



Mini Review

The risk of cardiovascular disease in patients with rheumatoid arthritis: A discussion of the link, response to treatment, and the path forward

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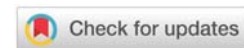
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Introduction

Increased risk of Cardiovascular Disease (CVD) in patients with Rheumatoid Arthritis (RA) has been well established for decades and bolstered by countless studies since the 1950's [1,2]. Numerous papers have explored the pathogenesis and have demonstrated that the systemic inflammation caused in RA increases arterial stiffness, which may result from loss of elasticity and stenosis [3,4]. The inflammation also impairs cholesterol efflux and leads to destabilization of coronary plaque, increasing the risk of rupture and infarction [5,6]. Studies have further demonstrated that active RA causes an imbalance in the dilatation and vasoconstriction of the endothelium, and enhanced residence of reactive oxygen species and proinflammatory factors within the endothelial walls, leading to barrier permeability and leakage of inflammatory mediators into the Cardiovascular (CV) tissue [7,8].

Epidemiology of cardiovascular disease in rheumatoid arthritis

The elevated risk of developing CVD is associated with significant morbidity and mortality as well as high healthcare related costs [9]. Prior research has shown a mortality that is 1.5 times higher in patients with RA compared with the general population and that CVD is the leading source of mortality, accounting for 30–40% of deaths [10]. Despite more aggressive strategies of early RA treatment, increased premature mortality persists [11].

Impact of rheumatoid arthritis disease management on cardiovascular risk

Multiple studies have shown that effectively combatting RA decreases the risk of clinical CVD [12]. Dampening of articular inflammation has been shown to improve arterial stiffness [13]. Moreover, disease control results in lowered levels of N-terminal pro-brain natriuretic peptide (NT-proBNP), homeostasis model assessment–estimated insulin resistance, total cholesterol, and high-density lipoprotein cholesterol (TC/HDL-C), all validated biomarkers of CVD [14,15].

The Cardiovascular Inflammation Reduction Trial showed that treatment with methotrexate (MTX), the gold standard choice for initial therapy in RA, in particular, reduces the risk of congestive heart failure (CHF) related hospitalizations [16]. MTX also reduces all-cause CVD. Furthermore, studies have illustrated its role in reducing levels of high sensitivity C-reactive protein, interleukin (IL) 6, and tumor necrosis factor α (TNF- α) [17]. MTX also helps to restore vascular endothelial vasodilation, most likely as a result of its potent anti-inflammatory effects [18].

Role of cytokine inhibitors in lowering cardiovascular risk

The cardioprotective effect provided by use of MTX is enhanced by the use of anti-TNF- α agents in treating patients with RA. Use of TNF- α blocking agents is associated with a



decreased risk of composite CV outcomes which is most notable in patients who are 65 years or older [19]. Similarly, a meta-analysis found that anti-TNF- α therapy results in a reduction in the risk of all CV events, including Myocardial Infarction (MI) and stroke [20]. Moreover, utilization of anti-TNF- α agents results in improvement in parameters of arterial stiffness and improves endothelial function and flow-mediated vasodilation [21,22].

Tocilizumab, an antibody targeting the IL-6 receptor with well established efficacy in the management of RA, has also been shown to harbor cardiac benefits and has been illustrated to reduce NT-proBNP levels [23,24]. Moreover, treatment with tocilizumab results in an increase in endothelial glycocalyx thickness, enhancing arterial elastic properties and improving the efficiency of myocardial work [25]. This effect is explained by tocilizumab's role in reducing inflammation and oxidative stress [26].

Abatacept, a novel RA medication which binds to antigen presenting cells preventing delivery of the co-stimulatory signal to T cells, also possesses cardioprotective effects. It is associated with a reduced risk of composite CV events. Moreover, the risk of MI and coronary revascularization is lower in patients treated with abatacept compared with TNF- α inhibitors [27]. This may be related to its downstream anti-inflammatory effect, beyond cytokine-mediated pathways, as demonstrated by a prevention in the progression of atherosclerosis in mouse models [28].

Use of Janus Kinase Inhibitors (JAKi) in the medical treatment of RA results in an unfavorable lipid profile, which may be caused as a result of reducing lipid accumulation in the synovium, promoting an increase in circulating cholesterol [29]. Despite these shifts in lipid levels, studies have shown that they are not associated with an increased risk of CVD [30]. In fact, JAKi agents improve arterial stiffness in patients with RA and attenuate the development of atherosclerosis in rabbits [31,32]. Tofacitinib in particular reduces levels of NT-proBNP and improves endothelial function [33,34]. Furthermore, upadacitinib, a newer JAKi, has been shown to assist with efflux of cholesterol, in parallel with a rise in high density lipoprotein and a drop in C-reactive protein [35].

The influence of patient-physician communication

Detection of CV events is frequently delayed or even missed as clinical CVD can present both atypically and at younger ages in patients with RA [36]. Strikingly, between 70 and 90 percent of RA patients have not been made aware of the increased incidence of CVD, especially among those at highest risk [37]. Prior papers have illustrated that insufficient information regarding the link between CVD and RA is being conveyed to the relevant patients, explaining in large part the poor awareness [38].

At the same time, enrollment in programs which provide clear information about the increased risk of CVD have result in feelings of relief, motivation, and control in patients with RA [39]. Patients with greater awareness tend to modify

lifestyle risk factors and advocate for risk-reducing medical treatments [40]. Furthermore, increased knowledge is linked with increased adherence with medical therapy [41]. Moreover, reduced rates of MI and CHF have been detected in patients who have been provided with an educational intervention [42].

Conclusion

Early treat-to-target therapies, as recommended by the American College of Rheumatology and European League Against Rheumatism, are fundamental to providing optimal care to patients with RA in order to control disease activity, providing symptom relief and preventing progression of disease [43,44]. Furthermore, such strategies, with the currently available arsenal of conventional and biologic disease modifying agents, is essential for modulating the increased risk of CVD in this disease population [45]. Moreover, the development and increased use of diagnostic tools and clinical disease scales allow for continued re-assessment and effect disease course management [46].

At the same time, pharmacotherapy must be combined with a patient-centered approach in which physicians educate patients on the nature of their disease and its link to CVD. In this way, patients may take a more active approach in controlling their illness and mitigating the associated risks. In an era where novel educational instruments are increasingly being integrated into clinical practice, especially in response to the COVID-19 pandemic, further studies are warranted to assess for which tools are most effective in providing clear information to patients and result in demonstrable markers of quality improvement.

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