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Cardiovascular Comorbidity in Rheumatic Diseases A Focus on Heart Failure

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INTRODUCTION

The increased risk of cardiovascular disease (CVD) associated with rheumatologic conditions is well recognized and has been described extensively in systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and, more recently, ankylosing spondylitis (AS) and psoriatic arthritis.

There is evidence to support the role of inflammation in the pathogenesis of CVD in this population, but the exact mechanism remains incompletely understood. Given the mortality gap that exists between patients with rheumatic diseases and the general population, early recognition, modification of risk factors, and control of disease activity will likely be pivotal in improving outcomes in this population.¹

RA

Epidemiologic Insights

RA is a common rheumatic disease, estimated to have a prevalence of approximately 1%, and is seen 2 to 3 times more frequently among women.² The lifetime risk of RA has been estimated as 3.6% in women and 1.7% in men.³

Cardiovascular-Related Mortality and Ischemic Heart Disease in RA

Patients with RA have a higher risk of mortality when compared with the general population, which is largely a result of increased cardiovascular (CV) death (Fig. 1).^{4,5} There is a 50% increased risk of CV mortality among patients with RA compared with the general population, with heart failure (HF) being a significant contributor to the observed excess mortality.^{6,7}

The risk of ischemic heart disease (IHD) is significantly higher among patients with RA when compared with the general population.^{8–10} In a large prospective cohort study of

114,342 women with RA and no prior CVD, the relative risk of myocardial infarction (MI) (after adjusting for CV risk factors) was 2.0 (95% confidence interval [CI] 1.23–3.29) compared with the general population.¹¹ Population-based studies have also shown that patients with RA are more likely to have unrecognized coronary heart disease (CHD) and are almost twice as likely to experience sudden death when compared with the general population (hazard ratio [HR] 1.94, 95% CI 1.06–3.55).¹⁰

The increased risk of coronary artery disease among patients with RA has been attributed to accelerated atherosclerosis in the presence of systemic inflammation.^{12,13} Although coronary artery disease is the major cause of HF in the general population, accounting for 62% of all cases, its contribution to the development of HF in RA is not as compelling.¹⁴ The excess risk of HF is not explained by clinical IHD.¹⁵ Patients with RA presenting with incident HF are less likely to have a preceding history of IHD compared with non-RA patients (24% compared with 35% among non-RA patients, $P = .02$).¹⁶ This fact may be explained, in part, by the increased risk of unrecognized CHD described earlier.

HF in RA

The increased risk of developing HF among patients with RA is well described.^{9,17,18} A population-based incidence cohort of patients with RA over a 40-year period demonstrated a higher incidence of HF among patients with RA compared with a cohort of non-RA patients. After adjusting for age, sex, IHD, and traditional CV risk factors, the risk of developing HF (defined according to the Framingham Heart Study Criteria) among patients with RA was almost twice that of non-RA patients (HR 1.87, 95% CI 1.47–2.39), with an increase in cumulative incidence observed over time (Fig. 2). The higher incidence of HF was seen among all age groups, but it tended to be increased in women compared with men (relative risk [RR] 1.9, 95% CI 1.4–2.5 vs RR 1.3 95% CI 0.9–2.0).¹⁵

Compared with the general population, HF in patients with RA seems to be more frequently associated with diastolic dysfunction.^{19,20} After adjusting for age, sex, and history of IHD, patients with RA have been shown to be twice as likely to have preserved ejection fraction (odds ratio [OR] 1.90, 95% CI 0.98–3.67) (Fig. 3).¹⁶ When HF with reduced ejection fraction does occur in patients with RA, it is seen much more frequently in men (HR 3.7, 95% CI 1.8–7.7).²¹ Diastolic dysfunction is a predictor for incident HF independent of the traditional CV risk factors, including age, hypertension, diabetes, and coronary artery disease (HR 1.81, 95% CI 1.01–3.48).^{22,23} Echocardiographic findings of diastolic dysfunction have also been shown to be associated with an increase in all-cause and cardiac mortality.^{24–26}

Role of Traditional CV Risk Factors

The increased risk of CHD and HF among patients with RA is not explained by an increased incidence of the traditional CV risk factors; in fact, some traditional risk factors may play a paradoxical role in RA.^{10,18,27}

Age is a major determinant for CVD risk in the general population. Indeed, the impact of aging on the CV risk in patients with RA may be even greater than for the general population. Recently, a population-based inception cohort of patients with RA with no prior CVD history demonstrated that the effect of age on CVD risk was almost twice that in the general population in men and more than twice that in women. The impact of age on CVD risk in seronegative patients and among patients younger than 50 years was similar to that seen in the general population.²⁸

Diabetes mellitus, hypertension, dyslipidemia, and alcohol use/abuse have not been described more frequently in patients with RA when compared with patients without RA.^{15,16,18,29} The prevalence of smoking is higher among patients with RA, but this risk factor alone is unlikely to account for the increased CVD risk.^{27,29,30}

Obesity seems to play a paradoxical role in its contribution to CVD risk in patients with RA, with a lower body mass index (BMI) associated with increased CV risk in one study.²⁹ Davis and colleagues¹⁶ also described a lower prevalence of obesity at baseline among subjects with RA with incident HF compared with non-RA subjects (60% vs 71%, $P = .03$). Patients with RA with a higher BMI have lower mortality rates than that seen in thinner patients independent of RA onset, age, duration, and smoking status.³¹

Lipids also seem to play a paradoxical role with respect to CV risk among patients with RA, with lower total cholesterol being significantly associated with a higher CV risk (Fig. 4).³² High-density lipoprotein, low-density lipoprotein (LDL), and total cholesterol levels may be reduced in patients with untreated RA and later increase with suppression of inflammation through treatment, although the increase in LDL cholesterol associated with RA treatment does not seem to confer a higher CV risk.^{33–35} Patients with RA tended to have a lower likelihood of achieving therapeutic LDL goals following statin use. Increased erythrocyte sedimentation rate (ESR) is associated with a lower likelihood of achieving LDL targets, which underscores the importance of control of disease activity in risk-factor modification.³⁶

Screening for Traditional CV Risk Factors in RA

Despite the increased awareness of the higher risk of CVD among patients with RA, screening and management of traditional CV risk factors in this population remains inadequate.³⁷ In one study, a significant proportion of patients with RA and hyperlipidemia with sufficiently high risk to warrant statin use were not receiving treatment with statins.³⁸ Similarly, hypertension among patients with RA remains underdiagnosed and undertreated.³⁹

The association between CV risk factors and CV events seems to be weaker among patients with RA compared with the general population. Male gender, smoking, and personal cardiac history have a weaker relative association with CV events in patients with RA compared with non-RA patients.²⁹ Overall, the proportion of risk attributable to traditional CV risk factors was 23% lower in subjects with RA than in non-RA subjects in one study.¹⁸

Taken together, these data suggest that the higher risk of CVD in RA is not explained by a higher prevalence of CV risk factors or an increased impact of CV risk factors. Instead, recent data have suggested that RA may be an independent CV risk factor. Notably, the magnitude of risk conferred by RA as an independent CV risk factor is comparable with the magnitude of risk associated with diabetes mellitus.^{40,41}

Because RA disease activity has repeatedly been shown to be significantly associated with higher CVD risk, modification of traditional risk factors alone, in the absence of effective control of disease activity is unlikely to be sufficient for CV risk reduction.^{29,42} Thus, the impact of aggressive control of traditional CVD risk factors in patients with RA remains unclear. Nonetheless, the current recommendations support screening and management of patients with an elevated CV risk when identified.³⁸ The management of CV risk factors in patients who would not otherwise be deemed to be high risk based on the use of the traditional Framingham risk score (FRS) remains an unresolved question.⁴³

Prognosis/Outcomes of Patients with RA

Studies have suggested that patients with RA have worse short- and long-term outcomes following MI compared with the general population.^{44,45} Mortality after the first MI has been shown to be significantly higher in people with RA compared with non-RA subject controls (standardized mortality ratio [SMR] 1.47, 95% CI 1.04–2.08).⁴⁶ Patients with RA are also less likely to undergo coronary artery bypass grafting than patients without RA.¹⁰ A retrospective chart review of hospital records of 90 patients with RA treated for MI compared with matched controls suggested that patients with RA were less likely to receive acute reperfusion (OR 0.27, 95% CI 0.10–0.64) and treatment with beta-blockers and lipid-lowering therapy while in the hospital.⁴⁷ These findings were not reproduced in a recent larger cross-sectional study of 13,029 patients with RA conducted between 2003 and 2005, which, in contrast, demonstrated a higher rate of percutaneous intervention (OR 1.27, 95% CI, 1.17–1.39) and a greater likelihood of thrombolytic use (OR 1.38, 95% CI 1.10–1.71) compared with the general population. This study also suggested improved in-hospital mortality when compared with the general population.⁴⁸ It is unclear if the observed disparities are a reflection of different practice patterns based on the different populations in which these studies were conducted, and further investigation is warranted.

The prognosis of patients with HF and RA is also worse compared with non-RA patients based on population-based data derived from Olmsted County, Minnesota, which demonstrated a higher 30-day (15.5% vs 6.6%, $P = .001$) and 1-year mortality (35% vs 19.3%, $P = .01$) after the onset of HF among patients with RA compared with non-RA subjects. The risk of death at 30 days was 2.39 fold higher (95% CI 1.36–4.18) and 2.02 fold (95% CI 1.40–2.90) higher at 1 year. Among those subjects who survived the first year, there was no difference in overall survival after the onset of HF.¹⁶ Patients with RA seem to have less aggressive management of HF and CV risk factors when compared with non-RA subjects. Patients with RA and HF were less likely to receive treatment with angiotensin-converting enzyme inhibitors (15% vs 30%) and beta-blockers (10% vs 23%) compared with non-RA subjects in one study.¹⁶

PATHOPHYSIOLOGIC INTERACTIONS BETWEEN RA AND CVD

Innate and adaptive immune mechanisms shared by atherosclerosis and RA have emerged as possible contributors to the increased CVD risk seen in this population. There is evidence from both human and animal studies that toll-like receptor signaling plays a role in driving the production of cytokines in synovium and in the activation of atherosclerotic lesions.⁴⁹ HLA-DRB1 is a major gene that has been shown to be associated with RA susceptibility and has also been shown to potentially confer an increased risk of CHD, suggesting a role for adaptive immunity in the pathogenesis of both diseases.^{50–52} The loss of expression of CD28, which is a costimulatory molecule present on CD4 T cells (CD28 null cells), has been associated with RA and, in particular, with more aggressive disease manifestations.⁵³ Higher levels of CD28 null cells have been seen in patients with RA with evidence of preclinical atherosclerosis compared with controls.⁵⁴ CD28 null cells identified in atherosclerotic plaque has been shown to play a role in the mediation of the inflammatory process.⁵⁵

Chronic inflammation plays an important role in development of HF, but the mechanism by which this increases the risk of myocardial dysfunction and HF remains incompletely understood. Elevated inflammatory markers (C-reactive protein [CRP], interleukin 6 [IL-6], and tumor necrosis factor [TNF] alpha) are associated with an increased risk for left ventricular (LV) hypertrophy, diastolic dysfunction, and development of HF in the general population, with higher levels conferring greater risk.^{56–58} Among patients with advanced

HF, higher levels of TNF alpha and IL-6 have also been associated with increased mortality.⁵⁹

In patients with RA, elevated levels of IL-6 have also been demonstrated to confer a higher risk of diastolic dysfunction (OR 1.2 per 2.8 pg/mL, 95% CI 1.02–1.4) and have been associated with premature coronary atherosclerosis, even after adjustment for CV risk factors.^{13,60}

Systemic inflammation as evidenced by persistently elevated ESR levels among patients with RA has been shown to confer a 2-fold increased risk (HR 2.03, 95% CI 1.45–2.83) for CV death among patients with RA even after adjustment for traditional CV risk factors. There also seems to be an increasing risk with higher ESR levels.^{21,61} Among patients with RA, higher ESR levels were seen in the 6-month period before the development of HF than any other time during the follow-up period, which also supports the potential for inflammatory mechanisms to be involved in the pathogenesis of HF (Fig. 5).⁶²

Abnormal Myocardial Structure and Function in RA

Patients with RA are more likely to have abnormal LV geometry (higher LV mass and LV hypertrophy) than healthy people without RA. These abnormalities are associated with an increased risk of CVD. For example, there is a strong association between increased LV mass (seen in patients with RA) and incident HF (HR 1.4 per 10% increment, $P < .0001$).^{63,64} Patients with RA with abnormal LV geometry are also significantly more likely to have LV concentric remodeling (OR 4.73, 95% CI 2.85–7.83), which is associated with a higher risk of incident CHD.^{64,65}

Speckle tracking echocardiography is an advanced echocardiographic modality for detection of myocardial changes during contraction and relaxation (ie, myocardial strain).^{66,67} A recent population-based study of 87 patients with RA using this imaging modality showed a reduction in LV and right ventricular strain among patients with RA when compared with the general population, which correlated with markers of disease severity.⁶⁸ Although larger studies are needed to confirm these findings, this modality may be useful in detecting early myocardial changes in RA.^{66,67}

Impact of Disease Characteristics of RA

The disease characteristics of RA seem to influence the risk of development of CVD and CV mortality, with rheumatoid factor (RF) positivity and disease severity conferring the greatest risk.^{61,69}

RF positivity is a significant predictor of CV events including HF all-cause and CV mortality among the general population, suggesting a role for antibodies in the pathogenesis of CVD.^{69,70} Among RF-negative subjects, after adjusting for age, sex, IHD, and CV risk factors, the increased risk of HF was no longer significant in a population-based cohort study but remained significant with a 2.5-fold increased risk among RF-positive subjects (adjusted HR 2.59, 95% CI 1.95–3.43).¹⁵ Severe extra-articular manifestations of disease are associated with a higher likelihood of developing HF (HR 3.1, 95% CI 1.9–5.1) even after adjustment for CV risk factors.²¹ The presence of rheumatoid lung disease and RA vasculitis, which are markers of disease severity, has also been associated with a greater likelihood of CV death.⁶¹

Impact of Disease Duration

There is evidence to suggest that the increased CVD risk in RA may predate the clinical manifestations of the disease, with evidence of atherosclerosis and coronary artery disease

predating the diagnosis.⁷¹ Following the diagnosis of RA, the relationship between the disease duration and CVD outcomes is less clear. A recent metaanalysis suggested that the SMR was higher among noninception cohorts. A population-based inception cohort study of patients with RA did not identify an association with risk of coronary artery disease and disease duration, but there was an increased risk of events in the 2-year period before meeting the American College of Rheumatology's (ACR) criteria for RA.⁶¹ Another population-based study found no increased risk of IHD in the 5-year period before the RA diagnosis (adjusted OR 1.2, 95% CI 0.6–2.4).⁷² However, this population noted a significantly increased risk of IHD in years 1 to 4 after the RA diagnosis (RR 1.5, 95% CI 1.2–1.7).⁷³ The risk of diastolic dysfunction in patients with RA may be associated with the duration of disease based on data derived from a population-based cohort study that showed that after adjusting for CV risk factors, there was a significant association between the duration of the disease and diastolic dysfunction (OR 3.2, 95% CI 1.8–5.4), similar to that seen in other studies.^{74,75}

DIAGNOSTIC ISSUES

Patients with RA are less likely to have angina pectoris as a manifestation of coronary artery disease (OR 0.58, 95% CI 0.34–0.99), more likely to have silent MI (OR 5.86, 95% CI 1.29–26.64) compared with the general population, and less likely to have typical electrocardiogram findings at presentation.^{10,45} The difference in clinical presentation may contribute to delays in the recognition and treatment of patients with RA and emphasizes the importance of a high index of suspicion in these patients.

Clinical features of HF typically seen in the general population are less likely to be evident at presentation in patients with RA. Population studies of incident HF in patients with RA showed that they are less likely to have dyspnea on exertion, orthopnea, or paroxysmal nocturnal dyspnea at presentation. Patients with RA in this study were also more likely to have rales compared with non-RA subjects and less likely to have elevated blood pressures at presentation.¹⁶

B-Type Natriuretic Peptide

Elevated levels of B-type natriuretic peptide (BNP) are predictive of LV diastolic dysfunction (LVDD) on echocardiography in the general population and are useful in the evaluation of suspected HF.⁷⁶ Among patients without clinical CVD, those with RA were more likely to have elevated BNP than non-RA subjects (16% vs 9%, $P < .001$). Patients with RA with abnormal BNP are more likely to have LVDD compared with those with normal BNP, but the specificity compared with non-RA patients (89% vs 94%, $P = .02$) and the positive predictive value (25%) of elevated BNP in patients with RA is low (25%) and is, therefore, not a good screening tool.⁷⁷ The duration of RA and CRP levels is independently associated with N-terminal proBNP.⁷⁸

CV Risk Scores in RA

There is a need for risk scores that accurately estimate the risk of CVD among patients with RA.

Given that the current risk scores do not take into account the RA disease characteristics that have been demonstrated to confer an increased risk of CVD,^{37,67} the application of a 1.5 multiplier to the FRS has been suggested by the European League Against Rheumatism (EULAR) as a means of estimating the CVD risk among patients with RA.⁴² This application was shown to inadequately estimate the risk in light of a re-equivalent or even lower risk seen in some patients with RA and the up to 3-fold increased risk seen in older

patients relative to that predicted by the FRS.⁷⁹ Future studies will be important to determine the validity of the use of this multiplier and to establish alternate tools for CVD risk prediction in this population.

IMPACT OF MEDICATIONS USED IN TREATMENT OF RA ON HF

Medications used for the treatment of RA may have opposing effects on CV risk; although a reduction in disease activity is associated with a lower risk of CV outcomes, the potential for increased CV risk remains with the use of certain drugs.

Glucocorticoids

Glucocorticoids are frequently used in the treatment of RA primarily for short-term control of disease activity but may also have disease-modifying benefits. The use of glucocorticoids has been associated with an increased risk of CVD based on observational studies in the general population.^{80,81} Among patients with RA, population-based studies have shown a higher risk of CV events (MI, HF, and CV death) associated with glucocorticoid exposure, with higher exposure associated with a 3-fold increased risk of CV events in one study (HR 3.06, 95% CI 1.81–5.18). The increased risk was not seen in patients who were RF negative and in those taking lower doses of glucocorticoids (average daily dose of 7.5 mg).⁸² Current use of glucocorticoids has been associated with a 2-fold increased risk of HF (HR 2.0, 95% CI 1.3–3.2) and increased risk of hospitalization for HF (HR 1.4, 95% CI 1.03–1.8).^{21,83} Glucocorticoid use in patients with RA, when indicated, should be limited in dose and duration given the dose-dependent increase in the risk observed.

Nonsteroidal Antiinflammatory Medications

The use of Cox-2 inhibitors and nonsteroidal anti-inflammatory drugs (NSAIDs) is associated with an increased risk of MI, relapse of HF, and hypertension, which are greatest in patients with a prior history of CVD.^{84,85} The use of nonselective NSAIDs, however, has not been shown to be associated with an increased risk of incident HF in patients with RA without a prior history. Use of NSAIDs and Cox-2 inhibitors should, therefore, be avoided in patients with RA with a history of CVD.

Disease-Modifying Antirheumatic Drugs

There is evidence to suggest that control of disease activity is associated with a reduction in CV risk. A case-control study of patients with RA with no history of HF showed that patients treated with disease-modifying antirheumatic drugs (DMARDs) had a 30% lower rate of hospitalization for HF when compared with no DMARD use.⁸⁶ Data from population-based cohort studies showed that patients treated with methotrexate were half as likely to develop HF compared with nonusers (HR 0.5, 95% CI 0.3–0.9).²¹ The use of methotrexate in patients with RA was associated with a 60% reduction in all-cause mortality and a 70% reduction in CV mortality in one study.⁸⁷ A reduction in CV events in patients treated with methotrexate was also suggested by 2 recent systematic reviews.^{88,89}

Methotrexate has been the most widely studied of the disease-modifying agents with regard to the impact on CV risk, but there is a suggestion that the use of other traditional DMARDs (hydroxychloroquine, sulfasalazine, and leflunomide) may also be associated with a lower CV risk.^{90,91}

Biologic Response Modifiers

Of the biologic response modifiers used for the treatment of RA, anti-TNF agents have garnered the most attention for their impact on HF given the initial investigations into their role as a potential therapeutic agent. Trials of etanercept and infliximab failed to

demonstrate any treatment benefit and, in the case of infliximab, suggested a potential harm with a higher rate of HF and hospitalization.^{92–95}

Among patients with RA, the risk associated with the use of anti-TNF agents remains less clear. Data from observational cohort studies and long-term extension studies of patients with RA treated with anti-TNF agents have failed to show an increased risk of new or worsening HF. The possibility of a decreased risk associated with anti-TNF therapy has also been suggested.^{86,96} In a large observational cohort of 13,171 patients with RA, HF was significantly less common in anti-TNF-treated patients (3.1% [180/5832] vs 3.8% [281/7339], $P < .05$). Patients in this study who received infliximab were less likely to have a history of CVD than those who did not (47.8% vs 54.4% [4820/8864]), which may be reflective of the awareness of the treating clinician of the Food and Drug Administration's warnings that arose out of the trials of anti-TNF agents in HF.¹⁷ The applicability of these results to all patients with RA remains unclear in the absence of randomized controlled clinical trial data.⁹⁷ Nevertheless, the ACR's current recommendations for patients with HF recommend against the use of anti-TNF agents in patients with NYHA class III/IV HF with an ejection fraction of 50% or less.⁹⁸

SLE

Coronary artery disease is a well-recognized cause of morbidity and mortality among patients with SLE, with autopsy evidence of atherosclerosis in up to 50% of patients.^{99,100}

The risk of MI in patients with SLE (after adjusting for CV risk factors) has been estimated to be between 2 and 9 times greater than the general population depending on the study setting.^{101,102} The increased relative risk is especially striking in young women, with a prospective cohort study estimating that women in the 35- to 44-year-old age group were more than 50 times more likely to have an MI compared with women of a similar age.¹⁰²

Premature atherosclerosis is a recognized complication of SLE, which is associated with significant morbidity and mortality, with subclinical evidence detected more frequently among patients with SLE than the general population. Coronary calcification (a known marker of atherosclerosis) was seen more commonly among patients with SLE with no prior history of coronary artery disease when compared with control subjects (20 out of 65 vs 6 out of 69, $P = .002$).¹⁰³ Evidence of carotid plaque on ultrasound was more common in 197 patients with SLE compared with matched controls (37.1% vs 15.2%, $P < .001$).¹⁰⁴ Age, male gender, longer disease duration, higher damage scores, and longer duration of steroid therapy have been associated with a higher risk for subclinical atherosclerosis.^{103–106}

The role of the innate immune system in the pathogenesis of SLE and associated CVD is an area of ongoing research. Type 1 interferon has been implicated in animal studies through its impact on recruitment of T cells and macrophages into atherosclerotic lesions and endothelial dysfunction.^{107,108}

HF

The risk of HF is higher among patients with SLE. Women with SLE were 3.8 times more likely to be admitted to hospital for HF than age-matched patients without SLE in one study.¹⁰⁹ Tissue Doppler and strain imaging in patients with SLE with no signs of HF were more likely to show evidence of systolic and diastolic dysfunction when compared with a matched healthy control group.¹¹⁰

A total of 173 patients with SLE (with no evidence of coronary artery disease or valvular disease) compared with an age- and gender-matched reference group without SLE were

more likely to have increased LV mass (38.3 vs 32.8 g/m², $P<.001$) on echocardiogram, suggesting that this may be a possible mechanism behind the increased risk seen in this population.¹¹¹

Traditional CV Risk Factors

Studies of CV risk factors suggest that patients with SLE are more likely to be hypertensive than the general population, with an RR of 2.59 (95% CI 1.79–3.75) in one study.^{103,104,112} In a case control study of 250 women with SLE examining risk factors for CHD, hyperlipidemia and smoking were not seen more frequently compared with controls.¹¹² The prevalence of traditional CV risk factors is higher among patients with SLE, but the increased risk is not explained by traditional risk factors.^{113–115} Among 263 patients with SLE attending a lupus clinic, after adjusting for baseline CV risk using the FRS, the increase in the RR for nonfatal MI was 10.1 and 17.0 for death caused by CHD, suggesting that the increased risk is unlikely to be explained by traditional CV risk factors and is likely contributed, in part, by the chronic inflammation and the resulting increase in risk of atherosclerosis.^{116,117}

AS

AS represents the prototype of the spondyloarthropathies and is characterized by axial disease, enthesitis, and oligoarthritis. Although the risk of CVD in patients with AS has not been as well defined as in RA, there has been heightened awareness of the risk of CVD in this population.^{118–121} A recent retrospective cohort study using population-based administrative data from 8616 patients with AS reported, the sex standardized prevalence ratio for IHD was 1.37 (95% CI 1.31–1.44) and for HF was 1.34 (95% CI 1.26–1.42).¹¹⁹

PSORIASIS AND PSORIATIC ARTHRITIS

Both psoriasis and psoriatic arthritis have been shown to be associated with an increased risk of CV disease relative to the general population. The prevalence of traditional CV risk factors has been demonstrated to be higher among patients with psoriasis; but even after adjusting for these variables, the risk of IHD remains high (OR 1.78, 95% CI 1.51–2.11), with recent studies suggesting that psoriasis may be an independent risk factor for MI.^{122–124} Patients with psoriatic arthritis are more likely to have evidence of preclinical atherosclerosis and are at an increased risk of CVD relative to the general population.^{121,125–127} Among 648 patients with psoriatic arthritis enrolled in the University of Toronto database, the risk of MI (standardized prevalence ratio 2.57, 95% CI 1.73–3.80) and angina (1.97, 95% CI 1.24–3.12) was significantly higher than that of the general population, with increased risk seen in patients with more severe psoriasis.¹²⁸

Although data on the increased risk of CVD among patients with psoriatic arthritis and AS are emerging, they have been recognized to be important factors contributing to increased mortality and morbidity in this patient population and represent an area of ongoing research; the EULAR's current recommendations for CV risk management recognize these as risk factors.⁴²

SUMMARY

CVD remains a significant comorbidity associated with rheumatic diseases contributing to the higher mortality rate relative to the general population.

The risk of HF has been best described in RA, which is more frequently associated with diastolic dysfunction. Patients with RA are less likely to present with typical features of HF

or IHD, which underscores the importance of awareness on the part of treating clinicians for a high index of suspicion for CVD in the absence of the clinical features that are typically seen in the general population. The mortality rate after an MI is higher among patients with RA, which is potentially related to less aggressive treatment approaches in this population. Patients with RA and HF are treated less aggressively and have worse outcomes compared with the general population. Increased awareness of a higher CVD risk may ultimately translate into better treatment outcomes in the future.

The pathogenesis of the increased CVD risk seen in this population remains incompletely understood; but the role of systemic inflammation in the pathogenesis of premature atherosclerosis, IHD, and HF has been illustrated. Innate and adaptive immune mechanisms shared by CV diseases and systemic rheumatic diseases have been identified and are promising areas for expanding understanding of the pathogenesis of the increased risk as well as the identification of potential novel treatment targets.

It has been recognized that the increased risk of CVD in rheumatic diseases is not explained in entirety by the traditional CV risk factors. Isolated treatment of CV risk factors in the absence of adequate control of disease activity is unlikely to effectively reduce the CV risk; therefore, the current treatment strategies are focused on targeting both of these areas. Traditional CV risk factor identification and treatment is suboptimal among patients with RA; it remains unclear if the treatment targets used for the general population are applicable, especially in light of the paradoxical role of some risk factors.

Treatment strategies for the rheumatic diseases frequently involve the use of glucocorticoids and NSAIDs, both of which have been associated with a higher risk of CVD. Among patients with known CVD and rheumatic diseases, the use of glucocorticoids and NSAIDs should be avoided or minimized. There has been no increased risk associated with the use of traditional DMARDs; in fact, methotrexate use has been associated with improved CV outcomes, likely reflecting the impact of better control of disease activity. The safety of anti-TNF agents in patients with RA and HF remains less well defined and will warrant further study.

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KEY POINTS

- There is an increased risk of cardiovascular disease–related mortality associated with systemic rheumatic diseases, which is not explained entirely by traditional cardiovascular risk factors and is likely related to both inflammation and immune-mediated mechanisms.
- The risk of heart failure in rheumatic arthritis (RA) is almost twice that of the general population; although it has been associated with worse outcomes, the treatment of heart failure in RA remains less aggressive.
- Aggressive control of rheumatic disease activity in conjunction with traditional cardiovascular risk factor modification is important in the management of patients with RA, although the impact on long-term outcomes remains incompletely understood.

Fig. 1. Survival in RA compared with expected survival in the general population. (From Gabriel SE, Crowson CS, Kremers HM, et al. Survival in rheumatoid arthritis: a population-based analysis of trends over 40 years. *Arthritis Rheum* 2003;48(1):56; with permission.)

Fig. 2.

Comparison of the cumulative incidence of congestive HF in the RA cohort and the non-RA cohort, according to the number of years since the index date, adjusting for the competing risk of death. (From Nicola PJ, Maradit-Kremers H, Roger VL, et al. The risk of congestive heart failure in rheumatoid arthritis: a population based study over 46 years. *Arthritis Rheum* 2005;52(2):416; with permission.)

Fig. 3.

Distribution of ejection fraction (EF) between patients with RA and non-RA patients at the onset of HF. Data are presented as box plots: The boxes represent the 25th to 75th percentiles, the vertical lines represent the 10th and 90th percentiles, the diamonds represent the means, the lines within the boxes represent the medians, and the broken line represents the 50% EF reference. (From Davis JM 3rd, Roger VL, Crowson CS. The presentation and outcome of heart failure in patients with rheumatoid arthritis differs from that in the general population. *Arthritis Rheum* 2008;58(9):2606; with permission.)

Fig. 4. HRs for CVD in RA (*solid lines*) according to (A) total cholesterol (TCh) and (B) LDL. Shaded areas represent 95% CIs. (From Myasoedova E, Crowson CS, Kremers HM. Lipid paradox in rheumatoid arthritis: the impact of serum lipid measures and systemic inflammation on the risk of cardiovascular disease. *Ann Rheum Dis* 2011;70(3):484; with permission.)

Fig. 5. Erythrocyte sedimentation rate (ESR) levels before and after development of HF. (From Maradit-Kremers H, Nicola PJ, Crowson CS, et al. Raised erythrocyte sedimentation rate signals heart failure in patients with rheumatoid arthritis. *Ann Rheum Dis* 2007;66(1):76–80; with permission.)