

## Review Articles

# Rheumatoid arthritis and risk of cardiovascular disease

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### Abstract

In developing countries, rheumatoid arthritis (RA) remains a seriously under-prioritised disease, particularly among the underprivileged, often resulting in presentation of patients late in the course of their disease, further complicated by limited therapeutic options and inconsistent follow up. The consequences are often severe with irreversible disability, increased frequency of co-morbidities, especially cardiovascular disease (CVD), and higher mortality rates, relative to developed countries. Despite addressing traditional cardiovascular risk factors, the impact of subclinical or 'residual' inflammation from uncontrolled RA needs to be considered. This narrative review explores the prevalence and pathogenesis of CVD in RA, including the impact of tobacco use. It discusses pitfalls in the risk assessment of CVD in patients with RA, and the effect of disease-modifying anti-rheumatic therapy on cardiovascular co-morbidity.

**Keywords:** cardiovascular risk, chronic inflammation, rheumatoid arthritis, tobacco usage, effects of drug treatment

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### Overall mortality in rheumatoid arthritis (RA)

Despite innovative advances made in the management of patients with RA, premature mortality from co-morbid diseases remains a significant challenge. The disease is not only more common in females (gender ratio of 3:1), but they also tend to have more active disease and impaired function than males.<sup>1</sup>

A systematic review and meta-analysis of 11 longitudinal studies published in 2013, which covered the period 1955–1995, encompassing five different developed countries (the Netherlands, Spain, Sweden, UK and USA) and a total of 51 819 patients with RA, concluded that 'mortality has decreased among RA patients over the past decades but remained higher than in the general population as assessed by the incident mortality rate and the standardised mortality over time'.<sup>2</sup> This trend has continued in developed countries according to more recent studies from Canada,<sup>3</sup> France<sup>4</sup> and the UK,<sup>5</sup> all confirming a sustained increased mortality rate in RA sufferers relative to the general population.<sup>6</sup> According to the findings of the aforementioned systematic review and a meta-analysis reported by Dadoun *et al.*, the standardised mortality ratio is 1.47, meaning that patients with RA have a 47% higher risk of premature mortality relative to the general population when matched for age and gender,<sup>2</sup> with a decreased life expectancy of three to 10 years or more.<sup>7</sup>

A recent study from Spain covering the period 1994–2013 identified the following major independent risk factors for poor survival in RA: male gender, older age at diagnosis, the presence of rheumatoid factor (RF), [testing for anti-cyclic citrullinated peptide antibodies (ACPA) was unavailable in the early years of the study], higher number of hospital admissions, greater disease activity, and more severe radiographic joint damage.<sup>8</sup> In addition, genetic predisposition in Caucasian populations contributes significantly to the development and severity of, as well as mortality from, RA, this being conferred by the susceptibility genes known as the *HLA-DRB1* shared epitope (SE) alleles.<sup>9</sup> The influence of genetic susceptibility is particularly evident in RA patients who smoke, increasing the propensity for the development of ACPA-seropositive disease.<sup>9</sup> Indeed cigarette smoking, and possibly exposure to other types of inhaled irritants/toxicants, particularly in the context of expression of SE alleles, appears to promote the formation of ACPA by mechanisms that have been reviewed in detail.<sup>10,11</sup>

### Causes of mortality in RA

Cardiovascular disease (CVD) is well recognised as the most common cause of mortality in patients with RA, being associated with endothelial dysfunction and arterial stiffness due to inflammation-associated loss of elasticity of the vascular wall. This results from alterations in the structural proteins,

collagen and elastin, leading to accelerated atherosclerosis, usually detected by the measurement of carotid intima-media thickness.<sup>12-15</sup> One meta-analysis of observational studies undertaken by a Canadian group concluded that the CVD mortality rate was increased by approximately 50% in RA patients compared with the general population,<sup>16</sup> with neoplastic disease and respiratory disease, particularly pneumonia, being other significant contributors.<sup>4</sup>

Notwithstanding traditional risk factors for CVD common among RA patients in developed countries (smoking, obesity, type 2 diabetes mellitus, dyslipidaemia and others), those specifically associated with RA include the presence of extra-articular manifestations and erosions, as well as prolonged disease duration with accompanying systemic inflammation and endothelial dysfunction.<sup>12-18</sup> Given that increased risks for the development of myocardial infarction, heart failure/sudden death and stroke in patients with RA have been estimated to be two- to three-fold, two-fold and 1.7-fold, respectively,<sup>19</sup> it is hardly surprising that the European League Against Rheumatism advocates 'that early detection and pre-emptive treatment of high-risk (RA) patients is of great importance in reducing the excess risk of CVD in RA'.<sup>20</sup> In this context, RA-related CV screening in the developed world setting is considered to be a cost-effective strategy.<sup>21</sup>

The current methods used to assess cardiovascular risk do not accommodate long-term exposure to inflammation and tend to underestimate the risk. Different scoring mechanisms are used and under-estimations of risk as large as two-fold have been observed with the Framingham Risk Score (FRS) when applied to RA patients.<sup>22</sup> The European League Against Rheumatism (EULAR) working group has suggested that the Systematic Coronary Risk Evaluation (SCORE) scoring system risk value be multiplied by 1.5 in RA patients who show at least two of the following: (1) RA disease of more than 10 years, (2) positive RF, (3) positive ACPA, and (4) presence of extra-articular manifestations.<sup>23</sup> It is, however, possible that even with the modified SCORE, a large number of RA patients still may not be identified and are at high risk for CVD.<sup>24</sup>

In addition to ultrasound measurement of carotid intima-media thickness<sup>13</sup> and high-resolution ultrasound measurement of flow-mediated vasodilation in the brachial artery (measures arterial response to hypoxia) to evaluate endothelial function as a 'surrogate marker of subclinical atherosclerosis',<sup>25</sup> several systemic biomarkers of inflammation and cardiac dysfunction have also been reported to predict CVD risk and mortality in RA patients. Currently, the most promising of these is N-terminal pro-brain natriuretic peptide (NT-proBNP), a well-recognised, sensitive predictor of future CVD and mortality in general healthy populations, as well as in RA patients, according to the limited studies undertaken to date.<sup>26-28</sup> Measurement of cardiac troponin T may also have predictive potential in RA,<sup>28</sup> but interpretation of data is complicated by the influence of age and/or the presence of other co-morbidities.

## Pathogenesis of CVD in RA

Chronic, low-grade systemic inflammation leading to prolonged endothelial activation and an accompanying pro-thrombotic/pro-coagulant state is believed to be the major contributor to the increased risk of CVD in RA.<sup>19</sup> Some of the most prominent

proposed immunopathogenic processes underpinning these events are summarised as follows:

- increased systemic levels, presumably synovium-derived, of the endothelial-activating cytokines interleukin (IL)-1 $\beta$ , IL-6, tumour necrosis factor (TNF)- $\alpha$  and interferon (IFN)- $\gamma$ <sup>19,29-31</sup>
- binding and activation of neutrophils, monocytes and platelets to cytokine-activated, pro-adhesive vascular endothelium, potentiated by the neutrophil and monocyte chemokines, CXCL8 (IL-8) and CCL2, respectively<sup>19,29,30</sup>
- systemic activation of platelets, not only via interaction with cytokine-sensitised vascular endothelium and proximal neutrophils/monocytes, which may trigger further platelet activation via protease-activated receptors (PARs) 1 and 4, but also by exposure to ACPA<sup>32</sup>
- activation of vascular endothelium PAR-1 by adherent neutrophils/monocytes, thereby exacerbating systemic inflammation and endothelial dysfunction<sup>33</sup>
- creation of a pro-inflammatory milieu conducive to the formation of pro-atherogenic oxidised low-density lipoprotein<sup>29</sup>
- intra-vascular formation of neutrophil extracellular traps (NETs) via exposure of these cells to activated platelets<sup>34</sup>
- NETs, in turn, contribute to the intravascular, pro-inflammatory/pro-thrombotic/pro-coagulant environment via expression of endothelium-activating proteases<sup>33</sup> and histones,<sup>35</sup> as well as the expression and presentation of functional tissue factor.<sup>36</sup>

Although partially controlled by endogenous anti-inflammatory mechanisms,<sup>30</sup> this chronic, low-grade activation and dysfunction of vascular endothelium, triggered and sustained by synovial-derived mediators of inflammation, is likely to underpin the pro-atherogenic, pro-thrombotic changes that favour accelerated development of CVD in patients with untreated RA.

## Smoking, smokeless tobacco use, RA and CVD

Smoking is a well-recognised risk factor for the development of both RA and CVD, and in a recent study from the US, smoking was found to be an independent predictor, albeit somewhat weaker than age ( $p < 0.05$  vs  $p < 0.001$ , respectively), of the presence of atherosclerotic plaques in patients with RA.<sup>37</sup> As with RA, these atherothrombotic effects of smoking are also associated with 'multiple pathological effects in the endothelium', as well as activation of platelets and the coagulation cascade.<sup>38</sup>

However, less attention has been focused on the possible pro-atherogenic effects of usage of smokeless tobacco products, which is common among black South African females, with a recorded prevalence of 48% among RA participants in the Gauteng Rheumatoid Evaluation and Assessment Trial (GREAT).<sup>39</sup> Indeed, on the African continent, only Botswana and Mauritania have a higher prevalence of smokeless tobacco use than South Africa.<sup>40</sup> In a recently reported analysis of the global burden of disease, usage of smokeless tobacco products was estimated to account for 4.7 million disability-adjusted life years lost and 204 309 deaths, based on data from the benchmark 52-country INTERHEART study,<sup>40</sup> the risk being statistically significant with an adjusted odds ratio of 1.57.<sup>41</sup>

In this context, it is noteworthy that blood levels of the nicotine metabolite, cotinine, in South African female users of inhaled snuff products were found to be comparable with those of active smokers.<sup>39</sup> In the past, nicotine has been a

somewhat neglected component of tobacco usage with regard to pro-inflammatory activity. Recently, however, nicotine has been reported to possess endothelial disruptive, pro-inflammatory activity,<sup>42</sup> while exposure of isolated human blood neutrophils to nicotine *in vitro* has been reported to activate NETosis, which was augmented by the combination of nicotine with either TNF- $\alpha$  or APCA.<sup>43</sup> In this same study, administration of nicotine to mice was found to accelerate collagen-induced arthritis, which was accompanied by increased systemic levels of myeloperoxidase-DNA complexes, an *in vivo* surrogate of NETosis.<sup>43</sup> Moreover, chronic inhalation of nicotine by mice has been found to cause pulmonary injury associated with increased expression of pulmonary cytokines and proteases, mimicking the features of chronic obstructive pulmonary disease.<sup>44</sup>

Notwithstanding a high content of heavy metal toxicants, cured tobacco also contains high levels of pro-inflammatory microbial products, particularly bacterial endotoxins.<sup>10,45</sup> Endotoxins, which are potent activators of vascular endothelium, neutrophils, monocytes/macrophages and platelets, as well as other types of immune/inflammatory and structural cells, have also been implicated in the pathogenesis of atherosclerosis.<sup>46,47</sup> In this context, users of smokeless tobacco products may be particularly vulnerable to the pro-atherogenic effects of tobacco-derived endotoxins, since these are inhaled or ingested without modification by the combustion of tobacco. The impact of tobacco use in the context of RA disease progression and associated co-morbidity is often neglected by both patient and clinician, even though globally, a high percentage of patients with RA continue to smoke.<sup>10,48</sup>

### Effects of disease-modifying anti-rheumatic drug and cytokine-targeted therapies on clinical and systemic indices of CVD in patients with RA

Methotrexate (MTX) is the pivotal traditional disease modifying anti-rheumatic drug (DMARD) and has a proven track record for the cost-effective management of RA. In addition, MTX increases total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglyceride levels in RA, which might be attributed to the decrease in inflammation.<sup>24</sup> MTX treatment has been found to reduce mortality rate in RA patients by 70% and showed a decrease of 21% in total cardiovascular risk, including myocardial infarctions, congestive cardiac failure and strokes.<sup>49</sup> This information confirms the belief that if systemic inflammation in RA is reduced, the risk for CVD is also reduced. It is therefore important to achieve remission or low disease activity as soon as possible, not only to achieve better structural and functional outcomes, but also to reduce the risk of CVD in these patients.<sup>49</sup>

As alluded to above, TNF- $\alpha$  is pivotally involved in the pathogenesis of RA and is one of the main targets in the treatment of the disease. Anti-TNF biologics are now standard in the treatment of refractory RA. The main agents used in this group are etanercept, adalimumab, infliximab and golimumab. Treatment of RA with anti-TNF biologics may decrease CVD risk by inhibiting endothelial dysfunction, and the progression of atherosclerosis by decreasing the expression of pro-inflammatory cytokines and endothelial adhesion molecules.

No changes in the levels of LDL-C or the ratio between HDL-C and TC were found with long-term treatment of RA patients with these immunotherapies. However, evidence derived from clinical studies shows that TNF inhibitors can reduce the risk for cardiovascular events between 30 and 70% in RA patients.

Non-TNF biologics such as tocilizumab (TCZ), tofacitinib, rituximab, abatacept and anakinra act on different arms of the immune system and also demonstrate clinical efficacy in RA, but little is known about the effects of these drugs on CVD morbidity and mortality rates. In this context, evidence from a limited number of clinical studies has indicated that lipid profiles tend to alter when RA patients are treated with these drugs, but results are inconclusive and more research is needed.<sup>50</sup>

An important albeit unanswered question is 'can the remarkable advances in the management of RA be used to manage patients with non-RA associated CVD?' In this context, an unmet need in the management of patients with CVD is subclinical or 'residual' inflammatory risk, despite addressing other cardiovascular risk factors, in the management of patients with CVD. The identification of inflammatory mediators or other biomarkers associated with cardiovascular risk has the potential to stratify at-risk patients and develop novel therapies for CVD in general.<sup>51</sup> In this context, it is noteworthy that studies in cholesterol-fed rats have demonstrated anti-atherosclerotic effects of MTX,<sup>52,53</sup> while several clinical trials are currently exploring the role of anti-rheumatic drugs such as MTX and IL-1 antagonists as novel therapies for non-RA CVD.<sup>54,55</sup>

### Conclusion

Cardiovascular co-morbidity has a significant impact on overall prognosis in the management of patients with RA. It is important to emphasise that classical risk factors for CVD are common in RA patients and their treatment is as important as in the general population. Controlling disease activity with aggressive and early introduction of conventional DMARDs with escalation to targeted or biologic therapies if required will enable control of inflammation and lower the CVD burden.

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### Mortality outcomes of original ASCOT trial reported

In patients with hypertension, the long-term cardiovascular and all-cause mortality effects of different blood pressure-lowering regimens and lipid-lowering treatment are not well documented, particularly in clinical trial settings. Professor Peter Sever at the National Heart and Lung Institute, Imperial College London writes in *The Lancet* that the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) Legacy Study reports mortality outcomes after 16 years of follow up of the UK participants in the original ASCOT trial.

ASCOT was a multicentre randomised trial with a 2  $\times$  2 factorial design. UK-based patients with hypertension were followed up for all-cause and cardiovascular mortality for a median of 15.7 years (IQR 9.7–16.4 years). At baseline, all patients enrolled into the blood pressure-lowering arm (BPLA) of ASCOT were randomly assigned to receive either amlodipine-based or atenolol-based blood pressure-lowering treatment. Of these patients, those who had total cholesterol of 6.5 mmol/l or lower and no previous lipid-lowering treatment underwent further randomisation to receive either atorvastatin or placebo as part of the lipid-lowering arm (LLA) of ASCOT. The remaining patients formed the non-LLA group. A team of two physicians independently adjudicated all causes of death. Of 8 580 UK-based patients in ASCOT, 3 282 (38.3%) died, including 1 640 (38.4%) of 4 275 assigned to atenolol-based treatment and 1 642 (38.1%) of 4 305 assigned to amlodipine-based treatment; 1 768 of the 4 605 patients in the LLA died, including 903 (39.5%) of 2 288 assigned placebo and 865 (37.3%) of 2 317 assigned atorvastatin. Of all deaths, 1 210

(36.9%) were from cardiovascular-related causes.

Among patients in the BPLA, there was no overall difference in all-cause mortality between treatments [adjusted hazard ratio (HR) 0.90, 95% CI: 0.81–1.01,  $p = 0.0776$ ], although significantly fewer deaths from stroke (adjusted HR 0.71, 95% CI: 0.53–0.97,  $p = 0.0305$ ) occurred in the amlodipine-based treatment group than in the atenolol-based treatment group.

There was no interaction between treatment allocation in the BPLA and in the LLA. However, in the 3 975 patients in the non-LLA group, there were fewer cardiovascular deaths (adjusted HR 0.79, 95% CI: 0.67–0.93,  $p = 0.0046$ ) among those assigned to amlodipine-based treatment compared with atenolol-based treatment ( $p = 0.022$  for the test for interaction between the two blood pressure treatments and allocation to LLA or not). In the LLA, significantly fewer cardiovascular deaths (HR 0.85, 95% CI: 0.72–0.99,  $p = 0.0395$ ) occurred among patients assigned to statin than among those assigned placebo. Our findings show the long-term beneficial effects on mortality of antihypertensive treatment with a calcium channel blocker-based treatment regimen and lipid-lowering with a statin: patients on amlodipine-based treatment had fewer stroke deaths and patients on atorvastatin had fewer cardiovascular deaths more than 10 years after trial closure. Overall, the ASCOT Legacy study supports the notion that interventions for blood pressure and cholesterol are associated with long-term benefits on cardiovascular outcomes.

**Source:** Medical Brief 2018