Review

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Rheumatoid arthritis and cardiac disease

Maria Gonzalez-Mayda*[,1], Deepali Sen[1] & Richard Brasington[1]

[1]Division of Rheumatology, Department of Medicine, Washington University School of Medicine, 660 South Euclid Avenue, St Louis, MO 63110, USA

*Author for correspondence: mgonzale@dom.wustl.edu

Due to its chronic inflammatory state, patients with rheumatoid arthritis (RA) are more susceptible to developing atherosclerosis and other nonatherosclerotic cardiac issues. Management of cardiovascular risk factors and prevention of cardiovascular morbidity in RA has now become a key aspect in treating RA patients. It is imperative to evaluate patients with RA even during the early course of the disease for potential cardiac manifestations. In this article, we discuss the cardiac complications that can be seen in RA. We also review disease mechanisms and current recommendations on management of cardiovascular disease in RA.

Keywords: atherosclerosis • cardiovascular disease • inflammation • management • rheumatoid arthritis

Background

Cardiovascular disease (CVD) is a cause of significant morbidity and mortality in rheumatoid arthritis (RA). On autopsy series up to 60% of patients with RA have evidence of cardiac involvement including valvular and myocardial and pericardial disease [1,2]. Over the past decade tremendous progress has been made in understanding the link between inflammation and heart disease. It is now evident that the chronic inflammatory state in RA predisposes to early atherosclerosis. We discuss atherosclerotic disease in RA, including risk factors that are unique to RA followed by cardiac disease as a extra-articular manifestation of RA.

Atherosclerotic disease in RA

RA is associated with accelerated cerebrovascular and coronary artery atherosclerosis. Avina-Zubieta and colleagues conducted a meta-analysis that included 14 studies comprising 41,490 patients with RA. Their study showed a 48% increased risk of CVD compared with the general population. In this meta-analysis, RA patients were also noted to have a 68, 41 and 87% increase risk of myocardial infarction (MI), cerebral vascular accident (CVA) and congestive heart failure (CHF), respectively [3]. Patients with RA are also prone to recurrent cardiac events [4] and have a higher mortality after an acute cardiovascular (CV) incident [5].

Both traditional risk factors such as diabetes mellitus (DM), dyslipidemia, obesity, hypertension (HTN) and smoking, as well as nontraditional risk factors such as RA disease duration, disease activity and seropositivity, play a role in increasing the risk of CVD in this group of patients. The inflammation occurring in the synovium is very similar to the inflammation occurring in the atherosclerotic plaque [6]. Proinflammatory cytokines that lead to synovial inflammation in patients with RA likely mediate similar inflammatory effects on the CV system and other distant organs. Chronic inflammation can affect vascular wall stiffness, increasing thrombogenic potential and the formation of plaques.

Traditional risk factors for CVD in RA

Hypertension

HTN remains an independent risk factor for CVD in RA. HTN has been reported in 29–70% of RA patients [7]. The overall

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prevalence of HTN may be similar in patients with RA as compared with the general population [8]. Some studies, however, report a higher incidence of HTN in RA [9,10]. One possible explanation is that HTN may remain undiagnosed especially in younger patients with RA. Medications used to treat RA such as glucocorticoids, oral disease-modifying antirheumatic drugs (DMARDs) such as cyclosporine and NSAIDs, can also contribute to the development of HTN.

Dyslipidemia

In patients with RA, decreased lipid levels are associated with an increased risk of CV events. This is a contrast to the general population, where increased lipid levels, particularly low-density lipoprotein (LDL), can increase the risk of CV incidents. Lipid levels are affected by the inflammation associated with untreated RA, as well as medications used to treat RA. A longitudinal population-based study comparing the lipid profiles of RA patients to non-RA controls, 5 years before and after development of RA was conducted by Myasoedova and colleagues. There was a significant decline in LDL and total cholesterol levels in the RA group 5 years before they fulfilled American College of Rheumatology criteria, whereas no changes were noted in the control group. Five years after the diagnosis, LDL and total cholesterol levels became similar to the control group. The authors also noted a significant decrease in total cholesterol: high-density lipoprotein (HDL) ratio during the 5-year period before RA incidence [11].

The presence of underlying inflammation is thought to cause the decrease in the total cholesterol, LDL and HDL levels in patients with RA. As compared with total cholesterol levels, HDL levels are disproportionately lower, which leads to an increase of the total cholesterol/HDL ratio, also known as the atherogenic index. Myasoedova and collaborators followed 651 patients with RA for approximately 8 years. At each visit, CV risk factors, lipid levels, inflammatory markers and the development of CV events were monitored. They noted that the presence of an elevated erythrocyte sedimentation rate was associated with a significantly higher risk of CVD, (particularly CHF) and mortality after adjusting for sex, age and year of RA diagnosis. C-reactive protein (CRP) was also associated with risk of CHF and mortality; however, this was not statistically significant ($p = 0.07$). Elevated levels of triglycerides and lower LDL values were associated with higher risk of MI. Higher HDL levels and lower total cholesterol levels were also significantly associated with risk of CHF and persisted after adjustment for traditional CV risk factors [12].

Other qualitative abnormalities noted in RA patients include small-dense LDL molecules, which are considered more atherogenic, as well as lipoprotein A, which increases risk of CV incidents [13,14].

In the RA population, there is evidence to suggest that HDL molecules are both quantitatively low and qualitatively abnormal. Proinflammatory HDL molecules are seen in RA patients, which do not prevent LDL oxidation [15,16]. Oxidized LDL particles are highly antigenic and cause antibody formation. Anti-oxidized LDL antibodies are also positively correlated with carotid intima–media thickness (IMT) [17].

Treating RA also changes the lipid profile as cholesterol, especially HDL levels are known to increase in treated RA patients. This finding is more pronounced in responders to therapy [18,19]. A favorable shift in the total cholesterol/HDL ratio is noted in this group of patients. Hydroxychloroquine (HCQ) use is independently associated with lower LDL, total cholesterol, LDL/HDL and total cholesterol/HDL ratios in RA patients [20].

An increase in total cholesterol and HDL levels is seen with anti-TNF therapy; however, no equivalent effect is seen on LDL levels. van Sijil and colleagues conducted a meta-analysis of 766 patients, which showed that anti-TNF treatment led to a 7% increase in HDL levels and 10% increase in total cholesterol within the first 2–6 weeks of treatment [21].

Tocilizumab, the IL-6 receptor inhibitor, causes an increase in triglyceride, total cholesterol, LDL and HDL levels [22,23]; this effect is dose-dependent. Approximately 30% of patients treated with tocilizumab experience an elevation of lipid levels. Schiff and colleagues evaluated cumulative data from five Phase III trials and noted that 25.1% of patients treated with tocilizumab 4 mg/kg, 33.2% of patients treated with tocilizumab 8 mg/kg and 14.2% of controls had an increase in LDL levels from <130 mg/dl at baseline to ≥130 mg/dl with treatment. These elevations in LDL levels were seen within the first 6 weeks of therapy [24]. The ACT-STAR study, which was a postapproval study designed to evaluate the safety of tocilizumab in a setting mimicking clinical practice, showed that 11% of 886 RA patients had an elevation in LDL levels that required initiation of statin therapy [25]. Despite tocilizumab causing dyslipidemia, combined data from clinical trials suggest that it is not associated with an increased risk of CV events [26].

Tofacitinib, the Janus kinase inhibitor, increases both LDL and HDL levels [27,28]. A total of 7% of controls, 10.9% of patients treated with tofacitinib 5 mg and 10% of patients treated with tofacitinib 10 mg had elevations in LDL levels from a baseline of less than 100 mg/dl to greater than 130 mg/dl at 3 months of therapy as reported by Burmester and collaborators [29].

The diverse effects of the different biologic agents on lipids may be reflective of the role of individual cytokines on lipid metabolism.

Statin therapy in RA may alter lipid profile towards a favorable total cholesterol/LDL ratio thereby decreasing CV risk. Statin therapy also reduces inflammatory markers like CRP in RA [30]. In RA, statin therapy has a role in primary prevention of CVD, as well as in improving all-cause mortality [31]. Statins have both anti-inflammatory and immunomodulatory properties that can affect the inflammation associated with RA. A reduction in inflammatory markers and disease activity scores was reported by McCarey *et al.* with atorvastatin use in RA [30]. A small study looking at 100 RA patients reported a statistically nonsignificant improvement in disease activity in patients receiving simvastatin 20 mg [32]. Several studies have reported an improvement in surrogate markers of CVD such as flow-mediated dilatation and arterial stiffness in RA patients treated with statins [33–35]. An increased risk of MI was linked to the abrupt discontinuation of statins in RA by the TRACE-RA study [36].

BMI

A low BMI has been shown to be associated with an increase in CV events and mortality in patients with RA [37]. Chung *et al.* studied, 88 patients with early RA (defined as median disease lasting 2 years), 66 patients with long-standing RA (defined as median disease duration lasting 20 years) and 85 control subjects. Presence of metabolic syndrome was determined by both the WHO and National Cholesterol Education Program Adult Treatment Panel III (NCEP) criteria. Using the WHO criteria, 11% of control patients, 31% of early RA patients and 42% of patients with long-standing RA met the definition of metabolic syndrome ($p < 0.001$). Using the NCEP criteria, 22% of the controls, 30% of early RA patients and 42% of long-standing RA patients met the definition of metabolic syndrome ($p = 0.03$). An increased prevalence of metabolic syndrome was noted in individuals with RA whose BMI ≤30 kg/m^2. Contrary to the definition of metabolic syndrome in the general population, in which obesity is a major component, the statistical models used in this study suggested that in RA, metabolic syndrome was independent of BMI. Coronary artery calcification was measured by electron-beam computed tomography (CT) and was significantly associated with insulin resistance (odds ratio: 2.42; 95% CI: 1.22–4.79; $p = 0.01$) after adjustment for age and sex [38]. Of note, weight loss in RA termed as 'rheumatoid cachexia' is thought to be caused by TNF-α, and a lower BMI in RA could indicate higher cytokine levels that contribute to insulin resistance.

Insulin resistance

There is a strong association between RA and insulin resistance (IR), which has been found to be an independent risk factor of CVD in RA [39]. However, the incidence of diabetes has not been found be elevated in RA [40,41]. Inflammation likely plays a role in the development of IR as 51% of early RA patients and 58% of long-standing RA patients compared with only 19% in controls were noted to develop IR in a study performed by Chung *et al.* [38]. TNF-α is thought to contribute to IR [42]. TNF-α has been shown to be expressed in both adipose tissue and muscle [43–45] and may play a role in IR by decreasing insulin-dependent glucose uptake by inhibiting autophosphorylation of the insulin receptor [46].

TNF-α has also been implicated in IR in non-RA patients. Nilsson and colleagues compared 40 men with noninsulin-dependent DM, with 20 age-matched controls. Twenty of the 40 men with non-insulin-dependent DM had moderate IR, whereas the other 20 had severe IR. Serum levels of TNF-α were measured in all three groups. In the control group, the serum TNF-α level was 3.27 ± 0.29 pg/ml, which was similar to levels in healthy men in prior studies. In the moderate insulin-resistant group, the serum TNF-α levels were 23% higher, whereas it was 51% higher in the severe insulin-resistant group ($p < 0.001$) [47]. The above findings support the important role TNF-α plays in IR and DM, especially in RA. RA patients should therefore be screened at least annually, by checking a HbA1c level, fasting plasma glucose level or a 2-h postprandial glucose level, especially if other risk factors such as obesity, HTN and dyslipidemia are present.

RA has been considered an independent risk factor for the development of CVD similar to DM. Nondiabetic patients with RA were compared with patients with Type 2 DM and were found to have similar hazard ratios for CVD compared with the nondiabetic general population, with HR of 2.04 (95% CI: 1.12–3.67; $p = 0.019$) versus 2.16 (95% CI: 1.28–3.63; $p = 0.004$), respectively [48].

Age

Crowson *et al.* followed a cohort of 563 RA patients without a prior history of CV events for 8.2 years. In that time period, 98 of them (74 of them were seropositive, while 24 were seronegative) developed a CV event; the Framingham risk score for that same group, however, only predicted 59.7 events. The authors suggest that aging may have an accelerated effect on CV events in seropositive RA patients as the risk of CV events in seronegative RA patients was similar to the general population [49].

Smoking

It is well-established that there is a link between smoking and an increased susceptibility to developing RA [50,51]. Smokers also have more severe disease [52]. Elevated levels of IL-6 have been noted in past and active cigarette smokers [53]. Smoking is an independent risk factor for CVD in RA. Among their cohort of 101 RA patients, Gerli *et al.* found that smoking status, number of smoking years, number of daily cigarettes and 'cigarette years' were all associated with increased carotid mean IMT ($p < 0.05$ in all patients) when compared with nonsmokers [54].

CV risk factors associated with RA

Disease duration & its impact on CVD

It has been recognized that treating RA aggressively in its early stages is imperative as it has the potential to change the disease course. Several cohorts have suggested that CVD risk is increased in early RA [55,56]. Among 1236 early RA patients were followed by Goodson and colleagues over a median of 6.9 years, 160 patients suffered from a CV event; the majority were seropositive [57]. Carotid IMT, a surrogate marker of vascular disease is also abnormal in early RA as compared with controls [58,59]. The risk of CVD, although beginning early in the disease course, continues to increase with disease duration. CV mortality in established disease is known to increase in proportion to disease duration [60,61].

Seropositivity status

Severity of joint damage and extra-articular manifestations are associated with seropositivity in RA patients [62]. RF positivity has been associated with overall mortality [63]. Even in the earliest stages, patients with RF-positive arthritis have a higher risk of death from CVD causes than do RF-negative patients as reported by Goodson and colleagues [57]. The effect of anticyclic citrullinated peptide (CCP) on atherosclerotic damage in RA was evaluated by Gerli *et al.* by measuring the carotid IMT of 81 consecutive patients with RA without overt CVD using ultrasound. When compared with controls, IMT values were higher in the RA patients at all artery domains examined. RA patients with detectable circulating anti-CCP had higher IMT at the internal carotid arterial wall than patients without evidence of these antibodies [64].

Genetic risk factors

The relationship of shared epitope with anti-CCP antibodies in RA is well known. Shared epitope alleles have also been associated with ischemic heart disease and mortality in RA. Farragher *et al.* noted that the presence of two copies of the shared epitope was associated with highest all cause mortality [65]. The combination of shared epitope, anti-CCP antibodies and smoking predicted the highest risk of CV mortality in RA [65]. Certain shared epitope genotypes especially HLA-DRB1 0404 have been associated with increased risk in several studies [66,67]. This genotype has also been associated with endothelial dysfunction as measured by impaired flow mediated dilatation [68].

Several studies have linked genetic polymorphismsin various candidate genes with surrogate markers of CV risk such as flow-mediated dilatation. The polymorphism TNF-α -308 (rs1800629) in the TNF-α promoter region was found to be associated with a higher risk in RA patients who were also concomitantly carriers of the shared epitope [69]. Polymorphism in the IL-6 gene -174 (rs1800795) was associated with a lower flow-mediated dilatation in a small group of patients [70]. Lack of *MTHFR* has been associated with elevated homocysteine. Those patients with the A1298C polymorphism in the *MTHFR* gene had a higher risk of developing CV outcomes, which was depicted by a low flow-mediated dilatation [71]. The gene polymorphism in CD40 rs1535045 was linked to the development of subclinical atherosclerosis in RA patients [72]. On the other hand, a 32 base-pair deletion in the cytokine receptor *CCR5* gene, CCR5 rs333, those with a minor allele had a lower risk of CVD and normal flow-mediated dilatation [73].

Inflammation as a risk factor for atherosclerosis

Risk of CV death has been linked to elevated CRP levels, seropositivity may further increase this risk. Seronegative patients with a baseline CRP level of 5 mg/l or greater had a 1.5-fold increase risk of death from a CV cause as compared with a sevenfold increased risk of death from CV cause in seropositive patients [74]. Even in patients with clinically quiescent disease, high CRP levels conferred risk of CVD [75]. In a study involving 47 RA patients, high CRP levels were also found to correlate with higher carotid IMT [76].

Inflammation plays a role in the pathogenesis of atherosclerosis. It leads to plaque rupture, endothelial cell dysfunction, and subsequent thrombosis [77]. Persistent inflammation stimulates foam cell formation and arterial wall remodeling, both signs of early atherosclerotic lesions [78]. The inflammatory response in the rheumatoid synovium is similar to that found in an atherosclerotic plaques. Cytokines such as TNF-α and IL-6 contribute to the pathogenesis of joint inflammation and are also implicated in the increased CV risk seen in RA. IL-6 expression is seen in atherosclerotic plaques [79]. Vascular smooth muscle cells produce IL-6 and increased serums levels have been associated with IMT and proliferation of smooth muscle cells [80]. High

IL-6 levels are also associated with high CRP levels, a known association of CVD. A study by Cesari *et al.* showed that people with high levels of IL-6 are two- to five-times more likely to have a heart attack, stroke or other CV event [81]. TNF-α has also been detected in the smooth muscles cells, endothelium, and macrophages associated with coronary atherosclerotic plaques [82].

Role of medications in CV risk in RA

NSAIDs

Due to their potent anti-inflammatory mechanism of action, NSAIDs are commonly used to help treat arthritic symptoms. NSAID use, however, should be limited in patients with a history of a prior myocardial event as there is an increased risk of developing a recurrent MI. Trelle and colleagues, in their meta-analysis of 312 accumulated events from 26 trials, showed that NSAIDs were linked to 46% of all CV deaths. All drugs, except for naproxen showed evidence of an increased risk of CV death compared with placebo [83]. A total of 83,675 patients with a prior history of a MI were followed by Schjerning *et al.*, of which 42.3% were prescribed NSAIDs at least once during follow-up. NSAID treatment was associated with a significantly increased risk of death at the beginning of the treatment, and the increased risk persisted throughout the course of treatment (hazard ratio [HR]: 1.45; 95% CI: 1.29–1.62 and HR: 1.55; 95% CI: 1.46–1.64 after 90 days). Diclofenac was associated with the highest risk of death; however, naproxen was not associated with an increased risk of death or MI for the entire treatment duration [84].

Concurrent NSAID use may decrease the antiplatelet effect of an aspirin [85]. Hudson and colleagues showed there was a trend towards an increase in the rate of a recurrent acute MI in patients exposed to both aspirin and ibuprofen compared with those taking aspirin alone (HR: 1.01; 95% CI: 0.58–1.76). The risk increased with duration of exposure after 30 days of concomitant use; HR was 1.13 with a 95% CI between 0.54 and 2.39 and after more than 60 days, the HR increased to 1.83 with a 95% CI between 0.76 and 4.42. It is thought that ibuprofen blocks the binding channel so that aspirin is unable to bind to cyclooxygenase. Use of naproxen and aspirin, however, for a period of 60 days or more led to a decrease in the rate of a recurrent acute MI when compared with those patients who only took aspirin [85].

Lindhardsen and colleagues showed a modest CV risk in RA patients taking NSAIDs. A total of 6283 CV events occurred in a cohort of 17,320 RA patients followed on average for 5 years. Overall NSAID exposure was associated with a 22% risk increase in RA patients compared with a 51% increase in non-RA patients. Rofecoxib (which was removed from the market in 2004) was associated with the highest risk in both RA patients (HR: 1.57) and controls (HR: 2.19) [86]. Goodson *et al.,* however, conducted an inception cohort from the Norfolk arthritis registry that did not reveal an increase in CV risk in RA patients treated with NSAIDs [87].

Glucocorticoids

Traditional CV risk factors are also influenced by steroids and the risk is dose-dependent [88]. Greenberg and colleagues conducted a study which proved that daily dosages of prednisone between 1 and 7 mg had a HR of 1.78 (95% CI: 1.06–2.96) versus a HR of 2.62 (95% CI: 1.29–2.96) for dosages of prednisone 7.5 mg/day or greater [89]. Davis *et al.* retrospectively evaluated the use of corticosteroids in 603 RA patients, risk of CV events was assessed over a 13-year period. Interestingly, RF-negative patients who had been exposed to steroids did not have an increased risk of CV events, regardless of dosage or amount of use (HR: 0.85; 95% CI 0.39–1.87), whereas RF-positive patients with a high cumulative exposure to corticosteroids had a threefold-increased risk of CV events (HR: 3.06; 95% CI: 1.81–5.18) [90].

A total of 298 cases of MIs were noted in a study of 8384 patients with RA on corticosteroids conducted by Avina-Zubieta and collaborators. Current use of corticosteroids was associated with a 68% increased risk of an MI as shown by multivariable models. Current daily dose, cumulative duration of use and total cumulative dose were all associated with a significant increased risk of MI [91]. These same authors showed that steroid use was not associated with an increased risk of strokes (CVA) in a population-based cohort of 7051 RA patients followed over a median of 6 years. Although 178 incident CVA cases were reported, this was not considered a significant increased risk of CVA (HR: 1.41; 95% CI: 0.84–2.37). Models that accounted for daily dose, cumulative duration of use and total cumulative dose were also not significantly associated with CVA [92].

Risk assessment for CVD in RA

CV risk in RA patients cannot be measured with the same tools used to measure CV risk in the general population. For example, using the Framingham risk score in RA patients can underestimate the actual risk of developing a CV event as shown by Crowson *et al.*, where they conducted a study comparing the observed and predicted CV risk in RA patients versus controls using both the Framingham and the Reynolds risk score. The observed CV risk was significantly higher

than the predicted risk in patients, in those with persistently elevated erythrocyte sedimentation rates and in those older than 75 years. Using the Framingham risk score and the Reynolds risk score also underestimated the CV risk in women with RA who had elevated CRP. Overall the Framingham risk score underestimated CV risk by 102% in women and 65% in men with RA [93].

In Europe, the Systematic Coronary Risk Evaluation or SCORE is used to evaluate CV risk; it estimates the 10-year risk of a fatal atherosclerotic event such as a heart attack, stroke, other occlusive arterial disease and sudden cardiac death. A high CV risk was defined by a SCORE of ≥5% [94]. Gomez-Vaquero and colleagues found that SCORE also underestimated CV risk in a Spanish population of RA patients [95].

The European League Against Rheumatism (EULAR) proposing a risk score model where a multiplication factor of 1.5 is added to their risk score if a patient with RA meets two of the following three criteria: disease duration of >10 years; positive for rheumatoid factor or anti-CCP antibodies; and/or the presence of certain extra-articular manifestations [96].

So fa, the EULAR risk model has not been validated in large cohorts. The EULAR task force in its report mention that this correction of 1.5 is conservative. It is likely that the CV risk associated with RA may still be underestimated even after applying the numeric correction [97]. This may be especially true of patients with severe inflammation, but disease duration of less than 10 years who do have an increased risk of CV events [55,56]. Applying the correction will likely identify additional patients where aggressive risk management and primary prevention can be implemented.

Some studies suggest that measuring carotid IMT by carotid Doppler in conjunction with corrected CV risk scores may allow for identification of a larger number of patients with a higher risk of developing CV complications [98,99].

Management of CV risks in RA patients

In 2010, EULAR presented guidelines for management of CV risk in RA. They recommend that RA be considered as an independent risk factor for CVD. Adequate disease control is necessary for reducing CV risk. All patients with RA, especially those with active disease, should receive an annual CVD risk assessment and if they have inactive disease they could undergo CVD risk assessment every 2–3 years. Risk assessment should be adjusted for RA and total cholesterol/HDL ratios should be employed for assessing risk. Primary prevention strategies for CVD that are recommended for the general population should also be applied for RA patients [96].

Blood pressure, weight, physical activity, smoking status, and comorbidities such as dyslipidemia and DM should be monitored and discussed at each clinic visit. Fasting lipid panels should be checked on a regular basis and treatment with statins should be implemented if necessary. Statin therapy is useful for management of dyslipidemia, as well as modulation of inflammatory response associated with atherosclerosis as evidenced by lowering of CRP levels. Some studies suggest that with adequate risk stratification, up to 22% of RA patients without known CVD may meet indication for statin therapy, most of these patients however do not get treated adequately with statins [100]. Angiotensin-converting-enzyme inhibitor and angiotensin-receptor blockers should be used for HTN due to their effects on the vasculature and endothelial stability in RA patients [101–103]. NSAID use should be judicious in patients with known CVD. As discussed above, high doses of steroids have been associated with an increased risk of CV events in patients with RA. It is therefore recommended that if steroids are deemed necessary as part of the management, low doses should be used for the shortest period of time. Treatment should also include a multidisciplinary approach to ensure that all comorbidities are being addressed and appropriately controlled. Smoking cessation should be strongly advised at each visit and the emphasis on its detrimental CV outcomes if they continue to smoke should be discussed.

CV risk reduction by disease control

Effective treatment of RA is associated with reduction in CV risk. While both DMARD and biologic DMARD therapy has been associated with benefit, some studies suggest that the benefit may be larger in patients treated with biologics especially anti-TNF therapy [89].

Several studies however have documented CV risk reduction with methotrexate. Choi *et al.* conducted a prospective study of 1240 RA patients followed for an average of 6 years while being treated with various oral DMARDs including methotrexate, sulfasalazine, HCQ, penicillamine and intramuscular gold. They noted that CV deaths were decreased by 70% in patients treated with methotrexate [104]. Several meta-analysis looking at data from large cohorts have also confirmed the lowering of CV risk with methotrexate [105,106]. El-Barbary *et al.* showed that IL-6 and TNF-α are both elevated in early active RA and these levels decrease and sometimes normalize with MTX therapy [107].

Greenberg and collaborators however found that treatment with TNF antagonists, but not methotrexate was associated with a reduced risk of CV events

when compared with nonbiological DMARDs. This risk reduction was observed for both MI and CVA as individual outcomes [89]. TNF inhibitors (TNF-I) are known to have favorable effects on IR and lipid profiles in RA, which may explain this finding. Treatment with infliximab led to a statistically significant reduction in both serum insulin levels, IR and insulin sensitivity in RA patients with severe joint disease [108]. Similar results have been seen with other, such as etanercept [109].

In a recent study, the HR for CV events was 20–29% lower in patients receiving as compared with DMARD therapy; however, this benefit was only seen up to 12 months of therapy [110]. This effect may be attributable to better and earlier disease control with biologic agents rather than a class effect of biologics themselves [111,112]. They have also shown to have beneficial effects on vascular stiffness as measured by surrogate markers like aortic pulse wave velocity [113–115]. Hürlimann and colleagues evaluated flow-mediated dilation and nitroglycerin-induced vasodilation of the brachial artery before and 12 weeks after standard treatment with infliximab by high-resolution ultrasound vessel wall-tracking device. Eleven RA patients with on average 9 years of disease duration with high disease activity despite high dose methotrexate and prednisone therapy were treated with three doses of infliximab. Endothelium-dependent dilation improved from 3.2 to 4.1 after 12 weeks of infliximab treatment ($p = 0.018$). Nitroglycerin induced vasodilation however remained unchanged [116].

In RA patients treated with infliximab every 8 weeks for at least a year, endothelial-dependent and -independent vasodilation was also evaluated by Gonzalez-Juanatey and collaborators. They noticed a rapid increase in the percentage of endothelial-dependent vasodilation in all patients with a return to baseline, however, by 4 weeks [117]. Adalimumab was also noted to lead to improvement in endothelial dependent vasodilation after 1 month of treatment and even better response at 1 year [118]. In the meta-analysis by Barnabe *et al.*, anti-TNF therapy was associated with greater risk reduction than DMARD therapy in observational cohorts but not randomized controlled studies [119]. Gonzalez-Juanatey and collaborators also showed similar improvement in endothelial-dependent vasodilation with rituximab [120].

Cardiac disease as an extra-articular manifestation of RA

Pericarditis

Pericarditis is a well-recognized extra-articular manifestation of RA. The incidence of pericarditis in RA depends upon the modality used for diagnosis. Clinically symptomatic pericarditis is uncommon and occurs in less than 5% of RA patients. If investigated by echocardiography 20–50% of patients show evidence of pericardial involvement [121–123]. Autopsy series in RA also reflect similar findings with 20–40% of patients showing histologic evidence of fibrinous pericarditis [2,121].

Risk factors for pericarditis in RA include seropositivity, male sex, and severe or active disease. Pericarditis can present with symptoms of chest pain or dyspnea. Pericardial rub may be present on auscultation. In rare instances patients without clinically significant joint disease may present with pericarditis in the setting of positive serologies for RA. Rheumatoid pericardial effusions tend to have elevated protein and lactate dehydrogenase levels, as well as low glucose levels. Cholesterol crystals may also be found [124]. Hemodynamic compromise due to pericardial disease infrequent, and is seen in approximately 0.5% of patients [125]. Pericarditis does not always parallel joint inflammation. Pericardial involvement can be either constrictive or effusive. Echocardiogram, chest CT or a right heart catheterization may be necessary to make a diagnosis of pericardial involvement if there is constrictive disease. A CT may show pericardial inflammation, fluid or calcification.

Treatment can include NSAIDs, steroids, DMARDs or biologic DMARD therapy. If pericarditis develops in patients receiving biologic therapy, infection and malignancy need to be ruled out [126]. Surgical intervention such as pericardiectomy or pericardial window may be needed in patients with hemodynamic compromise. Surgical intervention should not be delayed for a trial of medical therapy. In patients with RA who develop hemodynamic compromise due to pericardial effusion mortality may be as high as 100% at 2 years [125].

Valvular heart disease

Although valvular disease is not considered to be a major cardiac manifestation of RA, recent echocardiographic studies have revealed a higher than anticipated incidence of asymptomatic valvular involvement. Studies using transthoracic echocardiogram studies have estimated the incidence of asymptomatic valvular abnormalities in RA from 24 to 39% [123,127,128].

Mitral valve is the most commonly involved valve. Histologically valves may show fibrosis or nodules [121]. Sometimes disease may be severe enough to cause valvulitis, regurgitation or rupture. Studies using transesophageal echocardiography as imaging modality show an even higher incidence of asymptomatic valvular disease. A study by Guedes *et al.* found only two of 30 unselected RA patients without known cardiac disease, had normal transesophageal echocardiography

studies. This study reported that 83% of RA patients had evidence of valvular disease as compared with 53% of controls. Mitral regurgitation was the commonest abnormality, seen in 80% of patients. Nodular involvement of valves was identified in two patients, 37% had evidence of cardiomyopathy [129]. Another study of 34 RA patients by Roldan *et al.* found 20/34 (59%) had evidence of left-sided valvular involvement, 11/34 (32%) had valve nodules, one patient had evidence of Libman-Sacks endocarditis [130]. A recent meta-analysis of ten echocardiographic studies in RA patients reported four times the incidence of valvular thickening and calcification, and five times the incidence of valve nodules in RA patients as compared with controls [131]. Valvular disease is more frequent in patients with nodular as compared with non-nodular RA [132]. Calcific valvular deposits suggest concomitant presence of coronary atherosclerotic disease [133].

Myocardial disease

Myocardial involvement is found in up to 30% of cases in autopsy series. Histologically the myocardial disease can be diffuse or focal. Myocardial granuloma's, fibrosis or necrosis may be present [121].

There is an increased incidence of CHF in RA, accounting for approximately 20% of mortality in RA patients [134]. Several risk factors for myocardial disease such as DM, HTN, dyslipidemia and ischemic heart disease are increased in RA. However, studies suggest that the risk of CHF in RA is higher than accounted for these traditional risk factors including ischemic heart disease [135]. This suggests that RA is an independent risk factor for CHF. In a study by Nicola *et al.,* among a cohort of 575 RA patients and 583 controls who were followed for 30 years, the incidence of CHF was 34% in RA versus 25.2% in non-RA patients ($p < 0.001$). RA increased the risk of CHF even after adjusting for demographics, ischemic heart disease and other risk factors [136]. Myasoedova *et al.* followed 795 RA patients for an average of 9.7 years. Erythrocyte sedimentation rate, RF positivity, extra-articular involvement and steroid use were the factors that remained associated with risk of CHF after adjusting for traditional CV risk factors [137].

Diastolic dysfunction is another commonly found cardiac abnormality in RA patients. Several large studies using transthoracic echocardiogram as imaging modality have documented higher rates of diastolic dysfunction in patients with RA as compared with controls [128,138–143]. Incidence as high as 66% have been reported; however, most patients tend to be clinically asymptomatic. There is no conclusive data linking diastolic dysfunction to either the duration or severity of RA [144].

In a meta-analysis of 25 studies that included 1614 matched RA patients, the most frequently reported echocardiographic abnormality was impaired ventricular relaxation [145].

Progression of diastolic dysfunction to clinically significant CHF is uncommon. A study by Correa de Sa *et al.* suggest only 1.9% of patients with diastolic dysfunction progressed to CHF at the end of 2 years, 31.1% were likely to develop a cardiac-related symptom [146]. The rate of progression of diastolic dysfunction may be independent of the RA disease activity, and similar to progression in non-RA patients [142].

Diastolic dysfunction in the general population is associated with increased left ventricular mass. Associations of left ventricular mass to diastolic dysfunction in RA has yielded mixed results. In a meta-analysis, Corrao *et al.* analyzed the data from four echocardiographic studies and concluded that patients with RA tended to have an increase in left ventricular mass [147]. This is in contrast to the study by Giles *et al.*, using cardiac MRI as imaging modality, which showed that patients with RA tended to have 18% lower left ventricular volumes, as compared with age matched controls ($p < 0.001$). Of interest, the ventricular volumes were inversely associated with anti-CCP antibody titers and with biologic use [148].

Inflammatory cytokines such as TNF-α, IL-1, IL-6 are thought to cause microvascular disease, which leads to myocardial remodeling and diastolic dysfunction. In a study by Davis *et al.* of 212 RA patients, the severity of diastolic dysfunction correlated to cytokine levels. They reported that an 11-cytokine profile was able to distinguish RA patients with moderate-to-severe diastolic dysfunction as compared with patients with normal heart function [149]. More recently, myocardial tissue from RA patients was found to have higher levels of citrullinated proteins as compared with controls, which may account for myocardial involvement in RA [150].

Another aspect of myocardial dysfunction in RA is medication associated toxicity, especially TNF-I and antimalarial agents. Antimalarial medicationsare commonly usedin RA. Antimalarial cardiotoxicity is generally linked to chloroquine [151], although there are several case reports of cardiotoxicity with HCQ [152–159]. Cardiotoxicity has been reported with variable cumulative doses and sometimes occurs early in the treatment course [151,160]. Antimalarial cardiotoxicity may result in restrictive cardiomyopathy or ventricular enlargement and biventricular failure. Histopathology is required to make a definitive diagnosis, with vacuolar changes being typical. Myelin figures and curvilinear bodies that represent abnormal lysosomes are also specific to antimalarial cardiotoxicity. Biopsy may also be necessary to rule out other diagnoses like

myocarditis and amyloidosis. In the literature review by Costedoat-Chalumeau *et al.*, antimalarial-associated cardiotoxicty had high mortality rates (11/25 patients). Withdrawal of medication resulted in stabilization in some cases [151]. There are case reports of patients who have required heart transplantation after antimalarial cardiotoxicity [161].

TNF-I are also associated with heart failure. Attention to possible worsening effects of agents on CHF were ironically brought into focus by two randomized controlled trials of TNF-I agents as therapy for heart failure. TNF inhibition in CHF was attempted as high levels of TNF were found to be associated with heart failure [162]. Animal models suggested TNF may be involved in remodeling of the heart, and that TNF inhibition may be beneficial in heart failure [163,164]. This was supported by a successful Phase I study of etanercept in heart failure [165]. Large randomized controlled trials of TNF-I agents in advanced symptomatic heart failure were conducted. Two studies were carried out using etanercept: the North American RENNAISSANCE and the European RECOVER, which together had a total of 2048 patients [166]. The ATTACH trial looked at the efficacy of infliximab in CHF [167]. All studies showed unfavorable outcomes including clinical worsening and increased mortality leading to early termination. This lead to the US FDA issuing a warning against use of anti-TNF agents in symptomatic CHF. Subsequently, about 47 cases of new or worsening cases of CHF were noted in 300,000 patients treated with worldwide [168].

There are, however, contrasting results from observational cohorts and various RA registries, which do not show an increased risk of CHF in RA patients treated with TNF-I. These data from several registries around the world suggest that patients with RA who are treated with TNF-I have an overall lower or comparable prevalence of CHF as compared with patients not treated with TNF-I [135,169–173]. A recent meta-analysis of data from these registries also concluded that RA patients treated with TNF-I had a lower incidence of CHF than patients who did not receive this agent [174]. This benefit may be reflective of the overall better control of inflammation, rather that effects specific to the class of drugs.

As RA is itself associated with CHF, it is unclear if the unexplained cases of CHF were truly related to TNF-I [172].

Cardiac amyloidosis

Chronic, uncontrolled inflammation in RA leads to reactive amyloidosis with deposition of amyloid A in various tissues. The incidence of amyloidosis is likely related to the severity and duration of inflammation. A large series of 369 autopsies from 1952 and 1991 showed a 30% incidence of amyloidosis with approximately 28% having cardiac involvement [175]. Similar incidence has been reported by others [176].

The clinical significance of these post-mortem findings on autopsy series is unclear as symptomatic disease leading to pre-mortem diagnosis is rare. Incidence of amyloidosis in the biologic DMARD era may also be lower due to better control of disease activity. Studies looking at abdominal fat pad aspirates for diagnosis estimate the incidence of systemic amyloidosis to be between 7 and 78% in RA patients [177,178]. Cardiac amyloidosis leads to biventricular enlargement and diastolic dysfunction. 'Sparkling' pattern in the myocardium is characteristic finding on cardiac MRI. Evidence of renal or other organ involvement may be apparent in most patients. There is evidence that biologic therapy especially with anti-TNF agents can reverse amyloid deposition [179,180].

Coronary arteritis

Before the advent of DMARD therapy coronary vasculitis was reported in up to 20% of cases based on autopsy series [181,182]. Coronary arteritis may result in cardiac ischemia and should be considered as a differential diagnosis in patients who present with ischemic events. An endomyocardial biopsy may be needed to differentiate cardiac ischemia due to vasculitis from a similar picture due to atherosclerotic disease [183].

Conclusion

CVD is prevalent in RA. RA in itself is a risk factor for atherosclerotic disease. Onset of atherosclerotic disease occurs in early RA and progresses with disease duration especially in uncontrolled disease. Seropositivity and high disease activity are disease specific factors that correlate with high CV risk. Some traditional risk factors such as BMI and lipid levels apply differently to the RA population. Medications including NSAIDs, steroids, DMARDs and biologic DMARDs can modify risk factors and some are implicated in the development of CVD. Control of disease activity lowers the CV risk in RA. Extracardiac manifestation of RA include pericarditis, valvular disease, cardiomyopathy, subclinical involvement is significant when detected by imaging modalities. Attention to risk stratification and prevention of CVD in RA is imperative and can significantly affect outcomes in RA patients.

Future perspective

Going forward, we anticipate that there will be reduction in CV morbidity in RA due to increased awareness amongst physicians, better control of CV risk factors and better control of disease activity. Further research into genetic polymorphisms and their effects

on CV outcomes in RA may allow for personalized medicine, where the risk of developing cardiac disease may be accurately predicted and interventions based on individual profiles may be instituted. Further insights into disease mechanisms, including the role of protein citrulination in CVD in RA may allow for more effective interventions. Development of clinically meaningful markers of atherosclerosis may allow for early detection and intervention in preclinical patients.

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Executive summary

Atherosclerotic disease in rheumatoid arthritis

- Traditional risk factors in rheumatoid arthritis (RA)
  - Lipid levels can be lower than anticipated in RA patients due to inflammation. Atherogenic index, which is a ratio of total cholesterol to high-density lipoprotein cholesterol can be used a marker of cardiovascular (CV) risk in RA.
  - Metabolic syndrome is prevalent in RA and can be present in patients with low or normal BMI.
- RA-specific risk factors
  - CV risk increases in early RA and is proportionate to the duration of disease.
  - Seropositivity increases risk of CV disease in RA.
  - Presence of shared epitope may increase CV risk in RA.
  - Medications used in RA including steroids and NSAIDs may contribute to the CV risk and should be used judicially.
- Risk assessment in RA
  - Traditional risk models like Framingham score underestimate CV risk in patients with RA.
- Management of CV risk in RA
  - Patients with RA should have routine assessment for CV risk.
  - Statin therapy for dyslipidemia and angiotensin-converting-enzyme inhibition for hypertension control are recommended.
  - Adequate disease control is important to reduce CV risk in RA.

Cardiac disease as an extra-articular manifestation of RA

- Subclinical pericardial involvement in RA is common.
- High incidence of subclinical valvular abnormalities seen in RA patients with imaging modalities such as transthoracic echocardiogram and transesophageal echocardiography.
- Increased incidence of CHF in RA patients, accounting for up to 20% of mortality in RA patients.
- Myocardial involvement and diastolic dysfunction is common in RA.
- Cardiac amyloidosis and coronary arteritis are rare cardiac complications of RA.

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