Patients with a range of rheumatic diseases are at increased risk of cardiovascular disorders

Towards a re-evaluation of the European League against Rheumatism (EULAR)'s recommendations for cardiovascular risk management?

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The notion that patients with rheumatic disorders are at increased risk of developing cardiovascular diseases has been ongoing for many years and has sparked much debate concerning whether and when to initiate cardiovascular prevention therapies.

The initiation of preventive therapies, such as blood pressure lowering drugs or statins, is usually recommended in patients at high risk of developing adverse cardiovascular outcomes. Accurately assessing an individual's cardiovascular risk is hence important. Until now, the modest size and duration of follow-up of available cohorts have been a barrier to precise quantification of cardiovascular risk in specific rheumatic disorders.[1] In particular, there is a lack of robust evidence about the rates of cardiovascular morbidity and mortality among people with diseases such as vasculitis, systemic sclerosis, or Sjögren's syndrome, and emerging evidence for excess risk in patients with systemic lupus erythematosus has not been validated in external cohorts.[2] The best evidence is available for rheumatoid arthritis, which has been shown to increase cardiovascular risk by approximately 50% beyond that explained by established risk factors.[3] As a result, the current cardiovascular disease prevention guidelines from the European Society of Cardiology (2021) recommend a lower threshold for the initiation of preventive therapies in adults with rheumatoid arthritis, by multiplying patients' calculated risk score by 1.5, but make no mention of risk multipliers for other rheumatic diseases.[4] The recent update of the European Alliance of Associations for Rheumatology (EULAR)'s recommendations (2022), did not endorse the use of any specific cardiovascular risk assessment tool nor risk multipliers for conditions beyond rheumatoid arthritis – although a thorough assessment of cardiovascular risk is recommended.[5]

A recent large-scale epidemiological study brings new evidence to this important clinical challenge. Using electronic health record data from 22 million individuals in the UK,[6] Conrad and colleagues examined 19 autoimmune disorders, including seven rheumatic diseases – axial spondyloarthritis, polymyalgia rheumatica, rheumatoid arthritis, Sjögren's syndrome, systemic lupus erythematosus, systemic sclerosis, and vasculitis – and described their association with a broad range of cardiovascular outcomes.[6] This study showed that patients with rheumatic (or "connective tissue") diseases, collectively, had an average 68% higher risk of cardiovascular disease over the period studied. Greater magnitudes of cardiovascular risk were observed for individuals with lupus and systemic sclerosis, for whom hazard ratios were two to four times higher than in the general population. The study also demonstrated a "dose-related" increase in cardiovascular risk with the number of autoimmune disorders present.

Two findings were particularly striking. First, the earlier age of onset of cardiovascular disease in individuals with rheumatic and musculoskeletal diseases (RMD) – about 3 years earlier than controls. Second, the association between RMD and the full spectrum of cardiovascular diseases that emerged extended beyond atherosclerosis. The risk of thromboembolic disorders and degenerative heart disease, such as heart failure or non-rheumatic valve disorders, was substantially elevated, as were infectious and inflammatory cardiac diseases, including endocarditis, pericarditis, and myocarditis. Importantly, the higher incidence of cardiovascular events in patients with rheumatic diseases was not sufficiently explained by differences in the prevalence of traditional atherosclerotic risk factors (which included elevated systolic and diastolic blood pressure, body mass index, smoking status, cholesterol, and type 2 diabetes) (Table 1), although it must be noted that these variables were missing for a significant proportion of patients. In view of the similarity of trends in cardiovascular disease aetiology and population structure between the United Kingdom and other European countries, North America, and Australasia,[7,8] these findings are likely to be broadly applicable to many high income countries.

Chronic inflammation is proposed as a major driver of cardiovascular disease pathogenesis and is a common denominator across many RMDs.[9] Associations between inflammatory markers and cardiovascular disease observed in the general population[10,11] and the efficacy of anti-inflammatory therapy in reducing cardiovascular disease[12–14] further support this hypothesis. Several effector pathways likely play a role, including endothelial damage and impaired repair, altered stromal components of vascular tissues, cytokine, chemokine, immune complex and myeloid cell driven local inflammation, thrombocytopenia, thrombosis, and interference with lipid profiles, in particular concerning their pro-inflammatory functional capacity. This plethora of potential mechanisms belies specific pathway understanding that can explain the observed epidemiology. Moreover, specific RMDs may accelerate cardiovascular risk by distinctive mechanisms.

These complex pathophysiological mechanisms in RMDs suggest that specific cardiovascular prevention measures might be needed for this patient population but also that due consideration across discrete conditions may be essential. Clinical trials are needed to test the effectiveness of existing and new cardiovascular prevention therapies specifically in patients with RMDs, and potential cardiovascular side effect of commonly prescribed antirheumatic drugs, NSAIDs, biologics, and corticosteroids must also be elucidated fully. Whilst more cardiovascular outcome trials would also be useful in patients with RMD testing differing anti-inflammatory agents, placebo-controlled trials are near impossible given the need treat the systemic inflammation in patients with active disease. This means drug comparator trials are

the best options, but these have generally been underpowered, and robust inferences become difficult.[15,16]

Nevertheless, evidence from previous trials justifies using existing cardiovascular disease prevention measures. The JUPITER trial has shown that statin therapy improves cardiovascular outcomes among individuals with elevated inflammatory markers, even in subgroups with no other risk factors.[17] The CANTOS, COLCOT and LoDoCo2 trials have shown that inhibiting chronic inflammation, even without altering lipids or other risk factors, lowers rates of cardiovascular events.[12–14] Finally, the TRACE-RA trial has shown that statins are safe in patients with rheumatoid arthritis, although caution is needed for women of childbearing age, and the same is likely to be true in other rheumatic conditions.[18] Although TRACE-RA was underpowered, the point estimate provides preliminary evidence that statins are likely to be as effective in reducing cardiovascular risk in rheumatoid arthritis patients as they are in other populations.[18] Classical cardiovascular risk factors, such as blood pressure, obesity or smoking, are likely to interfere with disease-specific ones in patients rheumatic disease and deserve to be managed carefully.

In light of these newly available large-scale epidemiological data and strong evidence of excess cardiovascular risk in several rheumatic conditions, we suggest a re-evaluation of EULAR's recommendations for cardiovascular risk management in patients with RMDs. We argue that recommendations should consider this new evidence of poorer cardiovascular health in numerous RMDs that should prompt cardiovascular screening and consequent prevention measures. The risk threshold for initiation of cardiovascular preventative drug therapies could be lowered for patients with RMDs, a step already taken by the European Society of Cardiology for rheumatoid arthritis by introducing a risk multiplier.[4] Risk multipliers are arguably an imperfect model adjustment and insufficiently account for individualised aspects of risk management and interactions with other risk factors, in particular age. Nevertheless, risk multipliers appear as the best available option until personalized risk prediction tools are developed specifically for patients with RMD. To reflect the different orders of magnitude in cardiovascular risk between RMDs, we advocate a tailored approach, with different risk multipliers considered for each disease (**Table 1**). The proposed risk multipliers were chosen to reflect the precise hazard ratios for cardiovascular risk from the Conrad analysis and were calculated using the lower end of the adjusted hazard ratios' 95% confidence interval, rounded down to the next half integer. This conservative approach in part reflects potential overestimation of hazard ratios from missing risk factors in adjustment and a possible declining trend in excess cardiovascular risk

over time with better control of inflammation in many RMDs with disease-modifying biologics over this period, perhaps coupled to lower use of corticosteroids in many patients. One exception was made for polymyalgia rheumatica, for which we propose a risk multiplier of 1.5 despite a slightly lower hazard ratio, a decision which was taken to simplify use in routine clinical practice.

Insufficient evidence remains for cardiovascular risk in other inflammatory RMD, particularly gout and psoriatic arthritis, two common conditions, and further studies are assuredly needed to address this gap.

Finally, although individually considered as rare disorders, collectively these conditions likely result in a high cardiovascular burden.[6] In post hoc analyses performed for the present editorial, we calculated the collective prevalence of seven RMDs (axial spondyloarthritis, polymyalgia rheumatica, rheumatoid arthritis, Sjögren's syndrome, systemic lupus erythematosus, systemic sclerosis, and vasculitis) in the UK in 2018, and found it to be 2.6% (3.2% in women, 1.9% in men).[19] This means that there are about a third as many people living with RMDs as there are of type 2 diabetes, which currently affects 6.28% of the worldwide population,[20] and further supports the strong public health imperative to protect these patients from cardiovascular disease.

Contributions

All authors contributed to designing the report, drafting the manuscript and the revisions. NS and NC had full access to the data in the study and had final responsibility for the decision to submit for publication. All authors gave final approval of the version to be published.

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Table 1: Proposed multiplication factors for baseline cardiovascular risk score in individuals with rheumatic disorders

Rheumatic disease	HR 95% CI*	Adjusted HR 95%CI**	Proposed risk multiplier
Axial spondyloarthritis	1.97 [1.65, 2.35]	1.91 [1.60, 2.28]	1.5
Polymyalgia rheumatica	1.47 [1.40, 1.54]	1.42 [1.36, 1.49]	1.5
Rheumatoid arthritis	1.83 [1.74, 1.92]	1.76 [1.67, 1.85]	1.5
Sjögren's syndrome	2.08 [1.81, 2.39]	2.15 [1.87, 2.46]	1.5
Systemic lupus erythematosus	2.82 [2.38, 3.33]	2.79 [2.37, 3.29]	2
Systemic sclerosis	3.59 [2.81, 4.59]	3.60 [2.81, 4.62]	2.5
Vasculitis	1.87 [1.73, 2.01]	1.78 [1.66, 1.91]	1.5

Hazard ratios (HR) and 95% confidence interval (CI) for incident cardiovascular disease among patients with rheumatic disorders compared to matched controls, as reported by Conrad et al[6], and proposed multiplication factors for cardiovascular risk scores informing the initiation of preventive therapies.

** Matched on age, sex, socioeconomic status, and region. ** Further adjusted for systolic and diastolic blood pressure, BMI, smoking, cholesterol, and type 2 diabetes (sensitivity analysis).*

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