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### **Chapter 3. Managing cardiovascular risk in patients with rheumatic disease**

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## **KEY WORDS**

RA, SLE, gout, cardiovascular disease (CVD), inflammation

## **KEY POINTS**

- Rheumatoid arthritis, gout, and systemic lupus erythematosus are associated with increased cardiovascular disease (CVD) risk compared with the general population.
- This risk is related to a combination of traditional cardiovascular risk factors, disease specific factors, and some medications including NSAIDs and prolonged use of relatively high-dose corticosteroids.
- CVD risk should be assessed using relevant national or international risk assessment tools. These may need to be adapted in RMDs with a multiplication factor.
- Management includes lifestyle modifications and pharmacological treatment of traditional cardiovascular risk factors, as well as tight control of disease activity with disease-modifying-anti-rheumatic drugs.
- Nonsteroidal anti-inflammatory drugs should be used with caution. Corticosteroids should be prescribed at the lowest effective dose for the shortest possible duration.

## INTRODUCTION

Individuals with chronic inflammatory rheumatic and musculoskeletal diseases (RMDs), most notably rheumatoid arthritis (RA), Systemic Lupus Erythematosus (SLE), and gout, are at increased risk of cardiovascular disease (CVD) compared to the general population. Central to all three conditions is chronic inflammation. Many of the cellular and molecular features of RMDs are now also recognised to be operant in the pathogenesis of CVD, especially in the local lesions of atherosclerosis and in promoting wider endothelial and microvascular dysfunction. The combination of RMD-specific factors, coupled with a higher prevalence of traditional cardiovascular risk factors e.g. smoking, hypertension, dyslipidaemia, diabetes, and obesity, and certain medications e.g. several NSAIDs, as well as the COX-2 inhibitor rofecoxib, and prolonged use of relatively high-dose corticosteroids, all contribute to greater CVD morbidity and mortality in chronic RMDs (Figure 1).

In this chapter, we will review the evidence base for CVD risk in RA, SLE, and gout, drawn largely from observational studies, and consider potential mechanisms for such increased risk. We will then discuss how best to manage cardiovascular risk in chronic RMDs by addressing traditional risk factors through lifestyle and pharmacotherapy, as well as treating underlying systemic inflammation through anti-rheumatic therapies.

## DISCUSSION

### 1. CVD risk in RA

RA is associated with increased CVD risk. Previous meta-analysis has shown those with RA have a 48% higher risk of incident CVD, 68% higher risk of myocardial infarction, and 41% higher risk of stroke, compared with the general population<sup>1</sup>. More recent estimates suggest this excess risk may be less than previously estimated, with data from the QResearch database in the UK suggesting around a 24% greater CVD risk in RA compared to the general population<sup>2</sup>. While this may relate to better treatments now available for RA, individuals with RA still remain at greater cardiovascular risk than their non-RA counterparts, likely related to a combination of a higher prevalence of traditional cardiovascular risk factors e.g. smoking, obesity, physical inactivity, hyperlipidaemia, type 2 diabetes mellitus and hypertension, as well as underlying chronic inflammation<sup>3</sup>. A large international study, A Trans-Atlantic Cardiovascular Consortium for Rheumatoid Arthritis (ATACC-RA), revealed around 49% of CVD events in RA were attributable to traditional CVD risk factors (in particular smoking and hypertension) and 30% to RA characteristics (elevated DAS28, RF/ACPA positive, raised ESR and CRP)<sup>4</sup>. Cardiovascular mortality is also increased in RA, in the order of 43 to 66% higher than the general population, even after adjustment for age, sex, and traditional cardiovascular risk factors<sup>5</sup>.

#### 1.1 Traditional cardiovascular risk factors

Prior meta-analysis of RA patients revealed those with concomitant hypertension and diabetes were at 84% and 89% higher risk of MI respectively compared to those without these risk factors<sup>6</sup>. CVD morbidity in RA was greater in those with hypertension (RR 2.24), type 2 diabetes (RR 1.94), smoking (RR 1.50), hypercholesterolaemia (RR 1.73) and obesity

(RR 1.16) <sup>6</sup>, highlighting the important contribution of traditional cardiovascular risk factors to overall CVD risk in RA.

While dyslipidaemia, in particular elevated low-density lipoprotein (LDL)-cholesterol, is strongly associated with increased CVD risk in the general population, its role in RA is more complicated. Indeed, those with RA may display an apparent ‘lipid paradox’, with reduced total cholesterol and LDL cholesterol, despite RA being an independent risk factor for CVD <sup>7</sup>. This may relate to the state of active inflammation in RA with activation of the mononuclear phagocyte system that ‘scavenges’ LDL particles, resulting in lowered serum LDL-cholesterol concentrations <sup>8</sup>. Subsequent treatment to reduce inflammation generally leads to a rise in serum LDL-cholesterol concentrations <sup>9</sup>, especially apparent with the IL-6 receptor antagonist tocilizumab <sup>10</sup> and is thought to be linked to a reversal of IL-6-induced LDL-cholesterol clearance from the circulation <sup>8</sup>. Similar patterns of lipid changes have been observed across studies of Janus kinase inhibitors, which inhibit signalling downstream of IL-6 <sup>11,12</sup>. For example, treatment with tofacitinib resulted in reduced clearance of LDL-cholesterol particles from the circulation and an increase in circulating cholesterol concentrations <sup>13</sup>.

An ‘obesity paradox’ may also exist in RA with an inverse relationship between BMI and mortality. While increased BMI is associated with CVD mortality in the general population <sup>14</sup>, in contrast individuals with RA who are overweight or obese appear to have a lower relative risk of all-cause and CVD mortality than patients with a normal BMI (18.5–24.9 kg/m<sup>2</sup>) <sup>15</sup>. Importantly, a separate study demonstrated this inverse association between BMI and mortality was lost after adjustment for co-morbidities and RA severity <sup>16</sup>. This suggests the ‘obesity paradox of RA’ may be due to residual confounding and reverse causality whereby active inflammatory disease leads to unintentional weight loss <sup>17</sup>. Supporting this, evidence has shown weight loss, rather than current BMI, is a strong predictor of mortality in RA, with a fall in BMI of  $\geq 1\text{kg/m}^2$  associated with almost twice the risk of death <sup>18</sup>.

## 1.2 RA disease-specific factors

While traditional cardiovascular risk factors significantly contribute to CVD risk in RA, disease-specific factors also play an important role. Studies have demonstrated an association between higher cumulative inflammatory burden and increased CVD risk in RA <sup>19–23</sup>. While disease duration does not appear to affect CVD risk independently <sup>20</sup>, disease activity as well as the number and duration of flares over time may contribute to greater CVD risk in RA <sup>19–22</sup>.

The heightened state of chronic inflammation has long been hypothesised to contribute to increased CVD risk in RA. Indeed, both RA and atherosclerosis share similar underlying inflammatory pathways. These comprise T-cell and myeloid lineage cell activation, release of pro-inflammatory cytokines and increased leukocyte adhesion molecule expression <sup>24</sup>. Inflamed synovium in affected joints, as well as secondary lymphoid tissues including the spleen, lymph nodes, and adipose tissue, release pro-inflammatory cytokines such as TNF, IL-1 $\beta$  and IL-6 and immune complexes into the circulation. Complement activation is also a feature. This in turn can have numerous systemic adverse effects on skeletal muscle, liver, vascular tissue, adipose tissue, and circulating lipid profiles, leading to insulin resistance, increased CRP and pro-coagulant production from the liver, endothelial dysfunction, increased arterial stiffness, atherosclerotic plaque formation, and potentially altered body

composition with increased central abdominal fat and decreased lean mass. Collectively, these changes may culminate in CVD<sup>25</sup>.

Individuals with RA have been shown to have increased arterial wall inflammation on fluorodeoxyglucose (FDG) PET/CT imaging, which attenuated with anti-TNF therapy<sup>26</sup>. Further, RA is associated with greater atherosclerotic burden, including increased carotid intima-media thickness, carotid plaque burden<sup>27</sup>, and coronary plaques<sup>28</sup>, particularly non-calcified and mixed plaques, which appear more vulnerable to rupture than fully calcified plaques<sup>28,29</sup>.

### **1.3 Medications**

Some medications commonly used to treat RA, namely certain NSAIDs, particularly diclofenac, and the now with-drawn COX-2 inhibitor Rofecoxib, as well as prolonged use of relatively high-dose corticosteroids, also contribute to increased CVD risk in RA<sup>30</sup>. Their association is discussed in further detail in section 4.2.

### **1.4 Summary**

CVD risk is increased in RA and is related to a combination of traditional cardiovascular risk factors, disease-specific factors, namely chronic inflammation, and some commonly prescribed medications including certain NSAIDs as well as prolonged courses of relatively high-dose corticosteroids.

## **2. CVD risk in Gout**

In contrast to RA, studies examining the association between gout and incident coronary heart disease (CHD) have been more mixed. Two studies, The Meharry-Hopkins Study<sup>31</sup> and a separate Dutch primary care study by Janssens et al.<sup>32</sup>, did not show a significant independent association of gout with CVD. In contrast, a study of over 5,000 individuals from the Framingham Heart Study demonstrated men with gout had a 60% excess risk of CHD compared to men without gout<sup>33</sup>. This excess risk was related in part to a greater prevalence of traditional cardiovascular risk factors e.g. hypertension, hypercholesterolaemia, alcohol, and elevated BMI. However, even after adjustment for these risk factors, excess CHD risk remained. The reasons for such disparities between studies may relate to differences in underlying study populations, design, and sample size.

A separate study of over 51,000 men in the Health Professionals Follow-Up Study reaffirmed an independent association of gout with all-cause and CVD mortality<sup>34</sup>. After adjusting for traditional risk factors, men with gout (without prior CHD) had a 28% higher all-cause mortality, 38% higher CVD mortality, and 55% higher CHD mortality compared to men without gout. Similarly, data from the MRFIT study of over 12,000 men revealed gout was associated with a 26% higher risk of acute MI after adjustment for known cardiovascular risk factors.

Despite the earlier Framingham study demonstrating no association between gout and CHD in women, a later primary care study using the UK Clinical Practice Research Datalink (CPRD) demonstrated female patients with gout were at greatest risk of incident vascular events, even after adjustment for vascular risk factors, despite a higher prevalence of both

gout and vascular disease in men<sup>35</sup>. The reason for such sex differences in vascular risk remain to be fully determined but may include more prolonged exposure to hyperuricaemia in women, who generally require a higher mean serum uric acid level to develop gout<sup>36</sup>. Decreasing oestrogen during the menopause may also have a detrimental effect on renal uric acid excretion<sup>37</sup> and contribute to increased central (abdominal) obesity associated with increased cardiometabolic risk<sup>38</sup>. Finally, it is possible clinicians may be less vigilant in prompt diagnosis and treatment of gout and CVD in women due to the male preponderance of these conditions.

## 2.1 Potential Mechanisms

Central to gout pathogenesis is hyperuricaemia with urate crystal deposition in joints. Beyond acute joint inflammation, elevated serum urate levels have been associated with increased CHD incidence and mortality<sup>39</sup>. This may relate in part to the association of hyperuricaemia with traditional risk factors including hypertension, dyslipidemia, chronic kidney disease, and overweight/obesity<sup>40</sup>.

Hyperuricaemia is closely associated with endothelial dysfunction, an early marker of atherosclerosis<sup>41,42</sup>. In a study of 46 hyperuricaemic patients matched with 46 age and sex matched healthy controls, hyperuricaemic individuals had significantly lower flow mediated dilation (FMD) values than controls, indicative of worse endothelial function<sup>43</sup>. In a later study of post-menopausal women who underwent coronary microvascular function testing to assess for coronary endothelial dysfunction (CED), individuals with CED had significantly higher uric acid levels compared to those without CED<sup>44</sup>.

Elevated serum urate levels have been associated with greater amounts of smooth-muscle cell proliferation, low density lipoprotein oxidation and platelet activation, as well as a potential role in hypertension pathogenesis, suggesting an etiological role for hyperuricaemia in atherosclerotic disease<sup>45</sup>. However, it is also possible that hyperuricaemia may simply represent a surrogate marker for high levels of damaging oxidative stress associated with increased xanthine oxidase activity, rather than being directly responsible for vascular injury per se<sup>45</sup>.

A further potential mechanistic link between hyperuricaemia and CVD may include activation of the NLRP3 inflammasome by monosodium urate crystals. This may contribute to increased CVD through the release of IL-1 $\beta$ <sup>46</sup>. Indeed, inhibition of IL-1 $\beta$  receptor binding with canakinumab, used clinically to treat gout, has been shown to reduce recurrent vascular events in the Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS) trial<sup>47</sup>.

## 2.2 Summary

While some studies have been conflicting, there is now increasing evidence that gout is associated with increased CVD risk. This is related to both a greater prevalence of traditional cardiovascular risk factors including hypertension, hypercholesterolaemia, alcohol, and elevated BMI, as well as underlying hyperuricaemia and systemic inflammation.

### 3. CVD risk in SLE

Systemic lupus erythematosus (SLE), a multisystem autoimmune disease primarily affecting women of childbearing age, is associated with significantly greater cardiovascular risk. Although the exact frequency of cardiovascular events in SLE varies, an early study from Pittsburgh Medical Center found around 7% of SLE patients had a cardiovascular event, with patients in the 35- to 44-year old age group over 50 times more likely to have a myocardial infarction than those without SLE<sup>48</sup>. Factors associated with greater CVD risk included an older age at lupus diagnosis, longer disease duration, longer duration of corticosteroid use, hypercholesterolemia, and being postmenopausal<sup>48</sup>.

Despite improvements in disease management, a more contemporary study of individuals from the UK Biobank demonstrated SLE is still associated with significant cardiometabolic risk<sup>49</sup>. SLE participants displayed several traditional risk factors including hypertension, hypercholesterolemia, obesity, and smoking. After adjustment for age, gender, ethnicity, deprivation index, educational level, antihypertensive medications, and lipid lowering medications, SLE was associated with an almost 3 fold greater risk of CHD, over 4 fold greater risk of stroke, over 5 fold greater risk of VTE, and an over 15 fold greater risk of PAD<sup>49</sup>. Longer disease duration as well as NSAID/ corticosteroid use was associated with greater cardiometabolic risk<sup>49</sup>.

Corticosteroids are known to be associated with increased CVD risk in the general population, in the order of 58% to 81% for men and women respectively compared to those not taking corticosteroid medications<sup>2</sup>. However, even after adjusting for corticosteroid use, as well as traditional cardiovascular risk factors, data from The QResearch database showed women with SLE still had over double the risk of developing CVD, and men with SLE around 55% greater CVD risk, compared to the general population<sup>2</sup>.

#### 3.1 Potential mechanisms

In addition to traditional risk factors and NSAID/ corticosteroid use, several SLE-specific factors may contribute to heightened CVD risk in this group. Chronic damage, as assessed by the Systemic Lupus International Collaborating Clinics (SLICC) damage index, was found to be independently associated with increased carotid IMT scores, carotid plaque formation, and arterial stiffness<sup>50-52</sup>. The presence of lupus nephritis was also associated with greater odds of carotid plaque compared to age-matched non-nephritis SLE patients and population controls<sup>53</sup>. Certain genetic variants, such as those in the risk allele for SLE in the signal transducer and activator of transcription factor 4 (STAT4) gene, have also been associated with vascular events, in particular ischaemic cerebrovascular disease<sup>54</sup>.

Although the exact mechanisms underlying atherosclerosis in SLE remain to be determined, it is thought there is an imbalance between endothelial damage and atheroprotective mechanisms<sup>55</sup>. Damage to the endothelium may result from deposition of oxidised LDL and previous data have shown higher levels of oxidized epitopes on LDL in SLE patients compared to age- and sex-matched controls<sup>56</sup>. Several autoantibodies including anti-endothelial cell antibodies (AECs) and antiphospholipid antibodies (APLs) may contribute to endothelial injury in SLE<sup>55</sup>. APLs also contribute to a pro-thrombotic state<sup>57</sup>. Type 1 interferons (IFNs), involved in the pathogenesis of SLE, may promote premature vascular damage in SLE<sup>58</sup>. Neutrophil extracellular traps (NETs) may also play a role in SLE-related

atherosclerosis as they are thought to be prothrombotic and may impair anti-atherogenic HDL<sup>59</sup>. Immune complexes may also play a role in atherosclerotic lesion development<sup>60</sup>. Finally, impaired atheroprotective mechanisms including impaired endothelial repair and decreased production of atheroprotective autoantibodies may also contribute.

### **3.2 Summary**

In summary, SLE is associated with significantly increased CVD risk. This is related to a combination of traditional cardiovascular risk factors, NSAID/ corticosteroid use, and disease-specific factors including accumulating chronic disease damage, lupus nephritis, genetic factors, prothrombotic APLs, and imbalances between endothelial damage and atheroprotective mechanisms.

## **4. Managing CVD risk in Rheumatic Diseases**

There are two main approaches to targeting the increased CVD risk associated with chronic RMDs. These include targeting traditional CVD risk factors through lifestyle and pharmacological interventions, and tight control of underlying disease activity.

### **4.1 Traditional CVD risk factors**

Individuals with RMDs should be screened for traditional cardiovascular risk factors and their total cardiovascular risk assessed with the aid of a CVD risk prediction model. It is recognised that several of the risk prediction models designed for the general population e.g. Systematic Coronary Risk Evaluation (SCORE) or Framingham risk score may underestimate future CVD risk in individuals with RA as they do not include non-traditional risk factors<sup>61,62</sup>. However, at present there are no alternative CVD risk prediction models with proven accuracy and superiority in inflammatory joint diseases. In an attempt to address this issue, current EULAR guidelines recommend CVD risk prediction models should be adapted for patients with RA by a 1.5 multiplication factor (if this is not already included in the risk algorithm)<sup>63</sup>.

As in the general population, lifestyle interventions including smoking cessation and regular physical activity are important to lower CVD risk in inflammatory joint disease. Studies have shown exercise has several cardiovascular benefits in RA, improving cardiorespiratory fitness, microvascular and macrovascular function, and decreasing cardiovascular risk<sup>64,65</sup>.

In addition to lifestyle interventions, management of hypertension and dyslipidaemia with antihypertensive and lipid lowering therapies is also important. Data from the general population shows a 10-mmHg reduction in systolic blood pressure is associated with a 20% reduction in CVD events<sup>66</sup>, and a 1 mmol/l reduction in LDL-cholesterol with statin therapy is associated with a ~20% reduction in major adverse cardiovascular events (MACE)<sup>67</sup>. The benefit of statin therapy in CVD risk reduction in RA was recently demonstrated in the Trial of Atorvastatin for the Primary Prevention of Cardiovascular Events in Patients With Rheumatoid Arthritis (TRACE-RA study)<sup>68</sup>. This randomised placebo-controlled trial showed individuals with RA prescribed atorvastatin 40mg had a mean ( $\pm$  SD) reduction in LDL-cholesterol of 0.77 ( $\pm$  0.04) mmol/l compared to placebo ( $p < 0.0001$ ). Of the 1,504 patients receiving atorvastatin, 24 (1.6%) experienced the primary composite cardiovascular endpoint compared with 36 (2.4%) of the 1,498 receiving placebo (hazard ratio 0.66, 95% CI

0.39, 1.11;  $p = 0.115$ ). While this reduction was not statistically significant, likely related to the study have a lower than expected event rate, the reduction in CVD risk with the given reduction in LDL-cholesterol concentration was consistent with the Cholesterol Treatment Trialists' Collaboration meta-analysis of statin effects in other populations. There were also no significant differences in adverse event rates between statin and placebo, showing atorvastatin 40mg was safe in the setting of RA <sup>68</sup>.

## **4.2 Anti-rheumatic therapies**

Inflammation is central to RA, gout, SLE and atherosclerosis pathogenesis. Consequently, anti-rheumatic therapies that lower inflammation should lower cardiovascular risk, although this relationship may vary according to the medication chosen. The following sections outline the effects of current anti-rheumatic therapies on CVD risk in inflammatory rheumatic diseases.

### **4.2.1 NSAIDs and cyclooxygenase (COX)-2 inhibitors**

Several non-selective NSAIDs, as well as the selective COX-2 inhibitor rofecoxib, have been associated with increased CVD risk, although this relationship may vary according to the individual medication chosen <sup>30</sup>. For example, studies have shown diclofenac and the selective COX2 inhibitor rofecoxib were associated with increased risk of myocardial infarction and CHD death, particularly at higher doses <sup>69-71</sup>. Rofecoxib was withdrawn in 2004 when it was demonstrated to be associated with almost twice the risk of cardiovascular thrombotic events compared with placebo treatment <sup>72</sup>. On the other hand, moderate doses of the COX-2 inhibitor celecoxib were found to be noninferior to ibuprofen or naproxen with regard to cardiovascular safety, noting the limitations of a non-inferiority study <sup>73</sup>. A large, well-conducted meta-analysis of trial data found that treatment with naproxen resulted in no excess risk of major cardiovascular events (relative risk 0.93, 95% CI 0.69–1.27) <sup>70</sup>.

### **4.2.2 Corticosteroids**

While corticosteroids are effective at dampening inflammation in inflammatory joint disease, these drugs have notable long-term effects on morbidity and mortality. A large general population study demonstrated women and men prescribed long-term oral corticosteroids had an 82% and 58% higher cardiovascular risk, respectively, compared to those not prescribed corticosteroid therapy<sup>2</sup>. The adverse effects of corticosteroids in RA have been shown to be dose and duration dependent with relatively high daily prednisone doses (starting from 8 to 15 mg/day), a high cumulative dose, and a longer exposure to corticosteroids (in years) associated with greater CVD risk <sup>74</sup>. Other studies have also shown increased risk of type 2 diabetes, hypertension, thrombotic stroke or myocardial infarction, and death with corticosteroid use <sup>75,76</sup>.

Despite these findings, some argue that in patients with active RA, the anti-inflammatory benefits of corticosteroids may potentially counteract some of these detrimental CVD effects, and a study, the Glucocorticoid Low-dose Outcome in Rheumatoid Arthritis Study (GLORIS) is currently underway to address this issue <sup>77</sup>. For the meantime however, it is generally advised that clinicians should prescribe the lowest dose of glucocorticoids for the shortest time possible.

### **4.2.3 Conventional synthetic DMARDs**

Methotrexate has been associated with reduced all-cause and CVD mortality in individuals with RA<sup>78</sup>. Indeed, meta-analysis revealed methotrexate was associated with a 21% lower risk of total CVD and an 18% lower risk of myocardial infarction in patients with RA, psoriasis, or polyarthritis<sup>79</sup>. These observational findings suggest that methotrexate may reduce cardiovascular risk in inflammatory joint disease through targeting inflammation. However, in the Cardiovascular Inflammation Reduction Trial (CIRT), treatment with low-dose methotrexate did not reduce the rate of cardiovascular events in patients with established CVD<sup>80</sup>, leading some to question whether methotrexate is cardioprotective. It should be noted however that mean serum CRP concentrations in CIRT participants were substantially lower than those typically found in RA.

Conventional synthetic DMARDs may also have metabolic effects, including altering body composition and the risk of diabetes. For example, treatment with either methotrexate, prednisone or a TNF inhibitor may be associated with weight gain, whereas leflunomide is associated with modest weight loss in RA. In observational studies of patients with RA, patients taking hydroxychloroquine or abatacept were less likely to develop diabetes, while those taking glucocorticoids were more likely to develop diabetes, compared to patients prescribed methotrexate monotherapy<sup>81,82</sup>.

#### **4.2.4 Biologic therapies**

Anti-TNF therapy is effective at lowering inflammation and improving disease activity in RA<sup>83</sup>. As systemic inflammation is thought to drive cardiovascular risk, it follows TNF inhibition should lower this risk. In an observational study of patients with RA, while the rate of myocardial infarction was similar in patients taking a TNF inhibitor to those taking csDMARDs, those who clinically responded to anti-TNF therapy demonstrated a 64% lower rate of myocardial infarction compared to non-responders<sup>84</sup>. Meta-analyses have subsequently shown TNF inhibitors were associated with significant reductions in the risk of all cardiovascular events (RR, 0.70; 95% CI 0.54-0.90;  $p = 0.005$ ), including myocardial infarction, stroke, and major adverse cardiac events<sup>30,85</sup>.

While TNF-inhibitors may have beneficial effects on decreasing CVD risk, other biologics, notable the IL-6 inhibitor tocilizumab and the JAK-inhibitor tofacitinib, have been associated with an increase in total cholesterol and LDL-cholesterol concentrations<sup>10,13</sup>. This effect may simply be part of a compensatory response to dampened inflammation, but the long-term cardiovascular sequelae of these lipid alterations remain to be fully determined. One short observational study demonstrated the cardiovascular risk of patients prescribed a TNF inhibitor was similar to that of patients who had switched to tocilizumab<sup>86</sup>. Furthermore, in a prospective phase IV cardiovascular outcome trial (ENTRACTE), the risk of incident MACE was similar in those prescribed tocilizumab compared to patients given etanercept (HR 1.05, 95% CI 0.77–1.43)<sup>87</sup>.

#### **4.2.5 Gout medications**

Two landmark studies in assessing the inflammatory hypothesis of CVD have focussed on the gout treatments canakinumab and colchicine. In the Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS), directly reducing inflammation with canakinumab, a monoclonal antibody targeting IL-1 $\beta$ , reduced the incidence of recurrent vascular events in individuals with a previous MI and hsCRP  $\geq 2\text{mg/L}$  (HR 0.85, 95% CI 0.74–0.98;  $P = 0.021$ ),

independent of lipid lowering capacity<sup>47</sup>. While the benefit-to-risk ratio and cost effectiveness of canakinumab precluded its routine use in clinical practice for secondary prevention of CVD, this study was the first randomised controlled trial to prove the inflammatory hypothesis of CVD.

In the later Colchicine Cardiovascular Outcomes Trial (COLCOT), individuals with a recent MI treated with colchicine demonstrated a 23% relative risk reduction in the primary composite outcome of death from cardiovascular causes, resuscitated cardiac arrest, MI, stroke, or urgent hospitalization for angina leading to coronary revascularization (HR 0.77; 95% CI 0.61 to 0.96; P = 0.02), compared to placebo<sup>88</sup>. Overall adverse event rates were similar in colchicine and placebo groups. The primary outcome was driven mainly by a reduction in stroke events and urgent hospitalization for angina leading to revascularization (the latter a softer CVD outcome), with no statistically significant reduction in MI rate or mortality. Therefore, while colchicine may have a potential role in stroke warranting further study, it is not recommended at present as part of routine secondary CVD prevention<sup>89</sup>.

There has also been interest in the potential use of xanthine oxidase inhibitors (XOIs), such as allopurinol, in the treatment of cerebrovascular and cardiovascular disease through reduction of vascular oxidative stress and circulating uric acid levels<sup>45</sup>. Studies in individuals with hyperuricaemia and gout have shown mixed effects of XOIs on CVD outcomes<sup>90,91</sup>. In 2018, the CARES (Cardiovascular Safety of Febuxostat and Allopurinol in Patients With Gout and Cardiovascular Comorbidities) study compared cardiovascular outcomes between patients with gout and coexisting CVD receiving either febuxostat or allopurinol. While febuxostat was noninferior to allopurinol with respect to rates of adverse cardiovascular events, all-cause and cardiovascular mortality were higher with febuxostat than with allopurinol, raising potential safety concerns over the use of febuxostat in patients with existing CVD<sup>92</sup>.

## SUMMARY

In summary, this chapter has highlighted the heightened cardiovascular risk in inflammatory joint disease. This is related to a combination of an increased prevalence of traditional cardiovascular risk factors, disease-specific mechanisms, and certain medications commonly prescribed in RMDs including some NSAIDs as well as prolonged use of relatively high-dose corticosteroids. While CVD risk appears to be falling in RA, likely related to the availability of better treatments, CVD risk still remains elevated compared to the general population. In SLE, CVD risk remains substantially elevated, particularly in those with longer disease duration, more chronic organ damage, associated lupus nephritis, NSAID/corticosteroid use, and concomitant hypertension/ dyslipidaemia. Heightened CVD risk in gout is likely related to traditional cardiovascular risk factors, hyperuricaemia, and systemic inflammation.

Taken together, it is important to assess total CVD risk in individuals with inflammatory joint disease. At present, in the absence of disease-specific risk prediction algorithms, standard risk calculators such as SCORE may be used, with a 1.5 multiplication factor in those with RA suggested by current EULAR guidelines. Treatment should involve addressing traditional CVD risk factors including hypertension, dyslipidaemia, smoking, diabetes, and obesity with lifestyle interventions and pharmacotherapy, as well as dampening inflammation with disease modifying anti-rheumatic therapies. Medications associated with heightened CVD risk including certain NSAIDs (notably diclofenac) and some COX-2 inhibitors (namely

rofecoxib, now withdrawn from practice) should be avoided. In cases where corticosteroids are needed, the lowest effective dose should be prescribed for the shortest possible duration.

In conclusion, a holistic, multisystem approach is needed in the management of inflammatory joint diseases. This should include targeting underlying joint inflammation not only to minimise disease activity but also to help improve cardiovascular outcomes in conjunction with optimal management of traditional CVD risk factors.

### **CLINICS CARE POINTS**

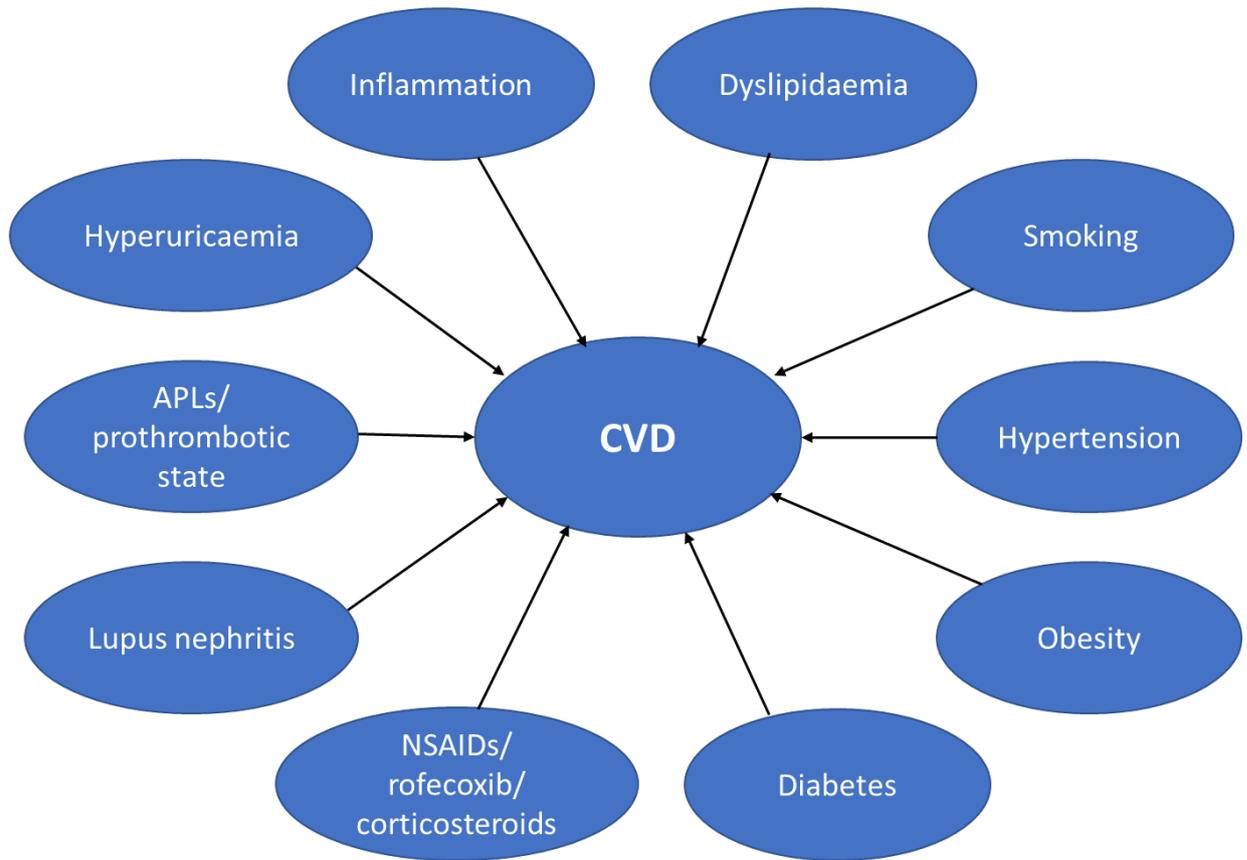
- RA, gout, and SLE are associated with increased CVD risk compared to the general population.
- This risk is related to a combination of traditional cardiovascular risk factors including hypertension, smoking, dyslipidaemia, diabetes, and obesity, as well as disease-specific factors including chronic inflammation.
- Common medications including some non-selective NSAIDs and the COX-2 inhibitor rofecoxib, as well as prolonged courses of relatively high-dose corticosteroids, can also contribute to heightened CVD risk in RMDs.
- CVD risk should be assessed using relevant national or international risk assessment tools e.g. SCORE or Framingham. Some of these general population tools may need to be adapted in RMDs with a multiplication factor.
- Cardiovascular risk management includes pharmacological and non-pharmacological management of traditional risk factors, as well as tight control of disease activity with disease modifying anti-rheumatic drugs.
- Lifestyle interventions should be encouraged including healthy eating, regular exercise, and smoking cessation.
- Antihypertensive and lipid lowering therapies should be prescribed according to national guidelines and risk assessment tools.
- NSAIDs should be used with caution. When required, naproxen appears to have the safest CVD risk profile. Corticosteroids should be prescribed at the lowest effective dose for the shortest possible duration.

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**RMD specific factors:**

**Traditional CVD risk factors:**



**Figure 1.** A combination of traditional cardiovascular risk factors, disease-specific factors, and some commonly prescribed medications, including certain NSAIDs, the COX-2 inhibitor rofecoxib, and corticosteroids (dose and duration dependent), contribute to increased CVD risk in Rheumatic and Musculoskeletal Diseases (RMDs).

Abbreviations: APLs – antiphospholipid antibodies; COX-2 – cyclo-oxygenase 2; NSAIDs – non-steroidal anti-inflammatory drugs.

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