

# Hands On

Practical advice on management of rheumatic disease



## MANAGEMENT OF CARDIOVASCULAR RISK IN RA AND SLE

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### Introduction

Each general practitioner with an average list size has approximately 15 patients with rheumatoid arthritis (RA) and one with systemic lupus erythematosus (SLE). Both diseases are associated with a marked increase in cardiovascular morbidity and mortality. Women with SLE <45 years old are 50 times more likely to experience a myocardial infarction (MI) in the next 8–10 years than healthy women of the same age.<sup>1</sup> Overall, patients with RA are twice as likely to experience an MI in the next 8–10 years as healthy age- and sex-matched controls.

Possible explanations for the link between inflammatory musculoskeletal conditions and accelerated atherosclerosis include shared genetic risk factors, an increased prevalence of traditional cardiac risk factors, and a direct consequence of the inflammatory process or its treatment. The inflammatory process is associated with a reduction in total cholesterol, but the high-density lipoprotein (HDL) cholesterol is particularly reduced, leading to an adverse total:HDL cholesterol ratio. High triglycerides are also associated with inflammation. Both low-density lipoprotein (LDL) cholesterol and triglycerides can be adversely affected by disease-modifying therapy.

Cardiovascular risk is strongly related to disease duration and cumulative disease activity in both RA and SLE. Systemic inflammation promotes endothelial dysfunction and oxidant stress, thus enhancing the accumulation of altered lipids in the vessel wall and the development of atherosclerosis. Many patients with SLE also have the lupus anticoagulant and/or anticardiolipin antibodies which promote thrombosis and increase the risk of developing coronary heart disease (CHD) and stroke. Renal impairment or proteinuria, where present, may also promote atherogenesis.

Primary and secondary prevention should focus on lifestyle advice, optimisation of traditional cardiac risk factors and tight control of disease activity.

### Screening

All patients with RA and SLE should be screened annually for cardiovascular risk factors. This should include:

- enquiring about symptoms suggestive of clinical cardiovascular disease (CVD)
- enquiring about family history of premature CHD in a first-degree relative (male aged <55; female aged <65)
- measurement of height and weight
- measurement of blood pressure (BP). Patients on non-steroidal anti-inflammatory drugs (NSAIDs) or steroids should have their BP checked at least twice a year and more often when such treatment has recently been changed.
- fasting lipids (cholesterol, HDL cholesterol, LDL cholesterol and triglycerides) and glucose
- electrocardiogram (ECG) if patient has hypertension, or symptoms or signs of recent onset or deteriorating CHD.

It is important to remember that CHD is more likely to be clinically silent or to present atypically in this predominantly female population and requires a low threshold for investigation.

### Secondary prevention of cardiovascular disease

SLE and RA patients with established CHD, cerebrovascular disease or peripheral vascular disease should be managed using the same guidelines as the general population.<sup>2</sup> The target BP is <130/80 mmHg and target LDL cholesterol is

<3.0 mmol/l (<2.6 mmol/l in SLE). All such patients should be on low-dose aspirin, angiotensin-converting enzyme (ACE) inhibitors and  $\beta$  blockers according to standard guidelines.

## Primary prevention of cardiovascular disease

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### Lifestyle advice

Primary care personnel are well placed to give lifestyle advice such as:

- Stop smoking
- Reduce weight
- Adopt a 'Mediterranean type' diet
- Moderate alcohol intake
- Take regular aerobic exercise.

### Primary prevention guidelines in RA

Although RA probably conveys a similar excess risk of CHD to diabetes, there is not yet sufficient evidence to support the similar adoption of secondary prevention targets for all patients with RA. RA patients without evidence of CVD should be managed according to the patient's 10-year CVD (i.e. CHD plus stroke) risk, which can be calculated from charts prepared by the Joint Societies ([www.bnf.org](http://www.bnf.org) or [www.bhsoc.org](http://www.bhsoc.org)). The most recent guidelines state that patients with a CVD risk  $\geq 20\%$  should be targeted for comprehensive risk factor reduction. These calculations do not allow for ethnicity or a strong family history of CVD. In addition, for RA we would recommend that the calculated 10-year risk is *doubled* to account for the excess risk associated with the chronic inflammatory condition. Such patients will therefore be much more likely to reach the threshold for interventions.

- **Blood pressure** All patients with a sustained systolic BP  $\geq 160$  mm and/or diastolic BP  $\geq 100$  mm should be treated regardless of their 10-year CVD risk. Patients with a systolic BP  $\geq 140$  mm and/or diastolic BP  $\geq 90$  mm should be treated if their 10-year CVD risk is  $\geq 20\%$ . The target BP is 140/85.
- **Dyslipidaemia** All patients with a total:HDL cholesterol ratio  $\geq 7$  should be treated with a statin regardless of their 10-year CVD risk. Patients with a total cholesterol  $\geq 5.0$  mmol/l or LDL cholesterol  $\geq 3.0$  mmol/l should be treated if their 10-year CVD risk is  $\geq 20\%$ . A statin should be considered if dietary change does not bring the total cholesterol down to the target of <5.0 mmol/l or LDL cholesterol to <3.0 mmol/l. A recent clinical trial showed that atorvastatin improved disease activity as well as reducing cholesterol in patients with moderately active RA.<sup>3</sup>
- **Low-dose aspirin** Low-dose aspirin should be prescribed, unless contraindicated, to patients aged  $\geq 50$  with a 10-year CVD risk  $\geq 20\%$ , providing that their BP is <150/90. Such RA patients should take low-dose aspirin in addition to any NSAIDs they have already been prescribed. The co-prescription of ibuprofen and low-dose aspirin

should be avoided. The majority of patients on aspirin plus a non-selective NSAID (nsNSAID) will also require some form of gastroprotection.

### Primary prevention guidelines in SLE

We consider SLE to be a CHD-equivalent condition similar to diabetes mellitus. As such, stringent targets should be employed in primary prevention in this population.<sup>4</sup>

- **Blood pressure** In SLE the ideal target BP is <130 mm systolic and <80 mm diastolic. Renal function should be closely examined and steroid therapy reviewed in patients with a sustained systolic BP  $\geq 140$  mm and/or diastolic BP  $\geq 90$  mm. If this, and attention to lifestyle factors, does not reduce systolic BP to <140 mm and/or diastolic BP to <90 mm then anti-hypertensive medication should be introduced appropriate to the patient's age, gender and ethnic background<sup>5</sup> and current guidelines.
- **Dyslipidaemia** In SLE the ideal target LDL cholesterol is <2.6 mmol/l. Statin therapy is indicated in patients with LDL >3.4 mmol/l but in patients with LDL of 2.6–3.4 mmol/l it may be possible to reduce the LDL to <2.6 mmol/l by dietary modification and the use of plant stanols, antimalarial drugs (hydroxychloroquine has a beneficial effect on the lipid profile) and steroid dose adjustment, although most will need statins.
- **Low-dose aspirin** Recent studies suggest that the risk:benefit of low-dose aspirin would favour its use in all patients with SLE.<sup>6</sup> Certainly as a minimum standard, patients with SLE and any additional cardiovascular risk factor and patients who are positive for antiphospholipid antibodies or the lupus anticoagulant should be treated with low-dose aspirin. There does *not* appear to be an additional benefit of aspirin in patients with the antiphospholipid syndrome already treated with warfarin.

### NSAID use in RA and lupus

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All nsNSAIDs and selective COX-2 inhibitors\* can adversely affect renal function, promote fluid retention and exacerbate hypertension. Nevertheless, these agents provide important symptomatic relief in patients with inflammatory rheumatic diseases. Recently, the newer selective COX-2 inhibitors have been associated with an excess of cardiovascular events which has led to the withdrawal of rofecoxib and significant changes to the labelling and use of celecoxib and etoricoxib. Observational studies have suggested that there may also be an excess of cardiovascular events in patients exposed to nsNSAIDs. It should be noted that several of these studies included patients who were treated for 'musculoskeletal pain' rather than specifically for RA or other inflammatory arthropathies. The risk:benefits of these agents with regard to cardiovascular health may not be the same in patients with RA and SLE where changes in, for example, blood pressure may be offset to some extent

\* Known variously as COX-2-selective NSAIDs, COX-2-specific NSAIDs, COX-2 inhibitors, coxibs, or simply COX-2s.

<b>TABLE 1. Primary prevention guidelines for RA and SLE.</b>		
	<b>RA</b>	<b>SLE</b>
Use Joint Societies calculator?	Yes – but double the result	No – inappropriate
<b>Blood pressure</b> Highest acceptable value	For all RA patients: 160/100 For patients with CVD risk $\geq 20\%$ : 140/90	140/90
Target value	140/85	130/80
<b>LDL cholesterol</b> Target value	For patients with CVD risk $\geq 20\%$ : <3.0 mmol/l	<2.6 mmol/l
<b>Fasting blood sugar</b> Target value	<7.0 mmol/l	<7.0 mmol/l

CVD cardiovascular disease; LDL low-density lipoprotein; RA rheumatoid arthritis; SLE systemic lupus erythematosus

by improved mobility. Nevertheless, the use of nsNSAIDs/selective COX-2 inhibitors should be considered carefully in patients with RA and SLE. The continued requirement for nsNSAID/selective COX-2 inhibitor therapy in some patients may indicate that further adjustment to their disease-modifying anti-rheumatic drug (DMARD) therapy is indicated to control inflammation better. In all cases the nsNSAID/selective COX-2 inhibitor dose should be reviewed and the lowest effective dose should be used for the shortest period of time.

The European Medicines Agency (EMA) advice states that selective COX-2 inhibitors must not be used in patients with established ischaemic heart disease and/or cerebrovascular disease (stroke), nor in patients with peripheral arterial disease.

## Control of inflammatory disease activity

Inflammatory disease activity in RA and SLE is related to the development and progression of atherosclerosis, and it is therefore important to strive to minimise inflammatory disease activity in these patients. Treatment with various disease-modifying therapies in RA has been shown to be associated with improved endothelial function and a rise in HDL cholesterol, especially in those patients with an improvement in disease activity. Treatment with methotrexate has been reported to be associated with increased life expectancy in RA patients.

Steroid therapy needs to be considered carefully. If steroids are needed to reduce disease activity then they are likely to be beneficial to cardiovascular health, but only if the dose is kept to the minimum necessary to achieve the treatment goal. The effect of more novel anti-tumour necrosis factor (TNF) and anti-B cell therapies on cardiovascular health is still to be established.

## Conclusions

Patients with RA and SLE should be viewed as being at high risk of CVD. The aetiology of CVD in this context probably represents a combination of the underlying inflammatory disease process, traditional risk factors and additional effects from therapies used. CVD often occurs at a younger age and may present atypically. Regular screening of all such patients and lifestyle advice to promote cardiovascular health seems justified. A lower threshold for interventions is recommended in both groups, with more stringent targets in SLE patients. Aiming to control disease activity by fine tuning of anti-rheumatic therapy is important. Steroid therapy may not always be harmful to cardiovascular health but nevertheless should be used judiciously. nsNSAIDs/selective COX-2 inhibitors need careful assessment in this population and their use should be tailored to the patient's individual needs.

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## COMMENT

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*The management of cardiovascular risk in RA and SLE patients is often overlooked in primary care because general practitioners concentrate on managing the primary disease process and do not realise that these patients often have as high a risk of cardiovascular disease as diabetic patients.*

*The underlying cause of the accelerated atherosclerosis is multifactorial but disease activity and duration is a major determinant, and therefore early diagnosis and referral of these patients into secondary care is vital – not just to prevent disease progression but also to minimise the development of cardiovascular disease.*

*General practitioners are ideally placed to screen these patients for cardiovascular risk factors because most of us are already providing an enhanced service of monitoring their DMARD therapy. The doubling of the 10-year risk in rheumatoid patients will take many patients over the threshold intervention level and they*

*will require treatment with anti-hypertensives, statins and low-dose aspirin.*

*Long-term treatment with non-selective NSAIDs and selective COX-2 inhibitors in all patients requires regular monitoring to detect deteriorating renal function or a rise in blood pressure, irrespective of cardiac risk factors.*

*When screening for the usual lifestyle measures, general practitioners should be aware that many of these patients will have an underlying depression which will have an adverse effect on their cardiovascular health unless recognised and treated.*

*Therefore, the care of these patients demands a truly holistic approach which we, as general practitioners, are ideally placed to provide. What is the point of treating these patients with very expensive biologic therapy if they die at an early age because of failure to manage their cardiac risk factors?*

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