Rheumatoid Arthritis and Cardiovascular Disease

Cynthia S Crowson, MS1, Katherine P Liao, MD MPH2, John M Davis III, MD1, Daniel H Solomon, MD MPH2, Eric L Matteson, MD MPH1, Keith L Knutson, PhD1, Mark A Hlatky, MD3, and Sherine E Gabriel, MD MSc1

1Mayo Clinic, Rochester, MN
2Brigham and Women’s Hospital and Harvard Medical School, Boston, MA
3Stanford University School of Medicine, Stanford, CA

Abstract

Background—Rheumatic disease and heart disease share common underpinnings involving inflammation. The high levels of inflammation that characterize rheumatic diseases provide a “natural experiment” to help elucidate the mechanisms by which inflammation accelerates heart disease. Rheumatoid arthritis (RA) is the most common of the rheumatic diseases and has the best studied relationships with heart disease.

Methods—Review of current literature on heart disease and rheumatoid arthritis

Results—Patients with RA have an increased risk of developing heart disease that is not fully explained by traditional cardiovascular risk factors. Therapies used to treat RA may also affect the development of heart disease; by suppressing inflammation, they may also reduce the risk of heart disease. However, their other effects, as in the case of steroids, may increase heart disease risk.

Conclusions—Investigations of the innate and adaptive immune responses occurring in RA may delineate novel mechanisms in the pathogenesis of heart disease, and help identify novel therapeutic targets for the prevention and treatment of heart disease.

Introduction

The role of inflammation in the development of heart disease has only been recognized relatively recently. Rheumatic disease can be viewed as a ‘natural experiment’ in the interplay between chronic inflammation and heart disease, which could elucidate the fundamental mechanisms by which inflammation accelerates development of atherosclerosis and heart disease. Rheumatoid arthritis (RA), systemic lupus erythematosus, Sjögren’s syndrome, systemic scleroderma, inflammatory myositis and psoriatic arthritis are characterized by chronic inflammation in various body systems, most often the joints, skin, eyes, lungs, and kidneys, but also in the heart and vascular system. RA is the most common and best studied of the autoimmune rheumatic diseases, and will be the primary focus of this overview.

The immune underpinnings of heart disease and RA share many similarities. In addition, circulating acute phase reactants, such as C-reactive protein (CRP), are substantially elevated in RA and are risk markers for heart disease in the general population. Understanding the factors responsible for heart disease in patients with RA, such as
abnormal immunity and chronic inflammation, may lead to novel therapeutic targets in the prevention of heart disease.

Epidemiology of heart disease in RA

Patients with RA have a 1.5–2.0 fold increased risk of developing coronary artery disease (CAD) compared with the general population (1,2), similar in magnitude to the risk imparted by diabetes mellitus (3). This increased CAD risk is evident even before the clinical recognition of RA: at diagnosis, individuals with RA were over three times as likely to have had a prior myocardial infarction (MI) than subjects without RA (2). An expert committee of the European League Against Rheumatism has recommended that CV risk scores (e.g., Framingham) be multiplied by 1.5 in some patients with RA to reflect their increased risk of heart disease (4).

Patients with RA also have twice the risk of developing heart failure (5). This risk is more pronounced in the RA patients who are rheumatoid factor positive than among seronegative patients. Patients with RA are less likely to have typical signs and symptoms of heart failure, tend to be managed less aggressively and have poorer outcomes (6). Importantly, patients with RA and heart failure are more likely to have a preserved ejection fraction (>50%), and less likely to have clinical evidence of CAD. Patients with RA may have a reduced likelihood of developing heart failure after MI (7). Collectively, these findings suggest patients with RA are more likely to have heart failure due to diastolic dysfunction, which may be related to systemic inflammation.

The possible effect of RA on the risk of non-cardiac vascular disease is less clear. Some reports have noted increased risks of cerebrovascular disease in RA (8), while others have not (9). Overt and subclinical peripheral vascular disease appears to be increased in patients with RA, and is associated with severity, particularly extraarticular systemic disease (10–12). The risk of venous thromboembolism appears to be increased 2–3 fold in RA compared with the general population (9,13).

CV risk factor profile in RA

Patients with RA tend to have a different profile of cardiac risk factors, including a higher frequency of smoking and an altered lipid profile, compared with the general population. The lipid profile in RA is characterized by suppression of total and LDL cholesterol levels during periods of high-grade inflammation, with a proportionately greater suppression of high-density lipoprotein (HDL) levels, yielding an unfavorable ratio of total to HDL cholesterol. Lipid levels have a paradoxical relationship with CAD risk in RA, since lower lipid levels are associated with more severe systemic inflammation, which in turn is associated with increased CAD risk (14). Inflammation in RA also appears to alter lipoprotein structure and function (15); the serum amyloid A load carried by HDL increases and Apolipoprotein A-I decreases, altering the usual anti-atherogenic effects of HDL and resulting in pro-atherogenic effects (16).

Patients with RA are more likely to have lower muscle mass and low body mass index, which may result from uncontrolled inflammation, limitations of physical activity, or both. Low body mass in RA appears to be associated with a worsened prognosis (17). Cachexia, characterized by low muscle and fat mass, is now uncommon in RA, but the combination of low muscle mass and high fat mass is more prevalent in patients with RA and may be even more problematic from a heart disease perspective (18). Visceral adiposity in RA is associated with insulin resistance, hypertension, metabolic syndrome, and a greater inflammatory load (18).
Hypertension is common and it appears to be underdiagnosed and undertreated in RA (19). Hypertension in RA may be exacerbated by inflammation and medications.

Increased risk of heart disease in patients with RA is associated with elevation of inflammatory markers, including CRP, erythrocyte sedimentation rate, rheumatoid factor, anti-citrullinated protein antibodies, and with more active or severe RA (20). Rheumatoid factor and anti-nuclear antibodies have been associated with heart disease and overall mortality, even in patients without rheumatic diseases (21).

**Heart Disease Management/Outcome in RA**

Patients with RA are typically managed by several physicians, and coordination of care may be suboptimal. Smoking cessation and control of standard risk factors are all indicated in patients with RA, but may be underused because of the understandable focus on management of RA itself. Despite the well understood benefits of exercise on general and cardiovascular health, the majority of patients with RA do not pursue a regular exercise program (22, 23). Both aerobic and resistance exercise training for patients with RA has been shown to be efficacious in improving overall well being, the muscle mass loss associated with RA, and markedly improving physical function without exacerbating disease activity and is likely to reduce cardiovascular risk, and should be part of routine care (24–29).

There is evidence that patients with RA are less likely to receive both primary and secondary heart disease prevention. Only 55% of RA patients in one study had lipid levels measured; management by rheumatologists was associated with less lipid screening (30). Rheumatologists were less likely to identify and treat cardiac risk factors than primary care physicians (31). Angina may also be under diagnosed, with chest pain attributed to RA instead of CAD, perhaps because the increased risk of CAD is not understood by treating physicians, and referral to a cardiologist is less likely. Patients with RA and an acute MI were less likely to receive reperfusion therapy and secondary prevention medications, such as beta blockers and lipid-lowering agents (32). Patients with RA were also less likely to undergo coronary artery bypass grafting than patients without RA (2).

**Effect of RA Therapies on CV Risk in RA**

RA therapies target inflammation, a CV risk factor that is also important in patients without rheumatic disease. Understanding how these therapies also modify CV risk in RA may provide insight into the inflammatory component of CV risk for all patients.

Glucocorticoids have been widely used in RA to acutely control pain and inflammation associated with RA flares. However, the beneficial anti-inflammatory effects of glucocorticoids, which can improve mobility, are also accompanied by adverse effects, including increasing CV risk factors and worsening heart disease outcomes. Glucocorticoid use is associated with carotid plaque and arterial stiffness, decreased insulin sensitivity, elevated lipid levels, and hypertension (33, 34). Patients treated with high dose steroids (>7.5mg/day prednisone) appear to have twice the risk of heart disease compared with those who do not receive steroids (35). Use of low-dose glucocorticoids to treat active inflammatory disease might have more benefits than harms, but this requires further investigation.

The long standing concern about CV risk with nonsteroidal anti-inflammatory drugs (NSAIDs) use was magnified after studies of the selective cyclo-oxygenase-2 inhibitors (coxibs). The VIGOR (Vioxx Gastrointestinal Outcomes Research) study found an increased risk of heart disease events with rofecoxib use, which led to its removal from the market (36). By contrast, another trial found no differences in heart disease events among subjects...
randomized to receive celecoxib or ibuprofen (37). Finally, a network meta-analysis of 7 NSAIDs, including 4 coxibs, suggested that naproxen conferred the lowest CV risk, while the remaining 6 NSAIDs appeared to confer similar risk for CVD (38). A large trial currently enrolling patients, including those with RA, will assess differences between NSAIDs and risk of heart disease (39).

Methotrexate, a first-line treatment for RA, has been associated with lower CV risk. A recent meta-analysis found that methotrexate use was associated with 21% fewer CV events (Figure 1)(40). Methotrexate does not appear to alter lipid profiles (41), and there is insufficient evidence about its effects on insulin resistance, hypertension or atherosclerotic plaque burden. Nevertheless, the apparent benefit of methotrexate in reducing heart disease risk in RA, and the strong evidence that CRP is a risk factor for heart disease, led to the development of a large randomized trial (http://ClinicalTrials.gov identifier: NCT01594333) designed to determine whether low dose methotrexate reduces heart disease risk in post-MI patients who have metabolic syndrome or diabetes mellitus (42).

Tumor necrosis factor (TNF) inhibitors are frequently used in RA patients who do not achieve adequate disease control with other therapies. Roughly 30–40% of RA patients in the US received a TNF-inhibitor either as monotherapy or in combination with other medications. TNF-inhibitor therapy in patients with RA appears to be associated with reduced risk of all heart disease events (Figure 1)(43). If this reduced CV risk is true, it may be mediated by effects on controlling inflammation, rather than by favorable modifications of CV risk factors. In general, TNF-inhibitors appear to elevate total and HDL cholesterol, resulting in a stable atherogenic ratio (44). In addition, since RA disease activity appears to be inversely correlated with HDL levels, treatments that control RA activity may favorably affect HDL levels (45). It is unclear, however, whether TNF-inhibitors exert a class effect on lipids, or if specific TNF-inhibitors achieve more favorable lipid profiles. TNF-inhibitors may improve endothelial function and insulin resistance; their effect on arterial stiffness is unclear, with one study showing improvement and another finding no change with therapy (44,46–48).

There is insufficient evidence regarding the effect of other disease modifying antirheumatic drugs and heart disease risk. Hydroxychloroquine is associated with a decreased risk of diabetes mellitus in patients with RA (49), and may also improve lipid profiles, with evidence of decreased LDL and total cholesterol/HDL ratios (50). Tocilizumab, a humanized antibody that targets the IL-6 receptor, increases LDL, HDL and triglyceride levels during clinical trials (51). The long term clinical significance of these perturbations in lipid levels remains unknown.

Effect of Heart Disease Therapies in Patients with RA

There have been relatively few patients with rheumatic diseases enrolled in major clinical trials of primary or secondary prevention. While commonly used CV therapies are presumed to be effective in patients with RA, there is little direct evidence of their efficacy.

Statins (hydroxymethylglutaryl CoA reductase inhibitors) appear to reduce vascular inflammation and, have been tested for efficacy in the treatment of RA. Atorvastatin treatment resulted in a small reduction in RA disease activity compared with placebo, suggesting that statins may reduce inflammation directly (52). Small studies in patients with RA have also shown improvements in arterial stiffness and endothelial dysfunction with atorvastatin (53,54). Statin discontinuation for ≥3 months in patients with RA resulted in a 2% increased risk of acute MI for each month of discontinuation (55). Notably, statin therapy has also been found to impair the effectiveness of rituximab (56), so drug interactions will be important to consider in the clinical management of patients with RA.
Aspirin was the mainstay of RA treatment until the development of prescription NSAIDs in the 1970’s. Aspirin has been highly effective in secondary and primary heart disease prevention, but few studies included patients with rheumatic diseases. Aspirin doses for heart disease prevention are far below those used for RA treatment in the past (ranging from 2600 to 4800mg/day) (57). Moreover, the gastrointestinal bleeding risks of chronic aspirin use in RA patients, who frequently use NSAIDs and glucocorticoids, may shift the balance away from CV benefit.

**Mechanisms of RA Pertinent to Cardiovascular Disease**

Emerging evidence suggests that T lymphocytes play a crucial pathogenic role in both RA and heart disease (58,59). The major risk gene for RA, HLA-DRB1, predisposes to disease by promoting the selection and survival of autoreactive CD4+ T cells. HLA-DRB1 alleles are also associated with increased risk of MI and various forms of non-RA-associated heart disease(60,61). As in heart disease, T cells isolated from the joints of patients with RA have enhanced production of interferon-γ and interleukin-17, which presumably mediate chronic inflammation (62,63). The proven efficacy of antagonizing T-cell co-stimulation is perhaps the most compelling evidence that T cells are pathogenic in RA (64). Similarly, percutaneous stents that elute T-cell inhibiting drugs (e.g., sirolimus) prevent in-stent restenosis and repeat re-vascularization in CAD(65).

In persons with either RA or heart disease, CD4+ T cells characteristically lose expression of the co-stimulatory molecule, CD28, which ordinarily provides the ‘second signal’ required for T-cell activation. So-called ‘CD28null’ T cells are believed to have undergone reprogramming, leading to premature senescence (66). Expansion of these senescent T cells among persons with RA is associated with extra-articular inflammatory manifestations, including vasculitis and lung disease, as well as CAD (67,68). In the setting of heart disease, CD28null T cells are identified in atherosclerotic plaque, where they are believed to contribute to the inflammatory process by producing cytokines and by killing vascular smooth muscle cells (69). Interestingly, HLA-DRB1, the aforementioned RA-risk gene, also predisposes to expansion of CD28null T cells in RA and in CAD(61,70).

Premature senescence of T cells in RA appears to be caused by fundamental defects in the hematopoietic system. CD34+ hematopoietic progenitor cells have accelerated telomere erosion, a sign of senescence (71). Naïve T cells in persons with RA also are prematurely aged, with increased fragility and damage of their DNA due to insufficient activity of basic DNA repair enzymes (72,73). Similarly, telomere shortening in hematopoietic progenitor cells correlates with myocardial dysfunction in patients with CAD (74). The onset of both RA and heart disease coincides with the loss of thymic emigration of naïve T cells in the fifth decade, suggesting that T-cell senescence may underlay the pathogenesis of both of these age-associated conditions. In the foreseeable future, rejuvenation of senescent T cells, using new drugs that restore genomic repair and integrity, could potentially be an effective strategy for the prevention and treatment of cardiovascular disease (75).

**CONCLUSION**

Heart disease remains a major problem for patients with RA. Systemic inflammation plays a major role, through direct and indirect effects on the vasculature (Figure 2). More research is needed to delineate the disease mechanisms, and to develop and evaluate risk assessment tools, biomarkers, prevention strategies and treatments that are specific to RA. The CV risk in patients with RA is not well recognized by practicing physicians, and better recognition and control of traditional risk factors in patients with RA is important. Coordination of care among rheumatologists, cardiologists, and primary care physicians will be needed for
optimal management of CV risk in patients with RA. Tight control of systemic inflammation among patients with RA may also reduce CV risk. Symptoms suggestive of CAD in patients with RA should be evaluated promptly, and early referral to a CV specialist for appropriate evaluation and treatment provides the best chance of optimizing outcomes.

Disentangling the relationship between inflammation, immune modulating treatment and CV risk in RA is difficult. Specific disease modifying drugs (e.g., methotrexate and TNF-inhibitors) effectively control inflammation in RA and also reduce CV risk. In contrast, glucocorticoids increase CV risk because of their adverse metabolic effects, which apparently outweigh their anti-inflammatory benefits. Common treatments to reduce CV risk (e.g., statins) are likely to be effective in patients with RA, but this supposition has little empirical support. Currently enrolling trials such as one administering methotrexate (a first-line treatment for RA) to post-MI patients without RA, should provide insight regarding whether reducing inflammation alone is associated with reduced CV risk (76).

Finally, similar pathways in RA and heart disease might be considered as therapeutic targets, such as T-cell-directed or anti-cytokine therapies (IL-1, IL-6, etc.) (77,78). Indeed, an anti-IL-1β monoclonal antibody (canakinumab) is being studied for heart disease treatment (79). These studies are anticipated to provide valuable new insights into the pathophysiology and treatment of heart disease.

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Abbreviations

- **CAD**: coronary artery disease
- **CRP**: C-reactive protein
- **CV**: cardiovascular
- **HDL**: high density lipoprotein
- **LDL**: low density lipoprotein
- **MI**: myocardial infarction
- **NSAID**: non-steroidal anti-inflammatory drug
- **RA**: rheumatoid arthritis
- **TNF**: tumor necrosis factor

Appendix

The studies included in this Review were identified by searching PubMed using an extensive list of phrases related to the topic of interest. The searches were restricted to full-text papers in the English language. This manuscript is not intended to be a systematic review or a meta-analysis. Papers cited in this Review were selected based on methodologic strength,
whereby evidence from randomized controlled trials and population-based studies were preferred.

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References


Figure 1.
Figure 2.