

Clinical update

# Cardiovascular disease in patients with chronic inflammation: mechanisms underlying premature cardiovascular events in rheumatologic conditions

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A variety of systemic inflammatory rheumatic diseases associate with an increased risk of atherosclerotic events and premature cardiovascular (CV) disease. Although this recognition has stimulated intense basic science and clinical research, the precise nature of the relationship between local and systemic inflammation, their interactions with traditional CV risk factors, and their role in accelerating atherogenesis remains unresolved. The individual rheumatic diseases have both shared and unique attributes that might impact CV events. Understanding of the positive and negative influences of individual anti-inflammatory therapies remains rudimentary. Clinicians need to adopt an evidence-based approach to develop diagnostic techniques to identify those rheumatologic patients most at risk of CV disease and to develop effective treatment protocols. Development of optimal preventative and disease-modifying approaches for atherosclerosis in these patients will require close collaboration between basic scientists, CV specialists, and rheumatologists. This interface presents a complex, important, and exciting challenge.

## Keywords

Inflammation • Coronary artery disease • Atherosclerosis • Rheumatic disease • Rheumatoid arthritis • Systemic lupus erythematosus • Risk factors

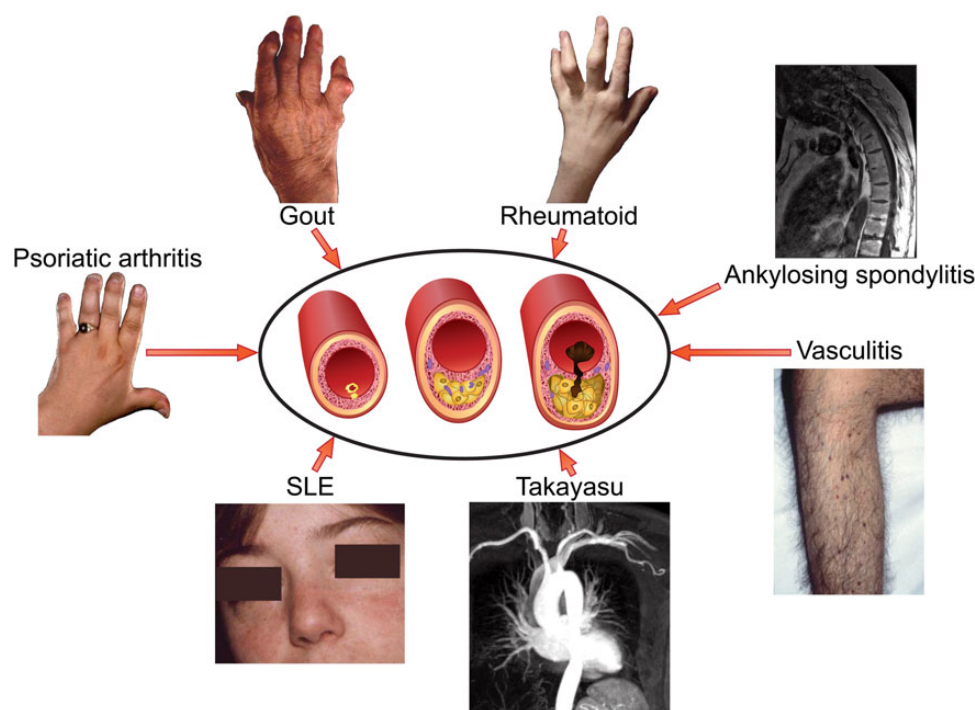
## Introduction

Recognition of the prominent role of inflammation at all stages of atherosclerotic plaque development highlighted the potential relationship between systemic inflammation and atherogenesis, and fuelled intense basic science and clinical research.<sup>1</sup> The rheumatology community has long recognized that patients with rheumatoid arthritis (RA) have heightened risk of premature cardiovascular (CV) death.<sup>2</sup> Indeed, a variety of systemic inflammatory diseases associate with increased risk of CV events including RA, systemic lupus erythematosus (SLE), ankylosing spondylitis, gout, psoriatic arthritis, and medium and large vessel vasculitides (Figure 1).<sup>3</sup> Emerging data suggest that systemic sclerosis (SSc) and inflammatory myositis also associate with an increased risk of atherosclerotic CV events. A meta-analysis of SSc studies recording myocardial infarction (MI), angina, and coronary intervention found an 82% increased risk of coronary artery disease compared with matched controls.<sup>4</sup> In dermatomyositis and polymyositis recent evidence also points towards an increased risk of coronary atherosclerosis-associated CV events.<sup>5</sup>

Patients with inflammatory rheumatic disease have a heightened risk of premature coronary heart disease (recorded as angina, MI, coronary bypass grafting, and coronary angioplasty) and stroke that associates with the degree of inflammation.<sup>6</sup> Although certain rheumatic conditions associate with coronary arteritis (Table 1),<sup>3,7,8</sup> atherosclerosis likely underlies the majority of the coronary artery-related events.<sup>9</sup> Notwithstanding, individuals with rheumatic diseases may not have accentuated atherosclerosis as estimated by angiography. Instead, autoimmune or other arteritides may aggravate lesional inflammation and so render plaques more vulnerable to rupture and thrombosis.<sup>10</sup> Cardiovascular events in patients with rheumatic diseases do not arise solely from atherosclerosis, as myocarditis and other non-ischaemic causes of heart failure also contribute to this burden.<sup>10</sup> Despite this recognition, the interactions of local vascular and systemic inflammation due to rheumatologic diseases with traditional coronary heart disease risk factors, and the degree to which these pathways contribute to adverse CV outcomes in this patient population remain unsettled.<sup>11</sup> Moreover, some of the medications employed in management of patients with rheumatic diseases may aggravate CV risk (e.g.

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**Figure 1** Atherothrombosis in the rheumatic diseases. Systemic inflammatory rheumatic disorders of various types predispose to premature, accelerated atherosclerosis and increased cardiovascular morbidity and mortality.

**Table 1** Coronary artery involvement and the rheumatic diseases<sup>4,5,7,8</sup>

Premature atherosclerosis	Coronary arteritis
Systemic lupus erythematosus	Systemic lupus erythematosus
Rheumatoid arthritis	Takayasu arteritis
Ankylosing spondylitis	Kawasaki disease
Psoriatic arthritis	Giant cell arteritis
Gout	Polyarteritis nodosa
ANCA-associated vasculitis	Granulomatous polyangiitis
Takayasu arteritis	Churg–Strauss syndrome
Giant cell arteritis	Rheumatoid arthritis
Inflammatory myopathies	

glucocorticoids), while other treatments may mitigate this risk [e.g. methotrexate (MTX), administration], as will be discussed below. These competing iatrogenic interventions render unravelling the pathophysiology of CV complications in patients with rheumatologic disease even more complex.

Although the various diseases considered here all qualify as autoimmune and/or inflammatory in nature (Table 1), they have individual attributes that render lumping all rheumatic disorders into one bin with respect to their contribution to CV events a vast oversimplification.<sup>12</sup> The differences among these diseases may provide important clues regarding their association with CV disease and to the aetiology

of these complications. Yet, atherosclerosis may represent a common response to arterial injury generated by different disease-specific upstream insults. These questions have generated considerable interest, and launched quests to understand the pathophysiologic links between these rheumatologic conditions and CV diseases.<sup>12</sup>

In parallel, clinicians need tools to identify those rheumatology patients most at risk of CV disease, to deploy most appropriately diagnostic and therapeutic measures, and aid management. Identification and validation of CV risk biomarkers in patients with rheumatic diseases would aid this practical clinical concern. Finally, the magnitude of this clinical problem demands the development and evaluation of combined therapeutic approaches aimed at minimizing inflammation, and limiting atherosclerosis and CV events in patients with rheumatologic diseases. This review will consider progress in this field, with a focus predominantly on CV disease in RA and SLE, two more common conditions for which the most reliable data exist in this regard. The review also briefly discusses the vasculitides and gout, two important but contrasting conditions associated with CV disease.

## Epidemiology of cardiovascular disease

### Rheumatoid arthritis

The recognition that patients with RA die prematurely dates back >50 years.<sup>2,13</sup> Cardiovascular disease causes >50% of these premature deaths.<sup>14</sup> Rheumatoid arthritis and diabetes mellitus elevate CV risk to a similar extent.<sup>15</sup> Risk factors associated with excess mortality

include female sex, raised erythrocyte sedimentation rate, persistent synovitis, erosions, extra-articular features including rheumatoid nodules, vasculitis and lung disease, and seropositivity including the presence of rheumatoid factor (RhF) and/or anti-citrullinated peptide (CCP) antibodies.<sup>16–18</sup> Despite transformation of RA drug therapy, the increased risk of CV mortality has not declined.<sup>16</sup> This situation may reflect in part the increased incidence of valvular heart disease, non-ischaemic cardiac failure, myocarditis, and pericardial disease in RA.<sup>10</sup>

Patients with RA exhibit impaired endothelial vasodilator function in response to acetylcholine, in association with reduced circulating endothelial progenitors.<sup>19,20</sup> Although these studies found no change in endothelial-independent vasodilation in response to glyceryl trinitrate, Bergholm *et al.* have reported attenuated responses to sodium nitroprusside.<sup>21</sup> Contrary to the previous studies, this investigation initially involved untreated RA patients. Thus, early uncontrolled RA might involve an endothelial-independent defect in arterial smooth muscle cell relaxation.<sup>21</sup> Patients with RA can also display augmented aortic stiffness.<sup>22</sup> These findings indicate the presence of wider vascular abnormalities beyond endothelial dysfunction. Such impairments may in turn predispose to atherosclerosis which progresses most rapidly during the first 6 years after RA diagnosis and more slowly thereafter.<sup>23,24</sup> Cardiovascular deaths increase 7–10 years following symptom onset.<sup>14,25</sup>

The increased risk of MI raises questions concerning the nature of the disease process in RA when compared with non-RA patients. The two groups share similar patterns of coronary disease angiographically. The clinical presentation, however, often has distinct features. Patients with RA may be more likely to exhibit silent or unrecognized ischaemia, to suffer MI, and to develop heart failure.<sup>26,27</sup> Compared with the general population, patients with RA have two-fold excess in sudden cardiac death.<sup>28</sup>

The study of plaque morphology in coronary arteries from patients with RA and age- and sex-matched controls has proved informative. Overall, RA patients had a reduced prevalence of multi-vessel disease and less severe coronary atherosclerosis than age- and sex-matched controls. In a post-mortem series, although the overall burden of plaques appeared similar, 48% of plaques in the LAD of patients with RA were graded unstable by histologic criteria compared with 22% in non-RA controls. Moreover, medial and adventitial inflammation appeared more prominent in subjects with RA than controls.<sup>29</sup> A recent study used ultrasound (US) to analyse carotid plaque in patients with active and inactive RA and non-RA controls. Measuring grey-scale median, patients with active RA had lower values, a characteristic ascribed to vulnerability to rupture and cause thrombosis.<sup>30</sup> The potential role of arterial inflammation in promoting plaque instability in RA also received support from a study that used <sup>18</sup>F fluorodeoxyglucose positron emission tomography with CT co-registration (<sup>18</sup>F-FDG-CT PET). <sup>18</sup>F-FDG-CT PET identified increased glucose uptake attributed to aortic inflammation and suggestive of sub-clinical vasculitis in patients with active RA, a finding not shared by non-RA patients with stable ischaemic heart disease (IHD).<sup>31</sup>

## Systemic lupus erythematosus

Evidence for a bi-modal mortality revealed the importance of CVD in SLE in the mid-1970s: early deaths reflected SLE disease activity, while the second peak associated principally with CVD, MI, or stroke.<sup>32</sup>

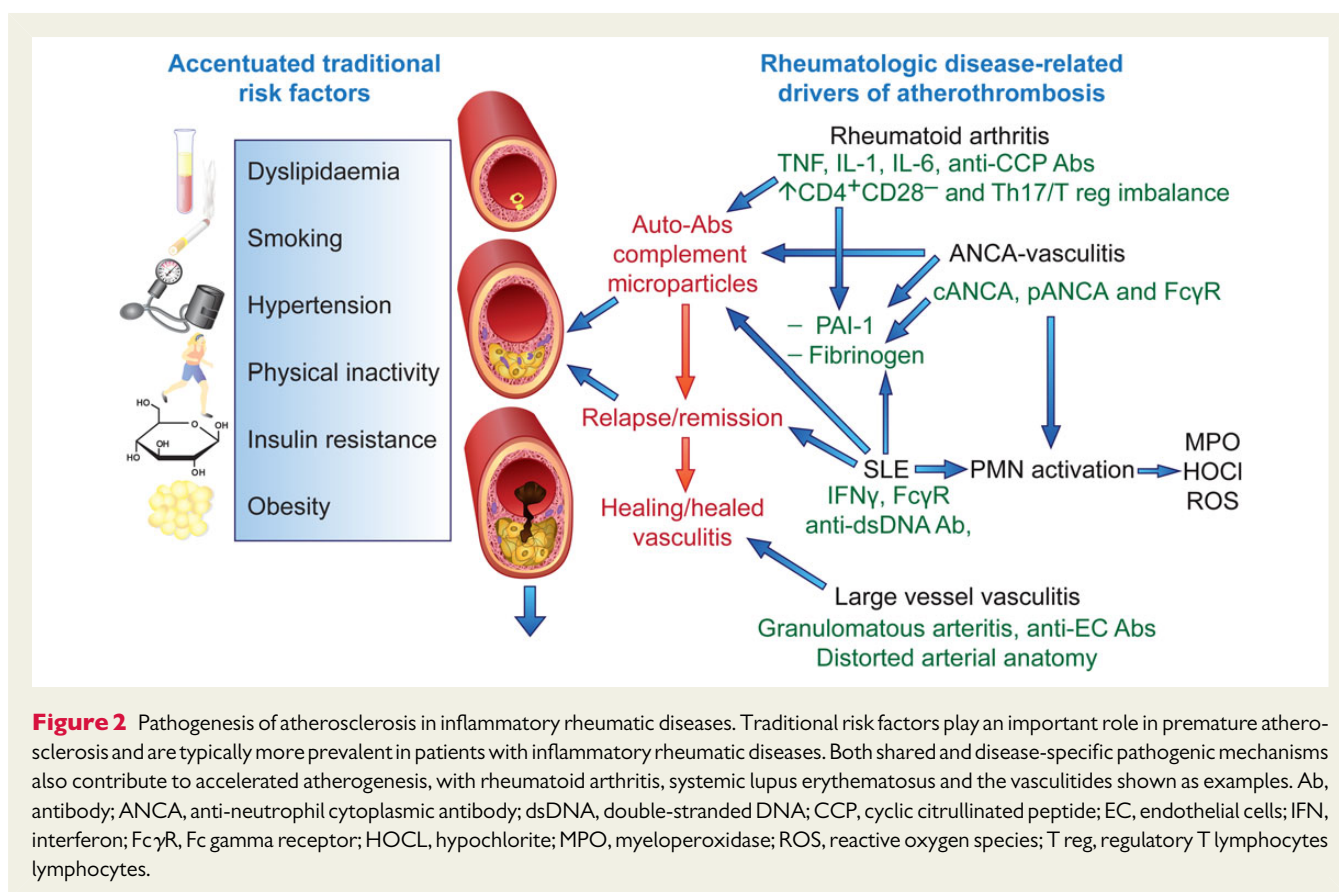
Since that time, improvements in the management of SLE have reduced mortality directly related to disease activity substantially, so that CVD and infection have emerged as the major cause of mortality.<sup>33</sup> Although RA and SLE each predispose to premature atherosclerosis, the pathogenic mechanisms differ. While TNF $\alpha$ , interleukin (IL)-1, and IL-6 play a central role in RA pathogenesis, type I interferons (IFNs) predominate in SLE (Figure 2).<sup>34</sup> The extent to which endothelial dysfunction, aortic stiffness, and atherosclerotic plaque instability seen in both of these diseases reflects increased traditional risk factors, common inflammatory mechanisms, or distinct disease-specific mediators remains unclear.

Despite the increased risk, the relatively modest absolute numbers of CV events in RA and SLE present a challenge to investigators.<sup>35</sup> Hence, the need to rely on biomarkers of disease activity or burden to probe disease mechanisms or to inform the development of treatments. More than 50% of SLE patients have impaired endothelial vasodilator function quantified as flow-mediated dilatation of the brachial artery compared with unaffected controls.<sup>36</sup> Likewise, cardiac PET revealed impaired microvascular blood flow and reduced coronary flow reserve following adenosine challenge in both RA and in SLE patients with angiographically normal-appearing epicardial arteries.<sup>37</sup> Single photon emission tomography demonstrated myocardial perfusion defects in 40% of SLE patients.<sup>38</sup> Carotid artery US revealed a marked increase in early plaque in patients with SLE compared with individually matched controls, and the plaque burden appeared related to SLE activity measured by the SLEDAI index.<sup>39</sup> The overall relative risk of carotid plaque in SLE patients was 2.4, peaking at 5.6 in those <40 years.<sup>39,40</sup> These non-invasive biomarkers of arterial abnormality generally indicate future CV events in non-SLE patients, but require further validation in this regard in patients with SLE or RA.

A recent study of 1874 SLE patients, accumulating 9485 person-years of follow-up, reported a 2.66-fold increased risk of total CV events (stroke, MI, angina, coronary intervention, and peripheral vascular disease) when compared with the general population based on Framingham risk scores.<sup>41</sup> Events were most frequent in those <40 years and were related to average disease activity measured by the SELENA-SLEDAI index, but not in this study to disease duration. Those taking corticosteroids at the time of analysis demonstrated a dose-dependent increased risk for CV events, reaching five-fold in those receiving  $\geq 20$  mg/day.<sup>41</sup> Other studies reveals broadly similar results, although the more recent have revised the overall rate of CV events downward, reflecting differences in study design, focus, and comparators.<sup>41–46</sup> The reported risk of MI in SLE patients ranges from 2- to 10-fold greater than the general population, with a peak of 50-fold reported in women of 35–44 years.<sup>44</sup> Relative risk values include 10.1 for non-fatal MI, 17 for death due to IHD, and 7.9 for stroke.<sup>42</sup> These data are particularly striking given that the majority of patients are female and that 67% presenting with a first event are <55 years of age.<sup>44</sup> Factors linked to the incidence of CV disease include disease duration, clinical activity, the titer of anti-dsDNA, the presence of lupus nephritis, and corticosteroid use.<sup>47</sup>

## Biomarkers

The role of auto-antibodies in CV events seen in patients with rheumatic diseases, either as biomarkers of or in the pathogenesis of CV complications remains uncertain. In RA, the presence of RhF and/



or anti-CCP antibodies associates with endothelial dysfunction and CVD, although a pathogenic link is unproven.<sup>34</sup> Similarly, although laboratory experiments suggest that anti-phospholipid Abs accelerate plaque development, we lack convincing evidence for a causal role in atherosclerotic CV events in patients with SLE or the anti-phospholipid syndrome.<sup>3,34</sup> Anti-apolipoprotein A-1 IgG associates with an increased systemic inflammatory response and major CV events, a finding that may reflect increased plaque vulnerability under these circumstances.<sup>48</sup>

Complement components and the adipocytokines leptin and resistin have also engendered interest as pro-inflammatory injurious factors, while adiponectin may exert anti-inflammatory effects on vascular endothelium.<sup>49</sup> In a variety of rheumatic diseases, leukocytes, platelets, and endothelial cells can release extracellular vesicles including exosomes and microparticles. Their ability to transport micro-RNA, auto-antigens, damage-associated molecular patterns, pro-inflammatory cytokines, and matrix metalloproteases may contribute to increased atherosclerotic plaque inflammation and vulnerability in patients with systemic inflammatory disease.<sup>50</sup> Thus, extracellular vesicles have the potential to act as biomarkers of endothelial injury and modifying their content and release may prove to be therapeutically important.<sup>50,51</sup>

### Traditional risk factors and atherogenesis in rheumatoid arthritis and systemic lupus erythematosus

As expected, traditional CV risk factors appear to contribute to atherogenesis in patients with systemic inflammatory diseases

(Figure 2). Yet, the relative contribution of specific risk factors remains uncertain. One recent study of micro- and macrovascular function in RA has suggested that traditional CV risk factors influence endothelial function more than disease-related inflammation.<sup>52</sup> Adjustment for traditional risk factors revealed a significant disease-specific effect in the pathogenesis of accelerated atherosclerosis in both RA and SLE.<sup>42,53</sup> The systemic and vascular inflammation may act synergistically with traditional risk factors to promote atherosclerosis in patients with RA or SLE (Figure 2).

Patients with RA or SLE have a higher burden of traditional risk factors than the general population. Tobacco smoking associates with both CV risk and the development of RA. Disability caused by RA can limit the ability to exercise. Elevated TNFα levels in RA patients may promote insulin resistance, which together with physical inactivity can favour development of the 'metabolic syndrome' risk factor cluster.<sup>34</sup> However, the metabolic syndrome may not influence CV risk beyond its individual components. Patients with RA may have dyslipidaemia characterized by increased triglycerides, decreased total cholesterol, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C).<sup>54</sup> Moreover, in both RA and SLE, a putative pro-inflammatory form of HDL-C (pHDL) increases.<sup>55</sup> The pro-inflammatory form of HDL-C reportedly promotes LDL oxidation and the development of foam cells. Patients with SLE commonly have hypertension, likely contributed to by renal involvement and the use of corticosteroid therapy. The heightened prevalence of insulin resistance and the metabolic syndrome cluster in SLE patients may also relate to renal impairment and higher corticosteroid doses.<sup>56</sup>



**Table 2** Anti-rheumatic drugs and cardiovascular risk

Agent	Effect on risk biomarkers	Effect on CV outcome
Glucocorticoids	↑BP, ↑TG, ↑glucose, ↓CRP	Prolonged high dose: worsen <sup>40,41,47</sup> Suppression of active SLE protective <sup>39</sup>
NSAIDs/COXIBs	↑BP, ↑thrombosis risk, ↓renal function	Worsen. May improve in RA <sup>83–85</sup>
MTX	↓CRP, ↑adenosine	↓Risk in observational studies <sup>66</sup>
Mycophenolate	↓CRP and plaque inflammation <sup>98</sup>	Minimal data <sup>47</sup>
Hydroxychloroquine	↓LDL, ↓thrombosis risk	Reduced risk in RA and SLE <sup>64</sup>
Anti-TNFα	↓CRP, ↑LDL, ↑TG <sup>54</sup>	Worsens cardiac failure. ↓May MI risk <sup>67,68,93,94</sup>
Anti-IL-6	↓CRP, ↓FN, ↑LDL, ↑TG <sup>54</sup>	No data <sup>64</sup>
Anti-IL-1	↓CRP, ↓FN, ↓IL-6 <sup>64</sup>	No data, study in progress
B-cell depletion	Long-term treatment may ↓LDL <sup>64</sup>	No data
Cyclosporine	↑BP, ↑LDL, ↓renal function	Worsen

BP, blood pressure; TG, triglycerides; LDL, low-density lipoprotein; CRP, C-reactive protein; NSAIDs, traditional non-steroidal anti-inflammatory drugs; COXIBs, COX-2 selective anti-inflammatory drugs; RA, rheumatoid arthritis; MTX, Methotrexate; SLE, systemic lupus erythematosus; FN, fibrinogen; IL-6, interleukin-6.

Outcomes

Optimizing CV prevention and care in this patient population should involve close liaison between cardiologists and rheumatologists.<sup>57</sup> Currently, RA patients with MI may less likely receive acute reperfusion therapy and secondary prevention measures and have worse outcomes than other MI patients.<sup>58</sup> Furthermore, although patients with RA have increased risk for heart failure, which may result in part from diastolic dysfunction, they typically receive less aggressive investigation and management.<sup>59</sup>

In SLE, despite a similar anatomic distribution of atherosclerosis to non-SLE patients, those with SLE may harbour more inflamed plaques considered more likely to cause thrombotic complications. Indeed, in experimental atherosclerosis, systemic or remote inflammation elicits an ‘echo’ of increased inflammation in the arterial lesions.<sup>60,61</sup> Rheumatoid arthritis or SLE increases the risk of mortality post MI.<sup>62</sup> Patients with SLE have poorer outcomes post percutaneous coronary interventions according to registry data, yielding a significantly increased risk of subsequent MI.<sup>63</sup> The poor CV prognosis in SLE may also reflect late diagnosis and a reluctance to treat immunosuppressed patients aggressively.

Treatment

The last 15 years has witnessed a remarkable transformation in drug therapy for many systemic inflammatory diseases. The use of combination disease-modifying anti-rheumatic drug (DMARD) therapy has increased, and a variety of biologic agents have become available.<sup>64</sup> Although these treatments produce clear benefits with respect to primary disease complications including rheumatoid erosions and lupus nephritis, they have shown a less dramatic impact on CV disease (Table 2). The limited long-term data have not conclusively demonstrated reduced CV events,<sup>34,65</sup> save for low-dose MTX.<sup>66</sup> This lack of evidence may reflect in part the low incidence of events and hence the need for large, long-term studies. Registries of patients treated with biologic agents in a variety of countries may prove informative in this regard. With respect to anti-TNFα

and anti-IL-6R strategies, an aggravation of dyslipidaemia may mitigate the anti-inflammatory effect of these agents with respect to atherosclerosis. In addition, anti-TNFα agents did not prove beneficial in patients with heart failure in large clinical trials. Indeed, some data indicate an increase in CV events in heart failure patients treated with anti-TNFα drugs.<sup>67,68</sup>

Advances in therapy would benefit from further understanding of disease-specific pathways involved in vascular injury and accelerated atherosclerosis. Moreover, the development and use of novel imaging and biomarker approaches could facilitate the identification of patients most at risk of CV disease and hasten the development and evaluation of new therapeutic strategies.

Traditional risk factors

Acknowledging that we lack sufficiently powered intervention trials in patients with RA or SLE, given their heightened CV risk they should receive aggressive management of conventional CV risk factors including cessation of smoking, control of weight and blood pressure, prevention/treatment of diabetes mellitus, and encouragement to engage in physical activity consistent with ability. Hypertension commonly complicates many rheumatic diseases including SLE, Takayasu arteritis (TA), SSc, and anti-neutrophil cytoplasmic antibody (ANCA) vasculitis and should receive aggressive treatment. In the absence of renal artery stenosis and provided the renal function allows, angiotensin converting enzyme inhibitors or receptor blockers are favoured, and many patients require additional therapy including vasodilators such as calcium channel antagonists. Some current CVD guidelines support the use of prophylactic anti-platelet medication in rheumatic disease patients.<sup>69</sup> Effective treatment of the primary inflammatory disease may mitigate dyslipidaemia, and some have proposed inclusion of the total cholesterol to HDL-C ratio as an appropriate measure for CV risk assessment in this population.<sup>54</sup> Ideally, disease-specific prediction tools should guide CV risk management. The availability and validation of such instruments, however, remain limited. Current CV risk models appear to underestimate risk in the RA population.<sup>70</sup> The EULAR guidelines for inflammatory arthritis have suggested adding a 1.5 ×

multiplier to standard CV risk calculations (mSCORE).<sup>71</sup> Some have suggested the addition of carotid artery US analysis,<sup>57</sup> particularly in those with a moderate mSCORE.<sup>72</sup> Endothelial dysfunction and aortic stiffness also predict CV risk and may merit inclusion.<sup>73</sup> As in the case of all risk prediction calculators, such instruments should undergo rigorous prospective validation.

Despite the overwhelming evidence for the benefit of statins for CV risk reduction in broad patient categories, we lack specific clinical trial evidence to support the routine use of statins in RA and SLE. In RA, recommended indications include an LDL-C  $\geq 190$  mg/dL (a somewhat conservative measure), a long history of RA, a family history of IHD or hyperlipidaemia, older age at disease onset and the presence of any other CV risk factor.<sup>74</sup> In SLE, some have proposed an LDL-C target of  $<100$  mg/dL, with statins the first choice therapy.<sup>75</sup> Nonetheless, statins have proved disappointing for CV event prevention in SLE, showing no benefit in primary or secondary endpoints in adult patients,<sup>76</sup> and no reduction in carotid intima-media thickness in a paediatric trial.<sup>77</sup>

## Treatment approaches in rheumatoid arthritis

Methotrexate is the most frequently used DMARD in the treatment of RA and has had remarkable impact since becoming widely used in the 1990s. The efficacy of MTX against RA-related CV disease remains undefined. An initial retrospective cohort study found that RA patients with known CV disease who subsequently started MTX had a higher risk of death during follow-up.<sup>78</sup> Despite this, subsequent clinical data and current opinion suggests that anti-inflammatory actions of MTX reduce the risk of CV disease and associated mortality.<sup>66,79–81</sup> Mechanistically, MTX may alleviate the dyslipidaemic profile associated with RA and *in vitro* limits foam cell development through promotion of macrophage cholesterol efflux.<sup>54</sup> A large-scale CV outcome study, the Cardiovascular Inflammation Reduction Trial, funded by the US National Institutes of Health, is evaluating the efficacy of weekly low-dose MTX in CV event reduction in MI survivors already receiving standard of care medication including high-dose statins but with residual features of inflammation indicated by the presence of elements of the metabolic syndrome cluster. Although this study will not enrol patients with RA or SLE, its results may nonetheless provide insight into the role of anti-inflammatory therapy in the prevention of recurrent CV events.<sup>82</sup>

The role of non-steroidal anti-inflammatory drugs (NSAIDs) and cyclo-oxygenase-2 selective antagonists (COXIBs) in RA has diminished. These agents cause a dose-dependent risk of CV complications. A recent network meta-analysis suggested that no traditional NSAID or COX-2 inhibitor is entirely safe and that naproxen has the best CV profile due to its anti-platelet effects.<sup>83</sup> Of note, in inflammatory arthritis, use of NSAIDs was not associated with an increased risk of mortality, and in fact reduces CV risk and mortality.<sup>84,85</sup> An ongoing large-scale critical trial is evaluating the CV safety of various NSAIDs in patients with rheumatoid and osteoarthritis.<sup>86</sup>

Corticosteroid therapy and accelerated atherosclerosis have a complex relationship. Corticosteroids increase insulin resistance, the risk of metabolic syndrome and hypertension, disturb the lipid profile and may promote CV disease in RA.<sup>16</sup> In contrast, in RA

patients with pre-existing IHD, corticosteroid therapy associated with a reduced risk of CV death.<sup>87</sup> Insufficient use of corticosteroids and persistent disease activity may increase the risk of CV disease. Current 'treat to target' paradigms, employing combination DMARDs and biologic therapy in those with persistent disease activity, should minimize corticosteroid requirement in the treatment of RA. Nonetheless, the impact of this approach on CV complications remains uncertain.

## Biologic agents

The introduction of TNF $\alpha$  antagonists transformed the management of RA and provided a catalyst for the development of further targeted biologics. Tumour necrosis factor  $\alpha$  blockade improves endothelial function<sup>20</sup> and reduces aortic stiffness,<sup>22,88</sup> although effects on these biomarkers vary<sup>89</sup> and may have limited durability.<sup>90</sup> Long-term data demonstrating a reduction in CV events are sparse, and some studies reported no significant effect.<sup>91,92</sup> Registry data show that RA patients responding to anti-TNF $\alpha$  therapy have a lower risk of future MI than non-responders.<sup>93</sup> A meta-analysis of both observational cohorts and randomized controlled trials suggests that TNF $\alpha$  blockade reduces the risk of MI, congestive cardiac failure, and stroke, while noting that studies lack sufficient power and include CV events as secondary endpoints only.<sup>94</sup> A retrospective review of 2000 patients suggests patients starting TNF $\alpha$  inhibitors have a reduced risk of CV events for 6 months when compared with those prescribed a conventional DMARD,<sup>92</sup> while a survey of 7704 patients revealed a significant reduction in risk of acute coronary syndrome in anti-TNF $\alpha$ -treated patients vs. the biologic naive group.<sup>95</sup> Abatacept, rituximab, tocilizumab, and the janus kinase inhibitor tofacitinib are now all licensed for the treatment of RA. The rigorous determination of the effects of all agents on CV outcomes will require randomized controlled trials with defined and adjudicated CV endpoints.

## Treatment approaches in systemic lupus erythematosus

Despite significant improvements in SLE therapies, their impact on CV risk remains uncertain. Hydroxychloroquine, currently widely prescribed, has lipid-lowering effects, reduces the risk of thrombovascular events, and associates with reduced plaque burden and improved survival.<sup>47</sup> Although under-treatment of SLE must be avoided as this increases the risk of CV events,<sup>39</sup> EULAR recommends that the minimal dose of corticosteroids possible should be used. High cumulative doses may associate with raised total cholesterol and increased atherosclerosis (Table 2).<sup>47</sup> Current use however seems to confer the maximal risk.<sup>41</sup>

Of the immunosuppressant drugs used in SLE, mycophenolate mofetil (MMF), a purine biosynthesis antagonist, has received most attention with respect to potential CV benefits. In mice with experimental SLE and atherosclerosis, MMF reduced oxidative stress, CD4+ T-cell recruitment and attenuated atherogenesis.<sup>96,97</sup> Of note, atorvastatin failed to do this in the same animals, indicating that statin treatment alone may not provide optimum CV protection.<sup>97</sup> In clinical studies, short-term treatment with MMF in patients with primary atherosclerosis and carotid artery stenosis, reduced inflammatory gene expression and T-cell activation in plaques.<sup>98</sup>

Although, a 2-year longitudinal cohort study in SLE using carotid IMT and coronary calcification as endpoints did not demonstrate an effect of MMF, only 25 patients received the drug and at variable doses.<sup>99</sup> The available data do not permit conclusions concerning the effects of azathioprine and MTX on CV events in SLE. The results of prospective studies with dedicated CV endpoints are awaited with interest and these include trials of IFN- $\alpha$  antagonists and new B-cell-targeted therapies.

## The vasculitides

Accelerated atherosclerosis and premature CV death has also been associated with the large, medium, and small vessel systemic vasculitides, the classification of which has recently undergone revision.<sup>100</sup> These conditions associate with accentuated traditional risk factors including hypertension, dyslipidaemia, and insulin resistance, as well as with indices of vascular dysfunction.<sup>8</sup> Both humoral and cellular immune mechanisms likely contribute to vasculitis pathogenesis. Hence, the vasculitides may involve multiple mechanisms of vascular injury, both distinct from and shared with those implicated in RA and SLE (Figure 2).<sup>101</sup>

The ANCA-associated vasculitides (AAV) comprise granulomatous polyangiitis (Wegener granulomatosis), microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome). Anti-neutrophil cytoplasmic antibodies bind proteinase-3 or myeloperoxidase and identify distinct autoimmune syndromes.<sup>102</sup> These antibodies may directly activate TNF $\alpha$ -primed neutrophils leading to a respiratory burst, generation of reactive oxygen species and subsequent endothelial damage. Immune complexes contribute to pathogenesis by fixing complement and by binding to neutrophil Fc $\gamma$  receptors and activating neutrophils.<sup>101,103</sup> The resultant systemic inflammatory response associates with endothelial dysfunction and increased aortic stiffness, and immunosuppression or TNF $\alpha$  blocker treatment may improve these biomarkers.<sup>104–106</sup> Associated vasculitides may follow a bimodal mortality pattern, with the second peak due to CV disease and malignancy. The risk of coronary heart disease increases up to four-fold and the relapsing and remitting nature of the AAV's may accelerate atherogenesis.<sup>107,108</sup>

The predominant large vessel vasculitides in the adult are giant cell arteritis (GCA), most common in the 6th decade and beyond, and TA that usually presents in those <40 years. Accelerated atherosclerosis and increased premature mortality may occur in TA.<sup>109,110</sup> Patients with TA have increased aortic stiffness,<sup>111</sup> early plaque and evidence of silent MI.<sup>112</sup> In addition to direct vasculitic injury to the arterial wall and pro-atherogenic effects of glucocorticoid therapy, the accelerated atherosclerosis may reflect distorted arterial anatomy leading to disturbed arterial blood flow shear stress patterns associated with pro-inflammatory changes in vascular endothelium.<sup>113</sup> Plaque in common carotid arteries, a site normally protected against atherosclerosis, was only seen in those TA patients with documented common carotid arteritis and increased intima-medial thickness.<sup>110</sup> Up to 40% of patients have demonstrable coronary artery abnormalities. These lesions comprise coronary arteritis with stenosis, typically ostial and non-calcified, and secondary atherosclerotic plaques typically with an irregular angiographic appearance and often calcified.<sup>7</sup>

In GCA, although not associated with increased long-term mortality,<sup>114,115</sup> an observational cohort study has identified a short-term increased risk of CV disease, when compared with the age-matched general population.<sup>116</sup> The predominant risk was within the first 2 months of diagnosis, with a two-fold risk of MI sustained up to 2 years. Likewise, a case–control study revealed increased early mortality.<sup>117</sup> Giant cell arteritis does not associate with accelerated atherosclerosis, and the increased short-term mortality seen likely relates to active arteritis, ischaemic complications of GCA, and adverse effects of glucocorticoid therapy.<sup>118</sup>

## Gout

Another rheumatologic condition, gout, affects up to 2% of individuals. Classical observational studies implicated gout and hyperuricemia as risk factors for atherosclerosis. In the Framingham Study gout associated with a 60% excess in coronary heart disease in men, but not in women, independent of traditional risk factors or diuretic use.<sup>119</sup> Interrogation of the US National Health and Nutrition Examination Survey showed an ~60% increase in risk for CV mortality in those with a history of gout.<sup>120</sup> This analysis also found a stepwise increase in CV mortality with uric acid concentrations in blood. A prospective examination of the Health Professionals Follow-up Study confirmed an ~60% increase in risk of fatal CHD coronary heart disease in men with a history of gout and a prior history of CV disease.<sup>121</sup> Several recent meta-analyses have confirmed an independent association between gout and increased CV risk.<sup>122,123</sup> The relationship of gout with the risk of CV events in women requires further study.<sup>124,125</sup> Uric acid crystals activate the NLRP3 inflammasome, a supramolecular complex within cells that generates the active form of the prominent pro-inflammatory cytokine IL-1 $\beta$ .<sup>126</sup> Thus, a strong pathophysiologic underpinning provides biologic plausibility for the association of gout and hyperuricemia with increased CV risk.

## Conclusion

Increasing scientific and clinical appreciation of the roles of inflammation and immunity in atherosclerosis and myocardial disease furnishes a mechanistic connection between the heightened risk of arteriosclerotic CV events and rheumatic diseases. Study of extreme cases of systemic inflammatory vascular disease (e.g. TA) may provide novel windows into the pathophysiology of arteriosclerotic CV disease in non-rheumatologic populations. In a similar manner, study of the mechanisms that provoke accelerated arteriosclerosis in solid organ allografts has illuminated the role of the adaptive immunity in usual atherosclerosis. Various pathophysiologic concepts originating from the study of rheumatic diseases have inspired pathophysiologic studies in the CV arena. For example, the role of matrix metalloproteinases in connective tissue breakdown in atherosclerotic plaques and in the remodelling of the left ventricle after MI has fundamental similarities with mechanisms often invoked in the joint destruction of RA. Anti-inflammatory therapies under exploration in CV patients have received inspiration from pioneering efforts in patients with rheumatologic diseases, for example, the attempt to lower atherosclerotic risk with MTX.

From a clinical perspective, gaps exist which require the attention of the medical community at large and rheumatologists and CV specialists in particular. The findings summarized in this review remind us that CV disease causes much morbidity and mortality in patients with rheumatic diseases, and that these individuals often do not receive appropriate management to lower vascular risk. This recognition requires aggressive treatment of conventional CV risk factors, and calls for additional investigation of ways to mitigate excess risk. The extent to which the anti-inflammatory therapies used to treat rheumatic diseases will improve CV outcomes requires further study. Whether we need to develop and validate novel biomarkers of risk to inform the intensity of therapy required to lower the CV risk of patients with rheumatologic diseases requires rigorous examination in clinical trials. Development and validation of optimal strategies for monitoring CV disease markers in patients with rheumatic diseases also requires an evidence-based approach. These strategies should strive to avoid complications associated with unnecessary invasive evaluation, prevent over-testing, and minimize imaging radiation exposure, as well as conserve healthcare resources.

Ultimately, close coordination between care-providers for patients with rheumatologic diseases should improve CV outcomes for this important population. The convergence of mechanisms shared by rheumatic and CV diseases should continue to shed light on fundamental mechanistic as well as therapeutic advances and help to address the unmet medical need for these patients.

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