Atherosclerosis in rheumatoid arthritis: is it all about inflammation?

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Abstract | Rheumatoid arthritis (RA) has long been associated with increased cardiovascular risk, but despite substantial improvements in disease management, mortality remains high. Atherosclerosis is more prevalent in RA than in the general population, and atherosclerotic lesions progress at a faster rate and might be more prone to rupture, causing clinical events. Cells and cytokines implicated in RA pathogenesis are also involved in the development and progression of atherosclerosis, which is generally recognized as an inflammatory condition. The two diseases also share genetic and environmental risk factors, which suggests that patients who develop RA might also be predisposed to developing cardiovascular disease. In RA, inflammation and atherosclerosis are closely linked. Inflammation mediates its effects on atherosclerosis both through modulation of traditional risk factors and by directly affecting the vessel wall. Treatments such as TNF inhibitors might have a beneficial effect on cardiovascular risk. However, whether this benefit is attributable to effective control of inflammation or whether targeting specific cytokines, implicated in atherosclerosis, provides additional risk reduction is unclear. Further knowledge of the predictors of cardiovascular risk, the effects of early control of inflammation and of drug-specific effects are likely to improve the recognition and management of cardiovascular risk in patients with RA.

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Introduction

Rheumatoid arthritis (RA) is associated with a significantly increased risk of cardiovascular mortality, accounted for mainly by increased atherosclerotic disease.[1,2] Although the prevalence of some traditional cardiovascular risk factors is increased in RA, adjustment for these factors does not fully account for the heightened risk, suggesting that RA itself is an independent risk factor for cardiovascular disease (CVD).[3] The prevalence of atherosclerosis is increased in RA, even in early disease,[4] and chronic inflammation is thought to promote atherosclerosis both by modulation of traditional risk factors and also possibly by direct biological effects on the artery. In this article, we discuss the potential mechanisms that might accelerate atherosclerosis in RA, with a particular focus on inflammation.

Atherosclerosis: an inflammatory state

At one time, atherosclerosis was thought to result from passive accumulation of lipids in the wall of the ageing blood vessel. Eventually, plaque would encroach on the lumen to such a degree that occlusion would occur, triggering clinical symptoms of ischaemia. However, atherosclerosis is now recognized as a chronic inflammatory condition with key roles for both the innate and adaptive immune systems in the initiation, progression and stability of lesions.[5] Furthermore, clinical events occur as a result of rupture of atherosclerotic plaque and consequential thrombosis, which, in turn, causes vessel occlusion. This rupture can often occur in a plaque that causes no substantial luminal stenosis prior to rupture.[6] Inflammation is an important trigger of plaque erosion and stability, and one focus of secondary prevention of coronary artery disease (CAD) in the general population is the development of anti-inflammatory agents for plaque stabilization.[7] Many aspects of the pathophysiology of atherosclerosis are mirrored in the inflamed RA synovium, including pronounced infiltration by macrophages and type 1 T helper (T_H1) cells, collagen degradation and neovascularization (Figure 1).

Cytokines such as TNF, IL-6 and matrix metalloproteinases are implicated in both processes.[8] To understand the influence of RA on atherosclerosis, it is important to understand the pathophysiology of the initiation, progression and rupture of atherosclerotic lesions.

Endothelial dysfunction

The earliest stage of atherosclerosis is when the innermost layer of the artery (the endothelium) becomes dysfunctional, often in response to factors such as hypertension or smoking. Rather than acting merely as an inert lining layer, the endothelium is responsible for regulating the vascular tone and has anticoagulant and anti-inflammatory functions. When the endothelium becomes dysfunctional, the expression of proinflammatory cytokine and cellular adhesion molecules is upregulated.[9]

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Key points

- The prevalence and rate of progression of atherosclerosis is increased in rheumatoid arthritis (RA), and atherosclerotic plaques in patients with RA might have a rupture-prone phenotype
- Atherosclerosis is a chronic inflammatory condition, and similarities exist in the cellular processes and cytokines involved in both atherosclerosis and rheumatoid synovitis
- Cardiovascular disease (CVD) and RA share genetic and environmental risk factors, including polymorphisms in genes within the HLA region, smoking and obesity
- The prevalence of some traditional CVD risk factors is increased in patients with RA, but traditional risk-prediction models perform poorly in this population
- Chronic inflammation is closely linked with atherosclerosis in RA; burden of inflammation is associated with clinical and subclinical CVD, and PET can reveal arterial inflammation in patients with active RA
- Although treatments for RA seem to have beneficial effects on cardiovascular event rates, mortality remains increased and further work is required to better estimate and treat cardiovascular risk in RA

The endothelium also becomes more permeable so that inflammatory cells (predominantly monocytes), attracted by cytokines, enter the vessel wall through a process facilitated by cellular adhesion molecules. Small lipid molecules can also enter the subendothelial layer (Figure 2).

In addition to traditional risk factors such as smoking, inflammation can lead to endothelial dysfunction.[10] *In vitro* and animal studies have shown that inflammatory cytokines such as TNF are associated with impaired endothelial-dependent vasodilatation.[11]

Atherosclerotic plaque development

On entering the subendothelial layer, LDL undergoes modification in the subendothelial layer, often becoming oxidized. Monocytes differentiate into macrophages, which take up modified LDL to form foam cells. Activated macrophages also secrete proinflammatory cytokines such as TNF and IL-6,[12] thus promoting further recruitment of inflammatory cells and amplifying the inflammatory process. Smooth muscle cell proliferation is also stimulated by cytokine signalling, causing intima-media thickening that progresses to plaque formation.

Other inflammatory cells, including T_H1 cells, infiltrate the nascent atherosclerotic plaque, enhancing uptake of oxidized LDL and foam-cell formation via secretion of IFN-γ and IL-1β. As the plaque grows it also becomes more complex. Neovascularization occurs, but the vessels are fragile and often bleed, causing intraplaque haemorrhage and exacerbating inflammation. Relative hypoxia and increased oxidative stress trigger foam-cell apoptosis; this apoptosis leads to deposition of lipids within the plaque and causes the formation of a necrotic core—a key step towards plaque instability (Figure 2).[13]

Plaque destabilization and rupture

As plaques become more complex, thinning of the fibrous cap occurs.[14] This thinning eventually causes rupture of the plaque, exposing its thrombogenic content to blood, resulting in acute thrombosis and a clinical event. Fibrous cap erosion is thought to be mediated by inflammatory cells, in particular macrophages and T_H1 cells, via secretion of matrix metalloproteinases.[15] Although atherosclerotic lesions develop over many years, the rate of progression is not uniform. Certain events, such as intraplaque haemorrhage, accelerate plaque growth and can hasten progression of atherosclerosis.[16]

Histological studies have demonstrated that 'unstable' and ruptured plaques contain high levels of inflammatory infiltrates and that plaque inflammation is strongly associated with clinical symptoms of stroke.[17] The histological evidence that inflammation has a key role in atherosclerosis is supported by findings in population studies. Levels of TNF and IL-6 are known to predict cardiovascular mortality in the general population, independently of traditional risk factors.[18,19] Additionally, studies using noninvasive imaging, including PET and MRI, have demonstrated high levels of inflammation and metabolic activity in symptomatic carotid plaques.[20,21]

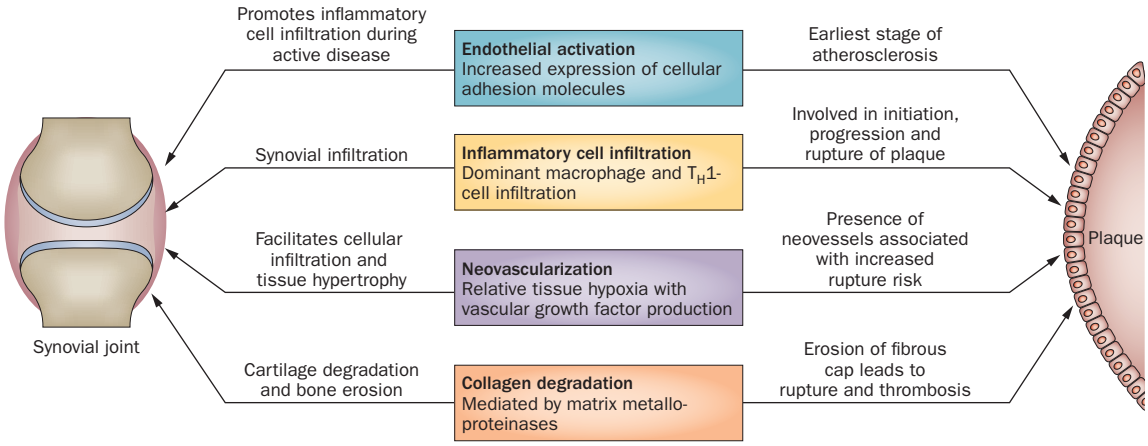

Figure 1 | Important pathological features common to both atherosclerotic plaque and the inflamed rheumatoid synovium. A number of similarities are found between the pathological processes seen in both rheumatoid synovitis and atherosclerosis. These processes might occur simultaneously in both the joint and vessel wall in RA, or mediators produced in the synovium might have distant secondary effects on the artery. Abbreviations: RA, rheumatoid arthritis; T_H1 cell, type 1 T helper cell.

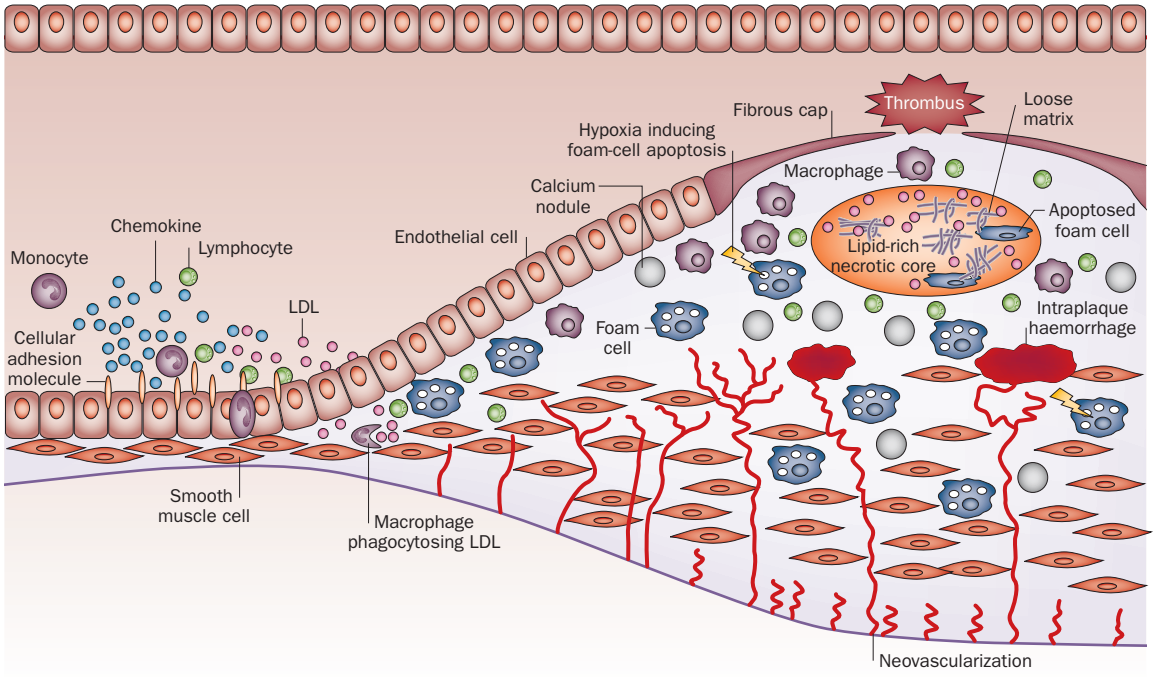

Figure 2 | Development of an atherosclerotic plaque. Endothelial activation leads to chemokine production and expression of molecular markers on the surface of endothelial cells, which cause migration and adhesion of immune cells, including monocytes, to the endothelium. Increased endothelial permeability enables cells and LDL to cross into the vessel wall. Monocytes differentiate into macrophages, which take up modified LDL to form foam cells. Proinflammatory cytokines promote cell recruitment, smooth muscle cell proliferation and neovascularization. Both foam-cell formation and smooth-muscle proliferation cause a localized thickening of the vessel wall, which becomes a plaque. The fragile neovessels can bleed, causing intraplaque haemorrhage that can accelerate growth. Hypoxia and oxidative stress lead to foam-cell apoptosis and the formation of a lipid-rich necrotic core. Calcium is deposited within the plaque and a fibrous cap forms over the top of the plaque, shielding the thrombogenic content of the plaque from the circulation. As the plaque enlarges, it not only causes narrowing of the lumen, but can also lead to outward vessel-wall remodelling, a feature of plaques at high risk of rupture. The fibrous cap thins and the plaque eventually ruptures, which can lead to acute thrombosis and clinical events. High levels of inflammatory cells are found in the plaque at the time of rupture.

Atherosclerosis in RA

Both endothelial dysfunction and atherosclerosis are more prevalent in the RA population than in the general population, and this increased prevalence is apparent early in the disease course.[4,22] The rate of progression of atherosclerosis is also accelerated in patients with RA compared with healthy individuals.[23,24] In addition to having a higher burden of plaque, patients with RA might also have a more unstable rupture-prone plaque phenotype.[25,26] Few histological studies have been done of atherosclerosis in RA, but two post-mortem studies of patients who died from myocardial infarction did demonstrate less-severe stenosis and more inflammation in coronary lesions in those with RA compared with patients without RA.[26,27] In a 2013 study, Karpouzas *et al.*[28] compared coronary CT findings in patients with and without RA who had no history of clinical CVD. They found not only an increased plaque burden, but also an increased prevalence in 'high risk' lesions in the RA cohort. High-risk lesions, defined as noncalcified plaque or mixed plaque (having both areas of calcification and of no calcification), were significantly associated with high disease activity after adjustment for traditional cardiovascular risk factors, sex and age (OR 4.5; 95% CI 1.4–14.4, $P = 0.01$). Although cross-sectional, this study does suggest an association between inflammatory burden and high-risk plaques. Semb *et al.*[25] also demonstrated, using ultrasonography, a more vulnerable plaque phenotype in patients with RA with active disease relative to those with low disease activity. This study was also cross-sectional, but the findings could suggest a link between disease activity and plaque vulnerability. The clinical trend of patients with RA having fewer 'warning' symptoms and higher risk of fatality also suggests the presence of a more rupture-prone plaque phenotype.[29,30]

Shared risk factors for RA and CVD

Not only are some pathological processes similar in RA and CVD, but the two diseases also share risk factors (Box 1). The presence of these risk factors could promote not just one but both conditions.

Genetic susceptibility factors

Both RA and CAD are accepted to be complex genetic conditions.[31,32] Genome-wide association studies (GWAS) have identified a number of novel genetic risk markers for both, but have not found substantial overlap in risk markers for the two diseases.[33,34] Although this approach

identifies loci with genome-wide significance, loci with smaller effect sizes might be missed. In complex conditions such as RA and CVD, the additive effects of multiple loci with small effects are likely to contribute to disease risk. New techniques enable genome-wide assessment of gene groups or pathways that might, together, confer susceptibility. For example, Torkamani *et al.*[35] examined common polygenic pathways in a number of complex diseases and found 55 disease-associated single nucleotide polymorphisms (SNPs) in common between RA and CAD. Karcezewski *et al.*[36] also examined the downstream effects of a range of polymorphisms associated with different diseases, and found that a number of SNPs linked to both RA and CAD were associated with enriched nuclear factor κB (NFκB) binding sites and dysregulation. Such novel approaches could clarify genetic susceptibility factors common to RA and CVD.

The importance of the *HLA-DRB1* gene in susceptibility to RA is well-recognized.[37] A 2012 paper by Paakkanen *et al.*[38] described an association of the DRB1*01 haplotype with acute myocardial infarction and with C-reactive protein (CRP) levels in the general population. They hypothesized that *HLA-DRB1*01* influenced the risk of myocardial infarction through increased systemic inflammation. Candidate-gene studies in RA and CVD have overlapped somewhat in the SNPs selected, such as those related to the MHC and interferon regulation.[39–43] Although investigations in this area are in the early stages, part of the increased risk of CVD in RA could be attributable to common genetic susceptibility factors.

Traditional cardiovascular risk factors

The link between smoking and both RA and CVD is well-established, and smoking is known to promote a pro-inflammatory environment.[44] Smoking has been shown to influence other risk factors for both diseases, including upregulating the expression of genes associated with the development of RA.[45] A 2014 prospective population study also demonstrated that both diabetes mellitus and obesity were risk factors for the development of inflammatory polyarthritis.[46] All three conditions (diabetes mellitus, obesity and RA) are known to be associated with chronic inflammation and increased levels of circulating adipokines, which might influence the initiation and course of both CVD and RA.

Novel risk factors

Periodontitis

Periodontitis, which occurs as a result of bacterial infection of the gingiva, has been linked with risk of RA and CVD. Periodontitis is more prevalent in patients with RA, in particular those with seropositive disease, than in healthy individuals, and circulating levels of *Porphyromonas gingivalis* have been associated with presence of anti-citrullinated peptide antibodies (ACPA) in persons with no history of RA.[47,48] Bahekar *et al.*[49] performed a meta-analysis of general-population studies examining the association between periodontitis and incident cardiovascular events. They noted an increased risk of prevalent and incident CVD in those with periodontitis that remained after adjustment for traditional risk factors, including smoking. In both RA and CVD, socioeconomic status might also be an important confounder in the relationship with peridontitis, but is more difficult to fully adjust for across studies. Nevertheless, plausible causal mechanisms exist that could account for the link with periodontitis in both diseases.

Box 1 | Shared risk factors for RA and CVD

Genetic risk factors
- *HLA-DRB1* polymorphisms
- Polymorphisms coding for NFκB signalling
- *MHC2TA* polymorphism coding for MHC expression
- *IFR5* promoter polymorphism coding for interferon production

Traditional cardiovascular risk factors
- Smoking
- Diabetes mellitus
- Obesity

Potential novel risk factors
- Periodontitis
- Rheumatoid factor and ACPA positivity

Abbreviations: ACPA, anti-citrullinated peptide antibody; CVD, cardiovascular disease; RA, rheumatoid arthritis.

RA-related autoantibodies

The presence of rheumatoid factor (RF) and ACPA in the asymptomatic population is a strong risk factor for subsequent development of RA, and these antibodies have also been associated with CVD. In a study within the Hertfordshire Cohort Study, Edwards *et al.*[50] found a significant association between RF positivity and prevalent ischaemic heart disease. The association persisted following adjustment for traditional risk factors and after removal from the analysis of patients known to have RA.

A subsequent study also demonstrated a similar association of CAD with ACPA, independent of traditional risk factors, smoking and CRP levels.[51] The authors hypothesized that the presence of ACPA might impair resolution of inflammation within the atherosclerotic plaque, enabling progression of lesions. The association of antibodies considered characteristic of RA with CVD again highlights the potential commonality in pathology between the two diseases.

Cardiovascular risk factors in RA

The prevalence of some traditional cardiovascular risk factors is increased in RA, but the relative contribution of such factors to the risk of CVD seems less in patients with RA than in the general population (summarized in Table 1). The prevalence and impact of cardiovascular risk factors in RA might be altered by inflammation. Gonzalez *et al.*[52] demonstrated that the association between traditional risk factors and cardiovascular events was weaker in patients with RA than in the general population. In accordance with this finding, traditional risk models underestimate the risk of cardiovascular events in the RA population.[53] After adjustment for traditional risk factors, such as those discussed in this section, the risk of CVD remains increased,[3] and

Table 1 | Traditional cardiovascular risk factors in RA

Risk factor	Prevalence in RA	Relationship with disease activity
Insulin resistance	Increased	Correlates with disease activity and improves with disease suppression
Dyslipidaemia	No hyperlipidaemia but increased prevalence of low levels of HDL cholesterol and adverse AI	Improvement in HDL cholesterol levels and AI following treatment of inflammation
Hypertension	Increased	No evidence of an association
Smoking	Increased	Might attenuate treatment response and thus perpetuate the effects of inflammation on cardiovascular risk
Metabolic syndrome	Increased, driven by increased waist circumference and low HDL cholesterol levels	Improvement in individual components but little evidence of the effects of treatment on metabolic syndrome as a whole

Abbreviations: AI, atherogenic index; RA, rheumatoid arthritis.

RA-specific factors probably make up a proportion of this excess risk.

Diabetes and insulin resistance

The prevalence of diabetes mellitus is increased in patients with RA relative to the general population (OR 1.74; 95% CI 1.22–2.50, $P = 0.03$).[54] Insulin resistance, a risk factor for the development of type 2 diabetes mellitus, is also more prevalent in RA and is associated with the presence of subclinical CVD.[55] Several studies have demonstrated that insulin resistance is associated with measures of disease activity, such as 28-joint disease activity score (DAS28), and also with seropositivity.[56] Insulin resistance has been shown to improve in parallel with disease activity;[57] however, the correlation seems most consistent in those with a high degree of insulin resistance at baseline, and the effects are attenuated by obesity.[58,59] The relationship between inflammation and insulin resistance is complex. Adipokines released from fat cells, such as adiponectin and resistin, regulate insulin sensitivity but can also have proinflammatory or anti-inflammatory effects on other tissues, including the synovium. Proinflammatory cytokines such as TNF and IL-6 can modulate adipokine production, thus influencing levels of insulin sensitivity. Some, but not all, studies have found altered circulating levels of adipokines in patients with RA, and associations of adipokine levels with disease activity and with anti-TNF treatment have been inconsistent.[60–62] Further research is required to elucidate the complex relationship between insulin resistance, adipokines and inflammation in RA.

Obesity and metabolic syndrome

Whereas some studies have found no significant increase in BMI in patients with RA, central obesity is more prevalent in this population relative to the general population in case–control studies.[63] Giles *et al.*[64] found that patients with RA had a higher proportion of abdominal visceral fat, which is associated with adverse outcomes of CVD, independently of BMI. Patients with a high level of disease activity are in a catabolic state whereby muscle is degraded more rapidly than fat. In this circumstance, patients often have normal or low BMI but body fat content that can be high relatively to lean mass. Indeed, studies have shown that low BMI can be associated with increased cardiovascular risk in RA, possibly owing to the association between high disease activity and catabolism.[65]

A 2013 meta-analysis by Zhang *et al.*[66] demonstrated that risk of metabolic syndrome is significantly increased in patients with RA compared to persons without RA. This increased risk is present in both early and established disease, and is driven by increased waist circumference, low HDL cholesterol level and insulin resistance.

Lipids

Although rates of hyperlipidaemia are not increased in RA, dyslipidaemia is more prevalent at the time of diagnosis compared with the general population.[54] Some studies have found that almost half of patients with RA have dyslipidaemia.[67] In active disease, levels of both LDL cholesterol and HDL cholesterol are reduced; however, the reduction in HDL cholesterol is greater, resulting in a more atherogenic total-cholesterol:HDL-cholesterol ratio.[68] One study, by Georgiadis *et al.*,[69] also demonstrated a strong inverse association between CRP and HDL cholesterol levels in a cohort of patients with early arthritis.

Some studies have also demonstrated that RA patients are more likely to have a 'proinflammatory' form of HDL, piHDL, which facilitates LDL oxidation and foam-cell formation.[70] This piHDL could accelerate growth of lesions and explain, in part, the higher rate of plaque progression in RA. Levels of piHDL seem to be related to disease activity.[71]

Whereas LDL cholesterol levels are a reliable marker of cardiovascular risk in the general population, they seem less reliable for patients with RA. One prospective study of patients with RA demonstrated a nonlinear association between LDL and subsequent cardiovascular events.[72] The group with the lowest LDL seemed to have an increased risk of cardiovascular events, although this finding did not reach statistical significance. A significant inverse (but nonlinear) association was noted between total cholesterol and cardiovascular events in the same study.[72] Few other studies have interrogated the predictive value of LDL in RA, but the need for further evaluation of the relationship between lipid profiles and cardiovascular events in the RA population is recognized.[73]

Anti-inflammatory therapies have also been associated with alterations in lipid profiles. A study of patients with untreated early RA participating in the TEAR trial measured changes in lipid profiles following treatment with methotrexate monotherapy, triple DMARD therapy or the combination of methotrexate and etanercept.[74] At baseline, no significant differences were found between the treatment groups in disease characteristics, lipid levels or CRP level. At 24 weeks, LDL and HDL cholesterol levels had increased and the total-cholesterol: HDL-cholesterol ratio had improved in all groups. Changes in lipid levels did not differ significantly between the

treatment groups, and improvements in lipid parameters were associated with an improvement in CRP level but were not associated with DAS28.[74]

Smoking

Smoking is more prevalent in patients with RA than in the general population[54] and has long been established as a risk factor for the development of RA. Smoking is associated with presence of both RF and ACPA, higher disease activity and more joint damage.[75] Evidence also exists that smokers are less likely to respond to anti-TNF treatment.[76] Therefore, in addition to its known adverse cardiovascular effects, smoking might further affect atherosclerosis by attenuating treatment response and thus increasing the burden of inflammation.

Hypertension

Although reports of hypertension among patients with RA are conflicting, a systematic review by Panoulas *et al.*[77] found an increased prevalence in this group compared with the general population. Despite this increased prevalence, the relative contribution of hypertension to risk of CVD seems lower in patients with RA compared with controls. To date, no significant relationship between hypertension and disease activity or suppression of inflammation has been demonstrated.[77]

Relative contribution to CVD risk in RA

Although some traditional risk factors clearly contribute to the increased risk of CVD in patients with RA, their prevalence and effect might be altered by inflammation. Gonzalez *et al.*[52] demonstrated that the association between traditional risk factors and cardiovascular events is weaker in patients with RA than in the general population. Smoking, for instance, has a weaker influence on cardiovascular risk in patients with RA compared with non-RA controls.[52] In accordance with this finding, traditional risk models underestimate the risk of cardiovascular events in the RA population.[53] After adjustment for traditional risk factors, the risk of CVD remains increased in patients with RA,[3] and RA-specific factors probably contribute to this increased risk.

RA-related factors

Genetic factors

Among patients with RA, the presence and copy number of certain alleles confer an increased risk of cardiovascular mortality. A number of studies have found that the presence of certain *HLA-DRB1* alleles (the shared epitope), including the aforementioned DRB1*01 haplotype that increases the risk of cardiovascular events in the general population,[38] are associated with increased cardiovascular mortality in patients with RA.[78,79] The risk associated with these polymorphisms is particularly high in patients who are seropositive or smokers, or both.[79] Of note, some of these alleles also are associated with more-severe joint disease and extra-articular disease,[80–82] which could suggest that the association with cardiovascular mortality is related to disease severity. However, a study by Mattey *et al.*[78] found no significant interactions of *HLA-DRB1* genotype with RA disease characteristics, including extra-articular disease and disease severity as measured by level of disability.

Box 2 | RA factors associated with increased CVD risk

- Disease duration
- Baseline and cumulative CRP levels
- Extra-articular disease
- Rheumatoid factor or ACPA positivity
- Disability (as measured by Health Assessment Questionnaire)

Abbreviations: ACPA, anti-citrullinated peptide antibody; CRP, C-reactive protein; CVD, cardiovascular disease; RA, rheumatoid arthritis.

Farragher *et al.*[83] examined the association of 19 SNPs in RA susceptibility alleles with cardiovascular mortality in a cohort of >2,000 patients with inflammatory arthritis. They found that a variant of *CCL21*, which encodes a C–C chemokine with functions including leukocyte trafficking, was associated with cardiovascular mortality. This association was independent of shared epitope, smoking and ACPA status. Other studies examining the cardiovascular risk conferred by non-HLA alleles, such as *TNF* and other cytokine-encoding genes, have had mixed results and, to date, the strongest genetic risk factors for cardiovascular mortality in RA are HLA-associated genes.[84]

Disease phenotype

RA is a heterogeneous disease with a range of outcomes for joint disease; the same variability is likely to apply to cardiovascular outcomes. A number of studies have found that risk of cardiovascular mortality is particularly increased in seropositive patients,[85,86] those with extra-articular manifestations[87] (such as nodules) and those with higher levels of disability[86] (Box 2). The increased in those with higher levels of disability could be attributed, in part, to their decreased physical activity. However, cumulative inflammatory burden, increased swollen-joint counts and CRP levels are also associated with increased risk of cardiovascular mortality, suggesting that inflammation has an important role.[88–90] Disease duration is also a strong predictor of cardiovascular events.[30] The severe and long-standing inflammation that causes damage and disability in the joints probably also stimulates the initiation and progression of atherosclerosis.

Vascular effects of RA inflammation

Cells and circulating factors implicated in atherosclerosis and thrombosis are known to be increased in RA and, although the primary stimulus for their production in RA might be in the joint, their downstream effects probably influence plaque progression and destabilization. A small pilot study that used FDG-PET to compare vascular inflammation in patients with RA, psoriasis and healthy individuals found that patients with RA had higher levels of vascular inflammation.[91] A larger study by Mäki-Petäjä *et al.*[92] used FDG-PET to demonstrate that aortic inflammation was increased in patients with active RA compared with patients with stable CVD and

no RA, and that this inflammation improved after anti-inflammatory therapy. These studies have provided, for the first time, *in vivo* visualization of vascular inflammation in patients with RA. In the general population, aortic inflammation evaluated using PET has been associated not only with traditional cardiovascular risk factors, such as obesity, but also with subsequent clinical cardiovascular events.[93,94]

Treating cardiovascular risk in RA

Cardiovascular risk estimation

As previously discussed, traditional risk factors account for only a proportion of total cardiovascular risk in RA and, thus, standard risk-prediction models underestimate cardiovascular risk.[53] Furthermore, although the importance of treating modifiable risk factors in patients with RA is well-recognized, some evidence suggest that traditional risk factors are underdiagnosed in patients with RA.[67,95] EULAR-issued recommendations included annual screening for traditional risk factors in RA patients.[96] To address the excess cardiovascular risk not accounted for by these factors, they also recommended that a multiplication factor of 1.5 should be applied to the risk model score if a patient meets two of the following three criteria: seropositivity, extra-articular features and disease duration >10 years.[96] Although this adjustment goes some way to addressing the increased risk, whether it accurately addresses risk prediction in RA populations remains unknown. For example, since risk is present even in early RA, this method could underestimate risk in those with shorter disease duration. Guidelines for the prevention of CVD published in 2014 by the Joint British Societies recognize the increased risk associated with RA and recommend use of the QRISK2 risk-prediction model.[97] This model, developed in a UK population, includes RA as a risk factor and incorporates a diagnosis of RA into the risk-prediction model. Currently, no RA-specific risk-prediction models incorporate both traditional risk factors and disease-related factors such as disease severity. A TransAtlantic Cardiovascular risk Calculator for RA (ATACC-RA) consortium has been formed with the aim of addressing this unmet need, and studies by this group are ongoing.[98]

Managing traditional risk factors

Evidence for the efficacy of treating traditional risk factors in patients with RA is lacking. Myasoedova *et al.*[99] compared total cholesterol and LDL cholesterol levels in patients with RA and non-RA controls before and after initiation of statin therapy. After treatment for >90 days, decreases in lipid indices were less pronounced in patients with RA, who were also less likely than non-RA controls to achieve target levels of LDL cholesterol. Although no prospective trials have evaluated statin therapy for patients with RA, *post hoc* analysis of two statin trials demonstrated equivalent reductions in lipid parameters in patients with RA and those without RA.[100,101] Whether these effects would translate to reduced cardiovascular risk remains unknown. Statins have a theoretical additional benefit in RA as they can have anti-inflammatory properties. In the JUPITER trial, therapy with rosuvastatin reduced cardiovascular events in patients with normal lipid levels and high CRP levels.[102] Additionally, imaging techniques have shown reduced plaque inflammation following statin therapy.[103] Despite the lack of evidence specifically in RA, a reduction in cardiovascular mortality can probably be achieved through better recognition and treatment of traditional cardiovascular risk factors.

Effects of treating inflammation

If inflammation is an important factor in cardiovascular mortality, then effective control of inflammation would be expected to reduce this risk. In addition, drugs targeting pathways involved in atherosclerosis, such as anti-TNF agents, could have beneficial effects on cardiovascular risk beyond those derived from controlling inflammation. Disappointingly, studies examining cardiovascular mortality have shown that although rates are falling in patients with RA, this decrease is no greater than in the general population, and the mortality gap remains wide.[104] The effects of the recent 'step-change' in RA management, involving treating to target and the more widespread and earlier use of biologic agents, might not yet be fully appreciated in such studies. Alternatively, some patients might have persistent low-grade inflammation that continues to drive atherosclerosis. Even in patients with RA deemed to have a low level of disease activity, CRP levels can be higher than those associated with increased cardiovascular risk in the general population, and it could be that a higher degree of disease suppression is required to reduce cardiovascular risk.[105,106]

Examination of the effects of specific drugs on cardiovascular risk has also given varied results. The most convincing evidence supports an association between lower risk and use of methotrexate. A 2011 meta-analysis found that methotrexate use was associated with a 21% lower rate of cardiovascular events compared with no methotrexate use (including use of other DMARDs or no DMARDs).[107] A systematic review by Westlake *et al.*[108] also found a similar association with methotrexate but not with other synthetic DMARDs.

Use of corticosteroids has been suggested to increase cardiovascular risk. Avina-Zubieta *et al.*[109] demonstrated that current and cumulative steroid use was associated with increased cardiovascular mortality in a large administrative database study; the association persisted even after adjustment for traditional risk factors and surrogate markers of disease severity. Indication could be a confounder in this study, as patients with more-severe disease are likely to receive corticosteroids. However, in a sensitivity analysis that added a hypothetical strong confounder, the association between glucocorticoid use and increased cardiovascular risk remained statistically significant.[109] Other studies have also found associations between corticosteroid use and cardiovascular events. Findings in a prospective cohort study by del Rincon *et al.*[110] support the association of corticosteroid use with cardiovascular mortality. However, van Sijl *et al.*[111] found that the association between cardiovascular events and

steroids use was no longer significant after adjustment for disease activity and severity markers. Davis *et al.*[112] also found an association only in those who were RF-positive. This previous finding could also point towards confounding, as seropositivity is associated with more-severe disease and higher cardiovascular risk.[86] Potentially, steroids could have a beneficial anti-inflammatory effect on vascular inflammation at low doses, which at high doses might be counter-balanced by adverse metabolic effects. However, the balance between risks and harms of steroids in RA requires further assessment. Current recommendations from the Joint British Societies for reducing cardiovascular risk in patients with RA suggest using the lowest dose of steroids required to control joint inflammation for the shortest time possible.[97]

Effects of biologic therapy

That anti-TNF therapy would have beneficial effects on cardiovascular risk in RA not only through suppression of inflammation, but also by blocking the deleterious effects of TNF on atherosclerosis, is a reasonable hypothesis. However, whereas the impact of TNF therapy on joint disease is clear, its effects on cardiovascular risk are less well-established. A meta-analysis by Barnabe *et al.*[113] examined the effects of anti-TNF agents on cardiovascular risk in randomized controls trials (RCTs; $n = 3$) and cohort studies ($n = 13$) separately. No significant reduction in risk was found in the RCT meta-analysis, although this lack of effect could be attributable to the short follow-up time and low absolute numbers of events in the RCTs. There was a significant relative risk reduction of 12% seen on meta-analysis of the cohort studies (RR 0.88; 95% CI 0.68–0.96). However, the cohort studies were heterogeneous and only two were deemed high-quality.[114]

One reason for the lack of clear evidence regarding the effects of anti-TNF drugs on cardiovascular risk could be that, when they were newly licensed, these drugs were offered to a cohort of patients who were likely to have accrued damage and have a high cumulative burden of inflammation. By contrast, biologics are now increasingly used earlier in the disease course and the cohort of patients now starting therapy with these drugs might have less exposure to uncontrolled inflammation. Hyrich *et al.*[115] demonstrated a gradual improvement in indices of disease severity and lower disease duration at the time of initiation of anti-TNF therapy in the British Society for Rheumatology Biologics Register (BSRBR). Two other studies, published 4 years apart, have also examined the effect of anti-TNF therapy in this same register. The BSRBR included patients starting anti-TNF therapy and a control cohort of patients using synthetic DMARDs. In the first analysis, published in 2010, Lunt *et al.*[116] found no differences in cardiovascular mortality rates between DMARD-treated and anti-TNF-treated cohorts, although the point estimate was similar to the one found in other studies (HR 0.73, 95% CI 0.44–1.23). In 2014, Low *et al.*[117] published (as an abstract) a further analysis of the same cohort but with a longer follow-up period and a larger sample size, and also with data linkage to a national registry of acute myocardial infarctions. They found a statistically significant 40% reduction in cardiovascular events (adjusted HR 0.61, 95% CI 0.41–0.89). This finding suggests that, with longer follow-up in a cohort of patients who have perhaps received earlier treatment with biologic therapy, a substantial reduction in cardiovascular risk might become more apparent.

Some studies have also shown short-term improvement in subclinical markers of cardiovascular risk with anti-TNF therapy, although others have not. In the previously described study by Mäki-Petäjä *et al.*,[92] arterial inflammation was significantly reduced after anti-TNF therapy. However, post-treatment levels of inflammation were still higher in patients with RA than in the control group, above levels considered to be associated with increased cardiovascular risk.[94] This study provides further evidence that low-grade vascular inflammation can persist even after biological therapy for RA.

Although work from large observational studies has suggested that anti-TNF therapy might have a beneficial effect on cardiovascular risk compared with synthetic DMARDs, inherent differences between the patients who receive the treatments could lead to bias, such as confounding by indication. Currently, insufficient evidence exists to suggest a drug-specific benefit of anti-TNF agents beyond effective treatment of inflammation, and further examination is warranted.

Compared with anti-TNF agents, less evidence exists of cardiovascular risk reduction with other biologic agents, probably owing to smaller cohort sizes and shorter follow-up time. Clinical trial data suggests that rituximab does not increase cardiovascular risk.[118] A study from the German biologics registry found significantly lower mortality rates in patients receiving rituximab compared with those treated with synthetic DMARDs, although cardiovascular mortality was not specifically assessed.[119]

Conclusions

The increased risk of cardiovascular mortality, and its close relationship with inflammation, in RA is clear. Despite great advances in improving joint-related outcomes, the heightened cardiovascular risk in RA remains unresolved. Current evidence and recommendations suggest that screening for, and intensive treatment of, traditional risk factors, alongside effective control of inflammation, is likely to improve cardiovascular risk in RA patients. Judicious use of corticosteroids is also advised.

Further research is needed to understand RA-specific mechanisms of atherogenesis. Advanced genetic and non-invasive imaging methods provide promising tools with which to investigate these mechanisms. Refinement of risk stratification and better use of existing drugs to treat cardiovascular risk factors might also improve outcomes, and work in these areas is ongoing. However, studies addressing questions regarding progression of atherosclerosis in states of low disease activity and drug-specific effects are required. In the future, the aim should be to identify high-risk patients early in the disease course and institute treatment(s) targeted at both improving joint disease and minimizing cardiovascular risk.

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Author contributions

Both authors contributed to researching data for the article, discussing the content, writing the article and review and/or editing of the manuscript before submission.