Disease modification and cardiovascular risk reduction: two sides of the same coin?

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Inflammatory rheumatic diseases are associated with a substantial increase in accelerated atherosclerosis, with complex interactions between traditional and disease-related risk factors. Therefore, cardiovascular risk reduction should be considered as integral to the control of disease activity in the care plans of patients with RA, SLE and, arguably any chronic inflammatory disease. Shared care structures, already established for the monitoring of DMARDs, could be adapted to communicate and monitor cardiovascular risk reduction objectives. We review the evidence for the efficacy of a range of therapeutic strategies, the majority of which impact on both disease activity and cardiovascular risk. The algorithm proposed here attempts to distill the latest advice from specialist panels at the National Cholesterol Education Program and the British Hypertension Society, as well as incorporating the existing data on SLE and RA patients. The algorithm is structured to minimize clinic time and resources necessary to stratify patients into groups for ROUTINE, SUBSTANTIAL or INTENSIVE risk management; the associated table summarizes optimal therapeutic objectives in each of these groups. The implication of this algorithm is that management of cardiovascular risk should be much more aggressive than is currently the norm in patients with chronic inflammatory diseases, such as RA and SLE. Long-term studies of such interventions are needed to further clarify the benefits of intensive cardiovascular risk management in these patients.

A number of recent observations indicate that chronic inflammation is not merely associated with accelerated atherosclerosis but that aberrant cellular and humoral immune responses are integral to its pathogenesis (reviewed in [1]). Therefore, therapeutic objectives in chronic inflammatory and cardiovascular disease converge, and agents prescribed as either immune or lipid modulators may be modifying both inflammatory and cardiovascular disease. The recent report that atorvastatin has disease-modifying activity in rheumatoid arthritis (RA) [2] emphasizes the relevance of this concept to rheumatology practice. This article summarizes the evidence for excess risk of accelerated atherosclerosis in inflammatory rheumatic disease with particular reference to RA and systemic lupus erythematosus (SLE). Recent insights into therapies which may modulate both articular and vascular disease are discussed, and an algorithm for managing cardiovascular risk in the context of inflammatory rheumatic disease is proposed.

Increased risk of atherosclerosis in patients with inflammatory rheumatic diseases

Numerous studies have demonstrated that mortality in patients with RA is increased compared with that of the general population, with standardized mortality rates ranging from 1.28 to 3.0 [3, 4]. Most of the excess mortality is cardiovascular [5, 6], resulting from accelerated atherosclerosis (reviewed in [7]). Morbidity related to acute coronary syndrome, stroke and other manifestations of accelerated atherosclerosis is also increased in patients with RA [8–12]. Non-invasive case–control studies have confirmed the increased risk of vascular dysfunction and subclinical atherosclerosis in RA [13–15].

SLE is also associated with an increased burden of accelerated atherosclerosis. This is particularly striking in young women; Manzi and co-workers estimated that the incidence of acute myocardial infarction in women with SLE aged 35–44 yr was 50-fold greater than that of the comparable cohort in the Framingham Offspring Study [16]. Again, even when studies control for classical risk factors, SLE is associated with excess risk. Esdaile and co-workers [17] estimated a 17-fold risk of mortality secondary to coronary heart disease, a 10-fold risk of non-fatal myocardial infarction and an 8-fold increase of stroke. Studies of subclinical cardiovascular disease substantiate the increased susceptibility in SLE. A case-control study in New York, using carotid ultrasound and echocardiography, reported an odds ratio for cardiovascular disease in SLE compared with controls of 4.8 [18] and a cross-sectional study in 214 women with lupus, using carotid ultrasound, revealed carotid plaques in 32% of patients [19].

Although less clearly defined, there is emerging evidence that accelerated atherosclerosis occurs in other inflammatory rheumatic diseases, such as sieronegative spondyloarthropathies (particularly psoriatic arthritis and ankylosing spondylitis) and ANCA-associated vasculitis [20, 21]. Interestingly, there have also been reports that an apparently 'non-inflammatory' rheumatic disease such as osteoarthritis is also associated with increased risk of cardiovascular mortality [22]. Whether this association reflects the recognized relationship between obesity/insulin resistance and osteoarthritis remains unclear.
Pathogenesis of vascular damage in inflammatory rheumatic disease

Inflammation is integral to the pathogenesis of atherosclerosis, and the interaction with chronic inflammatory disease and atherosclerosis has been the subject of several excellent reviews [1, 23, 24]. The paradigm of endothelial injury envisages that several classical risk factors, such as smoking, hypertension, diabetes mellitus and dyslipidaemia, can produce a state of endothelial dysfunction (ECD) and that this facilitates the infiltration of inflammatory cells. Several studies have indicated that traditional risk factors contribute to the development of atherosclerosis in RA [25] and SLE [26, 27]. Indeed, the prevalence and/or severity of traditional risk factors is increased in inflammatory rheumatic disease. For example, systemic inflammation contributes to pro-atherogenic lipid profiles. In RA, this lipid profile typically includes normal to low levels of total low-density lipoprotein (LDL), but reductions in apolipoprotein A1 and high-density lipoprotein (HDL) cholesterol [28]. Dyslipidaemia has also been demonstrated in SLE [29]. The prevalence of insulin resistance is increased in patients with RA and SLE [29, 30] and a risk-associated body habitus, with abdominal obesity, occurs more frequently in SLE [29]. Adipose tissue itself produces proinflammatory cytokines, or adipokines, and a relationship between insulin resistance and subclinical inflammation has recently been proposed (reviewed in [31]). Hypertension is clearly increased in SLE [29]. RA has been associated with a significant, albeit small, increase in systolic or diastolic blood pressure [11, 32]; however, other studies report no association with hypertension [25, 30]. The frequency of patients with RA or SLE who smoke appears to be comparable with that in the general population [29, 30].

In addition to the interaction of traditional risk factors with inflammatory disease, disease-related processes independently confer cardiovascular risk in RA and SLE. Systemic inflammation may be regarded as accelerating the atherosclerotic process. Indeed, systemic levels of soluble inflammatory mediators, such as C-reactive protein (CRP), have been associated with cardiovascular risk in the general population [33]. In RA, the severity of inflammatory disease correlates with the risk of vascular disease [13, 34–36]. In the accelerated vascular disease of SLE, CRP may be less important than other mechanisms. However, in the LUMINA study of cardiovascular disease in patients with lupus, CRP still emerged as a risk factor; the median CRP in all patients with vascular events was 12.6 mg/l compared with a median CRP of 4.8 mg/l in patients without vascular events [26].

ECD is common to many if not all inflammatory states [37]. Recent studies from Birmingham, Cambridge and other groups have demonstrated that ECD occurs in RA, SLE and primary systemic vasculitis (reviewed in [38]). It is probable that soluble inflammatory mediators contribute to endothelial damage and interact with the traditional risk factors at this level. In both RA and SLE, duration and activity of disease are associated with accelerated atherosclerosis [14, 18, 39], and it is intriguing that ECD correlates with disease activity in vasculitis and that it improves following tumour necrosis factor (TNF)-α blockade in RA and vasculitis [40, 41].

Although ECD occurs across the spectrum of systemic inflammatory diseases, distinct pathogenic mechanisms underlie individual disease states. For example, RA is associated with aberrant activity of CD4+ T cells, B cells and cells of the monocyte/macrophage lineage; Th1 cytokines predominate. Disease-specific risk factors include rheumatoid factor seropositivity, the presence of HLA-DRB1 alleles containing the shared epitope sequence, and extra-articular manifestations [14, 42, 43]. These factors are each associated with rheumatoid disease severity, and this may be a sufficient explanation for the accelerated atherosclerosis. CD4+ CD28− T cells have emerged as an intriguing commonality between RA and destabilized atheroma [44–46]. This population of T cells is increased in both RA and unstable angina; these T cells exhibit a lower threshold for activation and secrete a predominance of Th1 cytokines, which can promote endothelial injury and the release of metalloproteinases from macrophages. It is suggested that these properties lead to plaque rupture or haemorrhage, with resultant vessel occlusion.

Disease modifying anti-rheumatic drugs (DMARDs) may increase certain cardiovascular risk factors; for example, lefunomide and cyclosporin can cause hypertension. Cyclosporin is also associated with development of an adverse lipid profile and methotrexate increases homocysteine levels [47]. Non-steroidal anti-inflammatory drugs (NSAIDs) are also associated with hypertension. Indeed, relatively small changes in systolic blood pressure associated with use of NSAIDs may have a significant effect on the cardiovascular risk profile in RA [48]. Furthermore, it has recently become apparent that the COX-2-selective NSAIDs rofecoxib and celecoxib are associated with a 2- to 4-fold increased risk of thromboembolic events [49]. This may be a class effect and reflect the fact that COX-2-selective agents do not inhibit the platelet-derived prothrombotic thromboxane A2, whereas the endothelial production of the anti-thrombotic prostacyclin is suppressed.

The presence of IgM or IgG anti-phospholipid antibodies is an independent risk factor for cardiovascular disease in SLE [18, 50]. In this context, a susceptibility from thrombosis, in addition to accelerated atherosclerosis, may contribute to cardiovascular morbidity. Endothelial damage in SLE may also occur by other mechanisms distinct from those in RA, e.g. via immune complex deposition, local complement activation and anti-endothelial antibodies [51–53].

Therapies that may impact on both articular and vascular manifestations of inflammatory rheumatic diseases

Conventional DMARDs

In RA, circulating markers of inflammatory activity correlate with the presence of vascular disease, suggesting that suppression of inflammation may provide therapeutic improvements. Data on association of CRP with cardiovascular risk suggest that even minimal residual inflammatory disease is likely to confer significant additional risk of atherosclerotic morbidity. Effective control of RA using DMARDs is associated with improvements in CRP [54], and also in lipid profiles [55]. Epidemiological data indicate that mortality from acute myocardial infarction in patients with RA has declined over time as the use of methotrexate has increased [56]. Furthermore, Choi and colleagues [57] have demonstrated that in a prospective cohort study of 1240 patients with RA, methotrexate provided a substantial survival advantage, with reduction in overall mortality by 60% and cardiovascular mortality by 70%. These data suggest that suppression of systemic inflammation by methotrexate provides cardiovascular benefits that outweigh the risks related to hyperhomocysteinaemia [58]. However, folate supplementation is recommended, particularly in patients treated with a combination of methotrexate and sulphasalazine [47, 58].

In SLE, disease duration and damage index scores have been strongly associated with vascular disease [18, 39]. Roman and colleagues [18] have reported that the use of cyclophosphamide is independently associated with reduced risk of carotid plaque on ultrasound in SLE (odds ratio 0.3), indicating that more intensive control of disease activity may prevent atherosclerosis. In addition to disease-modifying effects in RA and SLE, hydroxychloroquine has been attributed with a beneficial effect on lipid profiles [59, 60] and an anticoagulant effect [61], the latter being of particular relevance in the antiphospholipid
syndrome. It is intriguing that non-use of hydroxychloroquine has been associated with vascular disease in at least two studies in SLE [18, 62].

**TNF-α blockade**

TNF-α plays a central role in the regulation of the inflammatory cascade, and has been implicated as a mediator of endothelial dysfunction, vascular instability and disease progression in atherosclerosis [63]. These observations raised the possibility that anti-TNF-α therapy would improve not only articular manifestations but also the vascular dysfunction associated with inflammatory arthritis. In active vasculitis and RA, treatment with infliximab has been shown to improve flow-mediated (endothelium-dependent) vasodilatation [40, 41, 64], albeit transiently in the latter. TNF-α blockade may also improve the lipid profiles of patients with inflammatory rheumatic disease [65]. Long-term studies are required to determine whether such laboratory findings translate into tangible improvements in cardiovascular morbidity and mortality.

However, there have been significant concerns regarding the safety of anti-TNF-α therapy in patients with accelerated atherosclerosis and associated cardiac failure. In patients with moderate to severe chronic heart failure (CHF), the RECOVER and RENAISSANCE randomized placebo-controlled trials of etanercept reported lack of benefit [66], and the ATTACH study of infliximab reported worse outcome with treatment [67]. These reports led to recommendations that anti-TNF-α therapy should be avoided in patients with NYHA Class III and IV CHF. However, a recent observational study of 13171 patients with RA reported that although CHF was more common in patients with RA compared with osteoarthritis controls, anti-TNF-α therapy was not associated with higher rates of CHF in RA [68].

**Corticosteroids**

The potent effects of corticosteroids on systemic inflammation suggest that these agents may have a therapeutic role in vascular disease. Early animal studies provided some support for this concept, demonstrating that experimental atherosclerotic plaque formation was partially suppressed by corticosteroids [69, 70]. However, chronic corticosteroid use may promote accelerated atherosclerosis in patients with inflammatory rheumatic diseases, through adverse effects on traditional risk factors such as hypertension, dyslipidaemia and, in particular, insulin resistance [71].

Several studies have attempted to address the role of corticosteroids in the pathogenesis of vascular disease of RA. A study of 138 patients with RA did not demonstrate an association between current prednisolone use and carotid artery intima–media thickness [15]. However, del Rincon and colleagues [72] have recently reported that, in a sample of 647 patients with RA, lifetime corticosteroid exposure was associated with carotid plaque and arterial incompressibility in a dose-dependent manner, irrespective of traditional risk factors or RA disease activity. Similarly, a number of other studies have reported that high cumulative doses of corticosteroids are associated with accelerated vascular disease in patients with SLE [16, 27, 39, 50, 73]. This finding is not universal, and indeed some studies have shown no association or a negative association between long-term corticosteroid use and vascular disease in SLE [18, 26, 74].

Overall, it seems likely that long-term high-dose corticosteroids do contribute to adverse cardiovascular outcomes in inflammatory rheumatic diseases [75]. However, it may be that low doses of corticosteroids that optimize suppression of systemic inflammation may be beneficial, and this possibility requires further investigation. Currently, we would recommend minimizing the corticosteroid dose by use of other DMARDs; in particular, we believe it would be prudent to use maintenance doses of prednisolone <7.5 mg, unless higher doses are required to avoid vital organ damage.

**Aspirin and NSAIDs**

Both primary and secondary prevention studies in the general population have demonstrated that low-dose aspirin reduces the risk of cardiovascular events (mainly myocardial infarction) by approximately 25% [76]. However, aspirin is also associated with increased risk of gastrointestinal bleeding and haemorrhagic stroke and, in 2002, the US Preventative Task Force recommended that low-dose aspirin should generally be reserved for individuals with a 10-yr risk of coronary heart disease (CHD) ≥6% [77]. Furthermore, in RA the risk of death from gastrointestinal causes has been estimated as 5-fold higher than in non-RA controls [6]; this has been attributed to gastrointestinal bleeding, probably due to use of NSAIDs and/or corticosteroids (reviewed in [78]). Further investigation is required to clarify the threshold of coronary heart disease risk above which low-dose aspirin is beneficial in patients with RA and SLE. At present, we suggest that aspirin be prescribed in RA patients only in cases where the 10-yr CHD risk is >20%. However, in patients with SLE or other vasculitides, aspirin should be considered in patients with estimated 10-yr CHD risk of <20%, especially in the presence of antiphospholipid antibody or lupus anticoagulant activity.

The coprescription of aspirin and NSAIDs requires careful consideration. Published data indicate that, in patients taking aspirin, ibuprofen antagonizes the irreversible platelet inhibition induced by aspirin, whereas other drugs with lower COX-1 inhibitory effects, such as meloxicam, do not interfere with aspirin [79, 80]. These results indicate a theoretical risk that use of some NSAIDs may limit the cardioprotective effect of aspirin. Although the COX-2 selective NSAIDs do not interfere with the anti-platelet effect of aspirin, the concerns surrounding the coxibs generally preclude their use in the context of patients with high cardiovascular risk [49]. The risk of cardiovascular events related to non-selective NSAIDs remains controversial, particularly in view of a recent report suggesting current naproxen use was associated with a small increase in serious coronary heart disease compared with remote NSAID use (odds ratio 1.14) [81], and the (currently unpublished) findings of the ADAPT study. Generally, therefore, we advocate minimization of NSAID doses by judicious use of DMARDs. If both aspirin and NSAIDs are indicated, a non-selective agent which does not antagonize the anti-platelet effect of aspirin should be prescribed, and the use of a proton-pump inhibitor should be considered.

**Statins**

Therapy with 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors (statins) is associated with a reduction in cardiovascular events of approximately 25% in most groups studied to date [82–84]. Inhibition of HMG-CoA reductase reduces not only cholesterol but also farnesyl pyrophosphate and the geranylgeranyl pyrophosphate, which are required for the post-translational prenylation of a range of proteins and lipids [85]. Unsurprisingly, therefore, statins have effects on cellular metabolism far beyond the reduction of cholesterol synthesis. The first suggestion that statins may be immunomodulators emerged in 1995, with the report that pravastatin reduced the incidence of haemodynamically significant rejection episodes in cardiac transplant patients, and that this effect was independent of the reduction in cholesterol levels [86]. Subsequent investigation has demonstrated a panoply of statin-sensitive immunological pathways [87, 88].

In a murine model of demyelination, atorvastatin prevented or reversed chronic or relapsing paralysis [89]. This was...
associated with a shift from Th1-type towards Th2-type immune responses. McInnes and co-workers [90] subsequently associated with a shift from Th1-type towards Th2-type of >20% [93] (Table 1). NCEP guidelines, and considering the increased risk in patients of >20% [93] (Table 1).

These encouraging observations on the effect of statins in RA prompt questions regarding use of statins in other inflammatory rheumatic conditions. Reports of drug-induced lupus [91] and the potential hazard of masking statin-induced myositis in patients with inflammatory myopathies (reviewed in [92]) should prompt careful monitoring for these complications. However, they appear to pose a small risk compared with the potential benefits of 25% reduction in risk of cardiovascular events. The National Cholesterol Education Program (NCEP) guidelines have recently been modified to reflect clinical trials which confirm the safety and efficacy of intensive lipid-lowering therapy in older persons, women and patients with non-coronary atherosclerosis [93]. In fact, the AFCAPS/TexCAPS study suggested that a 10-yr risk of CHD >0.6% is the threshold above which statins have a net population benefit [84]. This would include the majority of patients with chronic inflammatory disease, in whom the prospect of mild disease-modifying activity further increases their appeal. Based on the current NCEP guidelines, and considering the increased risk in patients with chronic inflammatory disease, we propose a two-tier target for LDL cholesterol: <2.6 mmol/l for patients with a 10-yr CHD risk between 1 and 20% and <1.8 mmol/l for a 10-yr CHD risk of 20% [93] (Table 1).

**Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers**

These agents have proven efficacy in the treatment of congestive cardiac failure, hypertension and renal disease [94–99]. Studies in animal models have indicated that angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) retard the progress of atherosclerosis [100, 101]. The influence of these agents on atherosclerosis in humans is controversial, as attested by the recent PEACE trial [102]. However, the HOPE, SECURE and EUROPA trials have demonstrated that ACE inhibitors have efficacy in the primary and secondary prevention of coronary artery disease in high-risk patients [103]. In both the HOPE and EUROPA studies, the reduction in cardiovascular events was greater than expected for the observed reduction in blood pressure. Indeed, according to the new British Hypertension Society guidelines, most hypertensive patients with inflammatory disease would be automatically eligible for ACE inhibitor therapy as first choice [104].

In addition to blood pressure lowering, ACE inhibitors may modulate the development of atherosclerosis through other mechanisms. Recent studies have emphasized the important autocrine and paracrine proinflammatory properties of angiotensin II. Within atherosclerotic plaques, there is accumulation of ACE and high expression of the type 1 angiotensin (AT1) receptor [105]. Angiotensin II promotes vascular smooth muscle proliferation, lipid peroxidation and endothelial dysfunction, all processes known to contribute to the development of atherosclerosis. In addition, angiotensin II signalling through the AT1 receptor leads to activation of the transcription factor NF-κB with subsequent production of proinflammatory cytokines, chemokines, reactive oxygen species and adhesion molecules [106–108]. Many of these abnormalities are reversed by ACE inhibitors or ARBs. [109–111].

The renin-angiotensin system is disturbed in RA. Elevated ACE activity has been demonstrated in blood monocytes, nodules, synovial fluid and synovial tissue of patients with RA [112–115], and AT1 receptors are present in human synovial tissue [116]. We have recently reported that both the ACE inhibitor quinapril and the ARB candesartan significantly diminish the activity of murine collagen-induced arthritis when given as prophylaxis or therapy [117]. Suppression of disease by quinapril was associated with reduction in both the antigen-specific humoral response and the production of proinflammatory cytokines.

There have been several small open-label trials of ACE inhibitors in patients with RA, with variable results. In an open study, 15 patients with active RA were treated with captopril and followed for 48 weeks [118]. Two-thirds of the patients reported improved arthritis symptoms and changes were seen in clinical scores, plasma viscosity and CRP. The clinical benefits of captopril have been attributed to structural similarities with penicillamine due to its thiol residue. A follow-up open study of the non-thiol ACE inhibitor pentopril in a further 15 patients with active RA reported lack of efficacy [119]. Interestingly, even with this small sample size, a significant reduction in CRP was observed, suggesting some benefit on inflammatory disease. However, this study’s power was again limited by the low numbers of patients and a high drop-out rate. Therefore, we believe that adequately powered and controlled clinical trials are required to clarify whether these agents have efficacy for both articular and vascular disease in RA.

The literature addressing the clinical use of ACE inhibitors or ARBs in SLE is surprisingly sparse but studies in murine models of lupus have indicated that captopril reduces disease severity [120, 121] and several case reports or small studies indicate that ACE inhibitors are beneficial in the context of lupus nephritis [122, 123]. However, despite these apparently beneficial effects on SLE, several ACE inhibitors have occasionally been associated with the occurrence of drug-induced lupus [124].

**Table 1. Proposed categories of risk reduction in patients with chronic inflammatory rheumatic disease**

<table>
<thead>
<tr>
<th>Risk reduction</th>
<th>INTENSIVE</th>
<th>SUBSTANTIAL</th>
<th>ROUTINE</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-yr CHD event risk</td>
<td>&gt;20%</td>
<td>1–20%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Target blood pressure</td>
<td>&lt;130/80</td>
<td>&lt;140/85</td>
<td>&lt;140/85</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Yes</td>
<td>Consider if 10 yr CHD risk</td>
<td>No</td>
</tr>
<tr>
<td>LDLc</td>
<td>OR if ACL/LAC +ve</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Target LDLc</td>
<td>&lt;1.8</td>
<td>&lt;2.6</td>
<td>&lt;3.4</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>Measure</td>
<td>Measure</td>
<td>Measure</td>
</tr>
<tr>
<td>Body mass index</td>
<td>LDLc</td>
<td>LDLc</td>
<td>25</td>
</tr>
<tr>
<td>Smoking</td>
<td>STOP</td>
<td>STOP</td>
<td>STOP</td>
</tr>
<tr>
<td>Disease activity</td>
<td>Minimize</td>
<td>Minimize</td>
<td>Minimize</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Minimize</td>
<td>Minimize</td>
<td>Minimize</td>
</tr>
<tr>
<td>Monitoring interval</td>
<td>3 months</td>
<td>6 months</td>
<td>1 yr</td>
</tr>
<tr>
<td>Fasting lipids</td>
<td>Yes</td>
<td>Yes</td>
<td>Optional</td>
</tr>
<tr>
<td>Screen for DM and hypothyroidism</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

ACEI as first-line agent.

Lifestyle advice and use of statin.

Modify this threshold according to any increased risk of gastrointestinal haemorrhage.

LDLc, low-density lipoprotein cholesterol; DM, diabetes mellitus; ACEI, angiotensin-converting enzyme inhibitor; ACL, anticonditiopin IgM or IgG; LAC, lupus anticoagulant.
This suggests that the immunomodulatory effects of ACE inhibitors may be beneficial or harmful in lupus-like disease, depending on unknown genetic or pathogenic factors.

**Fish oil**

The Western diet contains excess (n-6) fatty acids and low levels of (n-3) fatty acids. (n-3) Polyunsaturated fatty acids such as eicosapentaenoic acid (EPA) and docosahexaenic acid (DHA) are found at high levels in oily fish such as mackerel, herring, kippers, sardines and salmon. The benefits of (n-3) polyunsaturated fatty acids have been demonstrated in several secondary prevention trials of patients with ischaemic heart disease. The DART study in 2003 Welsh men following acute myocardial infarction demonstrated that dietary intake of approximately 0.3 g/day (n-3) polyunsaturated fatty acids over 2 yr reduced total mortality by 29% and coronary mortality by 33% [125]. Similarly, the GISSI-Prevenzione trial in patients who had survived recent myocardial infarction reported a 30% reduction in cardiovascular death following treatment with 1 g/day (n-3) polyunsaturated fatty acids for 3.5 yr [126].

(n-3) Polyunsaturated fatty acids have well-recognized anti-inflammatory effects on macrophages, lymphocytes and endothelial cells *in vitro*, including suppression of inflammatory prostaglandin, chemokine and cytokine production (reviewed in [127]). It is unknown whether the improvements in cardiovascular outcome in these studies are primarily due to these anti-inflammatory properties, or to other effects, such as changes in lipid profiles, reduction in blood pressure or increased threshold for ventricular arrhythmias (reviewed in [128]).

The effects of fish oil have also been studied in patients with inflammatory rheumatic diseases. A meta-analysis of 10 randomized controlled trials involving 395 patients with RA demonstrated improvements in tender joint count and duration of morning stiffness, but no significant improvements in swollen joint count, ESR or global assessments [129]. Supplementation with (n-3) polyunsaturated fatty acids may be particularly beneficial in patients with low background intake of (n-6) fatty acids [130]. However, the overall effect of these supplements in RA is modest [131]. Fish oils may also influence disease activity in SLE [132, 133]. Thus, the benefits of fish oils have been clearly demonstrated for secondary prevention of cardiovascular disease in the general population. The role of (n-3) polyunsaturated fatty acids in vascular disease associated with rheumatic disease requires further analysis.

**Mediterranean diet**

The benefits of the Mediterranean diet have been demonstrated as secondary prevention and primary prevention for patients at high risk of coronary artery disease. This diet replaces animal fat with polyunsaturated vegetable oil rich in α-linolenic acid, an (n-3) fatty acid. Meat, butter and cream are reduced and legumes, bread, fruits and vegetables are increased. The Lyon Diet Heart Study recruited patients after first myocardial infarction into a randomized single-blind trial [134]. Compared with the usual post-infarct prudent diet, the Mediterranean diet led to a significant reduction in the combined endpoint of cardiac death and non-fatal myocardial infarction (adjusted risk ratio 0.27) over 27 months. Similarly, in a study of South Asian patients with documented coronary artery disease or at least one risk factor for coronary disease, an ‘Indo-Mediterranean diet’ for 2 yr was associated with significant reductions in the combined endpoint of myocardial infarction and sudden cardiac death (adjusted risk ratio 0.48) [135].

The cardiovascular benefits of the Mediterranean diet may be due to a number of factors. This diet influences several recognized cardiovascular risk factors, including hypertension, dyslipidaemia, hyperhomocysteinaemia and insulin resistance. Adherence to this diet is also associated with improvements in circulating markers of systemic inflammation, such as CRP and IL-6 [136, 137].

These data may be of particular relevance to patients with RA in view of the recent report that the Mediterranean diet also has some clinical efficacy in suppressing disease activity in patients with RA. Skoldstam and colleagues studied 51 patients with active RA on stable DMARDs in a 12-week randomized single-blind trial comparing the Mediterranean diet with usual diet [138]. This study demonstrated significant improvements in DAS28 scores, HAQ scores and CRP in patients randomized to the Mediterranean diet. Whether such intervention has specific effects on the accelerated atherosclerosis of RA requires further assessment.

**Implications for the management of inflammatory rheumatic disease**

Within the general population, assessment of specific cardiovascular risk factors has allowed estimation of cardiovascular risk expressed as the percentage risk of a CHD-related event over a 10-yr period [139]. This can be performed using an online Framingham coronary risk calculator [http://www.cdburton.freeserve.co.uk/framcalc.htm] or by downloading an Excel-based program (available at [http://www.bnf.org/bnf/extra/48/ openat/450024.htm]). However, the existing calculations will underestimate the actual risk in patients with RA, SLE and other inflammatory diseases. This problem is compounded by a tendency to undertreat comorbid conditions in patients with chronic disease, including RA [140]. Consequently, we argue that rheumatologists should take responsibility for assessing cardiovascular risk in these patients, for determining optimal targets for modifiable risk factors, and for initiating preventative therapy. Shared responsibility with primary care and/or with specialist rheumatology practitioners could operate in parallel with the arrangements for the modification of DMARDs; indeed, existing shared care booklets could be modified to incorporate the patient’s individual targets.

We propose an algorithm to simplify the implementation of these targets and to minimize the clinic time required for risk assessment (Fig. 1 and Table 1). This algorithm is based on current available data and advice from specialist panels [77, 93, 139]. Using this strategy, patients would be assigned to ROUTINE, SUBSTANTIAL or INTENSIVE categories of cardiovascular risk reduction. We suggest that patients with one or less risk factor(s) for cardiovascular disease need not have formal calculation of the 10-yr CHD risk, but that they are assigned to the ROUTINE risk reduction category. Traditional risk factors include age (>55 yr in men, >65 yr in women), smoking, hypertension (or antihypertensive medication), family history of premature CHD in first-degree relative (male <55 yr; female <65 yr), diabetes mellitus and hypercholesterolaemia (total cholesterol >5.2 mmol/l) and hypertriglyceridaemia. To this list, we propose the addition of RA and other chronic inflammatory diseases, including SLE in young patients <50 yr or of <10 yr disease duration. Further investigation is required to assess whether risk factors should be extended to include disease-related variables, such as systemic corticosteroid therapy, CRP >10 mg/ml, HAQ >2, or threshold disease activity scores; at present these have not been incorporated into the algorithm. ROUTINE risk reduction would involve screening for traditional cardiovascular risk factors annually and minimizing both disease activity and corticosteroid dose. Patients should be encouraged to stop smoking and to maintain a body mass index <25. Advice regarding diet and exercise should be provided and blood pressure maintained at ≤140/85.
FIG. 1. Proposed algorithm to determine risk reduction category in patients with chronic inflammatory rheumatic disease. CHD, coronary heart disease; history of myocardial infarction, angina, coronary angioplasty or bypass, clinically significant myocar-
dial ischaemia; LDLc, LDL cholesterol. Traditional CHD risk equivalents: clinical manifestation of non-coronary athero-
sclerosis (peripheral vascular disease, aortic aneurysm, transient ischaemic attacks or 50% carotid occlusion, diabetes mellitus). Proposed additional CHD risk equivalent: SLE (if age 50 yr or disease duration 10 yr). Traditional risk factors: age (male 55 yr; female 65 yr), smoking, hypertension (or antihypertensive medication), left ventricular hypertrophy, family history of premature CHD in first degree relative (male 55 yr; female 65 yr). Proposed additional risk factors: RA, SLE (if age 50 yr or disease duration 10 yr), other chronic inflammatory rheumatic disease.

The target for LDL cholesterol should be <3.4 mmol/l (or total cholesterol ≤5.2 mmol/l).

This proposed scheme implies that even a single traditional risk factor in a patient with chronic inflammatory disease should trigger formal risk calculation. The majority of patients will fall into this SUBSTANTIAL risk reduction category. This would involve calculation of the 10-yr CHD risk and monitoring blood pressure and fasting lipid profiles at 6-month intervals. LDL cholesterol targets should be more stringent [93]; this will necessitate treatment with a statin, in addition to dietary modification, in the majority (Table 1). Use of aspirin should be considered in patients with a 10-yr CHD risk of ≥6% [77], but elevation of risk of gastrointestinal haemorrhage in specific patient groups should be used to adjust this threshold; in patients with RA, for example, we suggest that aspirin be used only if the 10-yr CHD risk is >20%.

A history of CHD or of any CHD-risk equivalent places the patient in the INTENSIVE category without need for further risk assessment. Established CHD risk equivalents are transient ischaemic attacks, >50% carotid artery occlusion, diabetes mellitus, peripheral vascular disease or aortic aneurysm [93]. Bruce has proposed that SLE be considered a CHD-risk equivalent, since it confers an overall 10-yr CHD risk of ~13% on a population of predominantly young to middle-aged women [141]. By analogy with current recommendations for diabetes, we suggest that SLE patients aged over 50 yr or with a >10-yr history of disease should be treated as CHD-risk equivalent [93]. In this INTENSIVE risk reduction group, the most stringent LDL cholesterol and blood pressure targets should be set. The LDL cholesterol target of 1.8 mmol/l has been drawn from the NCEP recommendations for high-risk patient groups [93] and the blood pressure target of ≤130/80 from cardiovascular risk reduction data in diabetes [142]. Although cessation of smoking and optimal body mass index (<25) are objectives in all the risk reduction categories, attainment of these targets assumes greater importance as the risk level increases. In the INTENSIVE category, we propose that particular emphasis be placed on cessation of smoking and on attaining the body mass index target (<25). It may be appropriate to provide or refer patients for specialist help in these areas, which may include prescription of nicotine replacement therapy or bupropion and/or prescription of orlistat respectively [143, 144].

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References

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