Editorial

Tackling ischaemic heart disease in rheumatoid arthritis

Rheumatoid arthritis (RA) is the commonest form of chronic inflammatory arthritis. It causes significant disability and the efforts of the scientific community have concentrated on controlling symptoms, decelerating joint damage and improving function. However, it has been known for 50 yr [1] that RA is also associated with increased mortality [2, 3]. For severe RA, this compares to that of major killers such as triple-vessel coronary heart disease (CHD) and some lymphomas [4, 5]. Despite advances in treatment, the mortality of RA does not appear to have changed over the last three decades [6, 7]. Its control, therefore, merits at least as much attention as the reduction of disability. An obvious target is reduction of cardiovascular mortality, which accounts for almost half of all deaths in RA [2, 3, 8]. In this article we describe the nature and significance of the problem, discuss the evidence for the involvement of atherosclerotic CHD, outline the role of classical and some novel cardiovascular risk factors, introduce potential lines for intervention, and provide a literature base for the interested reader.

With the exception of a few studies [9–13], most epidemiological work suggests that cardiovascular mortality is increased in RA, with standardized mortality ratios of between 1.13 and 5.15 [14–25]. This very wide range may reflect variable susceptibility of the populations studied (e.g. geographic, genetic and dietary differences), different management practices [for both RA and cardiovascular disease (CVD)] or dissimilar study designs (e.g. inception vs established disease cohorts) [7].

There are only two possible explanations for excessive cardiovascular deaths in RA: CVD is either more prevalent or more deadly in RA patients than in general population counterparts. CVD collectively accounts for much of the comorbidity of RA [26, 27]. Rheumatoid heart disease, although common on echocardiography or autopsy, rarely has haemodynamic consequences; it is therefore an unlikely cause for the increased cardiovascular mortality of RA [28]. Instead, evidence is mounting that the main cause of cardiovascular death in RA is ischaemic heart disease (IHD). This is supported by studies showing that the incidence and/or prevalence of ischaemic cardiac pathologies, such as myocardial infarction (MI), congestive heart failure (CHF) and coronary death, are increased in RA compared with controls [18, 20, 22, 29, 30]. Using myocardial perfusion SPECT (single photon emission computed tomography) scans under pharmacological stress, we have shown that the prevalence of stable IHD in RA (50%) is twice that of closely matched osteoarthritic controls (27%). RA was an independent predictor of IHD in the total population studied [31]. Half of the RA patients with confirmed IHD had clinically silent disease, which has also been noted using 24-h Holter monitoring [32]. In a separate study we found that a fifth of RA patients who sustained an acute coronary syndrome (ACS: unstable angina, Q-wave or non-Q-wave MI) did not have chest pain on presentation, compared with none of the controls. Recurrent ACS was more common, occurred earlier and was associated with more deaths in these RA patients than in case-matched controls [33]. There is therefore sufficient evidence to suggest that the major cause of increased cardiovascular death in RA is IHD rather than other cardiac pathologies, and that IHD is both more common and more likely to lead to death in RA than in the general population.

Interestingly, this general picture is reminiscent of type-2 diabetes mellitus (DM). Excessive cardiovascular morbidity (including silent IHD) and mortality in type-2 DM are of similar magnitude to those now emerging for RA. Like DM, RA appears to be an independent risk factor for the development of IHD. The prevalence of the two conditions is not dissimilar, particularly in the 45 to 75+ age groups (RA vs DM: females, 1.67–2.99% vs 1.0–2.9%; males, 0.58–2.18% vs 1.6–4.6%) [31, 34–39; D. Symmons, personal communication]. In the context of the prevention, diagnosis, therapy and socioeconomic consequences of IHD, RA may be of similar importance to type-2 DM.

In the general population, the commonest cause of IHD is atherosclerotic CHD. The higher frequencies of stable IHD, first and recurrent ACS, and related deaths in RA could all be explained on the basis of accelerated formation and increased instability of coronary atherosclerotic plaques, compared with the general population. There is currently very little direct evidence for this. Most work has concentrated on the intima-media thickness (IMT) of the carotid arteries. In the general population, IMT is a marker of early atherosclerosis and subsequent vascular events. Studies in RA suggest that IMT is increased compared with controls, indicating accelerated carotid atherosclerosis [40]. There are no comparative studies of the nature and extent of involvement of the coronary vasculature and the characteristics of atherosclerotic plaques between RA patients and controls. However, there are several overlapping lines of indirect evidence lending credence to this scenario. They point to potential causes (and therefore potential areas for intervention) and include (i) the presence of an adverse CHD risk factor profile in RA, (ii) evidence establishing chronic inflammation as a major pathogenic mechanism in atherosclerosis, and (iii) the association of...
inflammatory burden with cardiovascular events or death.

Several studies in the general population have identified classical risk factors for the development of CHD. These include modifiable factors, such as smoking, diabetes, hypertension, high total [or low-density lipoprotein (LDL)] and low high-density lipoprotein (HDL) cholesterol, and fixed factors, such as age and male sex. Put together, these factors account for about half of all CHD events in the general population. Obesity and sedentary lifestyle are also important. Many novel factors have been described and may account for events that cannot be explained by the presence of classical risk factors. These include, among many others, homocysteinaemia, prothrombotic factors and serological markers of systemic inflammation, such as C-reactive protein (CRP) and serum amyloid A.

Smoking may be a risk factor for the development of RA [41–47] and may be associated with its severity [48–50]. Although smoking was not found to be a predictor of cardiovascular events or death in a single study of seropositive RA patients [51], it is a logical target for modification in the RA population. The prevalence of diabetes is not increased in RA [51], but insulin resistance, itself thought to promote atherosclerosis [52], has been reported in RA and other systemic inflammatory diseases [53, 54].

Hypertension is common in RA [26, 27] but it is not clear whether it is commoner than in controls. We have found that more than half (56%) of RA patients with no known cardiovascular comorbidity (including hypertension) have a systolic blood pressure higher than 140 mmHg, but this is equally common in osteoarthritis controls. Other investigators have found higher diastolic blood pressure in RA patients than in community controls [55]. Many epidemiological studies have shown an association between non-steroidal anti-inflammatory drugs (NSAIDs) and hypertension, but clinical trials aimed at proving this relationship had mixed findings. Two large meta-analyses [56, 57] confirm that NSAIDs cause clinically significant increases in blood pressure in patients receiving antihypertensive therapy; increases in normotensive individuals are smaller and possibly clinically insignificant. The newer cyclooxygenase (COX)-2 inhibitors (coxibs) have effects on blood pressure similar to those of traditional NSAIDs. Both COX-1 and COX-2 are expressed in renal tissue. Blocking the production of renal prostaglandins, whether in a selective or non-selective manner, can lead to reduced renal function and fluid retention, which can aggravate hypertension [58].

This is important, because even a small increase of 5–6 mmHg in diastolic blood pressure increases the risk of cardiovascular and cerebrovascular events by 15 and 67% respectively [59]. Hypertension should therefore be actively sought and targeted as a risk factor in patients with RA. Use of NSAIDs and coxibs should be judicious, and hypertensive patients receiving such drugs should be monitored for loss of blood pressure control and have their antihypertensive therapy adjusted if necessary. The choice of antihypertensive agents may be problematic in this population, because of other comorbidities and polypharmacy. The combination of NSAIDs and ACE (angiotensin-converting enzyme) inhibitors, for example, is commonly nephrotoxic, particularly in the elderly [60].

In the general population, the risk of vascular events has a positive association with total or LDL cholesterol and an inverse association with HDL cholesterol. Dyslipidaemia has been well documented in RA [61] and appears to be associated with the acute-phase response. During active RA, total and LDL cholesterol may be elevated or reduced [62–64], but HDL is consistently reduced, leading to an unfavourable lipid profile [63–66]. Control of disease activity with several drugs [64, 67] or the use of cyclosporin [68] may lead to elevation of all lipid levels. This raises important issues about the optimal timing of lipid assessment and its utility in the cardiac risk assessment of rheumatoid patients, which need to be resolved in large prospective studies of cardiac risk factors specific to RA. However, some interventions may make sense at this stage. Studies in RA, lupus and even diabetes suggest that the antimalarials may both reduce the levels of total and LDL cholesterol and/or increase HDL, resulting in an advantageous lipid profile [66, 69–74]. This, together with a good safety record and the beneficial effects on RA control, when used in combination with other disease-modifying anti-rheumatic drugs (DMARDs) [75], suggests that antimalarials may be a good option in RA from the cardiovascular perspective. Hormone replacement therapy has mainly beneficial effects on lipids [68] and may be appropriate for many RA patients for osteoporosis prophylaxis. However, the recent Women’s Health Initiative study showed increased risk of CHD events among treated women [76]. An interesting option requiring evaluation in RA is the use of statins. Statins have a proven beneficial effect on lipid profiles and reduce cardiovascular events in the general population [77–79], irrespective of cholesterol levels [80]. They may also have anti-inflammatory and immunomodulatory effects [81–86] relevant to both atherosclerotic and rheumatoid pathology, they may have beneficial anti-hypertensive effects [87], and they may reduce the risk of osteoporotic fracture [88].

Lipids and hypertension may relate to obesity and the sedentary lifestyle, which are now considered major CHD risk factors in their own right. Modest reduction in weight and/or increase in physical activity may provide significant survival benefits [89–91]. Such lifestyle modifications may seem difficult but are not impossible in RA [92–94] and may lead to multiple benefits, including a reduction in cardiovascular risk.

Homocysteinaemia is an independent CHD risk factor, possibly through multiple effects on endothelial cells, LDL oxidation and haemostasis [95, 96]. Methotrexate (MTX) can reduce folate and thus increase homocysteine levels. High levels of homocysteine have been described in RA, including in patients receiving MTX or MTX and sulphasalazine [97–102]. It remains unclear whether this is important in the context of the cardiovascular mortality of RA. One study has shown a significant increase in the mortality of RA patients with pre-existing CVD treated
with MTX compared with other DMARDs [103]. In contrast, another study reported significantly reduced mortality in cardiovascularly unselected RA patients treated with MTX [104], probably because of its superior control of inflammation compared with other DMARDs. Further research is necessary to clarify this. For the time being, it makes sense to ensure that all MTX-treated RA patients receive adequate folate supplementation [105]; it may also be reasonable to avoid MTX, if possible, for the treatment of RA in patients with pre-existing CVD.

Inflammation in RA may have significant prothrombotic effects. These may contribute to both the severity of stable atherothrombotic coronary disease and worse outcome after ACS. Fibrinogen [106] and other thrombotic risk factors [107] (e.g. tissue plasminogen activator, D-dimers, von Willebrand factor) are elevated [55] and may associate with cardiovascular events in RA [108]. Several of the drugs used in RA may affect thrombogenic variables and, because of practice changes, there is an urgent need to define these effects. Antimalarials may have beneficial antithrombotic properties [72, 109] but this needs to be confirmed. NSAIDs (e.g. naproxen) have well-described aspirin-like antiplatelet effects and are reported to reduce vascular events in RA [110], slow atherosclerosis in animal models [111] and reduce mortality after MI as effectively as aspirin in the general population [112]. However, the evidence for this should be viewed with caution [113]. Some NSAIDs (e.g. ibuprofen) appear to antagonize aspirin-induced platelet inhibition, whereas others (e.g. diclofenac) do not [114]. The coxibs may [115] or may not [114] interfere with the antithrombotic effect of aspirin and may even have prothrombotic effects themselves [116], probably by decreasing vascular prostacyclin production [117]. Whether this leads to increased cardiovascular events [118, 119] is still a matter of debate. On current evidence, it would be inappropriate to withhold aspirin in patients receiving it for cardiovascular protection, whether or not they are receiving NSAIDs or coxibs. The administration of ibuprofen in patients receiving aspirin may also need to be avoided.

Atherosclerosis, like RA, is a chronic inflammatory condition [120] and may even have an autoimmune component [121]. Immunohistochemical studies suggest significant similarities between the mechanisms responsible for chronic synovitis and damage in the rheumatoid joint and the generation and rupture of the atherosclerotic plaque. These include the cellular infiltrates, adhesion molecule expression, the cytokine milieu and free radical and degradative enzyme release [3, 120–125]. The importance of inflammation is further supported by work in animal models [126–129] and epidemiological work in the general population showing that several serological markers of systemic inflammation may associate with cardiovascular outcomes [130–132]. The best studied is CRP: its level is a good predictor of future MI or ischaemic stroke in the general population, whether or not there is pre-existing CVD [130–133]. It remains unknown whether CRP reflects underlying inflammatory mechanisms or is itself pathogenically involved through effects on endothelial cells and macrophages.

It is obvious that the systemic inflammation of RA can be linked to accelerated atherosclerosis, IHD and cardiovascular death in many different ways. It follows that an increased inflammatory burden should be associated with more cardiovascular events and death, whereas its effective control should be associated with better outcome. The current evidence, although indirect, appears to support this. Disease activity, as assessed by the erythrocyte sedimentation rate [51], joint swelling [134] or a composite activity score [135], has been shown to be associated with cardiovascular events, cardiovascular death and overall mortality respectively. The effects of various treatments for RA are less clearly defined: DMARDs do not appear to increase overall mortality. In contrast, effective control of inflammatory activity appears to confer survival benefits [22, 104, 136–138], but it remains to be proven in most cases whether this is due to improved cardiovascular outcomes. It will be interesting to see the effects of the anti-tumour necrosis factor (TNF) agents in the future. At present, any assumptions would be premature. Treatment of CHF with anti-TNF agents has a sound theoretical basis (overexpression of TNF-α associated with negative inotropic effects, left ventricular dysfunction, cardiomyopathy and pulmonary oedema). Yet trials of the anti-TNFs in CHF suggest that they may lead to worsening CHF, increased hospitalization and more deaths rather than clinical improvement.

The cause of increased cardiovascular morbidity and mortality in RA is likely to be multifactorial. Further research is needed to disentangle the interdependence of most of the factors discussed above, separate cause from effect, and assign relative importance to them, so that informed interventions can be implemented. This may be a much greater challenge in RA than it is in the general population, but we can learn from work in other conditions. We have already drawn a parallel between RA and type-2 diabetes. The excess cardiovascular risk in DM is thought to relate partly to the direct effects of hyperglycaemia and partly to its adverse effects on risk factors [139]. Although strict glycaemic control showed a clear benefit in microvascular complications, it does not appear to affect macrovascular disease markedly [140]. Because of this, recent guidelines provide a framework for aggressive classical risk factor targeting and reduction in patients with DM and other high-risk groups [141]. We can follow a similar approach while we try to clarify the role of systemic inflammation in RA and find the best way to suppress it without compromising the vasculature. By recognizing that RA patients are a high-risk group, we can seek actively and treat aggressively their classical cardiovascular risk factors in both the primary and secondary care settings.

G. D. Kitas1,2 and N. Erb1

1Department of Rheumatology, Dudley Group of Hospitals NHS Trust and 2Department of Rheumatology, Division of Immunity and Infection, The Medical School, University of Birmingham, UK
Correspondence to: G. D. Kitas, Department of Rheumatology, Dudley Group of Hospitals NHS Trust, The Guest Hospital, Tipton Road, Dudley, West Midlands DY1 4SE, UK. E-mail: g.d.kitas@bham.ac.uk

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