Inflammation beyond the Joints: Rheumatoid Arthritis and Cardiovascular Disease

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Abstract
Rheumatoid Arthritis (RA), a chronic systemic inflammatory disease which affects approximately 1% of the population, is classically characterized by inflammation and synovitis that leads to cartilage damage and juxta-articular bone destruction. Accumulating evidence indicates that a major cause of death among RA patients is Cardio Vascular Disease (CVD), in excess of that in the general population. In this review, we discuss the epidemiology of CVD in RA populations, the underlying pathophysiologic mechanisms of CVD in RA including the role of chronic inflammation in driving accelerated atherosclerosis, the obesity paradox and altered metabolic pathways leading to pro-inflammatory HDL formation and insulin resistance. We also discuss the pitfalls in the evaluation of CVD utilizing traditional risk scores which tend to underestimate CVD risk in RA population and the efforts directed to find more accurate predictors for early CVD detection. Finally, we will present the latest developments in the evaluation and management of CVD in RA patients, given recent evidence on the role of inflammation and its impact on CVD.

Keywords
Rheumatoid Arthritis; Cardiovascular Risk Factors; Cardiovascular Disease; Risk Assessment; Cardiovascular Outcomes; Pathogenesis; Treatment; Evaluation

Introduction
Rheumatoid Arthritis (RA), a chronic systemic inflammatory disease which affects approximately 1% of the population, is classically characterized by inflammation and synovitis that leads to cartilage damage with joint space narrowing and juxta-articular bone erosions. CVD risk is increased among RA patients as demonstrated by numerous epidemiological studies, as the presence of traditional Cardio Vascular (CV) risk factors do not explain the higher rate of CV events seen in this population. The inflammatory milieu of RA, marked by elevations of serum inflammatory mediators and endothelial dysfunction, creates an opportune climate for the development of atherosclerosis and cardio myocyte dysfunction. Accordingly, CVD in RA is associated with active RA disease as measured by
joint swelling, extra-articular disease, and elevated serum inflammatory markers. Clinically, RA patients with CVD present with an increased rate of silent cardiac disease, atypical symptoms and diastolic heart failure. Predicting CVD and evaluating the risk have proven to be difficult in RA, in part due to the paucity of studies and challenges with risk calculator models. Imaging techniques and special functional tests may provide more reliable tools to assess risk and progression of CVD in this patient population. Optimizing prevention and management in RA includes a combination approach that addresses traditional risk factors and inflammation.

**Epidemiology**

The recognition that RA carries a heightened CVD morbidity and mortality derived from a number of reviews and meta-analysis. In a review that included 91,618 patients, CVD accounted for 39.6% of all deaths [1]. One meta-analysis comprising 111,758 patients found a 50% increased risk of CVD death, with Ischemic Heart Disease (IHD) and Cerebral Vascular Accidents (CVA) accounting for 59% and 52% increased risks, respectively [2]. Another meta-analysis of 14 observational studies concluded a 48% increased risk of incident CVD in patients with RA, with the risk of Myocardial Infarction (MI) and CVA being increased by 68% and 41%, respectively, with a single study identifying the risk of Congestive Heart Failure (CHF) increased by 87% [3]. These statistics are supported by a recent prospective population-based cohort study of CVD end-points showing that RA patients had higher rates, via adjusted incidence ratio (IRR) of MI (IRR: 1.43), unheralded coronary death (1.60), heart failure (1.61), cardiac arrest (2.26), peripheral arterial disease (1.36) and lower rates of stable angina (hazard ratio: 0.83) [4]. Increased incidence of CV events in RA patients have been linked to that in diabetics, with a two-fold increase compared to the general population [5].

Most recently, a large population-based study matched RA patient’s ≥15 years of age to individuals without RA. The mortality rate for RA patients was 232-compared to184 in the non-RA population (14% versus 9%). Overall, RA patients had increased all-cause mortality, but age specific mortality ratios suggested excess mortality among patients younger than 45 years due to respiratory and circulatory diseases [6]. The majority of population-based studies are derived primarily from European and North American cohorts. A recent cross-sectional study of Chinese patients showed an approximately two-fold increased risk of CVD, IHD and CHF in RA patients compared to age and sex-matched controls [7]. One South African study looked at CVD in RA patients belonging to an African Black population cohort. Their review argues that CVD in RA occurring in developed population cohorts cannot be extrapolated to developing countries population as further research is needed to ascertain the true disease prevalence given the degree of heterogeneity in ethnicity and geographic locations [8].

**Pathophysiology**

The pathophysiology of CVD in RA involves immune dysregulation and chronic inflammation which results from the interaction of genetic and environmental factors [9]. Inflammation favors atherosclerotic CVD, with inflammatory markers like C Reactive
Protein (CRP) considered independent predictors for coronary heart disease in the general population [10, 11]. Evidence supports that inflammation is the major driver of excess CVD in RA [12, 13].

Systemic Inflammation and Endothelial Dysfunction

Elevated levels of cytokines such as tumor necrosis factor-α (TNF-α), interleukin-17 (IL-17), interleukin-6 (IL-6), and interleukin-1β (IL-1β) are found in both RA and CVD, with higher levels being present in RA [10, 14–16]. These cytokines have been implicated in endothelial cell activation, a crucial step for pannus formation in the synovial tissue and in the pathogenesis of atherosclerotic CVD [10, 17, 18]. (Figure 1) Endothelial activation induces cellular expression of chemokines and adhesion molecules that enable leukocyte migration into the joint space or vascular intima which favor further neutrophil recruitment, activation and propagation of the local inflammatory process [19–21]. IL-17 induces endothelial cells to express chemokines that promote neutrophil recruitment [22]. Local T1 helper cells release interferon-gamma (IFN-γ) which, together with TNF-α and IL-17, causes endothelial cell apoptosis, [23, 24] eliminating the endothelial cells’ anti-thrombotic properties [25]. In the inflammatory milieu of RA, atherosclerotic plaques are particularly unstable and vulnerable to rupture [26, 27]. TNF-α and IL-17 also prevent nitric oxide and thrombomodulin synthesis and, along with IL-1, increase tissue factor production and activation [17, 28–31]. Similarly, IL-6 increases levels of fibrinogen and IL-6 receptor signaling pathways play a causal role in coronary heart disease [29, 32]. In concert, these actions create a hypercoagulable environment in the vascular lumen.

Results of cytokine-targeted therapy studies provide proof-of-concept in vivo, confirming the role of the cytokines and inflammation in RA pathogenesis. For example, TNF-α blockade improves endothelial-dependent vascular function in RA patients [33]. In patients with Coronary Artery Disease (CAD), anti-IL-1β therapy significantly reduced the rate of subsequent CV events, independent of lipid-lowering [34]. Furthermore, IL-6 receptor inhibition lessened the inflammatory response and release of troponin-T after acute MI [35].

In addition to direct pro-atherogenic effects, TNF-α and IL-17 increase insulin resistance, alter lipid levels and function, and create oxidative stress. IL-17 also affects cardiomyocytes by inducing inflammation and apoptosis which result in myocardial remodeling due to increased cardiac fibroblast activity and collagen production [36–39]. These processes likely contribute to the development of cardiomyopathy and heart failure [40].

There is also widespread vascular dysfunction with impaired vasodilation, which positively correlates with elevated inflammatory markers such as high sensitivity CRP (hsCRP) [41–43]. Furthermore, Coronary Flow Reserve (CFR) is decreased and carotid Intima-Media Thickness (cIMT) is increased in RA population [44].

Deranged Lipids and Atheroma Instability

RA and other systemic inflammatory conditions are associated with a unique type of dyslipidemia characterized by high levels of triglycerides and low levels of Low-Density Lipoproteins (LDL) and High-Density Lipoproteins (HDL). Although lipoprotein levels are
low, there is a paradoxical increase in CV risk [45]. This “lipid paradox” is explained by the fact that low lipoprotein levels are associated with inflammatory states, and inflammation is independently associated with CV events, and perhaps in a more causal fashion than cholesterol levels. Low lipoprotein levels are associated with elevations in ESR and CRP [46]. Furthermore, a clinically significant portion of HDL is altered in structure and function so that instead of being anti-inflammatory and atheroprotective, it enhances LDL-oxidation and foam cell formation [47–50]. This pro-inflammatory HDL has an altered proteome and does not bind efficiently with Lecithin-Cholesterol Acyl Transferase (LCAT) resulting in inadequate clearance of lipids from developing atheromas, a decreased efflux capacity. Pro-inflammatory HDL levels positively correlate with acute phase proteins, including serum amyloid A and complement factors, as well as RA disease activity [51, 52].

With increased control of inflammation, LDL levels rise while HDL production is shifted toward the anti-inflammatory form [53]. Accordingly, decreasing hsCRP by at least 10 mg/L over two years is associated with a rise in LDL and increased HDL cholesterol efflux capacity [54]. Lipid levels rise with the use of Disease Modifying Anti-Rheumatic Drugs (DMARDs), anti-TNF, anti-IL-6R, and Janus kinase inhibitors [53, 55–57].

The altered lipid profile in RA may be responsible for increased CVD events by causing increased instability of atherosclerotic plaques. A post-mortem study demonstrated lower overall grades of stenosis and fewer vessels with severe-grade stenosis, but significantly more vulnerable plaques, with increased medial and adventitial inflammation, in RA subjects compared to controls [27]. On ultrasound examination, RA patients had more carotid plaques than age and sex matched controls without RA. Controls were found to have more stable plaques [58]. Although RA patients had fewer atheromas and less severe stenosis, they had higher frequency of CVD events when compared to the general population suggesting that atherosclerotic plaques in RA are more prone to rupture.

**Hypercoagulability**

There is evidence that RA patients are hypercoagulable. Some of the related pathophysiology was discussed above in the context of the effects of cytokines on endothelial cells. To review, elevated concentrations of fibrinogen, von Will brand factor, fibrin D-dimer, tissue plasminogen activator antigen, and platelets are seen in RA patients [59]. Another pathway that contributes to hypercoagulability is the CD40-CD40L, which is upregulated in RA and associated with a genetic variant of CD40. Studies of this pathway in CVD have shown that levels of soluble CD40L are predictive of MI and associated with plaque rupture and thrombosis [60–62].

**The Role of T Cells**

The major risk allele for RA, HLA DRB1, is associated with the proliferation of an autoreactive CD4+CD28- T cell population [9]. These T cells are senescent meaning that, contrary to what the name suggests, they are terminal effectors that are highly active in secreting pro-inflammatory cytokines and resistant to apoptosis [63]. Significantly, the responsible allele has also been linked to increased CVD [64]. Expansion of the
CD4+CD28-T cell population is associated with preclinical cardiovascular disease; these T cells are found within atherosclerotic plaques [65] where they release IFN-γ and IL-17, promoting an inflammatory milieu [66]. In one study of RA patients, it was found that patients with greater expansion of this T cell population had increased atherosclerosis and endothelial dysfunction, as measured by carotid IMT and brachial artery Flow Mediated Vasodilation (FMV), than those with smaller populations [67]. TNF-α blocking therapy restored CD28 expression on T cells [68].

It is thought that activation of T cells and macrophages inside the atheroma by antigens generated from oxidized LDL may trigger macrophage-mediated destruction of the fibrous cap with erosion of the overlying endothelium, bringing thrombogenic particles from the endothelium into contact with blood, triggering the coagulation cascade and arterial occlusion, leading to dreaded cardiovascular events [69].

**Risk Factors**

CV risk scores valuable for the general population (Systematic Coronary Risk Evaluation score, Framingham Risk Score, Reynolds Risk Score) generally underestimate or overestimate (QRisk II) CV risk in patients with RA [70]. According to a recent, large, international cohort study, the Framingham Risk Score in Adult Treatment Panel (FRS-ATP), RA-related characteristics have been shown to account for roughly a third of CVD events in RA patients [71]. There have been many attempts to adjust pre-existing CVD risk calculators as well as to derive new risk calculators, but all have resulted in underestimations [72–74].

In 2015, the Extended Risk Score - Rheumatoid Arthritis (ERS-RA) was released. The project used data from the Consortium of Rheumatology Researchers of North America (CORRONA) cohort, the largest US-based RA registry to assess newly diagnosed RA patients without CVD for all possible traditional and RA-related CV risk factors. Factors such as age, sex, diabetes, hyperlipidemia, hypertension, and patient-reported tobacco use were included; in addition to, RA-related factors such as, level of disease activity, extent of functional disability, RA duration, presence of subcutaneous nodules, joint erosions on X-ray, RF or anti-CCP antibody positivity, any use of corticosteroids or DMARDS, and current use of methotrexate, NSAIDS, or anti-TNF drugs were also recorded. Race, education, physical activity, BMI, family history of early MI, and aspirin use were also considered. Patients were followed for a mean of 2.9 years. The researchers concluded that rather than multiplying by a correction factor [75, 76] or including inflammatory biomarkers in the calculation, using clinical disease activity (moderate or high instead of none or low), functional disability (moderate or high instead of none or low), disease duration greater than 10 years, and any prednisone use, in addition to traditional risk factors, resulted in an improved risk prediction model [77]. However, a later attempt to externally validate the ERS-RA algorithm found that the algorithm does not predict CVD in RA more accurately than risk calculators made for the general population [72]. Other recent efforts that used DAS28, ESR, or health assessment questionnaires in addition to traditional risk factors have also failed [73].
Abnormal Body Adiposity

CVD is traditionally associated with abdominal adiposity and increased BMI. While these associations hold true in RA patients, there is also an association between CVD mortality, weight loss and low BMI in RA [78–82]. One study found that obesity is associated with decreased mortality in RA patients, however, others have shown that obesity contributes the same or to a lower magnitude of CVD risk in RA patients compared to controls [83, 84]. The observed “obesity paradox” appears to be a consequence of the association between catabolic weight loss and increased inflammation and mortality [81]. Chronic inflammation in RA is associated with loss of lean body mass and increased fat mass, specifically abdominal adiposity and visceral fat; it has been termed rheumatoid cachexia, there is no net weight loss so that BMI is maintained. Rheumatoid cachexia may affect 10–67% of RA patients [85, 86]. Moreover, RA patients have decreased muscle and fat mass resulting in low BMI. Among RA patients, classical cachexia with BMI <20 is associated with increased CVD-related mortality [82]. Any seemingly protective effect of obesity likely represents the absence of intense disease activity [87].

Bioelectrical impedance studies have shown that RA patients may have more fat mass for a given BMI than controls, suggesting that BMI measurements may underestimate fat mass and CVD risk in RA [37, 88]. It has been suggested that the BMI cut-off for overweight and obesity should be 2 kg/m^2 lower in RA patients in order to appropriately estimate the health risks conferred by being overweight or obese [88]. Increased BMI in RA is associated with typical CVD risk factors, hypercholesterolemia, diastolic hypertension, and elevated CRP [78, 79, 89].

The relationship between BMI and CVD in RA is U-shaped in that at low BMI, inflammatory and RA-related factors predominate contributing to CVD risk whereas at high BMI, traditional CVD risk factors contribute significantly. This results in decreased CVD risk in RA patients with higher BMI compared to those with lower BMIs, supporting the postulate that inflammation associated with RA is a more powerful risk factor for CVD than traditional CVD risk factors. Additionally, hypertension and smoking confer attributable risk for CVD to RA patients as seen for the general population [73, 84].

Dyslipidemia

In RA, CVD risk is associated with lower than expected levels of LDL-C and Total-Cholesterol (T-C) which means that using LDL-C to extrapolate CVD risk in RA results in an underestimation [90]. Recent studies have shown that a U-shaped association between cholesterol levels and CVD risk also exists in non-RA population [90]. Low cholesterol levels may reflect chronic inflammation and are associated with high levels of triglycerides and LDL Particles (LDL-P) [54]. LDL-P and ApoB have been shown to be a better surrogate for estimating CVD risk than LDL-C when the two measures are discordant [91–95].

HDL-C also presents a challenge in RA patients. As discussed above, a significant portion of the HDL-C is pro-inflammatory and dysfunctional. HDL particles (HDL-P) concentration appears to be inversely related to carotid-IMT and CHD than HDL-C [96].
That the higher risk of CVD associated with lower cholesterol levels in RA reflects increased inflammation is supported by evidence. In patients receiving DMARDs, decreasing hsCRP correlated with improvements in HDL efflux capacity and rising LDL [54].

**Insulin Resistance**

Insulin resistance is more prevalent in RA with a rate of 54% in RA compared to 40–45% in the general population [97]. It has been hypothesized that the increased prevalence of insulin resistance is due to inflammation. In RA, insulin resistance has been shown to be associated with elevations in TNF-α, IL-6, ESR, and CRP, measures of RA disease activity and importantly, coronary artery calcification [97]. One study demonstrated no significant difference between the CVD risk conferred by diabetes to RA patients compared to non-RA patients [84].

**Smoking**

Smoking, a strong predictor of CVD in RA is also more prevalent in RA than in the general population, although it only contributes in a smaller magnitude to the CV risk [73, 84, 98].

**Genetic Markers**

One study demonstrated an increased risk of CV mortality in RA patients with HLA-DRB1*04 shared epitope alleles and the association was even stronger with HLA-DRB1*0404. The HLA-DRB1*04 allele is also associated with treatment resistant RA, endothelial dysfunction and extra-articular RA manifestations [12, 99–105]. The IL-6–174C allele is associated with increased CVD in RA patients and this corresponds with elevated IL-6 levels in the carrier’s serum [106].

**Clinical Disease Activity**

The CORRONA researchers found that per each 10-point reduction in Clinical Disease Activity Index (CDAI range 0–76) score there was a 21% reduction in CVD event risk, with a reduction of 53% between high disease activity and remission [107]. Similarly, other studies found Disease Activity Score 28 (DAS28), joint pain severity, functional disability, severe extra articular RA and, in some cases, disease duration were independently associated with increased risk of cardiovascular events and new onset CAD [108–110]. Absence of joint pain is associated with decreased cardiac risk [109]. Accordingly, a study of patients treated with anti-IL-6 therapy found that decreased risk of cardiovascular events correlated with the extent of reduction in disease activity measured by DAS28 [111]. There is a small but significant increase in CVD risk in RA patients for time spent in acute flare compared to time spent in remission. CVD risk for patients in remission is similar to the risk in patients without RA [112].

On the other hand, a higher score on the Health Assessment Questionnaire (score 0–3) at one year after RA diagnosis is an independent predictor of future CVD-related and all-cause mortality [113]. The association between CVD risk in RA and extra-articular disease has
been observed in patients with RA vasculitis, pulmonary disease, rheumatoid nodules among others, with a hazard ratio of 2.32 in patients with RA lung disease [45].

Disease severity is also associated with subclinical, premature atherosclerosis, as measured by Coronary Artery Calcification (CAC) score and cIMT [114, 115]. The greatest difference in CAC between RA and non-RA patients occurs in the youngest age group [114].

The “time-to-risk profile” depends on the CVD phenotype [116]. Risk for certain categories of CVD is increased even prior to RA diagnosis, while risk for others is not increased until years after diagnosis. For example, risks for IHD and venous thromboembolism are not increased prior to diagnosis but increase rapidly after RA onset [117–119]. The risk for ACS within the first year after diagnosis is particularly increased in patients with a high disease activity score [116, 120]. On the other hand, risk for ischemic stroke is first detectable at ten years after RA onset [121].

**Corticosteroids**

It is unclear how corticosteroid use affects CVD risk although it appears to be related to pre-existing heart conditions. Corticosteroid use has been shown to increase the risk of CVD death in patients with RA without CHD history, even after adjustments for CV risk factors. However, in patients with history of CHD, corticosteroid use actually decreases the risk of death from CVD [45, 122, 123]. Use of corticosteroids has been associated with an increased risk of CV events, as has use of COX-2 inhibitors and shorter duration of DMARD use [108]. On the other hand, studies have found no significant association between corticosteroids and CV events [124]. Low-dose corticosteroid use had no effect on atherosclerosis, ventricular function, heart rate variability or arterial stiffness however, an association with major CV events, including MI, stroke, and death was found [125]. Glucocorticoid use was associated with increased CVD risk and poorer survival for RA patients over age 65 at diagnosis, while methotrexate was associated with decreased CVD risk [126]. We hypothesize, that RA patients who required corticosteroid treatment had more active disease and higher levels of inflammation which in addition to the effects on insulin sensitivity and sympathetic tone from glucocorticoids led to an increased rate of cardiovascular events.

**Inflammatory Markers**

Inflammation is at the heart of the matter in RA patients. (Figure 5) This is reflected by the strong correlation between disease activity, quantified to some extent by plasma biomarkers of inflammation, and CVD risk. Seropositivity for Rheumatoid Factor (RF) and Anti-Citrullinated Peptide Antibodies (ACPA), along with higher white blood cell count at diagnosis, and higher cumulative C-Reactive Protein (CRP), Erythrocyte Sedimentation Rate (ESR) and pain-visual analog scale scores were associated with higher CVD risk among patient <65 years of age at RA diagnosis [126]. Inflammatory markers (ESR, CRP, WBC, IL-6, TNF-alpha) have a stronger association with fatal CVD and heart failure than with atherosclerosis and MI [45, 127].
C Reactive Protein (CRP)/High-Sensitivity CRP (hsCRP)

Elevated serum CRP levels are associated with increased CVD risk, including MI, heart failure, atherosclerosis, and mortality in RA [124, 128]. It is also an independent predictor of CVD risk, specifically of MI, in healthy people without RA. The association holds true even in sub-groups of patients with LDL cholesterol levels below 130 mg/dl and is a stronger predictor of CVD events than LDL-cholesterol, atherogenic cholesterol index, serum amyloid A, IL-6, homocysteine, and Inter Cellular Adhesion Molecule-1 (ICAM-1) [129]. An hsCRP level of >5 mg/dL has been shown to be an independent and statistically significant predictive marker of CV death in RA patients with a hazard ratio of 3.9 and 4.22 for men and women, respectively [128]. A CRP > 10 mg/L has been associated with increased MI with a hazard ratio of 2.12 (95% CI 1.02 to 4.38) [130].

Elevated CRP levels has also been associated with a significantly increased risk of heart failure and mortality with hazard ratios 1.25 and 1.08, respectively, in RA patients [131]. In both RA and the general population, elevated CRP is associated with number of atherosclerotic plaques and with increased carotid IMT. A proposed mechanism for these strong associations is that CRP promotes atherogenesis by increasing uptake of oxidized LDL cholesterol by macrophages and inhibiting cholesterol efflux from foam cells, and also promotes plaque rupture by promoting the production of matrix metalloproteinases by macrophages [132, 133].

ESR

Elevated ESR is independently associated with increased cardiovascular risk [108, 122]. Studies have shown that ESR > 42 mm/h carries increased MI and ischemic stroke risks [130] and ESR=50 mm/h is associated with approximately 10-fold increase in CVD risk [130, 131]. A 15 year follow-up study found increased risk for CVD death with a hazard ratio of 2.03 ((95% CI) 1.45–2.83) for patients with at least 3 ESR values of at least 60 mm/hr [45].

RF Positivity

Many studies have shown that RF positivity (+) is significantly associated with increased cardiovascular and all-cause mortality in RA [134, 135]. In fact, the mortality gap between RF (−) RA patients and the general population has remained stable in recent years while the gap for RF (+) patients has increased [136]. Interestingly, the association between RF (+) and increased CV and all-cause mortality holds true even in patients without RA [137]. RF (+) is positively associated with smoking and diabetes but correlates inversely with cholesterol levels [138]. Seropositivity confers increased cardiovascular risk and all-cause mortality, even after adjusting for smoking and diabetes [139]. RF (+) also strengthens the association between CRP levels and CV death [128] However, some more recent studies have not found an association between RF positivity and CVD risk [77, 120].
ACPA Positivity

Studies evaluating ACPA positivity as a risk factor for CVD in RA have produced mixed results. ACPA positivity was shown to be associated with increased risk of fatal CVD and death but lower or no increased risk of non-fatal CVD, CHD, or stroke compared to ACPA negative patients [108, 109, 140, 141]. Other studies found borderline associations with CVD events without statistical significance [120, 140]. Studies that looked at coronary atherosclerosis and ACPA positivity found no association even though citrullinated proteins were found within atherosclerotic plaques [142]. However, another study found that ACPA antibodies are independently associated with IHD (6.5% versus 2.6%) and higher mortality rates (11.2% versus 6.8%) compared to ACPA antibody negative RA patients [143]. Interestingly, an association between high levels of ACPA and reduced left ventricular mass, end diastolic volume, and stroke volume, but not reduced ejection fraction has been described.

Cytokines

Elevated levels of IL-6 are associated with CVD in RA and in the general population, and IL-6 receptor signaling pathways are known to have a causal role in the development of CAD [32]. Elevated levels of IL-6 predict cardiovascular event risk in healthy men and women. [129, 144, 145] Among women with RA, IL-6 is strongly associated with increased cardiovascular and all-cause mortality rather than non-fatal CVD or CHD [109].

Elevated cytokine concentrations are associated with subclinical CVD in RA patients. Elevated levels of inflammatory markers such as IL-6, Serum Amyloid A (SAA), intercellular adhesion molecule-1 (ICAM-1), E-selectin, TNF-α, and myeloperoxidase were found in RA, but only IL-6 and TNF-α concentrations correlated with high coronary calcium scores, independent of Framingham risk score and diabetes [146]. Elevated IL-6 is associated with higher levels of markers of endothelial dysfunction, ICAM-1 and Vascular Cell Adhesion Molecule-1 (VCAM-1) [147].

Other biomarkers being investigated are high-sensitivity cardiac troponin I (hs-cardiac troponin 1) and N-Terminal pro-Brain Natriuretic Peptide (NT-proBNP). Hs-cardiac troponin 1 has been shown to be independently associated with subclinical coronary plaques and a predictor of CV events in RA patients [148]. NT-proBNP is an independent predictor of CV mortality and has been shown to be most useful as a predictor when levels are at least 100 pg/ml [149–152].

Clinical Manifestations of Cardiovascular Disease in Rheumatoid Arthritis

Ischemic Heart Disease

RA is associated with an increased risk of IHD. Prospective cohort studies place the relative risk of MI in RA between 1.7 and 2.0, and meta-analyses data estimate a standardized mortality ratio of IHD between 1.59 and 1.77 [2, 153–156]. There is evidence that subclinical atherosclerotic disease is more common in RA. RA patients who underwent Computed Tomography (CT)-angiography for evaluation of coronary plaques had a
significantly higher proportion of plaques when compared with controls [157]. RA patients were also more likely to have single, double, and triple-vessel disease, >50% stenosis, and extensive segmental disease. Moderate RA disease activity (DAS28 ≥3.2) is most closely associated with non-calcified coronary plaque [157]. RA patients who were identified to have unilateral or bilateral carotid plaques by ultrasound examination were more likely to have newly incident Acute Coronary Syndrome (ACS) compared to RA patients without carotid artery plaques [115]. This may point to carotid artery plaque identification as a potential predictive tool for estimating CAD and CVD event risk in RA patients.

Just as higher RA disease activity has been associated with an increased risk of subclinical atherosclerotic disease, several studies have demonstrated that high disease activity is associated with an increased risk of incident IHD. RA patients with ACS have significantly higher DAS28 scores [116]. RA patients with IHD have more tender joints [158]. ACS and IHD are associated with elevated ESR in RA patients [116, 158]. A 10-point drop in Clinical Disease Activity Index (CDAI) resulted in a 21% decrease in composite cardiovascular risk. The effect of disease activity may be cumulative as increased risk with extended disease duration is observed; RA patients at >10 years after diagnosis had a significantly increased risk of MI, while those at <10 years after diagnosis did not have a significantly increased risk. These findings suggest that both disease length and severity affect the risk of developing IHD in RA. Furthermore, it has been demonstrated that the relative risk of MI, stroke, or CV death in RA patients is highest among young RA patients and lowest for those > 75 years old. This risk-age discrepancy could be explained by the fact that high-risk RA patients suffered premature CV death leaving a relatively healthy older population [107].

It appears that RA patients experience IHD differently from the general population. RA patients are five times more likely to have unrecognized MIs, identified by characteristic ECG findings in a patient with no documented history of previous MI) [45]. RA patients are more likely to suffer from sudden cardiac death and have increased frequency of ST-segment elevation MI, higher troponin levels, more inpatient complications, and higher short-term mortality after first acute MI or stroke than non-RA patients [45, 116, 159]. In addition, a review of Acute Coronary Syndrome (ACS) treatment patterns and outcomes among RA patients found not only a higher case fatality rate for MI but also that these patients were less likely to receive coronary artery bypass grafting, percutaneous reperfusion, and secondary prevention of MI including beta-blockers and lipid-lowering agents [116, 160]. On the other hand, one study that found no difference in ACS management still found worse mortality and increased recurrent ischemia in RA compared to non-RA patients [161].

**Congestive Heart Failure**

RA has also been associated with an increased risk of ischemic and non-ischemic CHF, with a more significantly increased risk for ischemic CHF [162–169]. RA patients have a higher rate of diastolic dysfunction, but no difference in left ventricular ejection fraction compared to the general population [137, 166, 170–175].

In non-RA populations, ischemic CHF can be attributed to hypertension, smoking, high BMI, and alcohol abuse however, in RA, those traditional risk factors do not fully explain
the occurrence of the disease prevalence and RA patients are less likely to have obesity and hypertension [176]. As in IHD, RA patients are more likely to experience CHF differently from non-RA patients with greater incidence of sub-clinical disease; they present with less orthopnea, dyspnea on exertion, and paroxysmal nocturnal dyspnea compared to controls. This absence of the cardinal symptoms of CHF could potentially delay diagnosis and treatment in RA patients [176]. Stroke and atrial fibrillation have also been found to be more prevalent in RA patients, with a 40% higher risk of atrial fibrillation and a 30% increased risk of stroke in RA compared to the general population [177].

**Evaluation and Workup**

It is of paramount importance that CV disease be promptly diagnosed and evaluated in patients with RA given the heightened risk of mortality [2]. The workup of CV disease in RA should include history, physical examination, laboratory tests, electrocardiography and echocardiography, with a specific focus on IHD, heart failure, myocarditis, micro-vascular disease and pulmonary hypertension, conditions more prevalent in RA [163, 178, 179]. Risk assessment tools, such as the Systematic Coronary Risk Evaluation (SCORE) index and Framingham models were developed to estimate CV risk in the general population [180, 181]. These tools underestimate the CV risk in RA largely due to the exclusion of non-traditional risk factors [70, 182]. Studies have shown that RA patients deemed to have moderate risk by these models, actually have carotid plaques which place them at a much higher CV risk [183, 184]. The QRESEARCH CV Risk Algorithm 2 (QRISK2), a risk calculator that incorporates RA in its assessment, was found to be of value in the determination of fatal versus non-fatal CV risk but appears to overestimate CV events in RA [70, 76].

The Modified SCORE (mSCORE) index, developed by the European League Against Rheumatism (EULAR), has shown a higher 10-year CV risk in patients with RA. This emphasized the need to include RA disease-specific factors to the estimation of CV risk in calculation tools [75, 185, 186]. The 2016 updated EULAR recommendations advised a multiplication factor of 1.5 for CV risk assessment calculators when used in patients with RA [186]. However, current research suggests that many of these risk assessment tools, including the Expanded CV Risk Prediction Score for Rheumatoid Arthritis (ERSRA), EULAR multiplier and QRISK2, are still not ideal [72, 77]. Future research is likely to provide a more accurate CV risk assessment calculator to be used among RA population.

Serum biomarkers have been studied as surrogate CV end points in RA [187] (Figure 6). The Reynold’s risk assessment incorporated hsCRP given its usefulness across a full range of CV risk profiles. However, the Reynold’s risk assessment failed to accurately predict CVD in RA [188–190].

Imaging studies are also useful in determining CV risk with high sensitivity and specificity. An ideal imaging tool would be able to provide: accurate prediction of CV mortality, early subclinical detection of atherosclerosis, longitudinal evaluation of interval changes in CVD and detection of impact of atherosclerosis and other manifestations of CVD [191]. Endothelial dysfunction has been reliably associated with impending atherosclerotic disease...
(See Figure 1) Flow-mediated dilation (FMD) and Brachial Artery Reactivity Testing (BART) can help estimate endothelial function [193, 194]. However, rigorous research found that of the parameters measured in BART, only forearm hyperemic flow could estimate the 10-year CV risk in RA by correlation with AHA/ACC risk categories [195]. While impaired in RA, FMD did not show significant correlation with estimated 10-year CV risk [195, 196]. Utilizing ultrasonography (US), the aortic Pulse Wave Velocity (aPWV) and augmentation index (AIx) can provide a measurement of arterial stiffness [193, 194]. A meta-analysis concluded that arterial stiffness was abnormal in patients with RA [197]. Studies have shown that although aPWV and AIx can predict CV risk in the general population, they are not useful to predict CV events in RA [198].

Carotid plaque and cIMT, as measured by US, have been independently associated with CV risk determination in the general population [199]. A 5-year prospective study of RA patients without CV risk factors showed that cIMT ≥0.90 mm, predicted CV events in >60% of the cohort. A cIMT ≥0.77 mm was associated with no CV events. cIMT is useful in estimating CV risk in RA patients who may be underestimated by conventional risk scoring calculators [115, 200]. Studies showed that 65% of patients classified as moderate risk and 85% of those in high or very high-risk categories have increased cIMT and/or carotid plaque, signifying its utility in re-estimating CV risk in this intermediate-risk cohort [183]. Carotid plaques, defined as a localized intima-media thickening of >1 mm, was shown to have significant correlation with poor CV survival and ischemic CV events. These findings are particularly important in the presence of bilateral carotid plaques, where the incidence of CV events rises by over a factor of 4 [115, 201]. The updated EULAR recommendations suggest that carotid US be used to screen for asymptomatic atherosclerotic plaques as part of CV disease evaluation in patients with RA [186].

Cardiac CT and CAC score are useful modern imaging techniques to quantify risk in RA patients. Similar to the ultra-sonographic techniques, CAC is well known to be a useful risk prediction marker of CV events in the general population [202]. A study of 227 patients showed that patients with both early and established RA had more severe CAC scores. Patients with established disease had an odds ratio of 3.42 for severe CAC when adjusting for CV risk factors, making cardiac CT a useful discriminator of CV risk in RA patients [203]. Cardiac MRI (CMR) can be used to quantify the extent of myocardial damage in patients with RA [204]. Although limited literature currently exists on CMR use in RA, patients tend to have reduced left ventricular mass and ejection fraction [172].

Myocardial strain imaging with the use of Speckle-Tracking Echocardiography (STE) is a new technique to evaluate myocardial function that can detect early myocardial dysfunction in patients with RA [205]. The Mayo Clinic used this modality to detect subclinical myocardial diastolic dysfunction in a retrospective study of 87 patients with RA without history of CV disease. Global left ventricular and right ventricular strain were reduced in RA patients, with worse strain correlating with other markers of RA disease severity [205]. An Italian study examining RA patients free of CV disease and normal transthoracic echocardiograms, demonstrated statistically significant reductions in LV end-systolic radial and longitudinal strains when compared to the general population controls [206]. Larger prospective trials are needed to confirm its usefulness as a routine modality and clinical
utility in predicting CV events. Table 1 for a summary of special tests that may be used to assess CVD in RA).

Additionally, genetic and serological markers are being studied to evaluate CV disease in RA patients. Human leukocyte antigens, cytokines, adipokines, endothelial cell activation markers, and their related genes all show a significant correlation with the development of CV risk in RA patients [206, 207] (See Figure 6). Age-adjustments should also be considered when evaluating CV risk in RA patient since younger RA patients tend to have higher rates of CAD, and dyslipidemia deserves special attention as previously discussed [208].

An accurate CV risk assessment tool would involve data, carotid US results and serological and genetic serum markers, providing a more individualized approach to CV risk for patients with RA [207]. We encourage clinicians to adopt a cautious approach when investigating patients with RA and maintain a low threshold for treatment and start prevention strategies to minimize the burden of CV disease in patients with RA.

Management

Chronic inflammation is now regarded as the driver of accelerated atherosclerosis in the RA population [209, 210]. Effective disease control seems to be pivotal to preventing atherosclerosis and its consequences. One of the first studies to show that disease control improved mortality was a retrospective review of RA patients receiving intramuscular gold therapy [211]. Disease Modifying Anti-Rheumatic Drugs (DMARD) and particularly methotrexate (MTX) soon were also found to reduce mortality up to 50%. In addition, MTX treatment reduced ESR and CRP, and raised TC and HDL levels [212, 213]. Hydroxychloroquine (HCQ) has also been found to have a favorable effect on lipid profile and has an additional antithrombotic effect [214]. HCQ reduces total cholesterol (T-C), LDL-C and increases HDL-C leading to a favorable atherogenic index [215–217].

The availability of DMARDs and anti-TNF therapies have been associated with decreases in CV fatalities in RA [218]. Clinical reports support the notion that arrhythmic events are significantly reduced in patients taking anti-TNF therapies or MTX [111, 219, 220]. Elevated levels of hsCRP and IL-6 were found to be strong and independent predictors of sudden cardiac death among a healthy cohort reinforcing the idea that inflammatory cytokines induce structural, chronic cardiac sympathetic activation, and myoelectrical alteration which favor arrhythmogenic events in the non-RA population [221, 222]. Moreover, triple therapy with MTX plus sulfasalazine and HCQ for 52 weeks was demonstrated to reduce disease activity and increase HDL-C, lower LDL-C, and lower the atherogenic index [223].

A five-year study that compared RA patients on synthetic DMARDs to those on anti-TNF therapy found that the risk of MI was decreased by 39% in the latter group. The study also demonstrated that 16 months of anti-TNF therapy was not only associated with a lower CV risk, but also influenced disease severity and mortality post MI. These findings reinforced the concept that a reduction of vascular inflammation in RA is linked to better outcomes by
decreasing atherosclerosis which entails improved endothelial function, plaque stabilization and post-MI remodeling [224, 225]. The randomized control trial of golimumab in MTX refractory RA patients (GO-FORWARD) revealed that at 14 weeks, the T-C, LDL-C and HDL-C, had increased in the MTX-golimumab group compared to the placebo-MTX control [226, 227]. In MTX naïve patients (GO-BEFORE), rises in the lipid parameters at 24 weeks were similar in the golimumab-MTX and placebo-MTX groups, which supported the notion that the improvements in lipid profile were due to MTX effectiveness in naïve patients [228, 229]. Tocilizumab (TCZ)’s effects (IL-6R inhibitor) on lipids and CV risk was examined in the MEASURE trial. TCZ resulted in a decrease of HDL-associated serum amyloid A, phospholipase A2, lipoprotein A, fibrinogen, D-dimer and elevation of paraoxonase while ApoB/ApoA1 ratio remained stable. This shows that TCZ induced elevations in LDL-C but altered HDL particles towards an anti-inflammatory composition, ameliorating many vascular risk surrogates [53, 229].

The relationship of TCZ and major CV adverse events (MACE) was studied in about 4000 RA patients with moderate to severe RA. TCZ’s ability to decrease disease activity positively correlated with a lower risk of future MACE. The higher the disease activity despite TCZ, the higher the risk of future MACE. Moreover, lipid parameters while on TCZ were not useful as markers of risk for MACE [111]. JAK inhibitors also increase HLD-C and LDL-C in a similar fashion as seen with tocilizumab, with a reduction in the CV risk and decreased cIMT despite the elevation in lipid profile. Pooled analysis found the MACE events were similar for patients on tofacitinib or placebo and this risk did not increase over time. However, in 2017 concerns for venous thromboembolic events led the FDA to establish mandatory reporting of all MACE for the JAK inhibitors class. Venous thromboembolism has been seen as an adverse effect with the entire class, and portal vein thrombosis was linked to ruxolitinib [230]. This should be kept in mind as pulmonary embolism appears to be a class-wide issue for JAK inhibitors.

The anti-inflammatory effect of statins was tested in the TARA trial (Trial of Atorvastatin in Rheumatoid Arthritis), in which RA patients ≥50 years old without known CVD or diabetes, who had RA for ≥10 years and were maintained on DMARD therapy, were initiated on atorvastatin or placebo as adjuvant therapy and followed for 6 months. Modest but significant improvements were seen in disease activity index and swollen joint count in addition to a decrease in ESR and CRP of 28% and 50%, respectively [231]. Furthermore, a large population-based study in which non-RA patients on statins were followed for 12 years looked at the crude incidence of RA in the population. It found that the high dose statin group (atorvastatin 20–80 mg, rosuvastatin 5–40 mg, or simvastatin 80 mg) was associated with a 23% reduction in the risk of incident RA, compared to the low-dose statin group, suggesting that statins may reduce inflammation directly [232]. Statins have also been demonstrated to improve arterial stiffness and endothelial dysfunction [233, 234]. Remarkably but not surprisingly, a population study of RA patients who had their statins discontinued for more than 3 months revealed a 67% increase in the risk of MI with a 2% increased risk of acute MI for each month of discontinuation [235]. The addition of a second non-statin lipid lowering therapy such as ezetimibe was also studied in patient with hsCRP >6 mg/dL, leading to significant reductions in LDL-C, hsCRP and disease severity [236].
propensity score analysis of RA patients on at least one DMARD demonstrated that the concomitant use of statins was associated with a 21% lower risk of all-cause mortality [237].

The benefits of early therapy in RA were confirmed by a 20-year follow up study of a cohort of RA patients who had low disease activity throughout, but in whom disability was apparent by year seven of disease and continued to rise regardless of whether they received treatment for their RA. In this study 44% of patients died, however, patients who had received DMARD treatment within 6 months of disease onset tended to have a lower risk of death that those who did not receive treatment [238]. Early initiation of statins should also be considered for patients with RA, even in the absence of dyslipidemia given that this patient population carries high risk features for CVD and statins have been demonstrated to have effective preventative and protective properties in RA patients [239].

A recent large population study encountered that the risk of ACS was increased 23% in the siblings of RA patients compared to the general population suggesting a possible shared susceptibility between RA and ACS. Therefore, inquiring about family history of RA during health maintenance visits might help detect and address subclinical CVD risk in patients otherwise considered low risk [240]. Rheumatology clinics also failed to discuss hypertension in 2 out of 3 visits, which represent a huge missed opportunity since 40% of RA patients met criteria for uncontrolled hypertension. Better strategies are needed to address modifiable risk factors such as hypertension, including prompt referral to primary care and patient education in order to improve outcomes in this vulnerable patient population [241].

**Conclusion**

While RA occurs in about 1% of the general population, CVD disproportionally affects RA patients and is currently the major cause of morbidity and mortality among RA patients. CVD presents much earlier in RA patients and has been reported even before full clinical presentation and diagnosis of RA. Among the major CVD presentations, silent MI, diastolic dysfunction, arrhythmias, stroke and sudden cardiac death appear to be prevalent and occur at a relatively younger age. Other features of CVD in RA include the obesity paradox and the lipid paradox making this disease a particularly interesting and rather challenging entity to diagnose and manage. Chronic inflammation appears to be the major underlying pathogenic factor linking RA and CVD. This is associated with endothelial dysfunction, lipid abnormalities, hypercoagulability and early atherosclerosis with unstable plaque formation. Physicians should be cognizant of RA disease activity as it correlates with higher CVD risk. The use of DMARDs and biologics have been shown to control not only RA but also CVD risk. Early detection and aggressive management of CVD should be employed in this high-risk population together with control of the traditional CVD risk factors including hypertension, hyperlipidemia, smoking and diabetes. Further research is needed to help characterize and establish the ideal management strategies in this vulnerable population and inform future guideline development in this field.

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Figure 1:
Shared Pathogenesis
Figure 2:
Risk Factors
Arrows Represent the Causal Relationship between the Activity of Inflammatory Factors, and the Development of Traditional Risk Factors (Increased Adiposity, Dyslipidemia, Insulin Resistance) and RA-Specific Risk Factors that Reflect Disease Activity. Hs-CRP High Sensitivity C Reactive Protein, ESR Estimated Sedimentation Rate, TNF Tumor Necrosis Factor, IL-6 Interleukin-6, IL-1 Interleukin-1, IL-17 Interleukin-17
Figure 3:
Inflammation Alters Traditional Risk Factors

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Figure 4: The Good, the Bad, and the Neutral – A New Way of Thinking of Cholesterol

New evidence has shed light on the ambiguity of cholesterol and suggests that conventional categorizations oversimplify the matter. HDL-P High Density Lipoprotein-Particles, ApoA1 Apolipoprotein A1, T-C Total-Cholesterol, LDL-C Low Density Lipoprotein-Cholesterol, HDL-C High Density Lipoprotein-Cholesterol, LDL-P Low Density Lipoprotein-Particles, Apo B Apolipoprotein B
Figure 5:
Inflammation is the Hub of the Risk Factor Wheel
**Figure 6:**
Elevated Inflammatory Biomarkers Found in Rheumatoid Arthritis
These markers are being studied for their usefulness in contributing to cardiovascular disease risk assessment tools in rheumatoid arthritis patients. CRP: C-reactive protein, ESR: Estimated Sedimentation Rate, NT-proBNP: N-terminal pro brain natriuretic peptide, TNF-A: Tumor necrosis factor-alpha, IL-6: Interleukin-6, IL-8: Interleukin-beta, IL-17: Interleukin-17, ICAM-1: Intercellular Adhesion Molecule-1, VCAM-1: Vascular Cell Adhesion Molecule-1, Hs-cardiac troponin 1: high sensitivity-cardiac troponin 1, RF: Rheumatoid Factor, ACPA: Anti-Citrullinated Protein Antibodies.
## Table 1:

### Special Tests

| Predictive                              | Requires Further Testing                     | Not Predictive                                      |
|-----------------------------------------|------------------------------------------------|-----------------------------------------------------|
| Forearm Hyperemic Flow [195]            | Cardiac MRI [204]                              | Flow-Mediated Dilation [195, 196]                   |
| Carotid Intima Media Thickness [115, 183, 186, 201] | Brachial Artery Reactivity [195]               |                                                     |
| Cardiac CT and Coronary                 | Speckle-Tracking Echocardiography [205]        | Aortic Pulse Wave Velocity [198]                    |
| Artery Calcification Score [203]        | Augmentation Index [198]                       |                                                     |