Cardiovascular Disease in Inflammatory Arthritis: Getting to the Heart of the Matter
Patients with rheumatic disease are at increased risk for cardiovascular disease (CV). One of the first to describe this increased risk was Urowitz and colleagues in 1976 in a study that noted mortality from cardiovascular disease was substantially higher in patients with systemic lupus erythematosus (SLE) than in patients without SLE. In a long-term follow-up study of 81 patients, it was observed that a group of patients with inactive lupus symptoms had a higher rate of myocardial infarction (MI) due to atherosclerosis. Subsequently, well-controlled observational studies have confirmed this elevated CV risk in SLE and other rheumatic diseases in larger populations. Most studies have been conducted in patients with rheumatoid arthritis (RA) or SLE, although several other rheumatic diseases are also associated with CV risk (see Table 1).

### Table 1. Systemic rheumatic disease and cardiovascular risk

<table>
<thead>
<tr>
<th>Increased CV risk</th>
<th>No increased CV risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid arthritis</td>
<td>Giant cell arteritis</td>
</tr>
<tr>
<td>Lupus</td>
<td></td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>Not well studied</td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td>Polyaeritis nodosa</td>
</tr>
<tr>
<td>Wegener's granulomatosis</td>
<td>Henoch-Schönlein purpura</td>
</tr>
<tr>
<td>Takayasu's arteritis</td>
<td>Cryoglobulin-associated vasculitis</td>
</tr>
<tr>
<td>Kawasaki's disease</td>
<td>Cutaneous leucocytoclastic angiitis</td>
</tr>
<tr>
<td>Systemic sclerosis</td>
<td></td>
</tr>
</tbody>
</table>

### Rheumatoid Arthritis

In a systematic literature review of RA and cardiovascular risk, RA has been associated with increases in the standardized mortality ratio of 1.7 to 3.3 and decreases in life expectancy of 3 to 18 years. Data from the Nurses Health Study, a prospective observational study conducted in 114,342 women in Boston and followed for 2.4 million patient years, showed a 2.0 relative risk for myocardial infarction associated with RA. Active or uncontrolled RA disease has also been associated with increased CV risk.

### Systemic Lupus Erythematosus

In a comparative, population-based study, SLE patients were found to have a 5- to 6-fold increased risk of coronary artery disease compared with the general population and a 50-fold increase risk of MI in women in the 35- to 44-year age group; these risks persisted even after adjustment for traditional CV risk factors. Additional risks observed in this study included older age at diagnosis, longer disease duration, long-term steroid use, and postmenopausal status.

### Pathogenesis

Atherosclerosis is considered to be a chronic inflammatory process resulting from a complex interplay of innate and adaptive immune responses rather than a lipid storage disease (see Figure 1). In evaluating the pathogenesis of the increased CV risks associated with RA, researchers have identified several potential mechanisms. These include dyslipidemia, oxidative stress, insulin resistance, and endothelial dysfunction. Subclinical atherosclerosis has been linked to substantial increases in the prevalence of carotid plaque and coronary calcification compared with patients without rheumatic disease. In addition, chronically high inflammatory responses in genetically predisposed individuals (with HLA-DRB1 0404 allele) have been found to be associated with an increased risk of CV events and CV mortality in patients with RA. This raises the question of how early patients with systemic rheumatic disease develop this increased CV burden. Ultrasound studies have found that carotid plaque is significantly higher in patients presenting with early RA than in controls with matched CV risk factors. Some evidence has surfaced that indicates RA treatment in patients with early systemic disease can improve some CV risk parameters. Specifically, patients undergoing treatment for RA have a documented improvement in brachial artery responses that signify that both functional and structural artery abnormalities may be attenuated.
**Effect of RA disease-related factors**

Enhanced mortality rates are seen after 10 years of RA disease. Factors related to disease duration that affect risks include length of RA medication use, concomitant medication use, and number of comorbidities associated with RA, which can increase with age.

Duration of RA disease also has an impact on CV risk. In a population-based cohort study examining the risk of coronary heart diseases in patients with RA, those with RA had significantly increased risks of being hospitalized for acute MI or experiencing an unrecognized MI compared with the general population. More established RA disease duration also increased the risk of sudden death and unrecognized MI in this population. Other studies have found that overall, patients with RA have twice the rate of multivessel coronary disease and a 2-fold greater fatality rate following MI.

The presence and amount of coronary calcification has also been associated with RA duration. But it is not known whether premature atherosclerosis is a general feature of inflammatory disease or whether it only affects a subgroup of patients, such as those with RA.

In another study, the existence of cyclic citrullinated peptide antibodies (anti-CCP) in patients with RA disease increased the risk of ischemic heart disease by nearly three times compared with those without the antibodies.

**Treatment effects**

The various treatment regimens for RA further complicate this CV risk. The disease-modifying antirheumatic drugs (DMARDs) may favorably affect the cardiovascular status, whereas prolonged use of nonsteroidal antiinflammatory drugs (NSAIDs) has been associated with several increased CV risks. Corticosteroid use also has observed effects that can increase the CV risk by producing a more atherogenic profile.

In general, these epidemiologic studies demonstrating increased CV risks are strong associations, not conclusively proven causations. Larger studies are needed to identify the specific patient subgroups, detailed CV risk stratification, and treatment effects that are more likely to result in progression to coronary artery disease.

**References**

In approximately two-thirds of patients, the first sign of coronary atherosclerosis is either MI or sudden cardiac death. Unfortunately, more than one-third of patients who suffer an acute MI die before reaching the hospital. Thus, CV mortality could be substantially reduced if coronary atherosclerosis can be detected at an early stage before symptoms occur.

Various techniques are available for noninvasive imaging to detect preclinical CV disease. Electron-beam computed tomography (CT) and multislice CT are radiographic techniques that can assess the extent and density of calcium in the coronary arteries. The coronary artery calcium (CAC) score is derived from CT and correlates well with the volume of atherosclerotic plaque. The accuracy of CT has been well validated across multiple instruments. New-generation CT systems that simultaneously acquire multiple slices were introduced into routine clinical practice in 1998. This multislice CT scanning is better able to define coronary luminal obstructions than electron-beam CT but is no better at detecting calcium and exposes patients to a greater radiation level.

Although the CAC provides an accurate measure of plaque volume, it has a poor correlation with luminal atherosclerotic narrowing. It is therefore not a substitute for invasive angiography in symptomatic patients. Furthermore, the CAC has no known value in patients who have suffered a heart attack or undergone coronary bypass surgery or coronary angioplasty. Radiation dose is a major concern for coronary CT angiography, especially in cases of multiple examinations or in particular patient subgroups, such as reproductive-age females.

The CAC score has predictive value regarding risk of CV events. In clinical practice, CAC scores are compared against age- and gender-matched averages to determine if levels are high or low. Higher CAC scores are associated with a greater risk for CV events. In turn, higher scores are linked to higher mortality. A study of more than 10,000 symptomatic women followed for 5 years found survival rates were proportionally worse as the patients’ baseline CAC scores increased.

A second technique for detecting preclinical atherosclerosis is using B mode carotid ultrasound to measure the carotid intima-media thickness (IMT). Carotid ultrasound does not use ionizing radiation and is therefore safer than CT. However, it is a technically challenging test that requires highly trained personnel and expensive equipment available only in specially equipped laboratories. In large studies, data have shown a significant association between increased carotid IMT and increased risk of MI or stroke.

Noninvasive imaging in rheumatic disease

An imaging study of coronary artery atherosclerosis in patients with systemic lupus erythematosus (SLE) found they had greater rates of atherosclerosis and earlier onset than matched controls without SLE. Patients with SLE had significantly greater scores for mean CAC and percentages with evidence of coronary calcification. When grouped by age, the prevalence of coronary calcification increased significantly in older patients, reaching 100% in the 60 years and older population (see Table 1). Although the study evaluated a relatively small patient population, the data suggest that patients with SLE develop premature atherosclerosis that can be tracked through assessment of coronary calcification.

<table>
<thead>
<tr>
<th>Age in years</th>
<th>SLE</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40</td>
<td>7%*</td>
<td>0</td>
</tr>
<tr>
<td>40-49</td>
<td>35%*</td>
<td>15%</td>
</tr>
<tr>
<td>50-59</td>
<td>79%*</td>
<td>21%</td>
</tr>
<tr>
<td>&gt;60</td>
<td>100%*</td>
<td>0</td>
</tr>
</tbody>
</table>

* statistically significant compared with controls

In a study of patients with RA, those with established RA had much higher incidences of coronary calcification than those with early RA or no RA, suggesting that duration of disease is a predictor of the likelihood of higher CAC scores. And similar to the age-dependency seen with SLE, older age was associated with greater prevalence of coronary calcification (see Table 2). In most age groups, existence of established RA was also associated with higher prevalence of calcification.

<table>
<thead>
<tr>
<th>Age in years</th>
<th>Early RA</th>
<th>Established RA</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td>15%</td>
<td>27%*</td>
<td>18%</td>
</tr>
<tr>
<td>50-59</td>
<td>53%</td>
<td>60%*</td>
<td>46%</td>
</tr>
<tr>
<td>&gt;60</td>
<td>81%</td>
<td>76%</td>
<td>61%</td>
</tr>
</tbody>
</table>

* statistically significant compared with controls

| Table 1. Prevalence by age of coronary calcification among patients with SLE |
|-----------------------------|-------------|-------------|-------------|
| Age in years                | SLE         | Controls    |
| <40                         | 7%*         | 0           |
| 40-49                       | 35%*        | 15%         |
| 50-59                       | 79%*        | 21%         |
| >60                         | 100%*       | 0           |

| Table 2. Prevalence of coronary calcification among patients with RA: Early vs established RA |
|-----------------------------------------------|-------------|-------------|-------------|
| Age in years                                | Early RA    | Established RA | Controls    |
| <50                                          | 15%         | 27%*         | 18%         |
| 50-59                                        | 53%         | 60%*         | 46%         |
| >60                                          | 81%         | 76%          | 61%         |
In a study evaluating carotid IMT in patients with RA, 44% had presence of plaque at study entry versus 15% in matched controls, a highly significant difference. Carotid IMT was also significantly greater. This study provides supporting evidence indicating that carotid IMT can detect the presence of premature atherosclerosis in these patients.

The study also illustrated the dramatic rise in existence of carotid plaque as patients with RA reach an older age group. After age 60, 80% of those with RA had documented plaque compared with 44% of controls (see Table 3). Age dependency was significant in all groups older than 40 years. This finding is significant because, rather than showing an increase in carotid IMT, it indicates the presence of actual plaque in the artery, which correlates with a very substantial risk of adverse cerebral vascular and cardiovascular outcomes.

Table 3. Prevalence by age of coronary calcification among patients with RA

<table>
<thead>
<tr>
<th>Age in years</th>
<th>&lt;40</th>
<th>40-49</th>
<th>50-59</th>
<th>&gt;60</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA</td>
<td>7%</td>
<td>52%*</td>
<td>52%*</td>
<td>80%*</td>
</tr>
<tr>
<td>Controls</td>
<td>0</td>
<td>12%</td>
<td>21%</td>
<td>44%</td>
</tr>
</tbody>
</table>

* statistically significant compared with controls

Further support comes from a study of patients with SLE in which 37% had carotid plaque versus 15% of controls, a significant difference. Age dependency was also significant with 73% and 71% of those aged 50 to 59 years and older than 60 years having carotid plaque versus 30% and 45% of age-matched controls, respectively. In all age groups, the SLE group was more likely to have carotid plaque than the control patients.

**Summary**

Based on the data, the following observations can be made:

- Multislice CT, which has replaced electron-beam CT, exposes patients to a higher radiation burden (and, thus, malignancy risk) than electron-beam CT.
- Changes in CAC scores do not correlate with disease progression. Thus, there is no rationale to support performing CAC imaging on more than a single occasion.
- Carotid IMT measurement imposes no radiation burden, but it is skill intensive and requires special laboratory equipment to perform the test, which limits its practical use.
- The ability of these noninvasive imaging modalities (multislice CT, CAC, and carotid IMT) to alter clinical outcomes in arthritic disease has not been established.

Although noninvasive imaging tests do have some predictive value for cardiac events, these tests do not provide consensus data to specify which patients to treat. In practice, patients with RA should be treated as if they have established CV disease — controlling blood pressure, starting cholesterol-reducing therapy, and eliminating adverse lifestyle risk factors, such as smoking.

**References**

There exists a heightened risk of CV disease in patients with RA. The primary cause of death in patients with inflammatory arthritis is CV disease. A recent meta-analysis\(^1\) of data on more than 100,000 subjects computed an overall hazard ratio for CV disease mortality of approximately 1.5 in patients with RA. These patients had increases of approximately 50% in ischemic heart disease, cardiovascular disease, and cerebral vascular disease. Inflammation has been linked to the development of atherosclerosis.

Traditional Framingham risk factors, such as age, gender, diabetes, blood pressure, smoking and dyslipidemia, do not fully capture the risks in patients with RA. Traditional risk factors only account for approximately 40% of the 10-year attributable risk for CVD, indicating other factors play a role in this patient population. Inflammation, which has been linked to the development of atherosclerosis, and oxidative stress are two factors thought to be involved.

In the past decade, studies have investigated the mechanisms of inflammation and how they are linked to atherosclerosis. Despite the investigations, there is no clear understanding of the precise underlying pathophysiologic mechanisms unique to RA that are linked to atherosclerosis.

**Myeloperoxidase**

One factor that may be involved in the development atherosclerotic plaque prone to rupture is the enzyme myeloperoxidase. Analysis of culprit lesions from coronary plaques in subjects with sudden cardiac death show intense immunostaining with myeloperoxidase. Increased blood levels of myeloperoxidase are also seen in patients with acute coronary syndromes, as well as within those with inflammatory arthritis.

Myeloperoxidase is the most abundant protein in the granules of neutrophils and monocytes, accounting for 3% to 5% of the dry weight of those cells. Myeloperoxidase normally plays a role in host defense against pathogens. Neutrophils and monocytes make reactive chlorinating species when fighting infection, and myeloperoxidase is the mechanism for that. Also, a large array of other reactive species are formed by myeloperoxidase. These species can be microbicidal to the pathogen; however, if inappropriately generated, they also can be damaging to normal host tissues. In the setting of atherosclerosis, many specific oxidation products that are dramatically enriched in atherosclerotic plaque are directly attributable to myeloperoxidase.

The idea that this enzyme is genetically linked to the development of atherosclerosis is evolving, with numerous lines of evidence. A growing body of data suggests that myeloperoxidase is linked to various stages in the development of atherosclerosis. It can consume nitric oxide and help generate or participate in endothelial dysfunction. In the plasma, it is bound to HDL, inhibiting its ability to remove cholesterol from cells at the artery wall. In the atherosclerotic plaque, it modifies HDL. It also modifies LDL, enhancing its ability to deposit cholesterol.

Clinical data have linked myeloperoxidase to plaque development. Myeloperoxidase has been shown to activate tissue-factor pathway activity,\(^2\) which is a known rate-limiting factor in thrombosis phenotype as well as a cause of apoptosis and sloughing of endothelial cells. Myeloperoxidase is enriched in culprit lesions of subjects with sudden cardiac death, such as in sites where fissuring or rupture occurs and where superficial erosions occur, which is the most common cause of intercoronary thrombus in smokers.

In patients presenting with acute chest pain, higher baseline myeloperoxidase levels have been associated with increased risk for myocardial infarction at presentation (see Table 1).\(^3\) Those with the highest levels of myeloperoxidase had a 4- to 5- fold increased risk for myocardial infarction, need for revascularization, or death in the next 6 months. This held true even for patients with normal EKG readings and normal cardiac troponin levels. High levels of myeloperoxidase in smokers also significantly increase their 3-year risk for major adverse cardiac event.

<table>
<thead>
<tr>
<th>MPO levels at baseline by quartiles</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI at evaluation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>1.0</td>
<td>1.2</td>
<td>2.1*</td>
<td>3.9**</td>
</tr>
<tr>
<td>MACE, 30 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>1.0</td>
<td>1.7*</td>
<td>3.3**</td>
<td>4.9**</td>
</tr>
<tr>
<td>Tropin negative</td>
<td>1.0</td>
<td>2.2**</td>
<td>3.7**</td>
<td>5.7**</td>
</tr>
<tr>
<td>MACE, 6 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>1.0</td>
<td>1.6*</td>
<td>3.6**</td>
<td>4.7**</td>
</tr>
<tr>
<td>Tropin negative</td>
<td>1.0</td>
<td>2.5**</td>
<td>3.8**</td>
<td>5.8**</td>
</tr>
</tbody>
</table>

\(^*\) \(P < 0.05\) vs Q1

\(^{**}\) \(P < 0.01\) vs Q2

MACE = major adverse cardiac events
Anti-CCP

One pathway linking smoking to increased CV risk may involve anti-cyclic citrullinated peptide (anti-CCP), an assay that is gaining in use within the RA field. The structure of citrulline is very close to a related amino acid, homocitrulline. Many antibodies to citrulline also recognize homocitrullinated proteins, which are post-translational modifications of proteins catalyzed by myeloperoxidase. Myeloperoxidase catalyzes the carbamylation of proteins (which forms carbamyllysine, which is identical to homocitrulline), particularly when thiocyanate levels are increased. Thiocyanate levels are increased in the plasma of smokers and individuals exposed to second-hand smoke. Leukocyte peroxidase-driven carbamylation serves as a mechanism linking inflammation, smoking, uremia, and atherogenesis.

Anti-CCP is a marker of RA in patients. Higher autoantibody titers to protein citrulline are associated with worse prognostic outcomes of RA and enhanced disease progression rate.

Myeloperoxidase-catalyzed carbamylation of LDL and HDL confers atherogenic properties. Carbamylated LDL has been shown to result in cholesterol deposition in the artery wall and several other factors associated with enhanced atherosclerosis.

Plasma levels of protein-bound carbamyllysine (homocitrulline) were increased in a case-control study of subjects with CV disease. This indicates that these levels serve as an independent predictor of CAD risk and burden.

The studies linking protein-bound homocitrulline levels to cardiac risks measure the antigen to protein-bound homocitrulline, not the antibody response. A higher systemic burden of these markers is associated with increased risk of adverse cardiac events. Plasma levels of protein-bound homocitrulline predict incident risks (3-year outcomes) for major adverse cardiac events: revascularization, non-fatal MI, stroke, or death (see Figures 1 to 3).

Figure 1. Plasma levels of protein-bound homocitrulline are increased in subjects with cardiovascular disease.

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Figure 2. Plasma levels of protein-bound homocitrulline are associated with increased risks for major adverse cardiac events (3-year outcomes).

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Since auto-antibodies titers of anti-CCP seen in RA also recognize homocitrulline, it may be that anti-CCP levels may not be measuring antibodies to citrulline but are actually measuring antibodies to carbamylated lysine, which is identical to citrulline in its chemical structure except that it has one more carbon. LDL modified by carbamylation has enhanced ability to be recognized by scavenger receptors, which leads to cholesterol deposition, the earliest step in the atherosclerotic process. Myeloperoxidase is a catalytic source for carbamylation at inflammation sites and in atherosclerotic plaque.

References
Rheumatoid arthritis is a disease of the synovial membrane. Patients with RA have an 8-fold increase in levels of proinflammatory cytokines in synovial fluid. C-reactive protein (CRP) is an acute phase protein that has been identified as a link to the underlying pathogenic cytokine events. The inflammatory events underlying the RA process lead to an increase in CRP, which is highly related to RA signs and symptoms. Higher CRP levels are highly correlated with higher disease activity and radiographic progression.1

Elevated levels of proinflammatory cytokines and CRP also play a significant role in the genesis of atherosclerosis and in plaque instability.2 A positive correlation of C-reactive protein (CRP) and coronary artery disease, which could be explained by the atherogenic effects of chronic inflammation, is well known. An association between minor but chronic elevation of serum CRP levels and future major cardiovascular events also has been shown.3

Baseline concentrations of CRP have been identified as an important predictor of subsequent mortality from CV disease in patients with new-onset rheumatic disease and are independent of other indicators of disease severity. This supports the theory that CRP may play a direct role in the pathogenesis of CV disease.4 Increased levels of CRP in patients with RA have been linked to dramatically reduced survival rates, primarily due to more CV disease.

Rheumatoid factor (RF) is also associated with more severe RA. Among patients with RA, those with RF-positive status have increased CV mortality.5 Because immune complexes are known to increase proinflammatory cytokine production in macrophage and RF participates in immune complex formation in the synovial fluid, this indicates that RF increases the inflammatory response in RA.

Circulating endothelial progenitor cells (EPCs) are another inflammatory factor thought to contribute to the increased CV risk in RA. Active RA has been associated with a depletion of these EPCs.6

**Link to CV events**

The classic outcomes of RA are joint damage and physical function, and more active disease is linked to increased joint damage.7 This link between active disease and reduced outcomes is also observed for overall mortality outcomes: the more joints affected, the lower the long-term survival rate.8 Similarly, CV morbidity and mortality is higher in patients with RA, especially in the context of higher disease activity. The odds ratio of having CV disease is higher in patients with RA, and increases with RA disease activity.

Since inflammation appears to have a role in the pathogenesis of CV events, measurement of markers of inflammation has been proposed as a method to improve the prediction of the risk of these events.9 High IL-6 and CRP and low EPC levels have been shown to be independent risk factors for future CV events. In patients with active rheumatoid disease, IL-6 and CRP are increased and EPCs are decreased. Significant associations of CV risk with IL-6 and CRP have been shown,9 probably due to the endothelial damage that occurs in the context of atherosclerosis and in the context of the overall inflammatory response that may induce apoptosis of endothelial progenitor cells. Similarly, EPCs are inversely correlated with risk and mortality in CV disease.10 Circulating EPC levels appear to be important for angiogenesis, and low levels of circulating EPC are associated with high CV risks.

**Treatment**

All therapies that induce RA disease remission halt the progress of radiographic joint damage. Observational retrospective studies indicate that effective RA treatments reduce CV risk, including the endpoints of MI, heart failure, and CV disease incidence as well as CV disease mortality (See Table 1).11-13 However, no formal outcome studies are available.

**Table 1. Reduced CV risks associated with effective RA treatments**

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>All CV disease</td>
<td>Adjusted Hazard Ratio (95% CI)</td>
</tr>
<tr>
<td>MTX</td>
<td>0.84 (0.80-0.87)</td>
</tr>
<tr>
<td>Anti-TNF</td>
<td>0.71 (0.56-0.89)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>Adjusted Hazard Ratio (95% CI)</td>
</tr>
<tr>
<td>MTX</td>
<td>0.82 (0.74-0.91)</td>
</tr>
<tr>
<td>Anti-TNF</td>
<td>0.42 (0.21-0.81)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>Incidence</td>
</tr>
<tr>
<td>No anti-TNF</td>
<td>3.8%</td>
</tr>
<tr>
<td>Anti-TNF</td>
<td>3.1%</td>
</tr>
<tr>
<td>Between groups</td>
<td>(P &lt; 0.05)</td>
</tr>
<tr>
<td>CV mortality</td>
<td>Adjusted Hazard Ratio (95% CI)</td>
</tr>
<tr>
<td>MTX</td>
<td>0.3 (0.2-0.7)</td>
</tr>
<tr>
<td>No MTX</td>
<td>0.6 (0.2-1.2)</td>
</tr>
<tr>
<td>MTX vs no MTX</td>
<td>0.4 (0.2-0.8)</td>
</tr>
</tbody>
</table>
The effect of remittive therapy for inflammatory arthritis on CV risk is most likely due to effects on the inflammatory response, as evidenced by the reduction in CRP levels. In studies, anti-inflammatory agents (TNF-inhibitors, methotrexate, leflunomide, and other DMARDs) have been shown to improve (ie, reduce) CRP levels and raise EPC levels. With TNF inhibitors, the degree of prevention is greater, especially in patients with high disease activity. This suggests that TNF blockers (and possibly other biologic agents) could partly dissociate the link between inflammation and CV risk, as they do regarding joint damage.

Summary

Although the current evidence is primarily observational, several comments regarding proinflammatory cytokines and CV morbidity and mortality risks can be made.

- Cytokines mediate both the inflammation leading to RA characteristics and the RA-related CV risk.
- Rheumatoid factor is associated with both a higher activity and destructive propensity of RA as well as higher CV risk and higher mortality.
- Effective therapy reduces the signs and symptoms, joint damage, and disability associated with RA, and it appears to reduce mortality and the CV risk. Effective therapies include synthetic DMARDs, TNF-inhibitors, and, possibly, other biologics.
- The effect of RA therapies is probably mediated by the reduction of cytokine levels and CRP, and the normalization of EPC lengths.
- For TNF-inhibitors, the reduction in levels may be independent of the reduction in overall symptoms of RA and joint damage.

Disease activity drives the synovitis that drives disease damage and other systemic comorbidities, including CV disease, and eventually results in disability. Cytokines are the major culprits driving this cascade of disease activity. Thus, effective therapy that interferes with cytokines would interfere with all of these aspects, improving the overall disease outcomes.

References

The objective of this article is to look at what is known about CV in inflammatory arthritis, what is suspected but not proven, and what is not known but needs to be known.

**What is known**

Rheumatoid arthritis has been shown in cohort data to be an independent risk factor for accelerated CV morbidity and mortality, even after adjustment for conventional CV risk factors. This implies that the effect of RA is mechanistically different from conventional CV risk factors, although it has not been conclusively proven. The effect is customarily ascribed to rheumatoid inflammation. However, because there are very few well-designed studies linking RA disease activity with CV outcomes, the exact link can only be speculated.

**What is suspected but not proven**

Current hypotheses are that the increased CV risk associated with RA is due to inflammation. Epidemiologic studies, however, have not been able to define the pathogenesis of the inflammation. Is it in the vasculature, muscle, or fat? Is it mediated through the innate immune system or the adaptive immune system?

It is important to realize that in studies, the measures of disease activity and severity in inflammation are not correlating these with CV outcomes. Using a crude measure such as C-reactive protein (CRP) levels, it is not possible to distinguish what is due to rheumatoid inflammation and what is due to inflammation associated with conventional risk factors. Levels of CRP can be elevated in hypertension without RA and in diabetes without RA. Although studies have not been able to distinguish rheumatoid inflammation from conventional risk inflammation, the metabolic and inflammatory pathways are tightly linked.

Several conventional risk factors are known to be increased in patients with RA (see Table 1).1-4 Among these are higher rates of smoking and elevated dyslipidemia. Although body mass indexes are not generally increased, fat mass is greater. There is more insulin resistance and higher rates of the metabolic syndrome. Some evidence indicates increased prothrombotic disease. This shows that there are interactions between conventional risk factors and inflammation.

### Table 1. Frequencies of conventional risk factors for atherosclerosis in patients with RA1-4

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Prevalence in RA vs controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>Equivalent or increased</td>
</tr>
<tr>
<td>Smoking</td>
<td>Increased</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>Increased</td>
</tr>
<tr>
<td>Obesity</td>
<td>Equivalent or increased</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Equivalent</td>
</tr>
<tr>
<td>Insulin resistance (ie, metabolic syndrome)</td>
<td>Increased</td>
</tr>
<tr>
<td>Prothrombotic markers</td>
<td>Increased</td>
</tr>
<tr>
<td>Hyperhomocystenemia</td>
<td>Equivalent or increased</td>
</tr>
</tbody>
</table>

Evidence shows that increased fat mass is highly correlated with elevated CRP in women with RA.5 There is a linear relationship between CRP and fat mass, whether these patients have few or many swollen and tender joints. This indicates that body fat also contributes to CRP elevation in RA patients.

Evidence from animal and human studies shows that infusing TNF alpha can induce a state of insulin resistance. This insulin resistance is thought to be the basic pathology that leads to the metabolic syndrome and, ultimately, CV disease (see Figure 1).
Inflammation can drive this pathway and may be one of the major ways that RA conveys CV risk. Obesity is known to be associated with insulin resistance. It may be that there is a pathway through inflammatory cytokines. Adipose tissue produces inflammatory cytokines, so there is a pathway that obesity exerts through inflammation to insulin resistance. The point is that the metabolic pathways and inflammatory pathways can be very tightly linked. It is important to note that most well-designed studies do not associate CV risk with disease duration. This suggests that the risk for CV may occur early, even before joint symptoms appear. This implies that the risk for CV disease predates swollen joints. Also, there are RA factors that are not directly correlated with inflammation but that may contribute to the pathogenesis of CV disease in the RA population. It is unclear if there is an association between CV disease and CRP given that some studies show an association but others do not. The point is that there are RA-related factors that are not related to inflammation but that may contribute to the CV risk.

One might hypothesize that CV risk associated with RA is due to two processes. In the first, the disease has a direct effect on the vasculature in which it disrupts the endothelium and suppresses repair of the endothelium leading to accelerated atherosclerosis and, possibly, congestive heart failure. But there seems to be another process in which systemic inflammation induces metabolic risk through insulin resistance and dyslipidemia. Some evidence indicates that adverse body composition (increased fat mass and decreased muscle mass) also has some effect on the CV risk.

**Clinical implications**

1. Targeting and aggressively managing conventional CV risk factors in patients with RA might also reduce the effects of inflammation. Efforts are needed to manage both the rheumatoid inflammation and conventional CV risk factors because they intersect. When we treat one, we treat the other.

2. Nonspecific measures of inflammation cannot distinguish between RA inflammation and inflammation associated with CV risk. Thus, both RA and CV risk factors need to be treated aggressively.

3. There are other RA-associated risk factors that cannot be altered by treatment but that may be contributing to CV risk, such as genetic predisposition.

**What is not known but needs to be known**

Three things are not known regarding CV disease in patients with RA:

- Exact mechanisms of increased risk for CV disease,
- Effect of RA treatments on CV risk, and
- How to screen and quantify risk.

Few data are available to address these areas; however, given that patients with RA have increased risk of CV disease, it appears these patients should be screened for metabolic risk and, possibly, for the prevalence of clinical atherosclerosis. But how to screen and what tools to use remain to be determined. Few data are available to guide these decisions. The epidemiologic studies available lack detailed information on both risk factors and CV outcomes in RA, limiting their clinical usefulness. Nevertheless, subclinical data suggest that RA conveys the same amount of increased risk for coronary calcium and plaque as diabetes or male gender.

**Screening and assessing CV risk**

Two noninvasive methods are available to measure subclinical disease — coronary artery calcification (CAC) via CT scan and carotid IMT — but both have drawbacks. The CT scans subject patients to considerable radiation, and a carotid IMT is very difficult to measure in routine clinical situations. Nevertheless, they may have roles to play in predicting CV events. In the MESA study (MultiEthnic Study of Atherosclerosis) of nearly 7,000 patients aged 45 to 84 years, high CAC scores had high hazard ratios for predicting coronary events whereas carotid IMT was not as potent of a predictor. However, the changes to hazard predictions are modest in this study, indicating that the Framingham scoring system in the general population is still an accurate predictor of subsequent CV events. Adding the CAC, despite its exaggerated hazard ratios, does not add appreciably to the conventional risk factors that can be measured at the bedside.

**Treatment recommendations**

Regarding the effect of RA treatments on CV risk, data are not conclusive. A compilation of data from five studies measuring the effect of TNF inhibitors on risk of CV events found that there was no consistent effect (see figure 2). Therefore, at this time, there is no conclusive evidence that these agents definitely reduce CV risk.
Without data, how should patients with RA be screened and treated to reduce their CVD risk? Clearly, tight control of RA is needed. It has to be assumed that whatever the factor in RA that influences the CV risk, controlling RA will help control the CV risk. Tight control of conventional CV risk factors is also needed. In general, patients with RA have higher fat levels, more insulin resistance, and more dyslipidemia, and they are less physically active. Because inflammation and metabolic pathways are intertwined, treating one is going to help the other. Furthermore, RA drug therapies alone may not make much of a difference. Thus there is a need to continue to reduce CV risk by emphasizing lifestyle interventions such as exercise, weight reduction, and control of hypertension and lipids.

Traditional risk factor screening (see Sidebar) is needed every year in this patient population. Because of the increased risks seen with RA, RA should be considered to be a risk factor equivalent to diabetes and add one risk category to a patient with a low or medium Framingham score. That will change the lipid goals recommended by the ATP3 guidelines.

**Sidebar: Traditional risk factors screening**

- Fasting lipid profile
- Fasting glucose
- Resting blood pressure
- Review smoking history
- Calculate BMI
- Measure waist circumference
- Review family history

Higher level screening with carotid ultrasound to determine whether plaque is present or not may not be unreasonable, although there are no data that indicate it adds to prediction models in RA. The same is true for CT scans to measure coronary calcium; furthermore, most insurance companies will not pay for this test, so it may not be practical.

 Ideally, all patients with RA should be treated with aspirin. However, most of these patients are on NSAIDs, and aspirin will increase their risk of gastrointestinal bleeding. Proton pump inhibitors can reduce the risk, but it may still be elevated.

Use of statins should also be considered, based on clinical trial data showing that even in the absence of elevated low density lipoproteins, statin therapy reduces CV events. Exercise and weight control will help restore insulin sensitivity and reduce fat deposits in the belly, which make the most inflammatory mediators. Finally, it is important for practicing physicians to recognize the increased risk in patients with RA and take measures to reduce those risks.

**References**


