCD IN RA**

***Accelerated CAD, congestive cardiac failure and inflammation***

Whilst there is a higher incidence of ischaemic heart disease (IHD) in RA, several authors have shown that this increased incidence cannot be explained by traditional risk factors alone[5,29], as such there has been growing interest in the role of inflammation as novel risk factor for atherosclerosis[30]. Indeed, in the general population, modest increases in C-reactive protein (CRP) have been associated with increased cardiovascular events[31], and RA has been likened to diabetes as a risk factor for CAD[32].

Studies have also suggested different patterns of CAD in RA with chronic inflammation leading to early endothelial dysfunction[33,34], and a higher incidence of unstable plaques attributed to inflammatory cytokines[35]. Indeed TNF-a has been implicated in all stages of atherosclerosis including endothelial dysfunction, plaque formation, rupture and promotion of the clotting cascade[36,37]. Systemic inflammation has also been associated with dyslipidaemia, impaired glucose metabolism, platelet activation and increased clotting factors[36]. However, despite the evidence linking inflammation to accelerated atherosclerosis and IHD, Maradit-Kremers *et al*[8] demonstrated that the two-fold risk of SCD seen in the RA population persisted after adjustments for history of hospitalized, or unrecognized, MI, revascularization procedures and cardiovascular risk factors. This suggests that the increased risk of SCD in RA cannot be explained by increased rates of IHD alone[10,38].

Crowson *et al*[39] showed that the excess risk of congestive cardiac failure (CCF) among RA subjects[40] could not be explained by the increased frequency, or effect of, either cardiovascular risk factors, or IHD. In the same cohort, Gabriel *et al*[41] demonstrated that whilst 80% of CCF in the general population is attributed to classical CVD risk factors, in RA, classical risk factors only explained 40% of the incident heart failure.

Amongst RA patients experiencing new-onset heart failure, ESR levels were highest in the 6 mo immediately preceding diagnosis, suggesting that ESR may signal the onset of heart failure in patients with RA[42]. However, the relationship between SCD and severity of CCF is not as clear-cut as that seen with SCD and IHD, and less is known about RA and CCF. Data from the general population suggests that as left ventricular (LV) systolic function deteriorates, all-cause mortality and the absolute number of sudden deaths increases, but the proportion of deaths due to arrhythmias decreases[14,43]. Thus, the degree of LV systolic dysfunction lacks specificity as a predictor of death secondary to cardiac arrhythmias, because it is also powerful measure of the risk of death[12]. In line with these results, Nicola *et al*[44] found CCF contributed to the excess cardiovascular mortality in RA, primarily through the increased incidence of CCF in RA rather than increased case fatality. Studies have also shown that patients with RA have higher rates of diastolic dysfunction[45], and heart failure with preserved ejection fraction[46].

***Abnormal ventricular repolarization, autonomic dysfunction and inflammation***

Inflammation, as an independent predictor of cardiovascular mortality and sudden death, has been the focus of recent research[30,47,48]. Indicators of abnormal ventricular repolarization such as QTc prolongation, QT interval dispersion, and autonomic dysfunction have been implicated in the aetiopathogenesis of SCD. The QT interval represents the time from onset of ventricular depolarization (beginning of the Q wave) to completion of repolarization (end of T wave). The corrected QT interval (QTc) estimates the QT at a standardized heart rate of 60 bpm, while QT interval dispersion (QTd) is measure of the dispersion of ventricular repolarization (maximum QT interval - minimum QT interval). In the general population both prolongation of QTc and increased QTd are known risk factors for SCD[49,50], and there is data linking both CRP to prolongation of QTc[51] and to SCD[47]. In animal models, prolonged QTc is associated with depolarization during phases 2 and 3 of the action potential prior to completion of repolarization[52]. These premature action potentials also known as early after depolarizations (EADs) can generate fatal ventricular arrhythmias, such as torsade de pointes, which can progress to ventricular fibrillation and SCD[12,53].

Several studies have also shown an association between RA and prolonged QTc or increased QT dispersion variables, as well as an association between RA disease activity and QTc length[54-62] (Table 1), with the strongest evidence available for CRP as a marker of disease activity, compared with clinical scoring systems and ESR[10]. Moreover, there is growing evidence from basic science studies demonstrating that pro-inflammatory cytokines, particularly tumour necrosis factor alpha (TNF-α), directly prolong cardiomyocyte action potential duration (APD) by regulating ion channels involved in ventricular repolarization[10]. In particular, several experimental studies have shown that TNFα prolongs APD, triggering re-entrant ventricular arrhythmias[63,64]. TNFα prolongs APD by inhibiting both the transient outward potassium current[65], and the rapid delayed-rectifier potassium current[10,66]. Similarly, animal studies have shown that the pro inflammatory cytokines IL-1 and IL-6, prolong APD in ventricular myocytes *via* their effects on calcium channels[67,68]. Interestingly both levels of CRP[48] and levels of soluble tumour necrosis factor-α receptors (sTNFR) are strong and independent predictors of cardiovascular death amongst RA patients[69].

As early as 1998, a cross-sectional study by Göldeli *et al*[54], demonstrated a significant increase in QT dispersion variables when comparing RA patients with matched controls, as well as an increase in complex premature ventricular beats. More recently a large prospective study of 357 RA patients demonstrated that prolonged QTc was a strong predictor of death, with a 50 ms increase in QTc being associated with a doubling of the hazard for all-cause mortality[60]. The authors also showed that QTc prolongation was independently associated with CRP levels, and that the association between QTc and mortality was lost after adjustment for CRP, further supporting the role of inflammation in the increased rates SCD seen in this patient group[60]. No association was found between QTc and the presence of cardiovascular disease at baseline, ECG abnormalities suggestive of myocardial ischemia, LV hypertrophy, or the use of common cardiovascular medications[60]. Similarly, Chauhan *et al*[61] found a higher incidence of idiopathic QTc prolongation amongst RA patients and demonstrated that any cause QTc prolongation was significantly associated with all-cause mortality (HR: 2.99, 95%CI: 1.93-4.65) but only marginally associated with cardiovascular mortality (HR: 2.68, 95%CI: 0.84-5.6, *P* = 0.09). The authors used a cut off of ≥ 450 ms in males and ≥ 460 ms in females to define QTc prolongation[61], but interestingly, amongst the general over 55 population even a borderline increased QTc interval, defined as 451 to 470 ms in women, and 431 to 450 ms in men, was associated with a two-fold increase in the risk of SCD[53]. Following this, Lazzerini *et al*[62] showed that treating RA patients with 3 mo of the anti-IL 6-receptor antibody, tocilizumab, was associated with a significant reduction in the QTc interval. The fact improvement was seen in such a short time frame suggests that QTc prolongation is driven by an inflammatory process rather than subclinical coronary atherosclerosis[62].

There is also emerging data about the role of pro and anti-inflammatory cytokines in QTc prolongation amongst patients with RA. Lazzerini *et al*[62] recently demonstrated a strong association between QTc and circulating TNF-α levels, more so than CRP, although sample sizes were small. Adlan *et al*[70] performed a cross-sectional study of 112 patients with RA examining the relationship between QTc and cross-sectional sampling of several pro and anti-inflammatory cytokines. The authors demonstrated an association between QTcprolongation and CRP, TNF-α, IL-1ß and the anti-inflammatory cytokine IL10. A surge of IL 10 often follows the release of pro-inflammatory cytokines and its release is stimulated by adrenaline[70,71].

Sympathetic excitation has been associated with prolongation of the QTc[72], while cholinergic stimulation with pyridostigmine shortens QTc interval in patients with CAD[73]. RA has been associated with both reduced parasympathetic tone and increased sympathetic tone, with a recent systematic review demonstrating a 60% prevalence of autonomic dysfunction amongst patients with RA[52]. The majority of studies assessed autonomic dysfunction using clinical cardiovascular tests (CCTs) or by measuring HRV parameters[52]. CCTs include blood pressure and heart rate response to orthostasis, deep breathing and Valsalva manoeuvres, with many studies using Ewing’s battery of CCTs[74]. HRV analysis attempts to assess cardiac autonomic regulation through quantification of variation in sino-atrial activity with rapid variations reflecting vagal modulation and slower variations reflecting a combination of both parasympathetic and sympathetic modulation and non-autonomic factors. HRV can be measured using time domain methods or frequency domain methods. Examples of time domain measures include; mean heart rate, AVNN (Average of all the NN intervals, with “NN” used in place of “RR” to emphasize that these are normal sinus beats), and the difference between the longest and shortest NN interval[75]. More complex statistically derived time domain measures include either those, derived from direct measurements of the NN intervals, such as SDNN (standard deviation of all NN intervals), SDANN (standard deviation of the average of NN intervals in all 5-min segments of a 24 h recording) or those derived from the differences between NN intervals such as RMSSD (square root of the mean of the squares of the differences between adjacent NN intervals) and pNN50 (percentage of differences between adjacent NN intervals that are > 50 msec)[75]. Conversely, frequency domain methods assign bands of frequency, and through fast Fourier transformation quantify the NN interval in each band[75]. The bands are typically high frequency (HF) from 0.15 to 0.4 Hz, low frequency (LF) from 0.04 to 0.15 Hz, and very low frequency (VLF) from 0.0033 to 0.04 Hz. Vagal activity is the major contributor to the HF component with a combination of both sympathetic and parasympathetic activity contributing to the LF and LF/HF ratio[75].

In the general population reduced HRV has been associated with a significantly increased risk of death post MI[76], although as yet there are no studies demonstrating the association between autonomic dysfunction and mortality amongst RA patients. This said, there is data to show that autonomic dysfunction, namely reduced HRV is associated with prolongation of the QTc in patients with RA[59]. A study of 100 patients with chronic inflammatory arthritis (CIA) demonstrated that while CRP was independently associated with HRV, there was no association between CRP and QTc in the multivariate model, with HRV parameters and RR interval playing a predominant role in producing differences in QTc among the subjects[59]. These findings, together with the evidence that, even after sex-adjustment, QTc was correlated with heart rate and all HRV parameters suggests that the association between CRP and QTc prolongation is most likely an indirect consequence of the autonomic dysfunction and specifically increased sympathetic tone[59]. Indeed, there is growing evidence to show that the release of pro inflammatory cytokines in diseases such as RA increases sympathetic outflow activation *via* autonomic centres in brain[10]. This represents an adaptive response which dampens immuno-inflammatory activation and inhibits the release of further cytokines *via* stimulation of β2-adrenoceptors in circulating lymphocytes and monocytes[77,78]. This negative feedback loop is known as the inflammatory reflex. However, sympathetic activation does not only affect the immune system, but all the systems throughout the body, and its effects may either directly[79], or indirectly (by prolonging QT interval parameters *via* modification in calcium and/or potassium conductance) trigger the onset of arrhythmias and SCD[10].

**IMPACT OF DISEASE-MODIFYING ANTI-RHEUMATIC DRUGS AND BIOLOGICS ON CARDIOVASCULAR OUTCOMES?**

Disease-modifying anti-rheumatic drugs (DMARDs) are a category of otherwise unrelated drugs defined by their use in RA to slow down disease progression. Throughout this review the term DMARD will be used to refer to synthetic DMARDs such as methotrexate, whereas Biologic DMARDs will be simply referred to as Biologics.

Whilst currently there are no studies specifically evaluating the impact of synthetic DMARDS and biologics on the incidence of arrhythmias and SCD in RA, the European League Against Rheumatism advocate early aggressive treatment with these agents, for the purpose of reducing cardiovascular morbidity and mortality[3]. These agents are expected to exert their benefits *via* their direct effect on reducing inflammation, but also by improving joint inflammation and function they will potentially lead to increased levels of physical activity and reduce the incidence of other risk factors such as diabetes mellitus and hypertension[3] (Figure 1). Indeed, a prospective cohort study and concurrent literature review conducted by Meek *et al*[80] showed a trend towards reducing cardiovascular case fatality since the advent of DMARDS and biologics. However, no comparison was made to a control population, to ensure that the findings were not just tagging the observed reduction in cardiovascular disease burden, in the general population.

In this section, we will explore whether the advent of DMARDs and particularly Biologics, has indeed reduced cardiovascular mortality and morbidity. We will look closely at the data supporting both the anti-arrhythmic and pro-arrhythmic effects of Biologics, as well as their influence on cardiac autonomic dysfunction and repolarisation parameters such as the QTc.

There is growing evidence from observational studies, including observational meta-analyses, to suggest that DMARDs in particular methotrexate[81,82] and biologics, particularly TNF inhibitors (TNFi)[37,83,84] are associated with decreased cardiovascular mortality and morbidity. To date, the largest meta-analysis has been conducted by Roubille *et al*[84], and included 28 observational studies, over 200000 RA patients and over 5000 cardiovascular adverse events. The authors found that TNFi were associated with a significant reduction in the risk of all cardiovascular events (CVE) (RR = 0.70, *P* = 0.005), as well as MIs, strokes and major adverse cardiac events. Methotrexate was also associated with a reduction in the risk of all CVEs (RR = 0.72, *P* = 0.007) and MIs. Moreover, a large observational study by Dixon *et al*[85] suggested that patients who responded to TNFi experienced a 70% lower risk of MI than their non-responding counterparts. In addition, a recent retrospective post hoc analysis involving approximately 4000 patients with moderate to severe RA, demonstrated that during tocilizumab treatment, greater reductions in disease activity were inversely associated with future major cardiovascular events, including MIs and cardiovascular death[86].

The lack of randomized controlled trials (RCTs) specifically examining the impact of biologics and DMARDS on CVE is perhaps explained by the number of patients that would be required to adequately power the studies, and the duration of follow-up that would be needed to detect an effect. Some studies have examined the impact of biologics on surrogate markers of IHD such as carotid intimal thickness and brachial artery flow mediated dilatation (FMD) with conflicting results[87]. A single center RCT conducted by Hsue *et al*[88] demonstrated that depletion of B-cells with rituximab in RA patients improved both macrovascular (brachial artery flow-mediated dilation) and microvascular (reactive hyperemia) endothelial function, despite modest elevation in lipids. There is also an ongoing prospective imaging study, CADERA, bolted onto the single-center VEDERA RCT (very early *vs* delayed etanercept in RA, NCT 02433184), which will use cardiac MRI to explore the prevalence and change of cardiovascular abnormalities in patients receiving TNF inhibitors *vs* standard therapy over a 12-mo period[89]. The evidence for a link between inflammation and cardiovascular disease is so compelling that 2 RCTS, the Cardiovascular Inflammation Reduction Trial (CIRT) and the Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS), have been commenced. CIRT will investigate whether low-dose methotrexate will reduce rates of recurrent MI, stroke, and cardiovascular death among stable post MI patients with type 2 diabetes or metabolic syndrome, two conditions that are associated with an enhanced inflammatory response (NCT01594333). CANTOS will evaluate whether interleukin-1β inhibition as compared to placebo can reduce rates of recurrent MI, stroke, and cardiovascular death among stable CAD patients who remain at high vascular risk due to persistent elevations of CRP (NCT01327846). In addition, tocilizumab and anakirna have been investigated as treatment for acute MIs with RCTs demonstrating an attenuation in CRP levels, CCF and cardiac remodeling following ST elevation MI[90,91], and attenuation in CRP levels and post percutaneous intervention troponin release following non ST elevation MI[92]. There is a further ongoing trial TOCRIVA, which will assess the effects of tocilizumab on cardiovascular risk in RA patients (NCT 01752335).

The relationship between biologics and CCF is more complex and the data is conflicting. In the general population TNF-α levels are increased in CCF[93] and associated with severity of clinical signs and symptoms[94]. Experimental heart failure models have suggested that TNF inhibitors may improve ventricular dysfunction[95]; however, a large clinical trial assessing etanercept in the treatment of congestive heart failure showed no benefit[96], while another one found that high-dose infliximab 10 mg/kg worsened heart failure in patients with moderate-to-severe chronic heart failure[97]. Consequently, a “black box” warning was introduced not to use these medications in patients with pre-existing heart failure[98]. The most recent data from the United States, which compared 8656 new users of synthetic DMARDs with 11587 new users of TNFi, suggested that TNFi were not associated with an increased risk of hospital admissions due to heart failure (HR 0.85, 95%CI: 0.63 to 1.14), but identified that such a difference may well have existed prior to the introduction of the black box warning in 2002[99]. This study also noted a dose-dependent association between glucocorticoid use and heart failure. Importantly, the authors acknowledged that they were unable to adjust for potential differences in baseline disease severity between the TNFi and synthetic DMARD groups as this information was not collected[98]. The German RABBIT registry also reported similar results, with similar rates of heart failure reported in those receiving TNFi compared to those receiving combined synthetic DMARDs as well as a dose-dependent association with glucocorticoids[100]. The authors of that study suggested that the overall effect of TNFi is more beneficial than harmful, through improved control of disease activity and reduced need for glucocorticoid. Glucocorticoid use in RA patients has also been associated with a dose dependent increase in all-cause and cardiovascular mortality, at a threshold of 8 mg per day[101]. There is less data about the other biologics and CCF but a recent pilot study has shown that 12 mo of treatment with the anti-IL6 tocilizumab significantly increases LV ejection fraction and reduces LV mass index with a concomitant reduction in disease activity[102]. As aforementioned anakinra has also been associated with reduced heart failure following ST elevation MIs[91].

It has been suggested that by suppressing inflammation, biologics may attenuate the autonomic and electrophysiological disturbances that have been linked with SCD and arrhythmic risk amongst patients with RA. Indeed, in a small interventional study of 17 patients with active RA, 76% of which had a prolonged QTc, Lazzerini *et al*[62] demonstrated that tocilizumab was associated with significant shortening of the QTc within a 3 to 6 mo period. This was also correlated with a decrease in both CRP and TNF-α levels. Similarly, Senel *et al*[103] showed a reduction in both QTc interval, and inflammatory markers, amongst patients with Ankylosing spondylitis (AS), following 6 mo of treatment with infliximab. Amongst patient with CIA, infliximab therapy duration has also been shown to be inversely and independently associated with QTc duration[59]. Conversely, di Franco *et al*[104] found no significant difference in QTc interval duration amongst CIA patients treated with TNFi and rituximab. However, the authors did not report on disease activity and thus there may be have been a large proportion of patients who did not achieve adequate disease control[105]. In the Diana study, 12 wk of treatment with combination synthetic DMARDs or biologics significantly improved cardiac autonomic dysfunction (*P* < 0.05) in both RA and AS patients[106]. Inflammatory markers (ESR and CRP) correlated with variables of autonomic neuropathy before and after biologic treatment, suggesting that inflammatory markers may both predict the occurrence of autonomic neuropathy and response to treatment, especially with biologics[106]. Infliximab has also been associated with acute changes in HRV consistent with a decrease in sympathetic tone and shift towards relative vagal predominance[107]. Additionally, duration of treatment was also found to be correlated to increased HRV and improved cardiac autonomic function[59].

However, the use of biologics is not without risk, and beyond the well-recognized risks of malignancy and infection, there have been reports of cardiac arrhythmias, in some cases life threatening, particularly following the use of anti-TNF monoclonal antibodies and rituximab[105]. Case reports have described ventricular arrhythmias[108,109], supraventricular arrhythmias[110,111], and various degrees of heart block[112-114], associated with the use of infliximab, although in one case, the complete heart block did in fact resolve spontaneously[112]. It is thought that biologics and in particular TNF inhibiting monoclonal antibodies may be acutely unmasking the inflammation driven myocardial instability that characterizes RA, and other inflammatory conditions[105]. They could be doing this in one of three ways; firstly by worsening LV function, secondly by reducing coronary blood flow[115], and thirdly, a mechanism which would be exclusive to monoclonal antibodies, *via* complement-mediated cytotoxic or inflammatory damage to the myocardium[105,116]. This is supported by two interesting studies in the literature. The first, is a case report of 42-year-old AS patient who developed ventricular tachycardia requiring defibrillation following 3 doses of infliximab[117]. Despite this, the patient was retreated with infliximab given that there was no evidence of CAD on angiography and his inflammatory markers remained high. Over 2 mo a marked reduction in ventricular arrhythmias was noted with an associated attenuation of inflammatory response. The second study, a prospective, single-blind, crossover study of 75 patients with CIA, demonstrated that during acute infliximab infusion, there was 8% incidence of new-onset ventricular tachyarrhythmia *vs* 2.7% with placebo (OR 3.17, 95%CI: 0.61-16.26)[107]. Although the difference was not statistically significant, the study was likely underpowered to detect this. Interestingly, those patients that experienced new onset ventricular arrhythmia showed baseline QTc and HRV values that were significantly prolonged and depressed, respectively, as compared to the patients who did not develop ventricular arrhythmia. Translating this into clinical practice, rituximab and monoclonal TNFi should be avoided in patients with significant CV risk factors, known structural heart disease or ECG abnormalities (conduction disease, QTc prolongation and HRV depression). If these drugs are still required, careful ECG monitoring should be performed in the early phases of administration, until disease activity is adequately controlled, to detect and treat any complications[105].

**CONCLUSION**

RA is a chronic inflammatory condition, which is associated with significant cardiovascular mortality and morbidity. Data suggests that RA patients are twice as likely to experience SCD compared to the general population[8], a figure comparable to diabetics[9]. Whilst some of this excess risk can be explained by the higher rates of heart failure and IHD, thought to be partially trigged and mediated by inflammation, direct influence of inflammatory cytokines on electrophysiological parameters has been implicated in arrhythmogenesis leading to SCD in RA. Interest is growing in examining the interplay between QTc prolongation, autonomic dysfunction and the risk of SCD. Both autonomic dysfunction and QTc prolongation have been shown to be correlated to inflammation, with the best evidence in place for CRP[10]. The advent of DMARDS and biologics has improved cardiovascular morbidity and mortality[37,82], with novel evidence demonstrating a direct normalisation effect on repolarization parameters such as QTc[62], as well as improvement in parameters of autonomic dysfunction[106]. Randomised controlled trials assessing the impact of DMARDs and biologics on autonomic dysfunction and repolarization parameters, such as QTc or QT dispersion, are urgently required to demonstrate the potential for reduction of SCD in this patient population.

**KEY MESSAGES**

Patients with RA are twice as likely to experience SCD compared to the general population; This excess risk can be partially explained by the higher rates of heart failure and IHD, thought to be partially trigged and mediated by inflammation; Direct influence of inflammatory cytokines and autonomic dysfunction on electrophysiological parameters has been implicated in arrhythmogenesis in this patient group; Biologic agents and disease modifying anti-rheumatic drugs may have a role in reducing the burden of SCD by controlling inflammation.

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|  |
| --- |
| **Table 1 Studies demonstrating associations between rheumatoid arthritis and QT parameters, inflammation and mortality** |
| **Ref.** | **Design** | **RA patients** | **Controls** | **Impact of RA and QT dispersion (QTd) and QTc**  | **Association between QT parameter, and disease activity/duration (1), arrhythmia (2), autonomic dysfunction (3), mortality (4)** |
| [54]  | Cross-sectional | 42 | 42 | ↑ QTd variables (QTd, QTcD, JTD, JTcD) *vs* controlsNo difference in QTc *vs* controls | (1) ESR, CRP(2) Complex premature ventricular beats |
| [55]  | Cross-sectional | 40 | 48 | ↑ QTd variables (QTD, QTcD) *vs* controls | (1) Disease duration |
| [56]  | Cross-sectional | 40 | 40 | ↑ QTd *vs* controls | (1) Extra-articular manifestations, erosive disease |
| [57]  | Cross-sectional | 58 | 29 | ↑ QT *vs* controls | (1) Secondary Sjörgen’s syndrome |
| [58]  | Cross-sectional | 100 | 100 | ↑ QTd *vs* controls | (1) Disease duration, DAS28, ESR, number of joints involved |
| [59]  | Cross-sectional | 25 | 21 controls76 with spondylarthopathy | ↑ QTc *vs* controls and those with spondyloarthopathiesInfliximab therapy duration inversely correlated to Qtc (*P* < 0.01) | (1) CRP(3) ↑ QTC associated with ↑ HR, autonomic dysfunction, particularly sympathetic dysfunction as assessed by spectral parameters of heart rate variability |
| [60]  | Prospective Cohort | 357 | \_ | ↑ QTc 10% males (QTc ≥ 450 ms) and 5.6% of females (QTc ≥ 460 ms) | (1) CRP(4) Doubled risk of all-cause mortality per 50 ms increase in QTc, (lost after adjustment for CRP) HR 2.17 (95%CI: 1.21, 3.90) |
| [61]  | Retrospective Cohort | 417 | 422 | ↑ % of RA patients with QTc prolongation (> 450 ms males, > 460 ms females) *vs* controls 20 yr after disease onset (48% *vs* 38%, *P* = 0.004) | (1) ESR(4) Any cause QTc prolongation was associated with ↑ all-cause mortality HR 2.99 (95%CI: 1.93, 4.65) |
| [62]  | Prospective Cohort | 17 | \_ | ↑ QTc (> 440 ms) in 76% of patientsToclizumab associated with 47% ↓ in No. patients with QTc prolongation (*P* = 0.006) | (1) CRP and TNF-α  |
| [70]  | Cross-sectional | 117 | - | - | (1) CRP, TNF-α, IL-1ß and IL 10 ( QTc BAZ)(1) IL-1ß and IL 10, trend towards TNF-α (QTc FHS) |
| RA: Rheumatoid arthritis; QTd: QT interval dispersion; QTc: Heart-rate corrected QT interval; QTcD: Heart-rate corrected QT interval dispersion: JTD: JT interval dispersion; JTcD: Heart-rate corrected JT interval dispersion: DAS28: Disease activity score in 28 joints; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; ms: Milliseconds; QTc BAZ: QTc calculated using Bazett formula; QTc FHS: QTc calculated using Framingham formula. |

**] ↑ mobility + function should ↓ HTN + DM**

**Biologics + DMARDs**

**Arrhythmias & Sudden Cardiac Death**

Direct electrophysiological effects

&

Sympathetic overdrive

Congestive Cardiac Failure

Reduced HRV + Increased QTc/Qtd

Coronary Artery Disease

Myocardial Injury + Remodeling

Accelerated Atherosclerosis

Release of Pro-inflammatory Cytokines

(TNF-α, IL-6, IL-1ß)

**Chronic Systemic inflammation**

**Figure 1 Proposed Mechanisms by which biologics and disease modifying anti-rheumatic drugs will reduce the risk of sudden cardiac death in patients with rheumatoid arthritis.** DMARD: Disease modifying anti-rheumatic drugs; HTN: Hypertension; DM: Diabetes; TNF: Tumour necrosis factor; IL: Interleukin; HRV: Heart rate variability; QTc: Corrected QT interval; QTd: QT interval dispersion.