

# Managing Cardiovascular Risk in Patients with Rheumatic Disease



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## KEYWORDS

• 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-antirheumatic 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), notably rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and gout, are at increased risk of cardiovascular disease (CVD) compared with the general population. Central to all 3 conditions is chronic inflammation. Many of the cellular and molecular features of RMDs now also are recognized as 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

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with a higher prevalence of traditional cardiovascular risk factors, for example, smoking, hypertension, dyslipidemia, diabetes, and obesity, and certain medications, for example, several nonsteroidal anti-inflammatory drugs (NSAIDs), the cyclooxygenase (COX)-2 inhibitor rofecoxib, and prolonged use of relatively high dose corticosteroids, all contribute to greater CVD morbidity and mortality in chronic RMDs (Fig. 1).

In this article, the authors 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. Then how best to manage cardiovascular risk in chronic RMDs is discussed by addressing traditional risk factors through lifestyle and pharmacotherapy as well as treating underlying systemic inflammation through antirheumatic therapies.

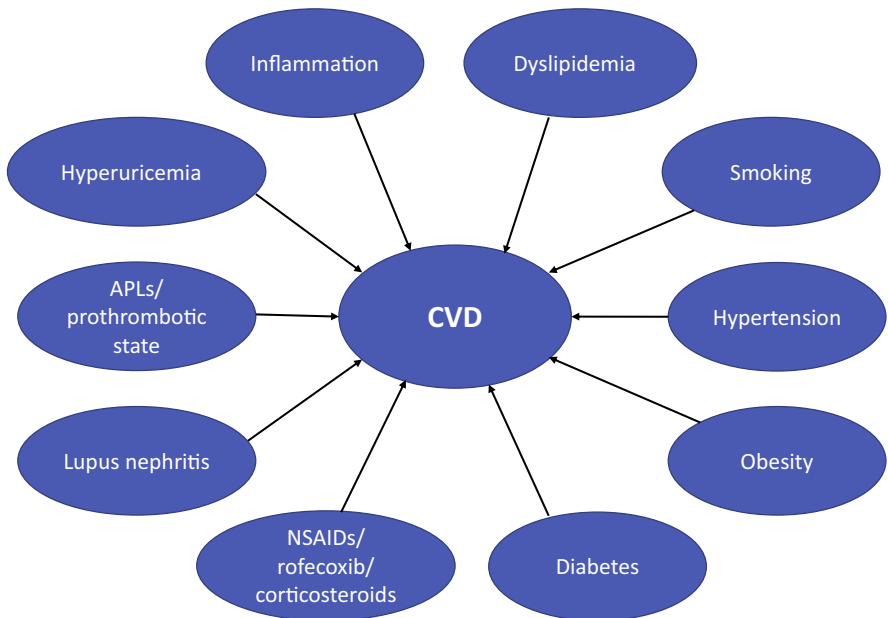
## DISCUSSION

### *Cardiovascular Disease Risk in Rheumatoid Arthritis*

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 (MI), 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 United Kingdom suggesting around a 24% greater CVD risk in RA compared with the general population.<sup>2</sup> Although this may relate to better treatments now available for RA, individuals with RA remain at greater cardiovascular risk than their non-RA counterparts, likely related to a combination of a higher prevalence of traditional cardiovascular risk factors, for example, smoking,

#### RMD specific factors:

#### Traditional CVD risk factors:



**Fig. 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 RMDs.

obesity, physical inactivity, hyperlipidemia, 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, revealed approximately 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, rheumatoid factor/anti-citrullinated protein antibody positive, and raised erythrocyte sedimentation rate and C-reactive protein [CRP]).<sup>4</sup> Cardiovascular mortality also is 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>

### **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 with those without these risk factors.<sup>6</sup> CVD morbidity in RA was greater in those with hypertension (relative risk [RR] 2.24), type 2 diabetes mellitus (RR 1.94), smoking (RR 1.50), hypercholesterolemia (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.

Although dyslipidemia, 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. 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 interleukin (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 signaling 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 also may exist in RA with an inverse relationship between body mass index (BMI) and mortality. Although 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 RR 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 comorbidities 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 greater than or equal to 1 kg/m<sup>2</sup> associated with almost twice the risk of death.<sup>18</sup>

### **Rheumatoid arthritis disease-specific factors**

Although 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> Although 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 hypothesized to contribute to increased CVD risk in RA. Both RA and atherosclerosis share similar underlying inflammatory pathways. These comprise T-cell and myeloid lineage cell activation, release of proinflammatory 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 proinflammatory cytokines, such as tumor necrosis factor (TNF), IL-1 $\beta$ , IL-6, and immune complexes into the circulation. Complement activation also is 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 procoagulant 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 PET/computed tomography imaging, which attenuated with anti-TNF therapy.<sup>26</sup> Furthermore, 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> in particular noncalcified and mixed plaques, which appear more vulnerable to rupture than fully calcified plaques.<sup>28,29</sup>

### **Medications**

Some medications commonly used to treat RA, namely certain NSAIDs, in particular diclofenac, and the now withdrawn COX-2 inhibitor rofecoxib, as well as the 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 later.

### **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.

### **Cardiovascular Disease Risk in Gout**

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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 and colleagues,<sup>32</sup> did not show a significant independent association of gout with CVD. In contrast, a study of more than 5000 individuals from the Framingham Heart Study demonstrated men with gout had a 60% excess risk of CHD compared with men without gout.<sup>33</sup> This excess risk was related in part to a greater prevalence of traditional cardiovascular risk factors, for example, hypertension, hypercholesterolemia, alcohol, and elevated BMI. Even after adjustment for these risk factors, however, 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 more than 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 with men without gout. Similarly, data from the Multiple Risk

Factor Intervention Trial (MRFIT) of more than 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 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 hyperuricemia in women, who generally require a higher mean serum uric acid level to develop gout.<sup>36</sup> Decreasing estrogen during the menopause also may 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.

### **Potential mechanisms**

Central to gout pathogenesis is hyperuricemia 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 hyperuricemia with traditional risk factors, including hypertension, dyslipidemia, chronic kidney disease, and overweight/obesity.<sup>40</sup>

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

Elevated serum urate levels have been associated with greater smooth-cell proliferation, LDL oxidation, and platelet activation as well as a potential role in hypertension pathogenesis, suggesting an etiologic role for hyperuricemia in atherosclerotic disease.<sup>45</sup> It also is possible, however, that hyperuricemia simply may 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 hyperuricemia 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> 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).<sup>47</sup>

### **Summary**

Although some studies have been conflicting, there now is 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, hypercholesterolemia, alcohol, and elevated BMI, and underlying hyperuricemia and systemic inflammation.

### ***Cardiovascular Disease Risk in Systemic Lupus Erythematosus***

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SLE, a multisystem autoimmune disease affecting primarily 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 the University of Pittsburgh Medical Center found approximately 7% of SLE patients had a cardiovascular event, with patients in the 35-year-old to 44-year-old age group more than 50 times more likely to have an MI 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 still is 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, a more than 4-fold greater risk of stroke, a more than 5-fold greater risk of VTE, and a more than 15-fold greater risk of PAD.<sup>49</sup> Longer disease duration as well as NSAID/corticosteroid use were 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 with those not taking corticosteroid medications.<sup>2</sup> Even after adjusting for corticosteroid use, however, as well as traditional cardiovascular risk factors, data from The QResearch database showed women with SLE still had more than double the risk of developing CVD, and men with SLE approximately 55% greater CVD risk compared with the general population.<sup>2</sup>

#### ***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 damage index, was found to be independently associated with increased carotid intima-media thickness scores, carotid plaque formation, and arterial stiffness.<sup>50–52</sup> The presence of lupus nephritis also was associated with greater odds of carotid plaque compared with 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, also have been associated with vascular events, in particular, ischemic 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 oxidized LDL and previous data have shown higher levels of oxidized epitopes on LDL in SLE patients compared with age-matched and sex-matched controls.<sup>56</sup> Several autoantibodies, including antiendothelial cell antibodies and antiphospholipid antibodies (APLs), may contribute to endothelial injury in SLE.<sup>55</sup> APLs also contribute to a prothrombotic state.<sup>57</sup> Type 1 interferons, involved in the pathogenesis of SLE, may promote premature vascular damage in SLE.<sup>58</sup> Neutrophil extracellular traps also may play a role in SLE-related atherosclerosis because they are thought to be prothrombotic and may impair antiatherogenic HDL.<sup>59</sup> Immune complexes also may play a role in atherosclerotic lesion development.<sup>60</sup> Finally, impaired atheroprotective

mechanisms, including impaired endothelial repair and decreased production of atheroprotective autoantibodies, also may contribute.

### **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.

### **Managing Cardiovascular Disease Risk in Rheumatic Diseases**

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There are 2 main approaches to targeting the increased CVD risk associated with chronic RMDs. These include targeting traditional CVD risk factors through lifestyle and pharmacologic interventions and tight control of underlying disease activity.

#### **Traditional cardiovascular disease 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 recognized that several of the risk prediction models designed for the general population, for example, the Systematic Coronary Risk Evaluation (SCORE) and Framingham risk score, may underestimate future CVD risk in individuals with RA because they do not include nontraditional risk factors.<sup>61,62</sup> At present, however, 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 European League Against Rheumatism (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 and microvascular and macrovascular function and decreasing cardiovascular risk.<sup>64,65</sup>

In addition to lifestyle interventions, management of hypertension and dyslipidemia with antihypertensive and lipid-lowering therapies also is important. Data from the general population show a 10-mm Hg 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 an approximately 20% reduction in major adverse cardiovascular events (MACEs).<sup>67</sup> The benefit of statin therapy in CVD risk reduction in RA recently was demonstrated in the Trial of Atorvastatin for the Primary Prevention of Cardiovascular Events in Patients with Rheumatoid Arthritis.<sup>68</sup> This randomized placebo-controlled trial showed individuals with RA prescribed atorvastatin, 40 mg, had a mean ( $\pm$ SD) reduction in LDL cholesterol of 0.77 ( $\pm$ 0.04) mmol/L compared with placebo ( $P < .0001$ ). Of the 1504 patients receiving atorvastatin, 24 (1.6%) experienced the primary composite cardiovascular endpoint compared with 36 (2.4%) of the 1498 receiving placebo (hazard ratio [HR] 0.66; 95% CI, 0.39, 1.11;  $P = 0.115$ ). Although this reduction was not statistically significant, likely related to the study having 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 also were no significant differences in adverse event rates between statin and placebo, showing atorvastatin, 40 mg, was safe in the setting of RA.<sup>68</sup>



### **Antirheumatic therapies**

Inflammation is central to RA, gout, SLE, and atherosclerosis pathogenesis. Consequently, antirheumatic 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 antirheumatic therapies on CVD risk in inflammatory rheumatic diseases.

**Nonsteroidal anti-inflammatory drugs and cyclooxygenase 2 inhibitors** Several nonselective 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 COX-2 inhibitor rofecoxib were associated with increased risk of MI 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 noninferiority 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 (RR 0.93; 95% CI, 0.69–1.27).<sup>70</sup>

**Corticosteroids** Although 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 82% and 58% higher cardiovascular risk, respectively, compared with 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 mg/day 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 also have shown increased risk of type 2 diabetes mellitus, hypertension, thrombotic stroke or MI, 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 potentially may counteract some of these detrimental CVD effects, and a study, the Glucocorticoid Low-dose Outcome in Rheumatoid Arthritis Study, currently is under way to address this issue.<sup>77</sup> For the meantime, however, it generally is advised that clinicians should prescribe the lowest dose of glucocorticoids for the shortest time possible.

**Conventional synthetic disease-modifying antirheumatic drugs** Methotrexate has been associated with reduced all-cause and CVD mortality in individuals with RA.<sup>78</sup> Meta-analysis revealed methotrexate was associated with a 21% lower risk of total CVD and an 18% lower risk of MI 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. 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. Mean serum CRP concentrations, however, in CIRT participants were substantially lower than those typically found in RA.

Conventional synthetic DMARDs also may 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, whereas those taking glucocorticoids were more likely to develop diabetes, compared with patients prescribed methotrexate monotherapy.<sup>81,82</sup>

**Biologic therapies** Anti-TNF therapy is effective at lowering inflammation and improving disease activity in RA.<sup>83</sup> Because systemic inflammation is thought to drive cardiovascular risk, it follows TNF inhibition should lower this risk. In an observational study of patients with RA, although the rate of MI was similar in patients taking a TNF inhibitor to those taking conventional synthetic DMARDs, those who clinically responded to anti-TNF therapy demonstrated a 64% lower rate of MI compared with nonresponders.<sup>84</sup> Meta-analyses subsequently have 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 MI, stroke, and major adverse cardiac events.<sup>30,85</sup>

Although TNF inhibitors may have beneficial effects on decreasing CVD risk, other biologics, notably 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 simply may 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 MACEs was similar in those prescribed tocilizumab compared with patients given etanercept (HR 1.05; 95% CI, 0.77–1.43).<sup>87</sup>

**Gout medications** Two landmark studies in assessing the inflammatory hypothesis of CVD have focused on the gout treatments canakinumab and colchicine. In 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 high-sensitivity (hs) CRP greater than or equal to 2 mg/L (HR 0.85; 95% CI, 0.74–0.98;  $P = 0.021$ ), independent of lipid-lowering capacity.<sup>47</sup> Although 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 randomized controlled trial to prove the inflammatory hypothesis of CVD.

In the later Colchicine Cardiovascular Outcomes Trial, individuals with a recent MI treated with colchicine demonstrated a 23% RR 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, 0.61–0.96;  $P = 0.02$ ) compared with 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, although 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 also has been interest in the potential use of xanthine oxidase inhibitors (XOIs), such as allopurinol, in the treatment of cerebrovascular disease and CVD through reduction of vascular oxidative stress and circulating uric acid levels.<sup>45</sup> Studies in individuals with hyperuricemia and gout have shown mixed effects of

XOIs on CVD outcomes.<sup>90,91</sup> In 2018, the 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. Although 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 article highlights 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. Although CVD risk appears to be falling in RA, likely related to the availability of better treatments, CVD risk still remains elevated compared with 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/dyslipidemia. Heightened CVD risk in gout likely is related to traditional cardiovascular risk factors, hyperuricemia, 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, dyslipidemia, smoking, diabetes, and obesity, with lifestyle interventions and pharmacotherapy as well as dampening inflammation with DMARDs. 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 minimize 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 with the general population.
- This risk is related to a combination of traditional cardiovascular risk factors, including hypertension, smoking, dyslipidemia, diabetes, and obesity, as well as disease-specific factors, including chronic inflammation.
- Common medications, including some nonselective NSAIDs and the COX-2 inhibitor rofecoxib, as well as prolonged courses of relatively high dose corticosteroids, also can contribute to heightened CVD risk in RMDs.

- CVD risk should be assessed using relevant national or international risk assessment tools, for example, SCORE and Framingham score. Some of these general population tools may need to be adapted in RMDs with a multiplication factor.
- Cardiovascular risk management includes pharmacologic and nonpharmacologic 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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## REFERENCES

1. Avina-Zubieta JA, Thomas J, Sadatsafavi M, et al. Risk of incident cardiovascular events in patients with rheumatoid arthritis: a meta-analysis of observational studies. *Ann Rheum Dis* 2012;71(9):1524–9.
2. Hippisley-Cox J, Coupland C, Brindle P. Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study. *BMJ* 2017;357:j2099.
3. Schieir O, Tosevski C, Glazier RH, et al. Incident myocardial infarction associated with major types of arthritis in the general population: a systematic review and meta-analysis. *Ann Rheum Dis* 2017;76(8):1396–404.
4. Crowson CS, Rollefstad S, Ik Dahl E, et al. Impact of risk factors associated with cardiovascular outcomes in patients with rheumatoid arthritis. *Ann Rheum Dis* 2018;77(1):48–54.
5. Ogdie A, Yu Y, Haynes K, et al. Risk of major cardiovascular events in patients with psoriatic arthritis, psoriasis and rheumatoid arthritis: a population-based cohort study. *Ann Rheum Dis* 2014;74(2):326–32.
6. Baghdadi LR, Woodman RJ, Shanahan EM, et al. The impact of traditional cardiovascular risk factors on cardiovascular outcomes in patients with rheumatoid arthritis: A systematic review and meta-analysis. *PLoS One* 2015;10(2):e0117952.
7. Robertson J, Peters MJ, McInnes IB, et al. Changes in lipid levels with inflammation and therapy in RA: a maturing paradigm. *Nat Rev Rheumatol* 2013;9(9):513–23.
8. Robertson J, Porter D, Sattar N, et al. Interleukin-6 blockade raises LDL via reduced catabolism rather than via increased synthesis: a cytokine-specific mechanism for cholesterol changes in rheumatoid arthritis. *Ann Rheum Dis* 2017;76(11):1949–52.
9. van Sijl AM, Peters MJL, Knol DL, et al. The effect of TNF-alpha blocking therapy on lipid levels in rheumatoid arthritis: a meta-analysis. *Semin Arthritis Rheum* 2011;41(3):393–400.

10. McInnes IB, Thompson L, Giles JT, et al. Effect of interleukin-6 receptor blockade on surrogates of vascular risk in rheumatoid arthritis: MEASURE, a randomised, placebo-controlled study. *Ann Rheum Dis* 2015;74(4):694–702.
11. McInnes IB, Kim H-Y, Lee S-H, et al. Open-label tofacitinib and double-blind atorvastatin in rheumatoid arthritis patients: a randomised study. *Ann Rheum Dis* 2014;73(1):124–31.
12. Taylor PC, Kremer JM, Emery P, et al. Lipid profile and effect of statin treatment in pooled phase II and phase III baricitinib studies. *Ann Rheum Dis* 2018;77(7):988–95.
13. Charles-Schoeman C, Fleischmann R, Davignon J, et al. Potential mechanisms leading to the abnormal lipid profile in patients with rheumatoid arthritis versus healthy volunteers and reversal by tofacitinib. *Arthritis Rheumatol* 2015;67(3):616–25.
14. The Global BMI Mortality Collaboration. Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents. *Lancet* 2016;388(10046):776–86.
15. Wolfe F, Michaud K. Effect of body mass index on mortality and clinical status in rheumatoid arthritis. *Arthritis Care Res (Hoboken)* 2012;64(10):1471–9.
16. Escalante A, Haas RW, del Rincón I. Paradoxical effect of body mass index on survival in rheumatoid arthritis. *Arch Intern Med* 2005;165(14):1624.
17. Sattar N, McInnes IB. Debunking the obesity–mortality paradox in RA. *Nat Rev Rheumatol* 2015;11(8):445–6.
18. Baker JF, Billig E, Michaud K, et al. Weight loss, the obesity paradox, and the risk of death in rheumatoid arthritis. *Arthritis Rheumatol* 2015;67(7):1711–8.
19. Ajeganova S, Andersson MLE, Frostegård J, et al. Disease factors in early rheumatoid arthritis are associated with differential risks for cardiovascular events and mortality depending on age at onset: A 10-year observational cohort study. *J Rheumatol* 2013;40(12):1958–66.
20. Arts EEA, Fransen J, Broeder AAD, et al. The effect of disease duration and disease activity on the risk of cardiovascular disease in rheumatoid arthritis patients. *Ann Rheum Dis* 2015;74(6):998–1003.
21. Myasoedova E, Chandran A, Ilhan B, et al. The role of rheumatoid arthritis (RA) flare and cumulative burden of RA severity in the risk of cardiovascular disease. *Ann Rheum Dis* 2016;75(3):560–5.
22. Zhang J, Chen L, Delzell E, et al. The association between inflammatory markers, serum lipids and the risk of cardiovascular events in patients with rheumatoid arthritis. *Ann Rheum Dis* 2014;73(7):1301–8.
23. Innala L, Möller B, Ljung L, et al. Cardiovascular events in early RA are a result of inflammatory burden and traditional risk factors: A five year prospective study. *Arthritis Res Ther* 2011;13(4):R131.
24. Libby P. Role of Inflammation in Atherosclerosis Associated with Rheumatoid Arthritis. *Am J Med* 2008;121(10):S21–31.
25. Ferguson LD, Siebert S, McInnes IB, et al. Cardiometabolic comorbidities in RA and PsA: lessons learned and future directions. *Nat Rev Rheumatol* 2019;15(8):461–74.
26. Maki-Petaja KM, Elkhawad M, Cheriyan J, et al. Anti-tumor necrosis factor- therapy reduces aortic inflammation and stiffness in patients with rheumatoid arthritis. *Circulation* 2012;126(21):2473–80.
27. Gonzalez-Juanatey C, Llorca J, Testa A, et al. Increased prevalence of severe subclinical atherosclerotic findings in long-term treated rheumatoid arthritis

- patients without clinically evident atherosclerotic disease. *Medicine (Baltimore)* 2003;82(6):407–13.
28. Karpouzas GA, Malpeso J, Choi T-Y, et al. Prevalence, extent and composition of coronary plaque in patients with rheumatoid arthritis without symptoms or prior diagnosis of coronary artery disease. *Ann Rheum Dis* 2014;73(10):1797–804.
  29. Pundziute G, Schuijff JD, Jukema JW, et al. Evaluation of plaque characteristics in acute coronary syndromes: non-invasive assessment with multi-slice computed tomography and invasive evaluation with intravascular ultrasound radiofrequency data analysis. *Eur Heart J* 2008;29(19):2373–81.
  30. Roubille C, Richer V, Starnino T, et al. The effects of tumour necrosis factor inhibitors, methotrexate, non-steroidal anti-inflammatory drugs and corticosteroids on cardiovascular events in rheumatoid arthritis, psoriasis and psoriatic arthritis: a systematic review and meta-analysis. *Ann Rheum Dis* 2015;74(3):480–9.
  31. Gelber AC. Gout and risk for subsequent coronary heart disease. *Arch Intern Med* 1997;157(13):1436.
  32. Janssens HJEM, van de Lisdonk EH, Bor H, et al. Gout, Just a nasty event or a cardiovascular signal? a study from primary care - PubMed. *Fam Pract* 2003; 20(4):413–6.
  33. Abbott RD, Brand FN, Kannel WB, et al. Gout and coronary heart disease: The framingham study. *J Clin Epidemiol* 1988;41(3):237–42.
  34. Choi HK, Curhan G. Independent impact of gout on mortality and risk for coronary heart disease. *Circulation* 2007;116(8):894–900.
  35. Clarson LE, Hider SL, Belcher J, et al. Increased risk of vascular disease associated with gout: A retrospective, matched cohort study in the UK Clinical Practice Research Datalink. *Ann Rheum Dis* 2015;74(4):642–7.
  36. Bhole V, de Vera M, Rahman MM, et al. Epidemiology of gout in women: Fifty-two-year followup of a prospective cohort. *Arthritis Rheum* 2010;62(4):1069–76.
  37. Stöckl D, Döring A, Thorand B, et al. Reproductive factors and serum uric acid levels in females from the general population: the KORA F4 Study. *PLoS One* 2012;7(3):e32668.
  38. Carr MC. The emergence of the metabolic syndrome with menopause. *J Clin Endocrinol Metab* 2003;88(6):2404–11.
  39. Kim SY, Guevara JP, Kim KM, et al. Hyperuricemia and Coronary Heart Disease: A Systematic Review and Meta-Analysis. *Arthritis Care Res* 2010;62(2):170–80.
  40. Kuwabara M, Niwa K, Hisatome I, et al. Asymptomatic hyperuricemia without comorbidities predicts cardiometabolic diseases five-year Japanese Cohort Study. *Hypertension* 2017;69(6):1036–44.
  41. Khosla UM, Zharikov S, Finch JL, et al. Hyperuricemia induces endothelial dysfunction. *Kidney Int* 2005;67(5):1739–42.
  42. Maruhashi T, Hisatome I, Kihara Y, et al. Hyperuricemia and endothelial function: From molecular background to clinical perspectives. *Atherosclerosis* 2018;278: 226–31.
  43. Ho WJ, Tsai WP, Yu KH, et al. Association between endothelial dysfunction and hyperuricaemia | *Rheumatology | Oxford Academic*. *Rheumatology (Oxford)* 2010;49:1929–34.
  44. Prasad M, Matteson EL, Herrmann J, et al. Uric acid is associated with inflammation, coronary microvascular dysfunction, and adverse outcomes in postmenopausal women. *Hypertension* 2017;69(2):236–42.
  45. Higgins P, Ferguson LD, Walters MR. Xanthine oxidase inhibition for the treatment of stroke disease: a novel therapeutic approach. *Expert Rev Cardiovasc Ther* 2011;9(4):399–401.

46. Martinon F, Pétrilli V, Mayor A, et al. Gout-associated uric acid crystals activate the NALP3 inflammasome. *Nature* 2006;440(7081):237–41.
47. Ridker PM, Everett BM, Thuren T, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med* 2017;377(12):1119–31.
48. Manzi S, Meilahn EN, Rairie JE, et al. Age-specific incidence rates of myocardial infarction and angina in women with systemic lupus erythematosus: comparison with the framingham study. *Am J Epidemiol* 1997;145(5):408–15.
49. Dregan A, Chowienczyk P, Molokhia M. Cardiovascular and type 2 diabetes morbidity and all-cause mortality among diverse chronic inflammatory disorders. *Heart* 2017;103(23):1867–73.
50. Manzi S, Selzer F, Sutton-Tyrrell K, et al. Prevalence and risk factors of carotid plaque in women with systemic lupus erythematosus. *Arthritis Rheum* 1999;42(1):51–60.
51. Roman MJ, Shanker B-A, Davis A, et al. Prevalence and correlates of accelerated atherosclerosis in systemic lupus erythematosus. *N Engl J Med* 2003;349(25):2399–406.
52. Valero-Gonzalez S, Castejon R, Jimenez-Ortiz C, et al. Increased arterial stiffness is independently associated with metabolic syndrome and damage index in systemic lupus erythematosus patients. *Scand J Rheumatol* 2014;43(1):54–8.
53. Gustafsson JT, Herlitz Lindberg M, Gunnarsson I, et al. Excess atherosclerosis in systemic lupus erythematosus, - A matter of renal involvement: Case control study of 281 SLE patients and 281 individually matched population controls. *PLoS One* 2017;12(4):e0174572.
54. Svenungsson E, Gustafsson J, Leonard D, et al. A STAT4 risk allele is associated with ischaemic cerebrovascular events and anti-phospholipid antibodies in systemic lupus erythematosus. *Ann Rheum Dis* 2010;69(5):834–40.
55. Giannelou M, Mavragani CP. Cardiovascular disease in systemic lupus erythematosus: A comprehensive update. *J Autoimmun* 2017;82:1–12.
56. Frostegård J, Svenungsson E, Wu R, et al. Lipid peroxidation is enhanced in patients with systemic lupus erythematosus and is associated with arterial and renal disease manifestations. *Arthritis Rheum* 2005;52(1):192–200.
57. Frostegård J. Systemic lupus erythematosus and cardiovascular disease. *Lupus* 2008;17(5 SPEC. ISS):364–7.
58. Somers EC, Zhao W, Lewis EE, et al. Type I interferons are associated with sub-clinical markers of cardiovascular disease in a cohort of systemic lupus erythematosus patients. *PLoS One* 2012;7(5):e37000.
59. Lewandowski LB, Kaplan MJ. Update on cardiovascular disease in lupus. *Curr Opin Rheumatol* 2016;28(5):468–76.
60. Mayadas TN, Tsokos GC, Tsuboi N. Mechanisms of immune complex-mediated neutrophil recruitment and tissue injury. *Circulation* 2009;120(20):2012–24.
61. Arts EEA, Popa C, Den Broeder AA, et al. Performance of four current risk algorithms in predicting cardiovascular events in patients with early rheumatoid arthritis. *Ann Rheum Dis* 2015;74(4):668–74.
62. Crowson CS, Matteson EL, Roger VL, et al. Usefulness of risk scores to estimate the risk of cardiovascular disease in patients with rheumatoid arthritis. *Am J Cardiol* 2012;110(3):420–4.
63. Agca R, Heslinga SC, Rollefstad S, et al. EULAR recommendations for cardiovascular disease risk management in patients with rheumatoid arthritis and other forms of inflammatory joint disorders: 2015/2016 update. *Ann Rheum Dis* 2017;76(1):17–28.

64. Stavropoulos-Kalinoglou A, Metsios GS, Van Zanten JJCSV, et al. Individualised aerobic and resistance exercise training improves cardiorespiratory fitness and reduces cardiovascular risk in patients with rheumatoid arthritis. *Ann Rheum Dis* 2013;72(11):1819–25.
65. Metsios GS, Stavropoulos-Kalinoglou A, Van Zanten JJCSV, et al. Individualised exercise improves endothelial function in patients with rheumatoid arthritis. *Ann Rheum Dis* 2014;73(4):748–51.
66. Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet* 2016;387(10022):957–67.
67. Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* 2005;366(9493):1267–78.
68. Kitas GD, Nightingale P, Armitage J, et al. A multicenter, randomized, placebo-controlled trial of atorvastatin for the primary prevention of cardiovascular events in patients with rheumatoid arthritis. *Arthritis Rheumatol* 2019;71(9):1437–49.
69. Fosbøl E, Gislason G, Jacobsen S, et al. Risk of Myocardial Infarction and Death Associated With the Use of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) Among Healthy Individuals: A Nationwide Cohort Study. *Clin Pharmacol Ther* 2009;85(2):190–7.
70. Coxib and traditional NSAID Trialists' (CNT) Collaboration, Bhala N, Emberson J, et al. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. *Lancet* 2013;382(9894):769–79.
71. Lindhardtsen J, Gislason GH, Jacobsen S, et al. Non-steroidal anti-inflammatory drugs and risk of cardiovascular disease in patients with rheumatoid arthritis: a nationwide cohort study. *Ann Rheum Dis* 2014;73(8):1515–21.
72. Bresalier RS, Sandler RS, Quan H, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *N Engl J Med* 2005;352(11):1092–102.
73. Nissen SE, Yeomans ND, Solomon DH, et al. Cardiovascular Safety of Celecoxib, Naproxen, or Ibuprofen for Arthritis. *N Engl J Med* 2016;2519–29.
74. del Rincón I, Battafarano DF, Restrepo JF, et al. Glucocorticoid dose thresholds associated with all-cause and cardiovascular mortality in rheumatoid arthritis. *Arthritis Rheumatol* 2014;66(2):264–72.
75. Wilson JC, Sarsour K, Gale S, et al. Incidence and risk of glucocorticoid-associated adverse effects in patients with rheumatoid arthritis. *Arthritis Care Res (Hoboken)* 2019;71(4):498–511.
76. Panoulas VF, Douglas KMJ, Milionis HJ, et al. Prevalence and associations of hypertension and its control in patients with rheumatoid arthritis. *Rheumatology* 2007;46(9):1477–82.
77. Hartman L, Rasch LA, Klausch T, et al. Harm, benefit and costs associated with low-dose glucocorticoids added to the treatment strategies for rheumatoid arthritis in elderly patients (GLORIA trial): study protocol for a randomised controlled trial. *Trials* 2018;19(1):67.
78. Choi HK, Hernán MA, Seeger JD, et al. Methotrexate and mortality in patients with rheumatoid arthritis: a prospective study. *Lancet* 2002;359(9313):1173–7.
79. Micha R, Imamura F, Wyler von Ballmoos M, et al. Systematic review and meta-analysis of methotrexate use and risk of cardiovascular disease. *Am J Cardiol* 2011;108(9):1362–70.



80. Ridker PM, Everett BM, Pradhan A, et al. Low-dose methotrexate for the prevention of atherosclerotic events. *N Engl J Med* 2019;380(8):752–62.
81. Ozen G, Pedro S, Holmqvist ME, et al. Risk of diabetes mellitus associated with disease-modifying antirheumatic drugs and statins in rheumatoid arthritis. *Ann Rheum Dis* 2017;76(5):848–54.
82. Wasko MCM, Hubert HB, Lingala VB, et al. Hydroxychloroquine and risk of diabetes in patients with rheumatoid arthritis. *JAMA* 2007;298(2):187.
83. Nam JL, Winthrop KL, van Vollenhoven RF, et al. Current evidence for the management of rheumatoid arthritis with biological disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of RA. *Ann Rheum Dis* 2010;69(6):976–86.
84. Dixon WG, Watson KD, Lunt M, et al. Reduction in the incidence of myocardial infarction in patients with rheumatoid arthritis who respond to anti-tumor necrosis factor alpha therapy: results from the British Society for Rheumatology Biologics Register. *Arthritis Rheum* 2007;56(9):2905–12.
85. Barnabe C, Martin B-J, Ghali WA. Systematic review and meta-analysis: Anti-tumor necrosis factor  $\alpha$  therapy and cardiovascular events in rheumatoid arthritis. *Arthritis Care Res (Hoboken)* 2011;63(4):522–9.
86. Kim SC, Solomon DH, Rogers JR, et al. Cardiovascular safety of tocilizumab versus tumor necrosis factor inhibitors in patients with rheumatoid arthritis: a multi-database cohort study. *Arthritis Rheumatol* 2017;69(6):1154–64.
87. Giles JT, Sattar N, Gabriel S, et al. Cardiovascular safety of tocilizumab versus etanercept in rheumatoid arthritis: a randomized controlled trial. *Arthritis Rheumatol* 2020;72(1):31–40.
88. Tardif JC, Kouz S, Waters DD, et al. Efficacy and safety of low-dose colchicine after myocardial infarction. *N Engl J Med* 2019;381(26):2497–505.
89. Newby LK. Inflammation as a treatment target after acute myocardial infarction. *N Engl J Med* 2019;381(26):2562–3.
90. Kim SC, Schneeweiss S, Choudhry N, et al. Effects of xanthine oxidase inhibitors on cardiovascular disease in patients with gout: A cohort study. *Am J Med* 2015; 128(6):653.e7-16.
91. Larsen KS, Pottegård A, Lindegaard HM, et al. Effect of allopurinol on cardiovascular outcomes in hyperuricemic patients: a cohort study. *Am J Med* 2016;129(3): 299–306.e2.
92. White WB, Saag KG, Becker MA, et al. Cardiovascular safety of febuxostat or allopurinol in patients with gout. *N Engl J Med* 2018;378(13):1200–10.