Reducing the cardiovascular disease burden in rheumatoid arthritis

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ABSTRACT

- Rheumatoid arthritis is associated with an increase in cardiovascular mortality and morbidity; this increase is independent of traditional cardiovascular risk factors.
- Effective treatment of rheumatoid arthritis with disease-modifying antirheumatic drugs appears to reduce cardiovascular mortality.
- The optimal approach to prevention of cardiovascular disease in rheumatoid arthritis is evolving, but will include a combination of:
  - cardiovascular risk factor screening and management;
  - effective and sustained control of joint and systemic inflammation; and
  - a high index of suspicion for silent cardiac disease.

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Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory disease that affects about 1% of Australians. It causes significant disability through synovial inflammation and eventual joint damage. In addition to these articular manifestations, there is substantial evidence of excess cardiovascular mortality in RA.[1] For example, a study of over 3000 RA patients followed up for as long as 35 years reported a standardised mortality ratio of 2.26, with most excess deaths being attributable to cardiac and cerebrovascular causes.[2] Similarly, a population-based study of 2.37 million participants in the UK General Practice Research Database showed an all-cause mortality rate ratio of 1.6 (95% CI, 1.6–1.6) and a vascular death rate ratio of 1.5 (95% CI, 1.4–1.6) in people with RA compared with those with no arthritis.[3] These figures roughly translate to an average 10–15 years loss of life for patients with RA.

Cardiovascular morbidity is also more frequent in RA patients. In the UK general practice study, the odds ratios for myocardial infarction and cerebrovascular events in RA were 1.6 (95% CI, 1.5–1.7) and 1.4 (95% CI, 1.3–1.5), respectively.[3] In a cross-sectional survey of 9000 patients with RA and 2400 with osteoarthritis, RA patients had a higher prevalence of myocardial infarction, congestive heart failure and stroke.[4] The most recent and compelling data come from a prospective cohort study conducted among the 114 000 women in the Nurses' Health Study.[5] These women were free of cardiovascular disease and RA at baseline in 1976 and were followed up for 20 years, or a total of 2.4 million person-years. The adjusted relative risk of myocardial infarction in women with RA compared with those without was 2.0 (95% CI, 1.2–3.3). Women who had RA for at least 10 years had a risk of myocardial infarction of 3.1 (95% CI, 1.6–5.9). In contrast to the previous studies, no increase in the risk of stroke was seen in these women with RA.

Cardiovascular disease may present differently in RA patients, making diagnosis more difficult. RA patients are less likely to report angina symptoms and more likely to experience unrecognised myocardial infarction and sudden cardiac death.[6] The increased risk of cardiovascular disease appears to precede the clinical diagnosis of RA in some patients.[6] Whether this relationship between RA and cardiovascular disease occurs because of a greater propensity for patients with RA to develop atheroma, or to suffer atheromatous plaque disruption and superimposed thrombosis, is not known.

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Traditional cardiovascular risk factors in rheumatoid arthritis (RA)

Cigarette smoking, diabetes mellitus, hypertension, dyslipidaemia, obesity and physical inactivity are important risk factors for cardiovascular disease which could, if more prevalent in RA patients, explain the excess cardiovascular burden in these patients. However, most studies have concluded that these risk factors are not increased in RA patients. In the Nurses' Health Study, women with RA were significantly more likely than women without RA to report past cigarette smoking (47.8% versus 38.0%). However, no significant differences between these groups were observed for current smoker status, body mass index (BMI), regular aspirin use, diabetes, hypertension, physical activity, or family history of early myocardial infarction.[7]

Furthermore, in a prospective study of 236 RA patients and 4635 community control participants, the age- and sex-adjusted incidence rate ratio of cardiovascular events associated with RA was 3.96 (95% CI, 1.86–8.43).[8] After adjusting for cardiovascular risk factors, the incidence rate ratio decreased only slightly, to 3.17 (95% CI, 1.33–6.36). This suggests that the increased incidence of cardiovascular disease in RA patients is not explained by an increase in classical cardiovascular risk factors.

Role of inflammation in atherosclerosis in RA

Atherosclerosis is an inflammatory disease, and there are striking parallels between the inflammatory and immunological mechanisms operating in atherosclerotic plaque and in rheumatoid synovitis. Common pathogenic features in affected tissues include an abundance of activated macrophages which release or induce inflammatory mediators, including cytokines (eg, interleukin-1, tumour necrosis factor), growth factors, adhesion molecules and matrix metalloproteinases and an infiltrate of T cells.[9] Both RA and atherosclerosis are associated with elevated serum levels of acute phase reactants, such as C-reactive protein, serum amyloid A and fibrinogen.[9] Several population studies of healthy men and women have

1 Strategies for reducing cardiovascular disease in patients with rheumatoid arthritis (RA)

General management strategies	*RA-specific strategies*
Traditional risk factors	
Cigarette smoking	
• Assess readiness for change • Counselling, referral to support services • Medical therapy: nicotine replacement, bupropion	• As for general population
Diabetes mellitus	
• Counselling, diet, weight loss and exercise • Hypoglycaemic therapy • Screen for diabetes complications	• Avoid corticosteroids • If corticosteroids required, consider intra-articular treatment, minimise dose and duration, monitor blood sugar levels, and alter diabetes therapy accordingly
Hypertension	
• Counselling, diet, weight loss and exercise • Antihypertensive therapy to achieve target blood pressure	• Minimise NSAIDs, corticosteroids • Avoid leflunomide, cyclosporin • Consider including calcium-channel blocker
Dyslipidaemia	
• Counselling, diet, weight loss and exercise • Lipid-lowering therapy if indicated	• Minimise corticosteroids • Avoid cyclosporin • Consider including hydroxychloroquine in disease-modifying drug regimen
Body mass index (high or low)	
• Counselling, diet, ideal weight, exercise • Dietitian referral	• Ensure rheumatoid arthritis controlled to prevent cachexia
Physical inactivity	
• Counselling, exercise	• Consider physiotherapist to tailor exercise program that ensures adequate joint protection
Rheumatoid arthritis-specific risk factors	
Inflammation	
• Specialist rheumatology referral for early and sustained control of inflammation with DMARDs • Consider using methotrexate in DMARD regimen • Tumour necrosis factor inhibitors useful for joint disease but may induce or exacerbate cardiac failure	
Homocysteine	
• Methotrexate and salazopyrine may increase serum homocysteine levels • Folic acid supplementation may reduce homocysteine levels but not proven to reduce cardiovascular risk	

NSAID = non-steroidal anti-inflammatory drug.
DMARD = disease-modifying antirheumatic drug. ◆

demonstrated a relationship between C-reactive protein (even within the population "normal" range) and risk of future myocardial infarction and ischaemic stroke.[10-12] A recent meta-analysis of 11 studies reported a risk ratio for coronary heart disease of 2.0 (95% CI, 1.6–2.5) in individuals in the top tertile compared with the bottom tertile for baseline C-reactive protein measurements.[13]

Given that even low levels of inflammation can predict cardiovascular events in the general population, it is reasonable to hypothesise that chronic, often high-level, systemic inflammation in RA may contribute to excess cardiovascular events in this population. This hypothesis is supported by the observation that various measures of disease severity (including decreased function, higher joint count, use of glucocorticoids, presence of rheumatoid nodules, seropositive status, extra-articular disease and higher erythrocyte sedimentation rate) are predictive of mortality in RA.[2,14-17]

Role of drug therapy for RA in cardiovascular disease

The aggregate effect of the drugs used to treat RA on cardiovascular risk is likely to be complex. Some of these drugs alter classical risk factors, but, as described above, most patient groups with RA that have been reported to have excess cardiovascular disease did not have abnormal risk factor profiles. Corticosteroids could increase the risk of cardiovascular disease via deleterious effects on lipids, glucose metabolism and blood pressure. However, these drugs could also decrease the risk by controlling inflammation and raising high density lipoprotein cholesterol levels. Equally, prescription of corticosteroids could be an indicator of more severe RA.

Conventional non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs) and cyclo-oxygenase-2 (COX-2) inhibitors have both recently been associated with an increased risk of myocardial infarction, especially in new users.[18,19] Antimalarials (such as hydroxychloroquine) appear to have a beneficial effect on lipid profiles and have also been postulated to have antithrombotic properties.[20]

Methotrexate treatment of RA has been associated with reduced cardiovascular disease (see below). However, methotrexate has also been shown to increase homocysteine levels (an independent risk factor for vascular disease) and has been associated with an increased risk of mortality in patients with pre-existing atherosclerosis.[21] Folic acid supplementation may reduce homocysteine levels, although the effect on vascular disease is not known. Tumour necrosis factor antagonists (etanercept, infliximab and adalimumab), which are now available for the treatment of RA in Australia, have been associated with new onset or exacerbation of congestive heart failure in a small number of RA patients.

Effect of immunosuppressive treatment of RA on cardiovascular risk

If RA-associated systemic inflammation accelerates cardiovascular disease in RA, then effective treatment might be associated with reduced cardiovascular risk; indeed, existing evidence supports this hypothesis. In an 18-year follow-up of 1240 RA patients, treatment with methotrexate reduced cardiovascular mortality by 70%.[22] Effectiveness of disease control with methotrexate appears to be important: in a retrospective study of 256 RA patients, the standardised mortality ratio was 1.5 (95% CI, 0.8–2.1) in patients who experienced a 50% or greater reduction in disease activity following treatment with methotrexate, compared with 4.1 (95% CI, 2.6–5.7) in those who continued taking methotrexate but had no response.[23] To date, no randomised controlled studies of methotrexate or other immunosuppressive drugs have examined cardiovascular end-points, and these observational data suggest the need for additional research.

2 Pharmaceutical Benefits Scheme criteria for lipid-lowering drugs

Patient category	Lipid levels for subsidy
Patients with existing coronary heart disease	Cholesterol > 4.0 mmol/L
Other patients at high risk with one or more of the following: diabetes mellitus, familial hypercholesterolaemia, family history of coronary heart disease (first degree relative aged under 60 years), hypertension, peripheral vascular disease	Cholesterol > 6.5 mmol/L or Cholesterol > 5.5 mmol/L and HDL < 1 mmol/L
Patients with HDL < 1 mmol/L	Cholesterol > 6.5 mmol/L
Patients not eligible under the above: men aged 35–75 years, postmenopausal women up to 75 years	Cholesterol > 7.5 mmol/L or Triglycerides > 4 mmol/L
Other patients not included in the above	Cholesterol > 9 mmol/L or Triglycerides > 8 mmol/L

HDL = high density lipoprotein. ◆

Strategies for reducing cardiovascular disease in RA

Traditional risk factors

Notwithstanding the data indicating that classical risk factors do not fully explain the risk of cardiovascular disease in patients with RA, the risks are likely to be additive. It is therefore important that clinicians are aware of the increased cardiovascular risk in RA patients and screen their patients for the presence of modifiable cardiovascular risk factors. At present, there are no evidence-based RA-specific cardiovascular guidelines, so the general management principles are the same as for the wider population. However, there are a number of RA-specific factors to consider when formulating the management plan. Box 1 outlines some recommendations for cardiovascular risk-factor management, which are based on the recent publication *Prevention of cardiovascular disease: an evidence-based clinical aid 2004*,[24] but incorporate RA-specific advice.

There is evidence that cigarette smoking, in addition to being a risk factor for vascular disease, may predispose to RA and increase RA disease severity.[1,25] An active approach to helping patients quit smoking is thus especially important in RA.

Steroid-induced diabetes can occur in RA patients treated with oral corticosteroids, and fasting blood glucose should be measured annually or in the event of significant weight gain. In RA patients who are diagnosed with diabetes, corticosteroids should be avoided if possible or used in the lowest possible dose.

Hypertension is a potential side effect of a number of the medications used to treat RA, including NSAIDs, corticosteroids, leflunomide and cyclosporin. Blood pressure should be monitored in RA patients before beginning these medications and then at regular intervals. NSAIDs reduce the antihypertensive effects of diuretics, β-blockers and angiotensin-converting enzyme inhibitors, but may be less likely to interfere with calcium-channel blockers.[26] In RA patients with hypertension who require continued NSAID treatment, it is usually possible to manage any increase in blood pressure with higher doses of antihypertensive drugs, or perhaps by including a calcium-channel blocker in the regimen. However, as with all RA patients, the need for continuing NSAIDs should be reviewed regularly, and alternatives considered, especially if hypertension or heart failure develops or worsens. The recent data suggesting an increased risk of myocardial infarction with both conventional non-aspirin NSAIDs and COX-2 inhibitors is of particular concern in RA patients, who already have increased baseline risk of cardiovascular disease.[18,19] In the absence of specific evidence-based guidelines, a reasonable approach is to minimise NSAIDs in all RA patients, especially those with cardiovascular risk factors.

In most cases, hypercholesterolaemia should be managed initially with dietary modification and weight loss. If levels are persistently elevated, statin therapy may be instituted according to the Pharmaceutical Benefits Scheme guidelines (Box 2). At present, RA is not considered to be an additional cardiovascular risk factor (in contrast to diabetes), and hence treatment criteria are the same as for the general population. We have previously demonstrated that atorvastatin can be safely used in RA patients and that it effectively reduces low density lipoprotein cholesterol and arterial stiffness, a surrogate marker of vascular disease.[27] Statins are postulated to have a number of immunomodulatory effects, and atorvastatin treatment may also lead to modest reductions in RA disease activity.[28] Further studies are required to confirm these findings and to determine if statins should be used in RA for the dual purpose of reducing both cardiovascular disease and RA disease activity.

Obesity, especially abdominal obesity, is a risk factor for cardiovascular disease in the general population. However, in RA the relationship between BMI and cardiovascular mortality appears to be reversed, with a number of investigators reporting increased mortality in RA subjects with a BMI $< 20\,kg/m^2$.[29,30] Given that uncontrolled systemic inflammation may result in cachexia (presumably from elevated levels of pro-inflammatory cytokines, including tumour necrosis factor) this finding is likely to reflect the association between severe disease and low BMI. RA patients should be encouraged to maintain a normal body weight, and this may be aided by dietitian referral. Regular physical activity is an important strategy to prevent cardiovascular disease. Weight-bearing exercise has been shown to be safe in RA and may also reduce disease activity, and therefore should be encouraged in patients with stable disease.[31]

Dietary supplementation with fish oil, rich in omega-3 fats, has demonstrated efficacy in the treatment of RA, can facilitate reduced use of NSAIDs, and may also reduce cardiovascular risk.[32] However, it is important that adequate doses (10–15 mL dose of fish oil per day) are taken. Useful practical advice for prescription of fish oil appears in a recent review of dietary manipulation in RA.[32]

Rheumatoid arthritis-specific risk factors

At present, the balance of evidence supports effective and sustained control of joint and systemic inflammation as an additional strategy to reduce cardiovascular mortality in RA. Although this remains to be proven conclusively, the approach is easily justified as there is ample evidence that early, aggressive and sustained disease-modifying antirheumatic drug (DMARD) therapy is safe in RA and highly effective in reducing joint destruction and long-term morbidity.[33] The relative efficacy of the various DMARDs (used alone or in combination) in preventing cardiovascular events in RA remains to be determined, ideally in prospective, randomised trials with hard endpoints, such as cardiovascular death. However, studies of this type will be difficult, because of the large patient numbers and long study periods required, and the fact that most RA patients need frequent adjustments to their DMARDs and concurrent medications to obtain and maintain disease control.

Early diagnosis and treatment

In addition to controlling cardiovascular risk factors, reducing the cardiovascular disease burden in RA requires early detection of symptoms and prompt intervention. There is some evidence that patients with RA receive suboptimal care for comorbid conditions, perhaps because the patient and physician are focused on the arthritis.[34] Furthermore, cardiovascular disease may present differently in patients with RA, with an increased frequency of unrecognised (or silent) myocardial infarction and a lower likelihood of angina symptoms.[6] Clinicians should therefore be alert for early or subtle manifestations of cardiovascular disease in their RA patients.

Conclusions

Cardiovascular disease is a major cause of morbidity and mortality in RA patients. Substantial evidence suggests that chronic systemic inflammation contributes significantly to excess cardiovascular disease in RA and that effective suppression of RA-associated inflammation appears to reduce mortality. Classical cardiovascular risk factors play a role and may, in some cases, be exacerbated by the medications used to treat RA. Prevention of cardiovascular disease in RA requires a combined approach incorporating cardiovascular risk-factor screening and management, effective and sustained control of RA disease activity, a high index of suspicion and prompt investigation of suspected cardiac disease.

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Competing interests

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