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The Epidemiological and Pathogenic Association of Rheumatoid Arthritis With Atherosclerotic Cardiovascular Disease

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ABSTRACT

Rheumatoid arthritis (RA) is associated with an approximately twofold increased risk of atherosclerotic cardiovascular disease (CVD) including myocardial infarction and stroke. The increased risk of CVD in RA is due to an interplay between traditional risk factors such as hyperlipidemia, hypertension, and smoking and disease-related variables such as the presence of rheumatoid factor and anticyclic citrullinated peptide antibodies, high erythrocyte sedimentation rate, and joint swelling. Systemic inflammation and immune mechanisms form a pathogenic link between synovitis and atherosclerosis in RA. Indeed, high levels of C-reactive protein, an inflammatory marker, predict cardiovascular mortality in RA. Furthermore, the risk of CVD is greatly diminished among patients who respond to disease modifying antirheumatic drugs and biological therapies such as tumor necrosis factor (TNF) alpha antagonists. Through adverse effects on lipid profile and blood glucose level, long-term use of high-dose glucocorticoids in RA also increases cardiovascular risk. However, through control of active disease, glucocorticoids may also indirectly attenuate cardiovascular risk. Through their lipid-lowering and immunomodulatory effects, statins may have a dual benefit in the treatment of patients with RA. However, data on cardiovascular risk reduction in RA through management of traditional risk factors remain scant. Current research efforts are directed toward elucidating the risk factors for CVD in RA and developing strategies to minimize this risk.

Keywords: rheumatoid arthritis, atherosclerosis, cardiovascular disease

INTRODUCTION

Rheumatoid arthritis (RA), an inflammatory rheumatic disease, is associated with increased risk of atherosclerotic cardiovascular disease (CVD) including myocardial infarction (MI) and stroke. The association of RA with CVD was first described over four decades ago. Increasingly, the role of inflammatory and immune mechanisms in the pathogenesis of atherosclerosis and CVD, even among the general population, is becoming apparent. Hence, the association of RA with CVD has two broad implications. First, as a disease model of accelerated atherosclerosis, RA has the potential to reveal important insights into the pathogenic mechanisms, risk factors, and biomarkers of CVD in general. Second, with advances in the treatment of musculoskeletal manifestations of RA through the availability of targeted immunotherapies, complications such as CVD assume renewed importance as major potential causes of morbidity and mortality among patients with RA.

In this article, we will summarize the evidence for the association of RA with CVD. We will review the risk factors for CVD in RA and present an overview of putative pathogenic mechanisms. We will discuss the impact of better control of RA disease activity on cardiovascular risk and outline current recommendations for screening and primary prevention of CVD in RA. Throughout this review, we will highlight areas that merit further investigation and research. Our article will conclude by summarizing key points of practical significance.

RHEUMATOID ARTHRITIS (RA) AND CARDIOVASCULAR DISEASE (CVD): THE ASSOCIATION, ITS MAGNITUDE, AND OUTCOME

With an estimated prevalence of 1%, RA is the most common inflammatory rheumatic disease. Over the past two decades, early and aggressive treatment with conventional disease-modifying antirheumatic drugs (DMARDs) and the availability of novel targeted biological therapies has changed the course and prognosis of RA dramatically, from a disease frequently resulting in joint deformity and disability to a disease wherein remission is an achievable target in a significant proportion of patients.

However, RA still confers excess mortality with a standardized mortality ratio (SMR) of 1.5–2.0. The majority of this excess mortality is attributable to CVD, which accounts for an estimated 40–50% of deaths in RA. Most studies comparing cardiovascular mortality in RA patients with the general population have included cardiac, cerebrovascular, and...
peripheral vascular disease-related deaths as a single composite outcome, while some studies have evaluated the incidence and mortality related to MI and stroke as separate outcomes. In a meta-analysis by Avina-Zubieta et al, the SMR for all cardiovascular deaths was 1.5 (95% confidence interval [CI]: 1.39–1.61), while for ischemic heart disease and stroke, SMRs were 1.59 (95% CI: 1.46–1.73) and 1.52 (95% CI: 1.40–1.67), respectively.11 When the analyses were confined to studies using inception cohorts of patients followed from diagnosis, the SMR for all cardiovascular deaths was lower at 1.19, possibly due to the more even spread of disease severities among patients in such cohorts.12 Similarly, in another meta-analysis, Meune et al reported a SMR for cardiovascular deaths of 1.6 (95% CI: 1.5–1.8) that was consistent over several time periods spanning 50 years. In a population-based cohort study, Sodergren et al found that patients with RA are almost three times more likely to have MI than the general population with a standardized incidence ratio (SIR) for MI of 2.9 (p<0.05).13 Two studies have shown that RA rivals diabetes as an independent risk factor for CVD, each associated with approximately twofold increased risk of cardiovascular events.14,15

CVD is not only more prevalent in RA, it is also accelerated, meaning that the rate ratio of cardiovascular events is increased particularly in younger patients. Solomon et al found that patients with RA aged 18–49 years were over three times more likely to experience a cardiovascular event than age and sex-matched non-RA patients (rate ratio 3.3, 95% CI: 2.4–4.5), while the incidence rate ratio of cardiovascular event for those aged ≥75 years was 1.6 (95% CI: 1.5–1.7).17 However, as the peak age of onset of RA is in the sixth decade, the majority of cardiovascular events in RA are observed among older patients.16,17

Compared with age and sex-matched controls, patients with RA are not only more likely to have a first cardiovascular event (MI or stroke), they are also more likely to die as a result of their first cardiovascular event or to have recurrent events if they survive their first event.3,19 Indeed, the 30-day mortality rate following a cardiovascular event in patients with RA is twice that of non-RA controls. Furthermore, patients with RA are at an increased risk of silent MI (odds ratio [OR] 5.86, 95% CI: 1.29–26.64) compared with controls and may, therefore, have unrecognized CVD.20

**PATHOGENIC MECHANISMS OF ACCELERATED CARDIOVASCULAR DISEASE (CVD) IN RHEUMATOID ARTHRITIS (RA)**

In a histological examination of coronary artery tissue obtained from 41 autopsied RA patients compared with age- and sex-matched controls who had a similar history of CVD, the anatomical extent of coronary artery stenosis did not differ between cases and controls.21 However, a larger percentage of RA patients had unstable plaque in the left anterior descending coronary artery compared with non-RA controls suggesting that in RA, coronary artery plaques may be more inflamed and vulnerable.

With regards to pathogenic mechanisms for accelerated atherosclerosis in RA, there are two broad lines of thought that overlap significantly. The first is a hypothesis based on the concept of shared risk factors and the other is the so-called inflammatory hypothesis.22,23 In the former hypothesis, it is proposed that many of the risk factors that predispose to RA also predispose to atherosclerosis such that in patients with RA the two processes occur in parallel. For example, smoking is a risk factor for the development of both RA and CVD.24,25 In addition, smoking is associated with more severe and erosive RA.26 Smokers are also more likely to have rheumatoid factor (RF) and anticyclic citrullinated peptide (anti-CCP) antibodies than nonsmokers; these antibodies are themselves associated with more severe disease.24,27,28 Dyslipidemia may also be present many years before the onset of RA and may be a key element of the pathogenic process that leads to both RA and CVD.29,30 Both RA and CVD may also share common susceptibility genes. The HLA-DRβ1 is a susceptibility gene for RA and is associated with a more severe disease.31 Certain HLA-DRβ1 genotypes are also associated with preclinical CVD in RA, manifested by endothelial dysfunction.32

The inflammatory theory links atherosclerosis to the burden of inflammation accrued over the course of RA. It is proposed that inflammation from the synovium may alter arterial biology and risk factors so as to promote atherosclerosis.33 Indeed many of the immunopathogenic processes seen in atherosclerosis are also observed in RA including macrophage, T- and B-cell activation, and increased expression of adhesion molecules including vascular cell adhesion molecule 1 (VCAM-1), intercellular adhesion molecule 1 (ICAM-1), endothelial adhesion molecule E-selectin, and P-selectin.34 The inflammatory cytokines TNFα and IL-6 are not only important in the pathogenesis of inflammatory arthritis, they also lead to elevation in total cholesterol (TC) and triglyceride (TG) levels and reduced high-density lipoprotein cholesterol (HDL-C) levels, thus playing an important role in atherosclerosis.35 Granzyme B, a macrophage product involved in extracellular matrix remodeling, is found in both the RA synovium and in vulnerable regions of atherosclerotic plaques, again pointing to common pathogenic processes involved in synovitis and joint damage, and atherosclerotic plaque instability and rupture.36

**THE ROLE OF TRADITIONAL RISK FACTORS IN RHEUMATOID ARTHRITIS (RA)-RELATED CARDIOVASCULAR DISEASE (CVD)**

Traditional cardiovascular risk factors do not fully explain the high incidence of CVD in RA.37 After adjustment for age, sex, smoking, diabetes mellitus, hypercholesterolemia, systolic blood pressure, and body mass index (BMI), the incidence rate ratio of cardiovascular events in an RA cohort compared with a non-RA cohort was 3.17 (95% CI: 1.33–6.36).37 In the Nurses’ Health Study, after adjustment for traditional risk factors, women with RA had a twofold increase in MI.38 Other studies have reported similar
findings. However, although traditional risk factors only partly account for the increased cardiovascular risk in RA, due to their modifiable nature, they play an important role.

Using the Framingham cardiovascular risk prediction model, patients with RA have been shown to have a higher overall 10-year cardiovascular risk than age- and sex-matched controls along with a higher prevalence of smoking, physical inactivity, and increased BMI. Similarly, in a population-based cohort study, over half of the patients aged over 50 years had accrued >10% absolute 10-year risk of CVD within a decade of the onset of RA.46 Hypertension is highly prevalent in RA, affecting up to 70% of patients.47 Systemic inflammation, inactivity, obesity, and medications such as anti-inflammatories and corticosteroids contribute to the high rates of hypertension observed in RA and make its treatment more challenging. However, other studies have reported contrasting findings, with Solomon et al showing a similar pattern of cardiovascular risk factors in women with RA compared to women without RA who participated in the Nurses’ Health Study.48 Notably, in the same study, women with RA had higher levels of several inflammatory biomarkers linked to CVD including C-reactive protein (CRP), soluble ICAM-1, sICAM-1, soluble tumor necrosis factor I and II (sTNFRI and sTNFRII), and osteoprotegerin.

The metabolic syndrome (MetS) comprises a constellation of features including abdominal obesity, dyslipidemia, hypertension, and insulin resistance.49 Depending on the definition used, the prevalence of MetS in RA varies from 12% to 45%.45,46 Physical inactivity and corticosteroid use contribute to the increased prevalence of MetS in RA. The MetS is a risk factor for subclinical atherosclerosis in RA patients.47 While in one study methotrexate therapy was associated with reduction in prevalence of MetS in RA patients aged over 60 years, this association was not supported by an analysis of a subgroup of patients in the Dutch cardiovascular research and rheumatoid arthritis (CARRE) study.45,46 While increasing BMI is independently associated with cardiovascular risk in RA,48 a low BMI, possibly indicating more severe active disease, is similarly associated with cardiovascular risk in RA.49

**LIPIDS AND CARDIOVASCULAR RISK IN RHEUMATOID ARTHRITIS (RA)**

There is evidence of the production of antibodies, an acute phase response, and dyslipidemia predating the onset and diagnosis of RA by up to 10 years.49-49 This pre-RA pattern is characterized by increased TC, elevated TG, depressed HDL-C, and raised CRP.50 However, these findings have not been consistent across all studies, with some investigators reporting no difference between cardiovascular risk factors of participants who do and do not subsequently develop inflammatory arthritis.51

Dyslipidemia in RA is related to disease activity such that more active disease is associated with a lower TC level and even more depressed level of HDL-C resulting in a higher and, hence, more atherogenic TC:HDL-C ratio.51,52 This effect on lipid profile is thought to be driven by inflammatory cytokines such as TNFα.51 Indeed, treatment of inflammatory joint disease leads to improvement in the TC:HDL-C ratio53,54 and an associated reduction in inflammatory markers CRP and erythrocyte sedimentation rate (ESR). Some studies have shown an improvement in dyslipidemia with TNFα blockade in RA and others have shown a more atherogenic lipid profile following prolonged treatment with TNF blockers.55,56 However, these findings must be interpreted with caution as the overall clinical impact of these changes in lipid profile on the incidence of CVD in RA is at present unclear.50,57

Oxidized LDL (oxLDL) and antibodies to oxidized LDL (anti-oxLDL) are both significant risk factors for CVD in RA, wherein oxLDL levels increase with active disease.58 The oxLDL plays a key role in atherogenesis and may promote inflammation by delaying engulfment of apoptotic cells by macrophages.59 Furthermore, macrophages containing oxLDL have been found in the synovium of patients with RA.59 These cells have the morphological characteristics of foam cells contained in fatty streaks, further highlighting the pathogenic similarities of RA and atherosclerosis.

Plasma HDL-C is involved in reverse cholesterol transport and its level is inversely associated with cardiovascular risk.50 However, treatments that raise HDL-C level may not necessarily confer cardioprotection as some types of HDL-C possess proinflammatory properties and may in fact promote atherogenesis.60 Furthermore, in inflammatory states, HDL-C function is impaired independently of HDL-C levels, thus leading to impaired reverse cholesterol transport.61 Compared with controls, patients with RA have increased levels of proinflammatory HDL-C (piHDL) and therefore higher levels of oxLDL.62 Patients with RA also have reduced paraoxonase enzyme activity resulting in decreased antioxidant and anti-atherosclerotic effects of HDL-C.63 Treatment with TNF inhibitors has been shown to increase paraoxonase activity and thus enhance HDL-C antioxidative capacity among patients with RA.64

Elevated CRP and anti-oxLDL have been shown to be associated with subclinical CVD in RA as determined by ultrasound measurement of carotid intima-media thickness (cIMT).58,66 The HDL-C levels are negatively correlated with CRP levels.67,68 These associations further support the pathogenic link between inflammation, dyslipidemia, and atherosclerosis. Indeed, just as treatment of inflammatory joint disease improves the lipid profile in patients with RA, lipid-lowering therapy reduces inflammation.65 A randomized controlled trial of atorvastatin versus placebo in patients with RA, who also received usual DMARD treatment, showed lower disease activity (measured using the Disease Activity Index 28; DAS28) and lower inflammatory markers (CRP, ESR, and IL-6) along with lower TC, low-density lipoprotein cholesterol (LDL-C) and TG in the atorvastatin arm.69 Furthermore, among patients with active RA, atorvastatin treatment over 12 weeks has been shown to reduce arterial stiffness, a marker of subclinical CVD.70
INFLAMMATION: THE PIVOTAL LINK IN THE ASSOCIATION of RHEUMATOID ARTHRITIS (RA) and CARDIOVASCULAR DISEASE (CVD)

Chronic systemic inflammation is thought to account for a large proportion of the unexplained risk of CVD in RA. After adjustment for demographic variables and traditional risk factors, higher ESR, joint swelling, rheumatoid nodules, vasculitis, and RA lung disease were all independently associated with an increased risk of cardiovascular death among RA patients. In a cohort study of RA patients enrolled in the Consortium of Rheumatology Researchers of North America (CORRONA) registry, the ability to predict cardiovascular events (including MI, stroke, and transient ischemic attack) as determined by the area under the receiver operating characteristic curve (c-statistic) improved from 0.57 for models with only traditional risk factors to 0.71 when age, gender, and markers of RA severity were added.

As discussed earlier, inflammatory infiltrates are abundant in atherosclerotic coronary lesions of patients with RA. Further support for the pivotal role of inflammation in RA-related CVD comes from the finding that the risk of CVD is greatly diminished among patients who respond to DMARDs and biological therapies. This is discussed in more detail below. While glucocorticoid use may promote accelerated CVD among RA patients with a known history of CVD, treatment with glucocorticoids reduces cardiovascular-related mortality, highlighting the underpinning importance of inflammation in the pathogenesis of CVD in RA.

OTHER RHEUMATOID ARTHRITIS (RA) DISEASE-RELATED RISK FACTORS FOR CARDIOVASCULAR DISEASE (CVD)

Other than markers of inflammation, notable disease-related risk factors for the development of CVD in RA include the presence of RF, nodular disease, and extra-articular manifestations. The association of RF with CVD mortality is thought to be due to more severe disease, and hence, increased inflammatory burden. Other markers of severe disease including anti-CCP and possession of two copies of the shared epitope are also associated with cardiovascular mortality in RA.

THE EFFECT OF NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs) ON CARDIOVASCULAR DISEASE (CVD) RISK IN RHEUMATOID ARTHRITIS (RA)

It is possible that both cyclo-oxygenase-2 (COX-2) selective and nonselective NSAIDs may elevate blood pressure and promote thrombosis, thus increasing the risk of cardiovascular events. In the VIGOR (Vioxx Gastrointestinal Outcomes Research) study of rofecoxib versus naproxen for osteoarthritis, patients receiving rofecoxib had a fivefold increased risk of acute MI. However, other studies evaluating the effect of anti-inflammatories on markers of subclinical CVD and also cardiovascular events have produced mixed findings. In a small double-blind randomized cross-over trial of patients with severe stable coronary artery disease, selective COX-2 inhibition by celecoxib resulted in improved endothelial function compared with placebo. However, in a small study of patients with RA, neither selective (rofecoxib) nor nonselective (indomethacin) COX inhibition was associated with improved endothelial function.

Generally, studies have shown an increased risk of MI with COX-2 selective NSAIDs compared with traditional nonselective NSAIDs. In a meta-analysis of 55 trials including over 99,000 patients receiving NSAIDs for various indications, the pooled odds ratio (OR) for MI risk for any COX-2 selective NSAID compared with placebo was 1.46 (95% CI: 1.20, 1.79). The pooled OR for MI risk for any COX-2 selective NSAID compared to nonselective NSAIDs was 1.45 (95% CI: 1.09, 1.93). Of note, rofecoxib, a COX-2 selective NSAID, was associated with a substantially higher risk of MI than naproxen (OR 5.39, 95% CI: 2.08, 14.02), but valdecoxib was associated with a lower MI risk than diclofenac (OR 0.14, 95% CI: 0.03, 0.73). There were no significant differences identified in the risk of MI in a head-to-head comparison of the COX-2 selective NSAIDs. Other studies have supported these findings with a meta-analysis of 14 trials among over 45,000 patients with arthritis revealing a similar increase in MI risk with COX-2 specific NSAIDs compared with nonselective NSAIDs (OR 1.6, 95% CI: 1.1, 2.4).

Therefore, the overall impact of NSAIDs on subclinical and clinical CVD may be dependent on the particular NSAID in question as well as patient characteristics. For example, in a large population-based study among patients with RA, Solomon et al found an increased risk of cardiovascular events (MI, stroke, congestive heart failure, and cardiovascular death) with celecoxib (incidence per 100 person years = 9.7, 95% CI: 7.0, 13.2), rofecoxib (incidence per 100 person years =18.9, 95% CI: 12.9, 26.9), valdecoxib (incidence per 100 person years =13.3, 95% CI: 5.8, 26.3), and diclofenac (incidence per 100 person years =10.3, 95% CI: 3.3, 38.0) but no significant increase in cardiovascular risk with ibuprofen or naproxen. In contrast, among all patients combined regardless of comorbidities, there was an increased risk of cardiovascular events with rofecoxib (relative risk [RR] 1.22, 95% CI: 1.14, 1.30) and a decreased risk of cardiovascular events with celecoxib (RR 0.89, 95% CI: 0.83, 0.94) and naproxen (RR 0.79, 95% CI: 0.67, 0.93). Several patient characteristics, namely age ≥80 years, hypertension, prior MI, prior CVD, RA, chronic renal disease, and chronic obstructive pulmonary disease increased cardiovascular risk among users of some NSAIDs. Interestingly, in a randomized controlled trial of colorectal adenoma prevention, celecoxib 200 mg daily was actually associated with an increased risk of cardiovascular events compared with placebo (RR 2.6, 95% CI: 1.1, 6.1), highlighting the importance of study design, patient population, and the particular drug when evaluating cardiovascular risk with NSAIDs.
THE EFFECT OF GLUCOCORTICOIDS ON CARDIOVASCULAR RISK in RHEUMATOID ARTHRITIS (RA)

In non-RA patients, glucocorticoids are associated with adverse lipid profiles and insulin resistance, and long-term use (>6 months) constitutes a risk factor for cardiac disease.88,89 However, through suppression of inflammation, corticosteroids may also have a beneficial cardiovascular effect in RA. For example, in the COBRA (Combination Therapy in Rheumatoid Arthritis) study, the combination of glucocorticoids, methotrexate, and sulfasalazine was associated with a more rapid and favorable impact on the TC:HDL-C ratio in RA patients compared with sulfasalazine alone.53 In contrast, Davis et al have shown an increased risk of cardiovascular events following exposure to glucocorticoids in RF-positive patients with RA.74 In this study, RF-positive patients in the highest tertile cumulative glucocorticoids exposure category (>7,000 mg) had a threefold increased risk of cardiovascular events (hazard ratio [HR] 3.06, 95% CI: 1.81, 5.18). However, it must be borne in mind that the glucocorticoid dose may be a surrogate for the degree of disease activity and, methodologically, it may be difficult to tease apart the effect of one from the other.

THE EFFECT OF RHEUMATOID ARTHRITIS (RA) DISEASE-SPECIFIC THERAPY ON CARDIOVASCULAR RISK

In the Questionnaires in Standard Monitoring of Patients with Rheumatoid Arthritis Program (QUEST-RA), after adjustment for traditional risk factors, prolonged exposure to methotrexate (MTX), leflunomide, sulfasalazine (SSZ), and biologic agents was associated with reduction in risk of cardiovascular morbidity, ranging from 8% for SSZ to 58% for biologics.90 Van Halm et al also reported similar findings with dramatic reductions in cardiovascular risk among patients who had ever been exposed to MTX alone or in combination with SSZ and hydroxychloroquine (“only MTX ever” adjusted OR for CVD 0.47, 95% CI: 0.07–2.33; “MTX and SSZ ever” adjusted OR for CVD 0.24, 95% CI: 0.07–0.85; “MTX, SSZ, and HCQ ever” adjusted OR 0.27, 95% CI: 0.07–0.99).94 In contrast, in a study by Solomon et al, wherein MTX monotherapy was the reference group, the immunosuppressive agents azathioprine, cyclosporine, and leflunomide (as mono- or combination therapy) were associated with an increased risk of CVD including MI and stroke (OR 1.85 [95% CI: 1.85–5.66] in those who had only 20–50% improvement, and a SMR of 4.11 [95% CI: 2.56–5.66] in patients who did not improve. The difference in SMR among responders and nonresponders was statistically significant (1.64 vs 4.11, p = 0.001). In a systematic literature review, Westlake et al concluded that overall, current evidence suggests that MTX is associated with a reduced risk of cardiovascular events.95

In systemic lupus erythematosus (SLE), a chronic inflammatory autoimmune disease similarly associated with increased cardiovascular risk, hydroxychloroquine (HCQ) use reduces overall mortality and risk of cardiovascular events.96 Its mechanisms of action include improved lipid profile, reduction in blood glucose level, and enhanced endothelial function.97 The potential cardioprotective effect of HCQ in RA merits further investigation.

Through control of inflammatory synovitis, biological agents such as TNFα, IL-1 and IL-6 antagonists, CTLA4-Ig, and B-cell depletion therapy may confer protection against atherosclerotic CVD in patients with RA. In addition, as discussed above, cytokines such as TNFα and IL-6 play a key role in atherogenesis as well as the pathogenesis of RA.98 Anti-TNF therapy has also been shown in several studies to improve vascular stiffness in patients with RA, but not carotid intima-media thickness (cIMT)—both indicators of subclinical CVD.99–105

In an analysis of data from the British Society for Rheumatology Biologics Register, Dixon et al found that RA patients treated with anti-TNFα drugs do not have a lower incidence of MI compared with RA patients treated with traditional DMARDs.72 However, the risk of MI was markedly reduced in those who responded to anti-TNFα therapy by 6 months compared with nonresponders (MI incidence rate ratio adjusted for baseline risk factors 0.36, 95% CI: 0.19–0.69 for responders compared with nonresponders). Similarly, in a study by Jacobsson et al, RA patients in the Swedish Regional Register who were treated with anti-TNF therapy had a significantly lower incidence rate of cardiovascular events compared to RA patients who were not treated (incidence rate ratio 0.46, 95% CI: 0.25–0.85 in anti-TNF treated versus untreated patients).106

At present, several questions remain unanswered. Are all remissions equally associated with a reduced risk of CVD regardless of the treatment used to attain this endpoint? Or, are remissions achieved through the use of potent biological agents associated with a more dramatic reduction in cardiovascular risk? Do all biologic agents improve endothelial function and reduce cardiovascular risk equally? Do patients with “burned out” (permanent remission) RA remain at increased cardiovascular risk?107 While at this stage the
answers to these questions are unknown, it is known that early treatment of inflammatory synovitis reduces cardiovascular risk in newly diagnosed RA patients. Along with evidence that radiographic joint damage occurs early in the disease course, this knowledge strengthens the case for early and aggressive treatment of RA.

**SUBCLINICAL CARDIOVASCULAR DISEASE (CVD) IN RHEUMATOID ARTHRITIS (RA)**

The evolution of clinical CVD is thought to be a continuum, wherein events are preceded by subclinical or “presymptomatic” disease. As such, markers of subclinical disease may serve as useful surrogates for early or preclinical CVD and enable identification of patients at high risk of cardiovascular events. Furthermore, there is currently significant interest in early RA as the events that occur in the early years following disease onset appear to have important prognostic consequences in terms of long-term physical function and comorbidities such as CVD.

In the general population, increased cIMT is a marker of early subclinical atherosclerosis and is predictive of future cardiovascular events. Patients with RA, including those with early disease of less than 12 months duration, have higher cIMT than controls. The cIMT has been shown to improve with RA treatment including a combination of MTX and prednisolone and the TNF antagonists. However, at present the predictive value of increased cIMT for cardiovascular events specifically in patients with RA remains unknown.

Inflammation leads to activation of endothelial cells and expression of leukocyte adhesion molecules thus creating a proatherogenic environment. In the general population, endothelial dysfunction predates the development of atherosclerotic plaques and is a surrogate marker of CVD. Small and large artery elasticity assessed by pulse wave analysis is significantly lower in RA patients than controls and associated with markers of inflammation, in particular CRP. Endothelial dysfunction, determined by reduced flow-mediated vasodilation of the brachial artery seen on ultrasound, is found in up to 66% of patients with RA. Therapeutic reduction of inflammation with anti-TNF treatment has been shown to reverse endothelial dysfunction.

**NOVEL RISK FACTORS FOR CARDIOVASCULAR DISEASE (CVD) IN RHEUMATOID ARTHRITIS (RA)**

As traditional risk factors only partly account for the increased risk of CVD in RA, there has been great interest in identifying novel risk factors. In the general population, high homocysteine levels have been associated with cardiovascular events including stroke. Although folate supplementation has been shown to reduce homocysteine level, this may not translate to an appreciable reduction in cardiovascular risk. Administration of the folate antagonist MTX in RA causes an elevation in serum homocysteine levels and it has been proposed that this in turn may play a role in the increased incidence of CVD seen in RA. After adjustment for age and male sex, high homocysteine levels have also been shown to be associated with atherothrombotic events in RA. In the same study, folic acid supplementation was associated with lower homocysteine levels and corticosteroid use was associated with higher homocysteine levels.

In the general population, elevated high-sensitivity CRP (hsCRP) level is associated with cardiovascular risk, pointing to low-grade inflammation as a pathogenic mechanism in atherogenesis. Furthermore, in the JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) study, treatment of patients (excluding those with systemic inflammatory conditions such as RA) who had low LDL-C (<130 mg/dL) but high hsCRP (>2 mg/L) resulted in a significant reduction in major cardiovascular events (including MI and stroke) compared with placebo. Prior to this study, a meta-analysis of over 50 randomized controlled trials showed that lipid-lowering therapies reduce the CRP level by an average of 28% (p < 0.0001). In RA, CRP has been shown to be associated with microvascular dysfunction independently of other traditional risk factors. In addition, CRP at baseline predicts cardiovascular mortality in RA.

Other candidate risk factors for CVD in RA include sICAM-1 and E-selectin, and thrombotic markers such as fibrinogen, von Willebrand factor, plasminogen activator inhibitor-1, tissue plasminogen activator, and D-dimer, found at higher levels in patients with RA compared with controls. The clinical utility of these novel and emerging risk factors remains to be seen. Importantly, there is a need to determine whether each of these markers contribute independently and significantly to cardiovascular risk assessment in RA.

**SCREENING AND MANAGEMENT OF CARDIOVASCULAR RISK IN RHEUMATOID ARTHRITIS (RA)**

As traditional risk factors only partly account for the increased risk of CVD in RA and many novel risk factors remain as yet undetermined, detection of subclinical disease using one or more of several modalities, such as ultrasound assessment of endothelial function and cIMT, may have a role in selecting patients at high risk who require more aggressive management of modifiable risk factors and tight control of inflammation and disease activity. However, the prognostic significance of these measures of subclinical CVD, specifically in patients in RA, is presently unknown. In addition, the need for expertise in the use of such techniques may limit their usefulness in a conventional clinical care setting.

Currently, reduction of LDL-C through the use of statins is considered the cornerstone of CVD prevention in the general population. In addition to lipid-lowering effects, statins have immunomodulatory properties including reduction of inflammatory cell recruitment and adhesion to endothelial cells, plaque stabilization, and suppression of IL-6-driven
CRP production. Given the important role of inflammation in atherosclerosis, control of disease activity may also be expected to lessen the risk of CVD in RA. Therefore, statins may be expected to have a dual benefit in the treatment of patients with RA, potentially making this therapy highly cost effective in this setting. Toms et al have shown that the majority of RA patients in their cohort who are eligible for statin therapy based on calculated cardiovascular risk were not in fact receiving this treatment. However, at present, data on cardiovascular risk reduction through management of traditional risk factors and tight control of RA are lacking. Furthermore, treatment targets specific to patients with RA are not known.

Control of hypertension, smoking cessation, increasing physical activity and combating obesity, and consequent MetS all constitute interventions that will reduce cardiovascular risk among patients with RA. The European League Against Rheumatism (EULAR) recommendations for cardiovascular risk management in patients with RA and other forms of inflammatory arthritis highlight the increased risk of CVD, particularly in those with long-standing disease (>10 years), RF or anti-CCP antibodies, and those with extra-articular manifestations. These recommendations also emphasize the importance of adequate control of disease activity while minimizing glucocorticoid use, and the crucial role of cardiovascular risk management using agents such as statins.

1. RA is associated with a 1.5 to 2-fold increased risk of atherosclerotic CVD.
2. The increased risk of CVD in RA is in part due to the inflammatory burden of the disease. This highlights the importance of adequate control of disease activity using DMARDs and biologics, while minimizing glucocorticoid exposure.
3. Traditional cardiovascular risk factors such hyperlipidemia and hypertension are also implicated in CVD among patients with RA, suggesting a role for statins and antihypertensives in prevention of CVD in RA.
4. Smoking is a risk factor for both atherosclerosis and more severe RA. Therefore smoking cessation should be encouraged and assisted.
5. Metabolic syndrome including obesity may contribute to CVD in RA. Therefore, weight control and physical activity may help prevent cardiovascular complications.
6. The impact of NSAIDs on CVD risk in RA is dependent on the particular NSAID and patient characteristics. Therefore, the choice of NSAID and duration of treatment must be assessed on an individual basis.
7. There are several novel and emerging markers of CVD risk in RA. However, with the exception of hsCRP, most of these markers have yet to find a place in clinical practice.
8. There is debate regarding the usefulness of screening for subclinical CVD in RA as only a proportion of these patients go on to develop symptomatic CVD and the optimal management of patient with subclinical CVD is as yet unknown.
In summary, epidemiological studies have shown that RA is associated with a 1.5- to 2-fold increased risk of atherosclerotic CVD. This increased risk may be in part due to the inflammatory burden of the disease itself and in part due to the presence of traditional risk factors such as hyperlipidemia, hypertension, and smoking. Furthermore, inflammation and traditional risk factors may act synergistically.

In Figure 1, we have summarized key points of practical relevance to clinicians with regards to CVD in RA. In Figure 2, we have proposed a research agenda for CVD in RA, which spans from elucidation of cardiovascular risk factors in RA to determining the impact of treatment of risk factors and RA itself and best management of symptomatic CVD in RA. Future efforts need to be directed toward discovery of novel risk factors and biomarkers for CVD in RA in order to enable better identification of patients who are at high risk. Randomized controlled trials are needed to evaluate the role of aggressive management of risk factors, including the use of statins and anti-platelets, in reducing the incidence of cardiovascular events in RA and defining RA-specific treatment targets. However, the feasibility of such trials presents a challenge. Finally, as cardiovascular events among RA patients carry a high case fatality, the best management approach for symptomatic CVD in RA needs to be determined so as to improve the short- and long-term prognosis of affected individuals.

In RA, remission is now an attainable target for a significant proportion of patients. It remains to be seen whether RA remissions obtained through the use of conventional DMARDs achieve the same reduction in cardiovascular risk as similar responses attained through the use of biological agents, and whether in this regard all biologic agents perform equally.

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Figure 2. Proposed research agenda for cardiovascular disease in rheumatoid arthritis. Abbreviations: CVD, cardiovascular disease; RA, rheumatoid arthritis; cIMT, carotid intima-media thickness; ACE, angiotensin converting enzyme; DMARDs, disease-modifying antirheumatic drugs.


