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Cardiovascular co-morbidity in early rheumatoid arthritis

Holly John, BMBS, MRCP, Clinical Research Fellow & Specialist Registrar [a,b], George Kitas, MD, PhD, FRCP, Professor of Rheumatology [a,c], Tracey Toms, MBChB, MRCP, Clinical Research Fellow & Specialist Registrar [a,c], Nicola Goodson, MBChB, PhD, FRCP, Senior Lecturer in Rheumatology [d,c,*]

[a] *Department of Rheumatology, Dudley Group of Hospitals NHS Trust, UK*
[b] *School of Sport and Exercise Sciences, University of Birmingham, UK*
[c] *ARC Epidemiology Unit, University of Manchester, UK*
[d] *Department of Rheumatology, University Hospital Aintree Hospitals NHS Trust, Liverpool, UK*

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Rheumatoid arthritis (RA) is associated with increased morbidity and mortality due to cardiovascular disease (CVD), mostly accelerated atherosclerotic CVD, and there is evidence that this occurs early in the inflammatory disease process. Both traditional and novel CVD risk factors as well as the effects of the RA disease process and its treatment interact and contribute to the development of CVD in RA. In this review we discuss the evidence for co-morbid CVD complicating early RA. This includes examining studies of mortality outcome and CVD events in cohorts of early RA patients as well as studies using surrogate markers for atherosclerotic CVD in RA. The evidence for shared risk factors for RA and CVD is presented. Screening and modification of CVD risk factors should be an integral part of care for any patient diagnosed with RA. Novel methods to diagnose CVD in high-risk asymptomatic RA patients need to be evaluated.

Medical care of patients with rheumatoid arthritis (RA) involves managing their joint disease but also addressing the co-morbidities associated with RA, such as osteoporosis, depression, cardiovascular disease (CVD) and malignancy [1]. Such co-morbidities may have a significant effect on quality of life, work disability, or mortality [1]. Indeed, the increased mortality of RA [2] is most commonly due to

* Corresponding author. Tel.: +44 151 529 5889; Fax: +44 151 529 5888.
E-mail address: nicola.goodson@liverpool.ac.uk (N. Goodson).

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co-morbidities such as infection, CVD, or respiratory disease [3]; in particular, CVD accounts for almost 50% of the excess mortality [3,4]. Given the frequency and impact of CVD co-morbidity in RA, this chapter focuses exclusively on this. We first summarize the epidemiological evidence for increased CVD morbidity and mortality in patients with established RA, and discuss possible mechanisms for increased CVD risk in this group of patients. We then focus on the evidence for concurrent CVD co-morbidity early in the RA disease process: we consider cardiovascular risk prior to the onset of RA, examine shared risk factors or predictors for both RA and CVD, and discuss an overall framework for incorporating these into the current drive for early diagnosis and management of RA.

Cardiovascular disease co-morbidity in established RA

Rheumatoid arthritis is associated with heart disease. Pericardial disease, including pericarditis and pericardial effusions, have long been identified as extra-articular manifestations of RA and were first described by Charcot in 1881 [5]. The true prevalence of pericardial disease in association with RA is difficult to determine as it often remains clinically silent. Echocardiographic studies in established cohorts of RA patients have reported prevalence rates of pericardial disease between 1 and 30%. Little is known about the prevalence of pericardial inflammation in the early years of RA. In addition, myocardial and endocardial disease have been described in association with RA. Again, these cardiovascular complications rarely cause clinical symptoms and are often identified as coincidental finding on autopsy or imaging studies. Whilst extra-articular RA is associated with mortality [6], this does not appear to be due to haemodynamic consequences of structural rheumatoid cardiovascular disease.

Many epidemiological studies have examined cardiovascular mortality in longitudinal cohorts of RA patients [7–10]. Overall, the consensus is that CVD mortality is increased in RA, with standardized mortality rates (SMRs) of 1.13–5.15 [11]. Studies that have explored cause-specific mortality in detail have highlighted that much of the excess CVD mortality is due to accelerated atherosclerotic CVD [12]. As expected, there is also evidence for increased CVD morbidity – namely myocardial infarction (MI), congestive heart failure (CHF), and stroke – in patients with RA [13–15], with their risk for MI or CVA being at least double that of the general population [15]. The relative risk for a CVD event is greatest in young adults, although in absolute terms the greatest difference in rates of CVD events was in older adults because CVD prevalence increases with age [15].

Not only is ischaemic heart disease (IHD) more prevalent in patients with RA, but also the clinical presentation of IHD appears to be different to that in the general population. Symptoms of IHD may be silent [16], or angina may be unrecognized medically [17]. Patients with RA are less likely to report chest pain or symptoms of angina associated with ambulatory ECG evidence of cardiac ischaemia than patients without RA [18]. Comparing clinical presentations in RA patients diagnosed with an acute coronary syndrome with age- and sex-matched non-rheumatoid controls showed that RA patients were less likely to present with chest pain and more likely to have an atypical presentation such as collapse or dyspnoea [19]. Other studies have demonstrated that patients with RA are more likely to experience unrecognized MIs or sudden death than non-RA patients [14]. The Stockport inception cohort study in England in the 1980s and 1990s supports this: although the SMR for CVD was increased in this RA cohort, admissions to hospital with a CVD event were not, suggesting that RA patients were less likely to seek hospital care due to any of the above reasons [9]. After an index CVD event, Douglas et al found that patients with RA were more likely to experience recurrent cardiac events or death [19]. The Stockport inception cohort revealed that, of those RA patients admitted to hospital, 70% only had one admission with a CVD event during the period of follow-up [9], which may also suggest that patients with RA were more likely to die during or after their first cardiovascular admission; others have also observed an increased 30-day mortality after a CVD event (including both MI and stroke) [15,20]. Therefore, overall, not only is CVD more prevalent in RA but it also associates with a higher case fatality [20,21].

Why is cardiovascular disease increased in patients with RA?

Accelerated atherosclerosis in RA [8] is thought to be due to the interplay between classical risk factors for CVD, which may be adversely affected by RA, as well as novel risk factors, particularly systemic inflammation [11,22]. This is summarized in Fig. 1.