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Cardiovascular complications of Rheumatoid Arthritis - Assessment, prevention and treatment

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Synopsis

Morbidity and mortality rates are higher in individuals with rheumatoid arthritis (RA) than in the general population. Ischemic heart disease and heart failure now represent one of the most common causes of death in RA. Indeed, RA appears to represent an independent risk factor for ischemic heart disease, similar to diabetes mellitus. However, no clear guidelines with regards to cardiovascular disease diagnosis and prevention in RA have been developed. This review highlights recent investigations on the assessment, prevention and treatment of cardiovascular disease in RA.

Keywords

rheumatoid arthritis; atherosclerosis; heart failure; inflammation; cardiovascular; cytokines

The impact of cardiovascular disease in the prognosis of patients with rheumatoid arthritis (RA)

RA, a chronic inflammatory disease that affects approximately 1% of the general population, is associated with increased mortality and reduced life expectancy, with standardized mortality rates ranging from 1.28 to 3.0[1–6, 7]. Despite remarkable improvements in RA treatment, there is evidence indicating that the mortality gap between patients with this disease and the general population is not closing. When patients in the Rochester RA cohort were grouped by the decade of disease incidence when they first met American College of Rheumatology criteria, no significant differences in survival were observed over four decades [8]. Since the control population showed decreases in mortality rate, these observations support the notion that the mortality gap between patients with RA and healthy controls is actually widening, particularly in patients who are seropositive for the rheumatoid factor (RF)[9].

This increase in mortality in RA is predominantly due to accelerated coronary artery and cerebrovascular atherosclerosis, as well as to other cardiovascular (CV) complications including heart failure [10–12]. Indeed, cardiovascular disease (CVD)-associated mortality risk is increased in both men and women with seropositive RA[13]. A recent meta-analysis indicated that the risk of CVD-associated death could be as much as 50% higher among patients with

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RA compared to controls, with the risk of ischemic heart disease and cerebrovascular diseases being elevated to a similar degree[14]. RA has also been shown to be an independent risk factor for multi-vessel coronary artery disease [15]. The enhanced vascular risk is not restricted to individuals with established RA, because increased mortality in patients who are positive for the RF and have early inflammatory polyarthritis has been reported[13, 16].

In men and women with RA with disease onset in the 1980s and 1990s, CVD mortality was significantly increased (standardized mortality rates of 1.36 and 1.93, respectively). However, standardized admission rates for CV complications were not raised in these patients, suggesting either that vascular disease in RA has a higher case fatality than in the general population or that it often goes unrecognized before the fatal event[17]. Patients with RA also have substantially increased 30-day mortality from all causes and from CVD following a first acute vascular event [18], as well as more frequent recurrent ischemic events after acute coronary syndrome[19]. RA extra-articular manifestations, usually related to uncontrolled inflammation, are also associated with increased CV mortality[20], suggesting that processes intrinsic to RA pathogenesis play important roles in CV damage and its clinical consequences.

CVD does not only impact mortality in RA, but also leads to significant morbidity. CV events occur approximately a decade earlier in RA than in controls [21] and RA patients are twice as likely to suffer a myocardial infarction [6, 8, 16] with the increased relative risk for CV events being concentrated in younger RA patients and individuals without known prior CV events [22]. However, in a population of male US veterans older than 50 years old, RA has also been associated with a higher risk of major adverse CV events, particularly in patients with increased disease activity independent of traditional risk factors [23].

Patients with prolonged arthritis have more atherosclerosis than patients of the same age with more recent disease onset, suggesting that atherogenesis accelerates after the onset of RA [24, 25]. The odds ratio for the likelihood of having more severe coronary artery calcification in established RA has been determined at 3.42, after adjusting for traditional CV risk factors[26]. Further, an increased prevalence of severe subclinical atherosclerotic findings in long-term treated RA patients without clinical evidence of atherosclerotic disease has been reported[27]. However, even patients with early RA show evidence of increased subclinical atherosclerosis[28], as assessed by carotid plaque, carotid intima media thickness and coronary calcification. Patients with RA also exhibit significantly increased arterial stiffness [29] and young to middle-aged RA patients with low disease activity and free from traditional CV risk factors and overt CVD have altered endothelial reactivity[30].

In many ways, CVD in RA shares similarities with CVD in diabetes mellitus (DM). Preclinical atherosclerosis and the risk of CVD appears to be of equal frequency and severity in RA and DM of similar duration[31]. Compared with nondiabetic controls, nondiabetic patients with RA and those with type 2 DM have comparable hazard ratios for CVD: 2.16 (95% CI 1.28–3.63, P = 0.004) and 2.04 (95% CI 1.12–3.67, P = 0.019), respectively[32]. Further, similar to what occurs in DM, patients with RA are less likely to report symptoms of angina and more likely to experience unrecognized myocardial infarction and sudden cardiac death[33]. However, despite the increased risk for vascular events, strategies to prevent CVD are similar among women with and those without RA[34].

Patients with RA are also at significantly higher risk for congestive heart failure (CHF) compared with those without the disease. CHF risk precedes the diagnosis of RA and cannot be explained by an increased incidence of traditional CV risk factors[35]. RA is associated with increased left ventricular mass which is independently related to disease duration, while systolic function is typically preserved [36]. Abnormalities of trans-mitral and pulmonary venous flow have been proposed as markers of altered diastolic function in long-standing RA patients

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with normal systolic function[37]. Both the clinical presentation and the outcome of CHF differ significantly between RA and control individuals. In the former, CHF presentation may be more subtle but mortality from this complication is significantly higher[38]. Even after adjusting for CV risk factors and ischemic heart disease, RA patients have almost twice the risk of developing CHF than patients without arthritis. Again, this increase has been seen primarily in patients who are seropositive for the RF[35]. In addition, patients with RA are at increased risk for death in the period immediately after CHF develops and this risk remains elevated for 6 months after[38].

Previous studies have suggested that traditional CV risk factors do not fully account for the increased propensity to vascular complications in RA[39] and that immune dysregulation, inflammation, and metabolic disturbances observed in RA could play an important role in accelerated atherogenesis and mortality. Indeed, histologic examination of coronary arteries in RA has revealed less atherosclerosis but greater evidence of inflammation and instability[40].

Pathogenic mechanisms involved in premature CVD in RA patients

Over the past few years, striking similarities in the inflammatory and immunologic responses in atherosclerosis and RA have been described[41]. While chronic inflammation can promote endothelial cell activation and vascular dysfunction, which leads to decreased blood vessel compliance and atheroma formation, the reasons for the dramatic increase in atherosclerotic disease in RA are not totally understood and appear to be fairly complex (Figure 1). It appears that variables that increase CV mortality in RA are present very early during the natural history of the disease, because patients with new onset, RF positive inflammatory arthritis exhibit evidence of abnormal endothelial function, which is considered a good predictor of future development of atherosclerosis [42]. Interestingly, RF as an independent risk factor for ischemic heart disease in the general population has been suggested by some studies. Indeed, the RF has been associated with increased all-cause mortality and CV mortality after adjustment for traditional risk factors, even among subjects without joint symptoms[43, 44]. Further, preliminary evidence indicates that patients with RA who are positive for anti-cyclic citrullinated peptide antibodies (Abs) (anti-CCP) have higher subclinical atherosclerosis than those who are not [45]. A recent study indicated that anti-CCP Abs in RA are independently associated with the development of ischemic heart disease (OR 2.8, 95% CI 1.19–6.56; P = 0.009)[46]. The precise role that autoAbs play in premature CVD in RA, however, remains to be determined.

1. Traditional CV risk factors

RA is associated with both traditional and nontraditional CV risk factors [39, 47–53]. Therefore, assessments based only on traditional risk factors are insufficient to capture the extent of CV risk in RA. A higher Framingham risk score is independently associated to coronary calcification in RA [54]. Age and hypertension correlate with increased CV risk RA, but so do factors associated with inflammation, including neutrophil count and radiographic score[13]. It also appears that physically inactive RA patients have significantly worse CVD risk profile compared with those who are physically active[55]. While smoking is associated with RF and anti-CCP Ab production and is now recognized as an independent risk factor for RA development[56, 57], it does not appear to predict CV events or cardiac-associated mortality in seropositive patients with inflammatory arthritis[58]. [13]. However, the prevalence and severity of coronary calcification in established RA has been linked in part to tobacco use [26]. Indeed, a personal history of ischemic heart disease, smoking, hypertension and diabetes mellitus has been found to contribute to CV death in RA[59].

A proatherogenic lipid profile has been reported in patients with RA [60]. Beyond the abnormalities in plasma lipids, increased levels of small, dense LDL are common in drug-naïve

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patients with early RA. The role that these particles may play in the atherogenic process in this disease is still unclear [61]. AutoAbs recognizing oxidized LDL are associated with atherosclerosis in the general population. These antibodies are present in RA and correlate with inflammation but their role in CVD in RA remains to be determined [62]. Serum lipoprotein A is significantly increased and high-density lipoprotein cholesterol (HDL) significantly decreased in women with RA. In addition, HDL function is abnormal in RA, because this molecule is unable to protect LDL from oxidation and is therefore considered proinflammatory[63]. Proinflammatory HDLs can contribute to oxidative damage and have been reported in approximately 20% of patients with RA[64]. Further, a recent study indicates that proinflammatory HDL in RA is associated with active disease and an altered protein cargo [65]. Interestingly, a recent study suggests that total cholesterol and LDL levels significantly decrease within 5 years prior to the diagnosis of RA. The mechanisms and significance of these findings remains to be determined [66].

2. Insulin resistance, body weight, homocysteine and thyroid function

Other metabolic abnormalities that predispose to vascular disease in the general population (microalbuminuria, insulin resistance and increased homocysteine) are prevalent in RA[67]. Insulin resistance is an important risk factor for CVD, and TNF-α and other proinflammatory molecules directly affect insulin sensitivity. Factors that lead to increased systemic oxidative stress and proinflammatoy cytokine overexpression may therefore promote insulin resistance. RA is associated with a higher prevalence of the metabolic syndrome than control subjects, which was present in about a third of patients with early disease and in 42% of patients with long-standing disease[68]. Patients with RA have evidence of impaired glucose handling which is secondary to peripheral insulin resistance mediated by the inflammatory response. Further, RA patients with carotid plaque have higher insulin resistance[69]. The precise role that corticosteroids play in insulin resistance development in RA remains to be determined [70]. Insulin resistance has been shown to improve with the use of DMARDS and biologics in RA[71, 72]. Increased trunk fat has been significantly and independently associated with increased arterial stiffness in postmenopausal patients with RA[73].

High homocysteine levels have been linked to atherothrombosis in RA [67]. A potential role of thyroid function in the development of subclinical atherosclerosis in this disease has also been proposed, as hypothyroidism in RA has been found to be an independent association with carotid plaque and this is enhanced in patients who also have other traditional CV risk factors or neutrophilia[74].

3. Family history

A parental history of death from CVD is associated with a 70% increase in risk for fatal CVD in RA and an increase in 10-year mortality from CVD from 5% to 10% in men and from 2% to 4% in women aged 50–67 years [75].

4. Genetic influences

Functional polymorphisms that relate to major histocompatibility complex (MHC) expression are associated with increased susceptibility to RA, myocardial infarction, and multiple sclerosis [76]. A –168A -> G polymorphism in the type III promoter of the MHC class II transactivator (MHC2TA) has been associated with increased susceptibility to these three diseases, as well as with lower expression of MHC2TA after leukocyte stimulation with interferon-γ. These polymorphisms may result in differential MHC molecule expression and could potentially be associated with susceptibility to common complex diseases with inflammatory components [76]. Interestingly, shared epitope alleles (*HLA-DRB1* genotype), particularly compound heterozygotes, are associated with death from all causes and from CVD, independently of autoAb status in RA. However, the combination of shared epitope, smoking, and anti-CCP

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antibodies is associated with a higher risk of premature death in patients with inflammatory polyarthritis and RA[77]. Other studies have also linked the shared epitope to ischemic heart disease in RA[78, 79]. The exact mechanisms by which the presence of the shared epitope may enhance premature vascular damage in RA remain to be determined.

A recent study suggests that the IL-6-174C-allele may associate with CVD in RA and possibly exerts its effect via increased inflammation[80]. RA patients who carry the TNF-α-1031 T/C polymorphism have smaller LDL particles that have greater affinity for extracellular matrix and higher susceptibility for oxidation[81]. Other genetic polymorphisms that have been proposed to be associated to the development of CVD in RA include plasminogen activator inhibitor I (PAI-1) and coagulation factor XIII[82]. Polymorphisms in TNF receptor type II are associated with hypertension in Scandinavian RA patients[83]. In another recent Scandinavian study, no increased occurrence of CVD prior to the onset of RA was detected. Authors then concluded that shared risk factors or susceptibilities for RA and CVD likely contributed less than RA-related factors to the increased occurrence of vascular complications in this disease[84].

5. The role of inflammation in CV disease in RA

Recent evidence indicates that there is a close temporal correlation between inflammation and morphologic features of rapidly progressive carotid atherosclerosis, which suggests that elevations in inflammatory biomarkers might help in predicting the presence of atherosclerosis[85]. Markers of systemic inflammation confer a statistically significant additional risk for CV death among patients with RA, even after controlling for traditional CV risk factors and comorbidities[59, 86]. Increased levels of proinflammatory mediators including TNF, interleukin-6 (IL-6), interleukin-17 (IL-17) and others could be detrimental to the endothelium and myocardium and promote insulin resistance. Levels of these cytokines are increased in RA [87–89]. The C-reactive protein (CRP) concentration at baseline is an important predictor of subsequent death from CVD in patients with new onset inflammatory polyarthritis, and is independent of other factors of disease severity[90]. High levels of CRP also correlate with carotid intima media thickness [91]. High sensitivity CRP and lower glomerular filtration rate have been independently predictive of endothelial dysfunction in RA[92].

Higher erythrocyte sedimentation rate, small and large joint swelling, rheumatoid nodules, vasculitis and rheumatoid lung have been independently associated with increased risk of CV death[59]. In a recent study comparing patients with RA and controls, TNF-α and IL-6 were significantly associated with the severity of coronary artery calcification in RA, independent of Framingham risk score [93]. Enhanced arterial stiffness in RA correlates with CRP and IL-6 levels[29]. Similarly, in those patients experiencing new onset CHF, the proportion of patients with very high sedimentation rate was greatest in the 6 months preceding the diagnosis of cardiac dysfunction. This indicates that an enhanced inflammatory process may promote the development of heart dysfunction in inflammatory arthritis[94] The magnitude and chronicity of the inflammatory response, as measured by circulating levels of inflammatory markers, correlates with carotid atherosclerosis development in RA[91]. Levels of adhesion molecules linked to vascular damage including soluble vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and endothelial–leukocyte adhesion molecule (ELAM) were higher in RA. VCAM-1 levels have been associated with carotid atherosclerosis in RA [92].

While the exact role of IL-17 in premature vascular damage in RA remains to be determined, recent work indicates that this cytokine may play a role in atherosclerosis development in murine models of vascular disease[95, 96] and elevated circulating levels of IL-17 have been reported in patients with acute coronary syndromes[97]. IL-17 is produced concomitantly with IFN-γ by coronary artery-infiltrating T cells and these cytokines act synergistically to induce

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proinflammatory responses in vascular smooth muscle cells[98]. IL-17 accelerates myocardial fibrosis in animal models of heart injury[99]. However, there is recent evidence that IL-17 may also play a regulatory role in atherosclerosis[100] and future studies should determine whether this cytokine plays or not a pivotal role in vascular damage in RA.

6. T cells

An expanded population of $CD4^+CD28^-$ T cells has been demonstrated in the peripheral blood of RA patients [101], and clonal expansion of a similar T-cell subset has been reported in the blood and atherosclerotic plaques of patients with unstable angina[102]. These cells can injure the endothelium and cause vascular damage. RA patients with persistent $CD4^+CD28^-$ expansion have presented with increased preclinical atherosclerotic changes, including endothelial dysfunction and carotid atherosclerosis, compared with those without expansion[102, 103]. TNF-α induces downregulation of the CD28 molecule in $CD4^+$ T cells, suggesting a pathogenic mechanism for the development of these cells [104]. Treatment with anti-TNF agents has been found to downregulate this cell subset in RA patients and in patients with unstable angina and no RA[104, 105]. The precise role that these cells play in the development of acute coronary events in RA requires further investigation.

7. Abnormalities in vasculogenesis

An adequate balance between endothelium destruction and regeneration is needed to maintain vascular health. Endothelial progenitor cells (EPCs) are present in the circulation of patients with different forms of vascular damage and are released from the bone marrow during acute vascular injury[106]. EPCs appear to be crucial in normal revascularization after endothelium damage occurs. Furthermore, reduced EPC numbers and abnormal EPC function correlate with increased incidence of atherosclerosis, impaired vasculogenesis after ischemia, and future CV events [106, 107]. Recent reports [108, 109] suggest that EPC numbers are decreased in the systemic circulation of patients with active RA and that their functions are impaired. Potentially, this phenomenon could contribute to atherosclerosis but further studies correlating abnormal EPCs with functional markers of endothelial dysfunction in RA are needed. Endothelial dysfunction in RA patients with low grade inflammation was associated with decreased EPC numbers and low grade dysfunction of these cells [109]. Interestingly, a single dose of infliximab significantly increases EPC numbers and improves their functional properties in RA [110]. Others have proposed that asymmetric dimethylarginine (ADMA), a major endogenous inhibitor of nitric oxide synthase associated with atherosclerosis risk in the general population[111], may contribute to EPC depletion in RA via depressed NO-dependent mobilization and/or survival of these cells [112].

EPCs can contribute to synovial neovascularization in RA [113]. Proinflammatory cytokines upregulate vascular endothelial growth factor, which increases synovial EPCs and is essential to the proangiogenic process. The discrepancy observed between decreased angiogenic responses in RA peripheral blood and enhanced angiogenesis at the level of the synovium has not been clarified but may be related to differences in EPC homing, perhaps driven by the proinflammatory milieu of the joint [113].

Effect of RA treatment on CVD risk

The lack of a unifying explanation for accelerated CVD in RA is reflected by the confusion that still exists regarding possible preventive measures aimed at decreasing atherogenic risk. There is still considerable uncertainty on how to manage RA patients effectively to reduce their risk for future CV events, because some of the medications used to treat RA might have dual effects on risk for CV morbidity. This is exemplified by the use of corticosteroids which on one hand may decrease CV complications in RA by decreasing inflammation, but on the other

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hand increase it by promoting proatherosclerotic lipid profiles, hypertension and insulin resistance[114]. Methotrexate can promote hyperhomocysteinemia (usually corrected by folic acid supplementation)[115] and cause endothelial damage[116]. However, long-term follow up of RA patients has suggested that methotrexate significantly reduces overall and CV mortality[117]. Furthermore, use of DMARDs is associated with reductions in risk for hospitalization for congestive heart failure in RA[118]. I will now discuss the role that various medications may play in CV risk and/or prevention in RA.

1. NSAIDS and CV complications in RA

Current and new users of all classes of non-aspirin NSAIDS, including RA patients, have an elevated relative risk estimate for myocardial infarction[119]. Several patient characteristics increase the risk of CV events among users of some NSAIDS including increased age, hypertension, previous myocardial infarction and CVD, chronic renal disease, chronic obstructive pulmonary disease and RA. This indicates that RA patients with various comorbidities and advanced age may be particularly prone to developed CV complications while on specific NSAIDS[120]. However, a large case–control analysis found that the risk for first-time myocardial infarction is increased for several weeks after the cessation of NSAID therapy, an effect that is more pronounced in RA or lupus patients and in individuals who discontinue NSAID therapy after previous long-term use[121]. These findings suggest that NSAIDs might have a role in suppressing the risk for myocardial infarction in patients with RA and other inflammatory conditions and that, ideally, abrupt discontinuation of NSAIDS in these populations should be avoided.

2. Role of corticosteroids in CVD in RA

Corticosteroids can induce hypertension, insulin resistance and disturbances in blood lipids; they induce obesity and may enhance hypercoagulability[122]. As mentioned above, whether glucocorticoids promote accelerated atherogenesis in RA is still a matter of debate. In one study, patients exposed to glucocorticoids had higher incidence of carotid plaque and arterial incompressibility, independent of CV risk factors and RA clinical manifestations[123]. A Scandinavian study reported that treatment with low-dose prednisolone did not influence endothelial function or carotid intima media thickness in RA, although it promoted higher levels of total cholesterol[124]. Interestingly, an increased risk of CV events with high cumulative exposure to corticosteroids has been found in RA patients who are seropositive for RF, but not on the patients who are seronegative[125]. However, in RA patients with a history of ischemic heart disease, use of corticosteroids attenuated the risk of CV death[59].

3. DMARDS

A recent study indicated that prolonged exposure to various DMARDS, including methotrexate, leflunomide and sulfasalazine, was associated with a reduction of CV risk in RA, and similar trends were observed with corticosteroid use[126]. Further supporting a beneficial effect of methotrexate treatment in CVD prevention, this drug reduced the incidence of vascular disease in veterans with psoriasis or RA[127]. Low to moderate cumulative doses appeared to be more beneficial than higher doses. In addition, a combination of methotrexate and folic acid led to a further reduction in the incidence of CVD, suggesting that the latter did not decrease the efficacy of methotrexate. Furthermore, methotrexate use was associated with a significantly lower risk for CV events in RA patients compared with patients who had never used DMARDs (odds ratio 0.16). Methotrexate use has also been associated with a decreased incidence of the metabolic syndrome, while corticosteroids or other DMARDS did not show a protective effect[72]. Adding additional DMARDS such as sulfasalazine and hydroxychloroquine appears to provide additional CV protection[128]. In a Canadian study, DMARD use was associated with a reduction in myocardial infarction risk in patients with

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RA, while corticosteroids showed an increased risk and coxibs did not change risk[129]. In a recent cross-sectional analysis, drugs used to treat RA did not have major adverse effects on CV risk factors and use of antimalarials was actually associated with beneficial lipid profiles and lower blood pressure[130]. As a potential antiatherogenic mechanism of methotrexate, Reiss et al have shown that through adenosine A2A receptor activation, MTX promotes reverse cholesterol transport and limits foam cell formation in macrophages[131].

4. Anti-TNF therapy

The effects of TNF-α blockers on CVD in RA are complex because these drugs may promote CHF and decrease heart compliance while controlling inflammation and decreasing risk for plaque formation[132]. Infliximab can improve endothelial function in RA after 12 weeks of therapy [89], and anti-TNF therapy also reduces aortic stiffness to a level comparable to that of healthy individuals by 4 and 12 weeks of treatment[133]. Prolonged effects on endothelial function (18 months of therapy) were recently reported with infliximab and adalimumab[134]. It appears that the risk to develop first CV events in RA is lower in patients treated with TNF blockers[135]. However, prospective, long-term, longitudinal studies are required to evaluate the precise role of anti-TNF therapy in atherosclerosis prevention. Anti-TNF therapy can also improve other risk factors for accelerated atherosclerosis, including promoting a decrease in insulin resistance[71], CRP, IL-6 and $CD4^+CD28^-$ T cells and an increase in HDL[132, 136]. However, it appears that at least some of the beneficial effects of anti-TNF agents on endothelial function are not sustained, have not been reported in all studies and are not seen in all patients populations (for example, in the case of diabetic patients treated with etanercept)[137–139]. In one study, although an initial improvement in RA endothelial function was observed with infliximab, values returned to baseline 4 weeks after the infusion in patients followed for 1 year[138]. Another report found that, although infliximab induces a transient increase in flow-mediated dilatation (FMD), the drug also induces vasoconstriction and increases in wall shear stress [140]. There is also evidence that biologics may induce elevations in blood lipids with a deleterious shift in the atherogenic index in RA[140]. It is possible that the various TNF antagonists have different effects on endothelial and smooth muscle cells and on vascular function. Animal studies suggest a negative influence of TNF-α inhibitors on collateral artery growth, and this observation deserves further investigation into the potential role of this therapy in decreasing alternative mechanisms of cardiac perfusion in individuals with impaired coronary circulation [141].

Previous studies in the general population have shown that short-term TNF-α antagonism with infliximab does not improve and high doses (10 mg/kg) adversely affect the clinical condition of patients with moderate-to-severe chronic heart failure[142]. Despite contraindication to the use of these agents in patients with moderate-severe heart failure, epidemiological studies in RA have not consistently substantiated this association[143, 144]. In fact, a recent German study has concluded that inhibition of TNF that effectively reduces inflammatory activity in RA is more likely to be beneficial than harmful with regards to CHF risk, especially when not combined with corticosteroids of coxibs[145]. Similarly, a recent study indicates that blocking TNF in RA patients without evident heart failure decreases N-terminal pro-brain natriuretic peptide pointing at no treatment-induced deterioration in cardiac function, and a potential CV risk benefit[146]. However, TNF-inhibitors may increase the risk of both first hospitalization and exacerbation of CHF in elderly RA patients[147]. Interestingly, a recent study indicates that, when compared with RA patients receiving MTX monotherapy, those receiving biologic immunosuppressive agents had no changes in the risk of experiencing a CV event, whereas use of oral glucocorticoids and other cytotoxic immunosuppressive agents (leflunomide, azathioprine) was associated with significant increases in the risk of CV events[148].

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5. Rituximab and other biologics

Preliminary data from various groups suggests that rituximab infusions exert early and sustained favorable effects on endothelial dysfunction and plasma lipids[149, 150]. The role of abatacept and anakinra in CV prevention in RA remains to be determined, although there is some preliminary evidence that chronic inhibition of IL-1 actions with anakinra improves left ventricle deformation in parallel with endothelial function and nitro-oxidative stress in RA[151].

Risk assessment and prevention of CVD in RA

Ideally, preventive strategies to decrease CV risk in RA should start shortly after its diagnosis. This statement is supported by observations that the factors that promote premature CV mortality in this disease are present early on, maybe even before overt clinical manifestations manifest. Clearly, a significant proportion of patients with RA have suboptimal management of CV risk factors. Depending on the risk stratification method used, it is considered that 2%–26% of RA patients without overt CVD have sufficiently high risk to require statin therapy, yet most of them remain untreated[152]. There is also evidence that target organ damage is highly prevalent in patients with RA and associates independently with hypertension, arterial stiffness and heart rate[153]. These observations indicate an urgent need for CV reduction strategies. However, specific guidelines that address the management of CV risk factors in RA are not available and a number of important questions with regards to prevention remain unanswered. It is unknown which levels of lipids or blood pressure should prompt pharmacologic intervention in RA and whether these interventions can modify CV risk. While RA and DM have a comparable enhanced CV risk, it is unclear whether guidelines similar to the ones developed for diabetes would lead to significant CV risk reduction in RA. Similarly, it is unknown which RA patients should be considered as candidates for subclinical and clinical coronary artery and carotid artery disease screening or for heart function screening.

The author suggests that CV assessment in RA should start by considering and detecting the presence other major comorbidities including hypertension, tobacco use, hyperglycemia, dyslipidemia, increased body mass index, central obesity, physical inactivity and family history of CV disease. Proper identification of these factors is crucial as a first step towards developing a plan for CV risk reduction in RA. It is unclear whether the presence of RA should be used as an additional risk factor during stratification; however, there are strong indications from the literature that this should be the case. Given the high prevalence of silent ischemia and decreased CV symptoms in RA, future prospective studies should investigate whether effective strategies for earlier detection of clinical CV disease will reduce morbidity and mortality in these patients. For patients that are deemed to be at high risk (seropositive for RF and/or anti-CCP Abs, aggressive erosive disease, extra-articular RA manifestations and high inflammatory markers) or for those with specific CV risk factors in addition to the arthritis, specialized testing including 24 hour monitoring of ambulatory blood pressure, stress test or echocardiography may be warranted. However, until clear guidelines are developed for CV prevention in this and other systemic autoimmune diseases, the justification for these tests remains unclear.

1. Targeting traditional CV risk factors in RA (Table 1)

Optimal blood pressure should be targeted with weight maintenance, physical activity, sodium control, judicious use of corticosteroids and, when indicated antihypertensive drugs. A recent study suggested that 10 mg/day of ramipril for 8 weeks in combination with standard of care markedly improved endothelial function in RA patients[154] and ACE inhibitors may be considered a good antihypertensive strategy in this disease. Intensive strategies for smoking cessation should be initiated early and aggressively. Weight loss and increased exercise are first-line strategies for reducing insulin resistance and hyperglycemia and should like be

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attempted in conjunction with good control of the inflammatory response. The role of thiazolidinediones in the improvement of insulin resistance and CVD in RA remains to be determined and is currently being investigated in controlled clinical trials. These drugs have pleiotropic effects on the endothelium which go beyond glucose control and may prove to have a dual beneficial effect in CV prevention and control of joint inflammation. There are hypothetical concerns with regards to thiazolidinedione use, specifically CHF and increased risk of fracture in RA, which should be explored.

Statins can mediate modest but clinically apparent anti-inflammatory effects in RA[155]. Atorvastatin, 20 mg/day for 12 weeks, resulted in significant improvements in arterial stiffness in RA patients, particularly in patients with active disease [156]. Similarly, RA patients treated with 40 mg simvastatin for 4 weeks had reduction in proatherogenic lipids and markers of oxidative stress, and improvement in FMD[157]. In another recent study, simvastatin 20 mg/day also improved FMD in RA. The drug also lowered CRP and TNF-α concentrations[158]. Ezetimibe and simvastatin treatment for 6 weeks similarly reduced disease activity and inflammatory markers in RA, and also reduced aortic pulse wave velocity and improved endothelial function[159]. While it is still unclear which levels of lipids are ideal for CV prevention in RA, optimal LDL and HDL cholesterol levels should be sought. A recommended LDL level of less than 100 mg/dL and HDL over 40 mg/dL, similar to what is recommended for patients with other CV risk factors, is warranted until more specific information becomes available for RA. Maximal dietary therapy should be tried with the addition of drug therapy when necessary. The benefit of use of anti-platelet agents in RA is unclear. A recent study indicated that statins may be protective for RA development in individuals with dyslipidemia[160].

2. Current and future strategies for targeting disease-specific CV risk factors in RA

As mentioned above, various therapies used in the management of RA may have a protective CV risk effect. In addition, patients with RA and prolonged exposure to hydroxychloroquine have a reduced risk of developing diabetes[161]. Studies have also suggested that antimalarials could have a vasculoprotective effect in inflammatory diseases, at least in part mediated by beneficial effects on lipids[162]. Further investigation is required to determine whether specific doses or duration of corticosteroid use is beneficial or harmful to the vasculature in RA. The deleterious adverse effects on the vasculature might be prominent in patients receiving over 7.5 mg per day of prednisone for at least 6 months[163]. There is some evidence that low dose corticosteroids could have a beneficial effect on lipid profiles [48]. Overall, as mentioned above, exposure to DMARDS appears to be associated with decreased CV morbidity and with decreased hospitalizations for heart failure [118, 128]. However, since the mortality gap between RA and the general population appears to be widening, it is unclear that the current use of DMARDS and biologics is effectively reducing CV risk. As new biologics become more widely available for use in clinical practice, assessment of their role in CV prevention and/or damage in RA should become possible. These strategies include anti-IL-6, anti-IL-17, other anti-B cell therapies, etc. Certainly, a better understanding of the mechanisms that promote RA development and severity may provide additional light into the most effective preventive strategies for vascular damage in this disease.

Conclusions

Given the serious impact of the increased risk of atherosclerosis in RA, future work should focus both on understanding the precise molecular mechanisms that lead to premature vascular damage in inflammatory arthritides, and on assessing the individual effects of various treatments on CVD in these patients by performance of rigorous studies. Future studies should also focus on the development of effective screening methods for the identification of those

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patients who are at the highest cardiovascular risk and who would benefit from early intervention. Clearly, the development of guidelines for the management of CV risk factors in RA, similar to those that have been developed for diabetes, is greatly needed. In the meantime, a combination of strategies that include appropriate control of the inflammatory cascade, immunologic diatheses and metabolic changes observed in RA should be sought. Finally, an increased awareness of the increased risk for silent ischemia, early myocardial infarction, heart failure and sudden death is warranted in this patient population.

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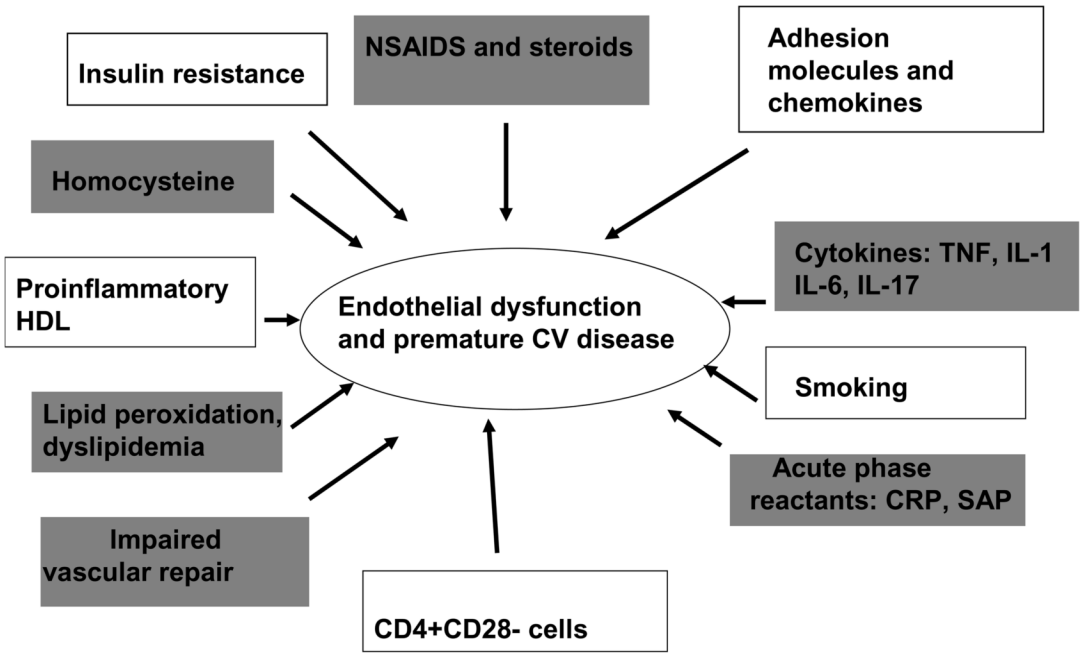

Figure 1.
Putative mechanisms leading to endothelial dysfunction and vascular damage in RA.

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Table I

Managing cardiovascular risk factors in rheumatoid arthritis

Risk factor	Cardiovascular prevention strategies
Smoking	Counseling, nicotine patches or gum, bupropion, varenicicline
Hypertension	Frequent blood pressure monitoring, diet, exercise, stress management, antihypertensives, minimize NSAID and corticosteroid use.
Hyperlipidemia	Diet, exercise, moderate alcohol use*, statins, minimize corticosteroid use, antimalarials*.
Diabetes	Counseling, diet, exercise, oral hypoglycemic agents and/or insulin
Insulin resistance	Counseling, diet, control of inflammation (DMARDS/biologics), PPAR-agonists*
Obesity	Counseling, diet, exercise, minimize corticosteroid use.
High homocysteine	Folic acid supplementation with methotrexate/sulfasalazine use
Family history of CVD	Counseling, monitoring risk factors
Inflammation	DMARDS, biologics, NSAIDS, statins*; PPAR-agonists*
Thrombotic risk	Low dose aspirin/consider anticoagulation when other risk factors for thrombosis are present

*not enough evidence to suggest as standard of care